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Ethics in musculoskeletal regenerative medicine; guidance in choosing the appropriate comparator in clinical trials

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SUMMARY

Background: Regenerative Medicine (RM) techniques aimed at the musculoskeletal system are increasingly translated to clinical trials and patient care. This revolutionary era in science raises novel ethical challenges. One of these challenges concerns the appropriate choice of the comparator in (randomized controlled) trials, including the ethically contentious use of sham procedures. To date, only general guidelines regarding the choice of the comparator exist.
Objective: To provide specific guidelines for clinical trial comparator choice in musculoskeletal RM.
Methods: In this manuscript, we discuss the ethics of comparator selection in RM trials. First, we make a classification of RM interventions according to different health states from disease prevention, return to normal health, postponing RM treatment, supplementing RM treatment, substituting RM treatment, improving RM outcome, and slowing progression. Subsequently, per objective, the accompanying ethical points to consider are evaluated with support from the available literature.
Results: a sham procedure is demonstrated to be an ethically acceptable comparator in RM trials with certain objectives, but less appropriate for musculoskeletal RM interventions that aim at preventing disease or substituting a surgical treatment. The latter may be compared to 'standard of care'.
Conclusion: From a scientific perspective, choosing the correct comparator based on ethical guidelines is a step forward in the success of musculoskeletal RM.

Introduction

Suppose a clinical scientist aims to investigate the efficacy of a (allogeneic) stem cell injection in patients with early stage intervertebral disc disease. Would it be ethically sound to allocate participants to an invasive placebo (sham) procedure in a randomized controlled trial (RCT)? Or suppose one participates in a Research Ethics Committee (REC) and has to review a research protocol in which participants with end-stage knee osteoarthritis are randomized to either a stem cell injection in the knee, or an injection with saline solution. How does one decide on ethical approval? These are two examples that illustrate the recent challenges clinical scientists and RECs face when choosing or evaluating the appropriate regenerative medicine (RM) comparator in a clinical trial for a musculoskeletal disorder. 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 application of such technologies in early stage disease, and the novelty and even hype of the field, a new light is shed on ethical challenges[5,6]. Here, ethical considerations go hand in hand with scientific questions. For example, is a sham procedure the most

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important comparator when introducing a new cell therapy for cartilage tissue engineering?[7–14] Although a guideline for products aimed at cartilage repair of the knee exists[15–17], it does not cover the wide range of other musculoskeletal RM applications. This lack of ethical standards creates difficulties for scientists and RECs when designing or evaluating RM clinical trials. In this paper, the ethics of comparator selection in musculoskeletal RM trials is discussed. First we make a classification of the disease development stages and show which objectives of RM interventions can be distinguished. Subsequently, per objective, the main accompanying ethical considerations will be shortly discussed. Here, the focus lies on the challenges in the choice of the comparator for trials aimed at showing efficacy of RM techniques.

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. In musculoskeletal disorders, four main stages can be identified: (1) *at risk of the disease*, (2) *early stage disease with minor symptoms*, (3) *intervention indicated* and (4) *late stage disease with severe symptoms (conservative measures only)* (Fig. 1).

Examples of disorders in which these stages can be distinguished are degenerative musculoskeletal disorders such as osteoarthritis and intervertebral disc degeneration. Not all disorders follow this disease pathway. Currently, musculoskeletal RM interventions are 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 based on disease stages. 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 slow the progression of disease. RM can be aimed at substituting the surgical treatment, or at supplementing treatment. Other interventions are aimed at postponing surgery. RM in a *late stage* disease, where an alternative is lacking, is aimed at slowing disease progression or restoration of function.

The main types of comparator in RM clinical trials

The preferred method of establishing an intervention and control group that allow an unbiased comparison regarding efficacy is via randomization[7,8]. Although conducting clinical trials for invasive interventions involve practical and ethical hurdles, the RCT is the default when the objective is to assess efficacy of an intervention[18–23]. The main types of comparators in RCTs are placebo, standard of care or no intervention. Examples of standard of care include; a conventional surgical procedure, another RM intervention, pain management and physiotherapy. 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. Placebos are assumed necessary to increase the validity of testing efficacy, particularly when clinical endpoints such as quality of life are incorporated in the trial[24]. A placebo allows for blinding which ensures that the participants and/or 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 requires an *invasive placebo*, or a *sham intervention*. For symptomatic patients, delayed treatment or historical control groups can be considered and approved by the Food and Drug Administration (FDA). However, optimal comparability with historical and delayed treatment control groups should be ensured to limit bias. This can be achieved by proper demographic analysis and ensuring comparability in follow-up. In this paper, we mainly focus on phase II–III (randomized) clinical trials. However, it should be acknowledged that the trial phase itself could influence the comparator choice. For example, a phase I trial is generally focused on safety and comprises a single-arm cohort. If a comparator is used, a (non-treatment) control is the comparator of choice. Similarly it is assumed that the clinical trials have undergone the necessary preclinical analysis along with relevant comparators. If the preclinical data is deemed insufficient by the REC, preclinical comparator selection may be advised prior to launching a clinical trial.

Ethical considerations in comparator choice in RM

The first human cartilage cell therapy was introduced over 30 years ago. Aimed at the regeneration of full-thickness focal cartilage

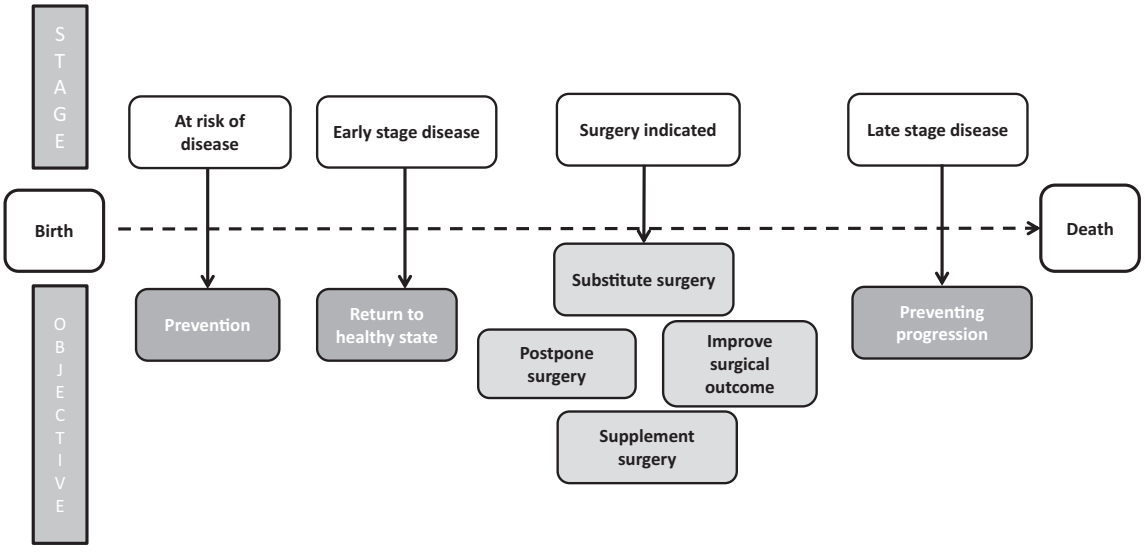

Fig. 1. Musculoskeletal disease stages with the therapeutic objectives.

defects, autologous chondrocyte implantation (ACI) was tested in a preclinical rabbit model before a first-in-man trial ($n = 23$) was launched[26]. In ACI, chondrocytes are harvested from a biopsy from healthy cartilage, expanded and re-implanted in a second surgical procedure. Although the above mentioned trial can be considered a phase I (safety) trial, no controlled (i.e., using a non-treatment or sham comparator) trials followed. Instead, the trial fueled the field of RM resulting in several advancements in ACI techniques[27]. RCTs followed, using microfracture as comparator. In this procedure, small penetrations are made in the subchondral bone during an arthroscopy, allowing a bone-marrow derived blood clot to stimulate fibrous tissue repair. As it is minimally invasive, straightforward and inexpensive, it has proven a valuable treatment option. Recently, a long-term follow-up of a RCT showed comparable outcomes for ACI and microfracture[28]. Currently, cell therapy is primarily indicated for larger defects, or defects which failed to respond to microfracture. Thus microfracture is considered a suboptimal comparator[27]. Because of the clinical trial experience and the known response to articular cartilage repair, it is suggested that a sham or non-treatment controlled trial has ethical flaws. Hence, the threshold to perform placebo or non-treatment controlled trials for RM interventions aimed at focal cartilage defects is high. For osteoarthritis, one placebo controlled trial was published showing superior clinical and radiological outcomes for an allogeneic Mesenchymal stromal/ stem cell (MSC) injection compared to hyaluronic acid with 15 patients in each arm[29]. As osteoarthritis is an end-stage disease, and the burden of injections is relatively low, the threshold to perform injection-based placebo controlled trials is relatively low. This is in contrast to focal cartilage defects, which are diagnosed in younger and active patients that require a surgical procedure, resulting in an invasive control such as a sham procedure. Thus the stage of the disease influences the ethical considerations in RM trial comparator selection. Again, the use of a sham intervention as a comparator raises ethical debate. In a letter to the editor, sham interventions were called 'ludicrous' based on the risks without potential therapeutic benefits for participants[30]. 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[31]. 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'[31]. 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. In addition, the use of a placebo should lead to scientific valid results[9,10].

Scientific validity

When performing an invasive placebo in RM trials, effects caused by the insertion of a surgical instrument (e.g., scope, needle) and/or its accompanying fluid or gel should also be considered[32,33]. Indeed, 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". Since the RM field is an upcoming field accompanied by new uncertainties[27] 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.

Risk-benefit assessment

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, i.e., the anticipated social value or aspirational benefits[9,10,32–34]. A risk-benefit assessment could include a sham modification plan to enhance the potential benefits[35]. For example, the risks 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].

Informed consent

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[38]. Here, the participant confuses care with research, which could compromise a valid consent. Therapeutic misconception may especially occur in the field of RM, where expectations of researchers and participants are high[39]. Therefore, in sham-controlled RM trials one should take safeguards to decrease the chance of therapeutic misconception, 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 in consent forms[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.

Methods: ethical points to consider according to disease stages

Defining specific study objectives and disease stages (Fig. 1), may allow for a standardized comparator choice (Box 1). The corresponding ethical considerations are provided below.

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 patients' do not yet suffer from symptoms. For the musculoskeletal system, examples are individuals with incidental findings of radiographic osteoarthritis without pain or dysfunction[45]. These risk factors could also include genetic mutations or elevated biomarker levels strongly related to disease[46,47].

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 as effective, one should provide the regime to the control group. However, when placebo effects or bias are expected, a sham-controlled

Box 1
Guidelines in trial comparator choice; ethical considerations per objective

RM aimed at prevention			
Comparator	**Sham**	**Risk/benefit assessment**	**Informed consent**
Standard of care	no	- Low anticipated social value - Risk of losing functionality	Acknowledge risk of misunderstanding due to uncertainty
RM aimed at returning to healthy state			
Comparator	**Sham?**	**Risk/benefit assessment**	**Informed consent**
- Standard of care - Placebo - Add on	yes	- Risk of losing functionality - Relatively high anticipated social value	Take safeguards on probabilities in disclosure
RM aimed at postponing surgical treatment			
Comparator	**Sham?**	**Risk/benefit assessment**	**Informed consent**
- Standard of care - Placebo	yes	- Risk of losing functionality - Relatively high anticipated social value if standard of care has risks	Take safeguards on probabilities in disclosure
RM aimed at supplementing surgical treatment			
Comparator	**Sham?**	**Risk/benefit assessment**	**Informed consent**
- Add on − Standard of care - Placebo	yes	High social value if: - suboptimal standard - need for improved clinical outcome	In acute stage of surgery consider impaired consideration due to: - Anxiety and stress - Limited voluntariness
RM aimed at substituting surgical treatment			
Comparator	**Sham?**	**Risk/benefit assessment**	**Informed consent**
- Standard of care - (delayed) Control - Historical control	No	High social value if: - completed early safety and efficacy stages - improved cost-effectiveness	Standard
RM aimed at improving surgical treatment			
Comparator	**Sham?**	**Risk/benefit assessment**	**Informed consent**
- Standard of care - Placebo	yes	Risk proportionate to social value if: - time between surgery and sham is relatively high - outcome of surgical treatment is currently suboptimal	In acute stage of surgery consider impaired consideration due to: - Anxiety and stress - Limited voluntariness
RM aimed at slowing progression			
Comparator	**Sham?**	**Risk/benefit assessment**	**Informed consent**
- Standard of care - Placebo	yes	- High social value as no other treatment options - Risks are relatively low	Consider risk of therapeutic misconception

(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 as healthy participants have much functionality to lose[9]. The anticipated social value of the intervention depends on the nature and magnitude of the improvement in the wellbeing[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. However, 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[48]. Hence, the benefits of these trials to society are relatively uncertain. 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. See Box 1.

Objective: return to healthy state − stage: early stage disease

Currently, RM interventions are mostly developed for early stage of disease with the aim to return these patients to a healthy state or slow disease progression. Although. these individuals mainly suffer from minor symptoms, activities of daily living can be impaired[5]. Examples in the field of musculoskeletal RM are patients with focal meniscal or knee and ankle cartilage injuries, tendon injuries and young patients with low back pain[5]. 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. When early disease stages are accompanied by more severe symptoms such as in early osteoarthritis, an add-on design can be considered, especially 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. See Box 1.

Objective: postpone surgical treatment – stage: intervention 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 long-term disadvantages. For example, using a RM intervention to delay the need for total knee arthroplasty in young and active patients falls into this category. 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, and 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 success 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. When the disease is far developed and painful, it is more urgent to conduct surgery.

The anticipated social value can especially be considered high when the standard surgical procedure has disadvantages. When these potential benefits to society are high, they could outweigh the risks. 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. See Box 1.

Objective: supplementing RM – stage: intervention 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 the RM field is the addition of autologous cells to core decompression surgery for osteonecrosis of the femoral head. 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, a sham procedure on top of the procedure is required to blind the participant. An accompanying advantage is that it allows blinding of 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, and if anxiety and stress may impede adequate consent. See Box 1.

Objective: substituting surgical treatment – stage: intervention indicated

RM interventions aiming at substitution are mainly developed to provide a more effective or efficient procedure. Examples are the development of a single stage (stem-cell based) treatment as a replacement for ACI, or the use of growth factors in spinal fusion procedures. From a scientific point of view, it is relevant to gain knowledge regarding relative efficacy, which can be achieved by comparing the RM intervention to the available surgical procedure, provided the latter has net clinical relevance. A sham comparator could be considered to limit bias. The choice for a standard of care comparator minimizes risks to the control group. Delayed treatment or historical control groups can be considered, although resulting in a greater risk of bias. Blinding patients and investigators is not always feasible since the procedures may require different surgical modalities[22]. In such case, one should consider blinding the outcome assessors, by allowing a separate team to perform the follow-up.

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 ensure that the RM intervention has completed early safety and efficacy stages to allow proper comparison with the existing procedure. In general, novel RM interventions aim at improving cost-effectiveness, resulting in high social value. The described challenges (and additional ones) are similar to trials testing existing surgical interventions against novel surgical procedures[22]. See Box 1.

Objective: improving outcome of surgical procedure – stage: intervention indicated

RM interventions may aim at improving the outcome of a procedure with application shortly after the intervention. A recent example for the musculoskeletal system is a RM trial that evaluated the effect of adult mesenchymal stem cells via intra-articular injection to the knee following partial meniscectomy[49]. Another example is patients elected for disc herniation surgery or spinal fusion surgery as these are on a higher risk of developing disc degeneration.

In order to gain knowledge on the efficacy of these interventions, a sham intervention as a comparator could be 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 latter could affect the recovery from surgical treatment. The burden for the participants may be 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 suboptimal. 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. See Box 1.

Objective: slowing progression – stage: late stage disease and no other options

For musculoskeletal disorders such as advanced intervertebral disc degeneration, no therapeutic options are available. In these disorders, a sham intervention as a comparator could be 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. Nevertheless, 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. 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 therapeutic misconception (TM). See Box 1.

Conclusions

As musculoskeletal 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 demonstrated that the appropriateness of the comparator for a RCT is largely determined by the objective of the RM intervention. A placebo or sham procedure is the most appropriate comparator for the majority of these objectives but is less appropriate when the trial is aimed at prevention or substituting surgical treatment. Adequate comparator selection reduces bias and corrects for insertion effects. Further, the inherent risks of a sham intervention could be acceptable when functionality remains unimpaired and there is a high anticipated social value. As sham interventions can give rise to misunderstanding of participants, extra safeguards should be taken to ensure a valid informed consent procedure. This is especially relevant for patients undergoing acute surgery and those suffering from late stage disease. Although no-treatment control groups and sham interventions are ethically contentious, they are essential to establish an evidence-based research field. If an alternative such as a delayed treatment or historical control group is considered, comparability between treatment arms should be prioritized to limit bias. Recent initiatives in the cartilage RM field to launch a global registry may aid in proper historical control group selection for novel RM procedures. Compared to available literature, this paper provides a comprehensive analysis of both the main ethical and methodological aspects of comparator selection in musculoskeletal RM trials. As a consequence, more similarity in the choice of the comparator in musculoskeletal 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, other determinants such as disease characteristics and treatment alternatives can influence the adequate choice of the comparator. Future ethics research should analyze to what extent these standards are applicable to disorders without a gradual disease progression. Finally, analysis should take place on when RCTs are scientifically necessary and feasible for testing the efficacy of orthopedic RM interventions, and when other trial designs such as observational cohorts are more appropriate.

Contributions

- Conception and design (TdW, SN, JvD, KR, WD, AB)
- Analysis and interpretation (TdW, SN, JvD, KR, WD, AB)
- Drafting of the article (TdW, SN, AB)
- Critical revision for intellectual content (TdW, SN, LV, JvD, KR, WD, DS, AB)
- Final approval of the article submitted (TdW, SN, LV, JvD, KR, WD, DS, AB)
- Obtaining of funding (SN, JvD, KR, WD, AB)

Conflict of interest statement

The authors declare that there is no conflict of interest.

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