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Personalized 3D printed scaffolds: The ethical aspects

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ABSTRACT

Personalized 3D printed scaffolds are a new generation of implants for tissue engineering and regenerative medicine purposes. Scaffolds support cell growth, providing an artificial extracellular matrix for tissue repair and regeneration and can biodegrade once cells have assumed their physiological and structural roles. The ethical challenges and opportunities of these implants should be mapped in parallel with the life cycle of the scaffold to assist their development and implementation in a responsible, safe, and ethically sound manner. This article provides an overview of these relevant ethical aspects. We identified nine themes which were linked to three stages of the life cycle of the scaffold: the development process, clinical testing, and the implementation process. The described ethical issues are related to good research and clinical practices, such as privacy issues concerning digitalization, first-in-human trials, responsibility and commercialization. At the same time, this article also creates awareness for underexplored ethical issues, such as irreversibility, embodiment and the ontological status of these scaffolds. Moreover, it exemplifies how to include gender in the ethical assessment of new technologies. These issues are important for responsible development and implementation of personalized 3D printed scaffolds and in need of more attention within the additive manufacturing and tissue engineering field. Moreover, the insights of this review reveal unresolved qualitative empirical and normative questions that could further deepen the understanding and co-creation of the ethical implications of this new generation of implants.

1. Introduction

One promising technology for personalized tissue engineering (TE) is additive manufacturing, also known as 3D printing. 3D printing is a manufacturing process that creates three dimensional solid objects by printing layers of material after a computer-designed digital model [1–3]. The convergence of 3D printing with medical scanning and 3D computer modelling enables bioengineers to make scaffolds designed to fit the patient's own body. This is especially helpful for non-standard size and unique pathology-related anatomical conditions [4,5].

Scaffolds are three-dimensional support mediums for cells, and can act as temporary implants in which new tissue can regenerate [6–9]. These scaffolds are made of materials that are biocompatible, ensuring that the scaffold interacts with living cells and tissues without inducing undesirable responses. The design can be biodegradable, meaning that it can break down over time into non-toxic by-products capable of being metabolised to later exit the body, leaving space for the new tissue to grow and gradually fill the defect [9,10]. Biodegradable scaffolds may also be perceived as a form of 4D printing, in which 'time' is considered the fourth dimension. Over time, their structure undergoes transformations after the initial 3D printing process, primarily driven by interactions between the materials and their surrounding environment once the scaffold is implanted. In 2013, researchers for instance created a 3D printed biodegradable airway splint that was used to treat tracheomalacia, a potentially life-threatening condition, in a 2-month-old child [11,12]. 3D printing in TE and Regenerative Medicine (RM) is thus rapidly progressing and promises to provide a life-long solution for tissue degeneration.

At the same time, this new technology raises many well-known and underexplored ethical questions. The early experimental stages of development in which the technology currently finds itself comes with well-known ethical issues regarding animal studies in the preclinical phase. Besides that, the subsequent clinical phase gives rise to challenges related to realising first-in-human trials and, in case of paediatric

Abbreviations: TE, tissue engineering; RM, regenerative medicine; COI, conflict of interest.

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diseases, how to include children in such trials [13–15].

Moreover, the development of these implants entails collaboration between various stakeholders with different interests. This leads to additional and more specific ethical and practical challenges regarding the commercialization of scaffolds, such as the occurrence of conflicts of interest (COI) and questions regarding the accessibility of this potentially expensive technology [16,17]. Due to the novelty of this technology, it is not yet clear how these scaffolds are perceived and understood, which raises new ethical questions concerning their ontological status and the influence on human identity and bodily experiences. This has further ethical implications for how such implants are tested and later used in clinical practice [7]. Last, less obvious and under-researched ethical topics also need to be considered, such as the inclusion of gender differences in implant design to provide optimal care for every patient. It is important to map all these aspects in the early development process rather than at the end of the pipeline in order to assist the development of personalized 3D printed scaffolds in a responsible, safe, and ethically-sound manner [18].

As of yet, no specific overview of the ethical implications of personalized 3D printed scaffolds has been published. While various articles have been published on the ethics of TE and *bio*printing [1,15,19,20], these technologies involve the use of living cells, and raise different ethical questions concerning the use of embryonic stem cells and donor cells [19]. This review focuses on 3D printing only and fills this gap in the literature by identifying key ethical themes that arise in the emerging technology of biodegradable implants for TE. The various ethical issues may differ for each phase of the life cycle of the scaffold, including the development process, clinical testing and the implementation phase. Consequently, these issues are discussed separately for each phase, and are summarized in Fig. 1.

2. Development process

In the early developmental process of personalized 3D printed scaffolds, ethical issues revolve mainly around digitalization, irreversibility, responsibility and ownership, and gender. In what follows, these ethical issues will be discussed in more detail.

2.1. Digitalization

A few authors argue that, within the field of 3D printing, the biological world and the digital space have become increasingly merged [21,22]. Raw digital scans and 3D models represent personalized human data, which may be sensitive, raising questions about confidentiality and privacy [2,21,23]. If the scan of a shoulder shows pre-existing osteoarthritis, this can for instance influence a patient's insurance coverage in certain countries [23]. This information warrants protection through de-identification and anonymization, and therefore requires extra regulations regarding the information storage, handling, processing and application [21,22]. While de-identification is the removal of personal identifying information, anonymization refers to data that cannot be re-identified [23]. The latter may be challenging, for example in case of facial scans, which show highly personal characteristics [23].

As part of the digitalization process, engineers could use algorithms, to go from patient-specific data to a printable 3D model [24]. Algorithms are often used to provide more personalized care [25]. Current literature has identified several ethical aspects of their use in medical settings [25,26].

Firstly, there can be several types of bias in the design or use of the algorithm. Selection bias may occur when the available data is incomplete or biased, for example when the data based on a study population that is not representative of the overall population, and algorithms might lead to outcomes that are irrelevant or unjustified [26]. Valid and accurate algorithm outcomes therefore require that datasets are complete, timely, correct and inclusive [26]. In the case of personalized 3D printed scaffolds, it is important that this is considered in the design of the algorithm, so the implant designs are correctly personalized. Another form of bias is transfer context bias. The development of scaffolds is a multidisciplinary and global endeavour that leads to the use of the same algorithm on different sites. Bias could emerge when an algorithm is used in a different context than the context for which it was developed, and to which these data may poorly generalize [26–28].

Secondly, it is questionable to what extent clinicians and radiologists can be held morally responsible for outcomes performed by algorithms, such as implant designs, which they cannot completely understand [25]. The lack of transparency and explainability of algorithms raises questions about the moral responsibility and accountability of actions performed by algorithms and clinicians [23,26]. Therefore, when algorithms become widely available, liability can shift towards companies or developers [29]. As a possible long-term solution to this technical complexity, it is of utmost importance that clinicians, like radiologists, are educated and informed about the workings of the algorithm to prevent computational and data illiteracy when designing an implant [25,26].

2.2. Irreversibility

Many authors have pointed out the irreversible nature of

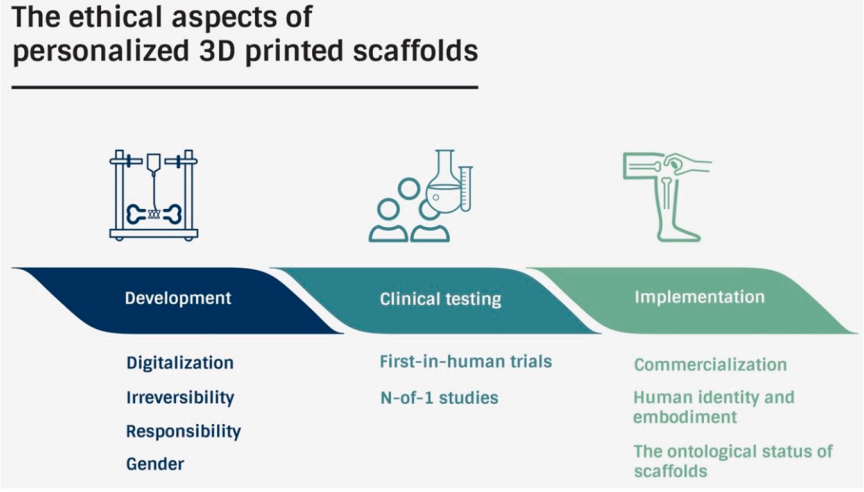

Fig. 1. Scheme depicting the ethical challenges and opportunities of personalized 3D printed scaffolds to assist their development and implementation in a responsible, safe and ethically sound manner.

biodegradable implants as ethically relevant [19–21,30,31]. Biodegradable implants are slowly broken down after implantation and thus integrate into the body and allow the body to regenerate healthy tissues. Therefore, it becomes almost impossible to remove them or rectify their effects [16,20,32]. When scaffolds are biodegradable, its irreversibility affects patients in three different ways.

Firstly, it has been argued that two principles are at stake, namely the autonomy of the patient and nonmaleficence of the clinician [30]. With regard to autonomy, it is difficult for a patient to exercise their right to withdraw from treatment or participation in a clinical trial when the implant already begins to integrate with the body [19,30,33]. With regard to non-maleficence, an attempted removal of the implant could lead to a state that is worse than if they never had an implant to begin with [19,30].

Secondly, for the same reason, patients may be ineligible to access future treatments [19,21]. Even if the implant stabilises the patient's condition, it may not be possible to replace the 3D printed scaffold with an improved treatment in the future when it has already become (partially) absorbed by the body. Therefore, it could in some cases preferable to have an implant that is not completely biodegradable because it can be more easily removed or upgraded in the future [31].

Lastly, Parry (2018) argues that the risks to humans that arise when such implants exceed their implantation sites and mode of actions and become fully integrated within the human body in irreversible ways need to be addressed. For example, if degradation products move through the bloodstream this may incur toxic effects elsewhere [19].

2.3. Responsibility

Responsibility is often mentioned in the literature and comes into play at various stages of the development and life cycle of the implant [1,21,34,35]. Due to the involvement of many stakeholders in the design process, it is unclear who can be held responsible and accountable, and to what extent, for the workings and outcomes of the personalized 3D printed scaffold.

In the field of 3D printing, tasks are commonly divided. In most countries, the clinician is responsible for the design, choice of biomaterials and their use. However, the implant may be manufactured in another country where other regulations apply resulting in the misalignment of regulatory requirements [36]. Similarly, an algorithm may be trained using data from one country, but marketed and used in another [27]. To ensure a clear distribution of responsibility and alignment of regulatory requirements, it is important to develop clear protocols and clarify blueprint and data responsibility.

In the last phases of development, questions about quality control and liability come into play [21]. Are medical organisations or manufacturers responsible for the final quality of the implant? And who should be liable in the case of claims from patients? Moreover, it is not evident who should be responsible for the further treatment and aftercare, for example in case of failed implants [34]. Therefore, the risks and performance of scaffolds should be managed and regulated within the field [35]. The question arises who compiles the feedback from surgeons and patients on performance and other data on the implant design [37]. To minimize the pain and suffering of patients, it is of utmost importance that an institution is appointed to have the professional responsibility for maintaining a shared record on medical implant failure [34,37]. These questions are in need of an answer now that the field is approaching clinical application.

2.4. Gender

Traditionally, gender is described as the socially constructed characteristics that are associated to being a woman or man. Sex refers to femininity and masculinity in terms of gonads, genes and genitals, i.e. 3 G-gender. While in health care this traditional distinction is made, here we understand gender to include sex also, unless otherwise indicated. This is because, as Judith Butler has argued, both sex and gender are socially constructed concepts, so sex falls under the scope of gender [38]. In the following paragraphs, we will discuss gender differences between men and women, because this is the focus of most research. However, it is essential to take differences between people of all genders into account.

Evidence shows that women's bodies, activities and experiences tend to be overlooked and not included in the design and clinical use of medical implants [39]. Hutchison and Rogers [40] discuss how previously implanted devices have led to disproportionate harm to women compared with men. As part of a personalized approach, it is important that gender differences are taken into account throughout the life cycle of the scaffold to promote efficient and accurate results and to prevent health inequities [41]. Gender differences can affect the design and clinical use of biodegradable implants in several ways.

Firstly, animal studies are primarily conducted on males and cell culture studies often ignore the sex of the individual from whom the cells were obtained [42]. The cisgender male body is still seen as the 'typical'/normal body, which results in an overrepresentation of cisgender men in human trials [40]. This, in turn, could affect the validity and reliability of trial results for people of other genders. For example, since women generally have a smaller blood volume than men [39], the same amount of by-products of a biodegradable implant may be toxic in women yet not in men. These differences need to be considered when designing personalized 3D printed implants by, for example, enforcing representation of people of all genders in clinical research.

Secondly, the past focus on cisgender males may still influence the outcomes of new devices in the present due to the market approval process [40]. Novel medical devices can be accepted via fast-track pathways, for which data of similar devices that were previously approved can be used and new data are not required [28,39,40]. Bias in the previously collected data could therefore also affect the design of the new implant [40]. Ordinary movements that put weight on joints may be different for people of different genders and negligence of these differences have let to complications in the past [39]. For example, a study from 2014, showed that the way in which female hips are positioned during heterosexual intercourse was not considered in the testing phases of previous hip implants, resulting in higher risk of dislocation of the hip in women [40,43]. For personalized 3D printed scaffolds, it is essential to consider such differences in lifestyle and movement by including people of different genders and sexual orientations in clinical research.

Thirdly, even when people of different genders are included in the research process, the research often fails to report on the sex and gender of participants or fails to conduct gender-specific analyses [39]. Reporting should thus be improved and analyses should be conducted so that potential differences can be taken into account in the implant design or – if this is not possible – by providing gender-related advice to their patients [39]. For example, people who often walk on heels could be advised not to do so if this damages the scaffold.

Finally, economic imperatives also interact with gender bias. In general, device trials are expensive to conduct and difficult to organise [40]. So, once a device is approved without specific obligations about the inclusion of patients of different genders, there is no financial incentive to undertake further gender-specific trials. Besides that, further research may find that the device is unsafe and ineffective in the new population, thereby limiting future profitability [40].

3. Clinical testing

In the clinical testing phase of 3D printed scaffolds first-in-human trials and N-of-1 studies raise ethical questions.

3.1. First-in-human trials

After the development process of the scaffold, the clinical testing phase begins, starting with first-in-human trials which raises various

ethical issues [13,14,19,20]. Participant selection is a key component of ethically sound first-in-human clinical trial design of personalized 3D printed scaffolds [14,44]. Phase I trials are often conducted on healthy individuals to test safety only. As these implants aim at restoring damaged, degenerated or diseased tissue they should not be tested on healthy individuals [20,45]. However, orthopaedic patients who need such scaffolds are generally relatively healthy. In this case, the question arises if the uncertainty of risks outweighs the potential benefits since the early phases of clinical trials tend to generate little benefit to the participant [14,20]. In general, the risks to participants during clinical trials must be reasonable and acceptable compared to the potential benefits of the research to science, society and the individual [20]. It could be a solution to add an assessment of therapeutic efficacy to the objectives of phase I trials, rather than focusing on safety testing alone [19].

Another ethical issue that arises in this context relates to testing scaffolds in children. Excluding children from first-in-human trials hinders potential benefits of new treatments to children that are seriously ill [13]. Several additional conditions need to be considered when conducting a first-in-human trial with children. For the inclusion of children informed consent of both parents or a legal representative and, if possible, valid assent (the agreement of an individual who has not reached the age of giving legal consent) of children is needed [13]. In general, the involvement of parents and (if possible) participants in reducing possible burdens by giving them the opportunity to give their opinions on the risk-benefit analysis, trial design and the participant selection is of utmost importance. Overall, there must be a scientific necessity [13]. In the case of a therapeutic intervention, it is ethically justified to include children when a favourable risk-benefit balance is present. This means that the possible harms should be minimised and a reasonable estimation of the possible benefits of the personalized 3D printed scaffolds should be made. Nonetheless, this estimation is complicated due to the poor translation of evidence of preclinical in-vitro and animal studies to humans [13]. During this process, all stakeholders should be aware of the possibility of a therapeutic mis-estimation in which researchers, participants and/or parents underestimate the potential harms and overestimate the potential benefits. The testing of nontherapeutic interventions in children is only morally justified if the condition affects only children, the necessary data cannot be gathered without their participation and risks are minimized [13].

3.2. N-of-1 studies

These biodegradable implants are uniquely tailored and designed to target a specific condition for a particular individual [19,21]. This might lead to different requirements and modifications to test each personalized implant design [21]. N-of-1 studies are such trials with a single patient. The literature mentions two important ethical issues related to n-of-1 studies [19,21].

Firstly, because each scaffold is unique, it would be ethically unjustified to test safety first on a person or population for whom the implant was not designed, given the possible harms and risks [19,46]. Secondly, as each treatment is unique and takes the conditions of only one person into consideration, the results cannot be generalized to future treatments and populations [21,47]. This means that each patient becomes its own testing subject, raising questions about efficiency and the protection of the individual [19,46]. Normally, the mechanical stability of an implant can be analysed via simulation or experiments. However, in the case of unique implants this needs to be repeated for each implant since anatomical shapes can differ and, therefore, weaken the overall structure [4]. In general, this inherent variation of a personalized approach affects the external validity, i.e. generalizability of the study results [47].

This calls for a different testing approach since the current evidence paradigm does not fit patient-specific implants [47]. Although the patient-specific shape and structure of the implants differs, the criteria, protocols and materials for making such a scaffold could be standardized and tested in different populations, and some of the obtained data could be generalizable for other populations [19,21]. However, more research is needed to improve safety and performance of such personalized scaffolds.

4. Implementation process

After a successful development and testing phase of the life cycle of the scaffold, these implants would be implemented into regular medical care, which could have implications for society at large. During this process, the most relevant ethical issues are commercialization, human identity and embodiment and debates on (un)naturalness and liveliness.

4.1. Commercialization

3D printing and RM are initially developed in an academic setting and will eventually be commercialized. According to the academic literature, financial incentives raise ethical issues related to COI, ethical marketing and distributive justice, which will be discussed below.

Firstly, the involvement of many stakeholders, like patients, clinicians, (device) manufacturers, universities and governments raises questions regarding how such collaborations are best shaped and managed. On the one hand, it has been argued that clinicians doubt the validity of results from industry-sponsored clinical trials and are less willing to apply the treatments from such trials [15,16]. On the other hand, if various stakeholders collaborate, their incentives and values may differ in important ways, and COI could occur. COI might have negative effects on the integrity of researchers and the scientific validity of the research outcomes and can result in a methodologically flawed study design [14].

Relatedly, it has been argued that the fiduciary responsibilities of device manufacturers to investors could produce potential conflicts for patient care [34,48–50]. It has been said that especially innovations in the field of RM are at risk of being pushed onto the market too early because they are often manufactured by small parties and sponsored by private equity investors, who need their money back as fast as possible [14]. Medical device manufacturers are strongly interested in the suppression of negative results to prevent financial risks through the publication of unfavourable results [14,49]. When individuals with a financial interest in a TE product are involved in the testing process or clinical translation, full disclosure should be given about the COI, including financial, personal, and those related to intellectual property [16]. Overall, stakeholders who have financial interests or lead clinical studies should not make the decisions alone when clinical results are evaluated [16]. Other forms of COI could occur in the interactions between clinicians and manufacturers regarding clinical education and training [31]. Good relationships between the manufacturer and clinicians could lead to brand loyalty which may lead to problems when the interests of manufacturers and patients are not aligned [31].

Secondly, ethical marketing plays an important role in the commercialization of medical implants. Device manufacturers provide an important source of information to consumers regarding their technological innovation through advertising messages [51]. The marketing of such implants must include full disclosure of all risks and benefits [51,52]. Manufacturers must also be willing to acknowledge potential cultural or social controversies surrounding an implant [51]. Honest and unambiguous marketing is the strongest strategy to fully meet the needs of customers and to build a trustworthy relationship with healthcare consumers [51].

Thirdly, multiple authors argue that there is a possible danger that 3D printing for TE purposes will only be accessible to the happy (wealthy) few and will further widen the gap between the rich and the poor and therefore evoke questions about distributive justice [21,32,53]. Products for TE, such as 3D printers with the ability to print implants with fine resolutions, are likely to be expensive [9,32].

Additionally, it costs money to ensure that such implants be routinely used in all clinical contexts and medical staff needs to be trained to handle such complex regenerative procedures [54].

Reimbursement and fair pricing may broaden access to this new technology [32]. Although the price of scaffolds could be low due to mass production, the scaffolds in question are personalized which makes mass production almost impossible. Even if the price is low, the question still exists whether the lowest price is affordable for disadvantaged patients [50]. Relatedly, in some countries specialised centres are only located in specific areas or only available in large teaching hospitals. These may be inaccessible for patients that are unable to travel from rural areas, such as older people, or people who are socioeconomically disadvantaged [17,31]. Creating a national system in which these procedures become part of a broader range of hospitals could ensure that citizens have access to this new technology [17].

4.2. Human identity and embodiment

It has been argued that implants can have an effect on embodiment and human identity and that it is important to consider these effects in the implementation process of the implant [33,55,56]. Personalized 3D printed scaffolds could make it possible to replace body parts with new ones. This has an effect on how the human body is perceived and how it is introduced and constructed into our lives and the social world [33]. Therefore, TE makes an appeal on a deep-rooted notion about our humanity: 'our integral embodiment' [33]. Embodiment is a concept derived from the work of Maurice Merleau-Ponty in which he tries to unify the mind-body dualism, the objective and experienced world. He argues that we all live as a being-in-the-world in which our body is not only 'a thing', an object of study, but a fundamental condition of experience. We live the world through our bodies [57,58]. New technologies in TE and RM challenge and refashion our embodied self and therefore our understanding of what it means to be human [33,59]. Because we are an embodied self, in which our own body is part of how we experience the world and therefore of our identity, implanting technologies into our body may affect our identity [59]. Oerlemans [60] poses the question if we will still give our body the same care and attention when a damaged tissue or body part can easily be replaced with a new one [60].

Two papers specifically elaborate on the effect of implants on the embodiment of patients [55,56]. If people feel estranged from their body and tend to look at the new implant as something foreign, as not part of their body, this could negatively affect rehabilitation outcomes [55,56]. Therefore, clinicians should not just focus on strengthening the joint and promoting full recovery to perform tasks, but also focus on the improvement of the conscious relationship between the patient and their new body part. This way, full incorporation or re-embodiment may be achieved, which can in turn improve the outcomes [55]. If personalized 3D printed scaffolds are biodegradable it makes this relationship even more complex because foreign material enters the body and dissolves after a period of time. To our knowledge, the effects of these new kind of implants on embodiment have not yet been investigated.

4.3. The ontological status of scaffolds

It has been argued that the introduction of regenerative devices interferes with the ontological and materialistic division between the human and technology, which is sometimes taken for granted [7,60]. 3D printed scaffolds blur the boundaries between older and seemingly fixed categories: the natural and the artificial, and the lively and inert [7]. The question arises: how do we perceive and understand personalized 3D printed implants? And what kind of implications does this have for regulations, responsibility, and values of society? In the literature these questions are related to two features: their (un)naturalness and liveliness.

Firstly, it is argued that two characteristics of TE explain how TE stays closer to our nature than 'bionic' technologies - artificial technologies inspired by the workings of nature such as an exoskeleton - do. On the one hand, TE intervenes with our 'fleshy' existence rather than simply adding something to the body [57]. On the other hand, it mimics nature by modifying parts of our body through modified tissue or biodegradable materials [57]. These two characteristics evoke questions about the natural body and artificiality. The bodily limits are blurred by surpassing the boundaries imposed by nature [61]. For a long time, the body was a clearly demarcated entity. Yet since the possibility of tissue replacement, it becomes rather vague where the technology ends and the body starts [7,60]. It has been mentioned that tissue engineers stress the 'naturalness' of TE to avoid certain fears and questions associated with biomedical engineering which is often perceived as unnatural and dangerous [57,60]. Whether people perceive the implant as natural or artificial can also affect the social acceptability and implementation of this new technology into society [1,15].

Moreover, (un)naturalness also relates to the debate on human enhancement versus self-preservation, i.e. restoration of function [7,21,62]. Since the traditional task of medicine is generally perceived to treat and prevent diseases and not to improve humanity in general, the question arises for what purpose personalized 3D printed scaffolds should be used: to merely replace and repair damaged tissue or to enhance human nature and physical capacities? [62]. Debate exists on whether human enhancement should be allowed or even promoted [35,62]. Some authors see room for improvement of humanity and promote human enhancement, whereas others argue that 3D printed technologies intervene with the natural order and lead to human enhancement which violates the intrinsic limit of human nature [35,62]. Hansson (2005) argues the best way to approach these problems is step by step, assessing each case based on our current values without considering future values.

Secondly, the ontological status of personalized 3D printed scaffolds affects classification and regulation and is defined by the key distinction between medicinal products and medical devices. Traditionally, medical devices are explained as materially bound mechanisms that are implanted in the body to repair localized sites [7]. Medicinal products, in contrast, are designed to diffuse and operate systemically throughout the body. The development of complex regenerative implants eliminates the ontological distinction between medicinal products and medical devices by creating devices that are systemic in action and that are neither object devices such as prostheses nor fully human body parts [7]. They become lively both in an ontological and material sense [7]. Currently, personalized 3D printed scaffolds fall under the scope of medical devices even though they are designed to be both dynamic and responsive to biofeedback.

There is a need to discuss the ontological status of 3D printed scaffolds because it shapes how the implants are tested and later used in clinical practice and has several other implications [7]. First, such status is later translated into norms relied on in court to understand the artifact-body interface and to determine where responsibility lies when complications arise [7]. Second, when the distinction between the materiality of the technology and the corporeality of the human becomes technically indistinguishable, it becomes more difficult to identify the causal link between the possible defective product and the adverse effect. This makes it difficult for patients to exercise their right to be protected from the insults of injury and distress caused by exposure to unsuccessful devices [7].

5. Discussion

Personalized 3D printed scaffolds are an emerging technological application with the potential to improve research and treatment in the field of TE and RM. An early assessment of their ethical aspects helps to shape the design and regulation of such implants in an ethical manner to ensure responsible development and implementation. This review is the first study that illuminates the ethical aspects regarding personalized 3D printed scaffolds along their life cycle.

Some of the well-known, i.e. familiar from other similar biomedical technologies, ethical issues raised by personalized 3D printed scaffolds are related to good research and clinical practices. These issues, such as privacy issues concerning digitalization, responsibility, first-in-human trials and commercialization, are often mentioned in the literature. At the same time, this review also creates awareness for underexplored, ethical issues, such as irreversibility, gender, embodiment and identity and the ontological status of these scaffolds, which are important for ethically-sound development of this new technology. As one might notice these issues go beyond good research and clinical practices and show the importance of considering the whole life cycle of the scaffold to provide the best care.

The insights of this review reveal many unresolved empirical and normative questions. For example, to further improve the performance and use of these scaffolds, qualitative empirical research, such as interview studies, is needed to gather different perspectives of stakeholders such as patients, clinicians, and engineers. Moreover, embodiment is an ethical aspect that needs further empirical investigation to gain insight into the perceptions of end users, i.e. patients. The current literature on embodiment is mostly focused on traditional, inert, implants and prostheses such as metal-on-metal hip implants or neural implants. The effect that these scaffolds, as discussed here, have on embodiment has not been researched before and should be further investigated to improve treatment outcomes. This also helps to further understand the ontological status of such implants which, in turn, benefits the process of regulation.

This review also exemplifies how to include gender in the ethical assessment of new technologies and is, to our knowledge, the first of its kind to analyze gender considerations with regard to implants in the TE and RM field. The emphasis on such gender-specific ethical aspects of technologies is important as gender bias is a worldwide problem in medical technology and (health) care, as well as in society at large. Important follow-up research could include an intersectionality approach that addresses even more inequalities and biases and could eventually improve the performances of such TE solutions.

5.1. Future directions

As TE continues to advance and its applications expand, it becomes increasingly imperative to systematically integrate ethical principles into research practices. One intriguing application is the development of scaffolds that have shape-morphing and self-sensing properties. This means for example that these scaffolds can evolve gradually or start to evolve after a longer period of time after implantation. This is particularly suitable for children, whose growth processes may necessitate this gradual or delayed transformation [63]. In some cases, this transformation and its therapeutic benefits may only become apparent when these children have reached adulthood [63]. At that point, the implant becomes impossible to remove, if that is desired by the now adult. However, the parents gave consent for implantation before the child reached the age to give consent themselves [63]. Consequently, the concept of irreversibility has a different impact to what was discussed earlier in this review.

Ensuring that ethical considerations are not an afterthought, but an integral part of the research process is essential to drive responsible innovation in TE and RM. Three key factors can facilitate the systematic application and integration of ethical principles in the field. First, incorporating ethics training and education at all levels of TE and RM research is crucial. Research institutions, universities, and organizations should develop and offer comprehensive ethics courses and workshops specifically tailored to TE and RM. These programs should cover a wide range of ethical topics, for which this review provides a useful starting point. Second, collaboratively developing and regularly updating ethical guidelines for TE and RM research is essential. These ethical guidelines are preferably added as an integral part of the current (regulatory) guidelines within TE and RM and should be accessible, clear, and adaptable to evolving technologies and practices. Third, promoting interdisciplinary collaboration between all stakeholders such as tissue engineers, ethicists, healthcare professionals, end-users (patients) and policymakers can foster a holistic approach to ethical considerations. These collaborations enable researchers to identify ethical challenges early in the research process and work collectively to address them.

Overall, this review can be of guidance in the successful and ethical development of 3D printing and TE along the life cycle of new implants. It can serve as input for discussion in both education and research contexts and addresses the benefit of multidisciplinary collaboration between ethicists, clinicians, scientists, (device) manufacturers, universities and governments.

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Author statement

MD, ALB and NG conceived the idea for this paper and MD and AJK analyzed the literature, with MD taking the lead in drafting the paper. All authors contributed to the intellectual content and authorship. All authors commented on and revised the article.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Manon van Daal reports financial support was provided by Horizon 2020. Annelien L. Bredenoord reports a relationship with Member of Dutch Senate that includes: board membership and employment.

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