I'm not a bot

24 Pages Posted: 14 May 2009 Date Written: May 13, 2009 Regenerative medicine describes a set of innovative approaches to the treatment of illness, injury, and disability, focusing on the growth, replacement, and repair of cells, organs, and tissues specific to the health needs of particular individuals. The extraordinary breadth of application of this approach is clear from an enumeration of just a few areas of regenerative medicine research, such as stem cells, including embryonic stem cells, pluripotent stem cells produced by genetic reprogramming, and multipotent stem cells from non-embryonic tissues; techniques for stimulating endogenous cell growth and repair for the kidney and pancreas in diabetes, or for digits and limbs injured as a result of trauma; and the growth of replacement tissues and organs, for example, blood vessels, hollow organs like the bladder, and even solid organs like the heart. This enormous diversity of applications, all currently in various stages of research and development, stems from a multidisciplinary research orientation incorporating genetics, informatics, basic research into the structure, mechanics, and development of different tissues, and creative production techniques. Despite its enormous promise, however, at this time regenerative medicines many applications constitute a very early step along the road to effective treatments. Most of the attention to ethical issues in regenerative medicine has been consumed by debate about the use of human embryonic stem cells in research, specifically, the destruction of embryos in order to create cell lines, disputes over the role of federal funding for research with human embryonic stem cells, and concerns about the safety, scientific purity, and adequacy of consent for the research use of human embryonic stem cell lines. Like other novel biotechnologies, however, regenerative medicine raises a number of additional critical research ethics issues that are not new, but that have not yet been adequately addressed. Instead, as is common in new science, familiar and longstanding questions appear in the fresh context of regenerative medicine research and renew old debates. Advances in regenerative medicine therefore provide a much-needed opportunity to reexamine important issues in human subjects research. Moreover, because regenerative medicine has taken a thoroughgoing translational perspective, seeking to anticipate and plan for the issues (scientific, policy, and practical) that are likely to arise along the full research trajectory from bench to bedside to clinical product, it presents a model system for comprehensively identifying and addressing issues and needs in ethics and policy as they arise in translational research involving this developing science. This article discusses some of the novel technologies within regenerative medicine. The article then examines the range of ethical issues raised by each novel regenerative medicine technology, including but not limited to: the ethics of research design; issues to consider in first-in-humans regenerative medicine research; and informed consent and the therapeutic misconception. The article further considers whether regenerative medicine helps to blur any distinction that may exist between medical treatment and enhancement, possibly creating more ethical issues to address in the long term. The article concludes by advising scholars and policymakers in bioethics to take the opportunity offered by regenerative medicine to move research ethics and policy forward by examining these issues anew through the lens of this groundbreaking medical science. Hermern, Gran (2021) The ethics of regenerative medicine. Biologia Futura, 72 (2). pp. 113-118. ISSN 2676-8615 (print), 2676-8607 (online) Preview Texts42977-021-00075-3.pdf Download (533kB) | Preview Official URL: Abstract Most developments in regenerative medicine have in common that there are many uncertainties and knowledge gaps. These features make the evaluation of long-term consequences of the available options difficult and have consequences for the ethical issues raised. This paper presents an overview of ethical issues raised in regenerative medicine, using as a starting point a list of stakeholders and their interests. Ethical issues are introduced via a simplified account of a project that focuses on several difficult problems, as well as a conceptual framework consisting of the following key concepts: present situation, goals, difficulties on the road toward the goals, and strategies for dealing with the difficulties. The list of ethical issues discussed includes safety and efficacy, patient consent, information, professional responsibilities, as well as equity and fairness. The issues and the underlying values need to be clarified, specified, debated, and ranked in order of importance. A particular problem is that values sometimes clash: Certain values can be achieved only at the expense of others. If and when values clash, principles are available that can guide the decision making. The paper comments on two such principles with implications for the particular issue of patient access to experimental treatments: the precautionary principle and the principle of proportionality. The paper ends with some conclusions for the future. Actions (login required) Edit Item Most developments in regenerative medicine have in common that there are many uncertainties and knowledge gaps. These features make the evaluation of long-term consequences of the available options difficult and have consequences for the ethical issues raised. This paper presents an overview of ethical issues raised in regenerative medicine, using as a starting point a list of stakeholders and their interests. Ethical issues are introduced via a simplified account of a project that focuses on several difficult problems, as well as a conceptual framework consisting of the following key concepts: present situation, goals, difficulties on the road toward the goals, and strategies for dealing with the difficulties. The list of ethical issues discussed includes safety and efficacy, patient consent, information, professional responsibilities, as well as equity and fairness. The issues and the underlying values need to be clarified, specified, debated, and ranked in order of importance. A particular problem is that values sometimes clash: Certain values can be achieved only at the expense of others. If and when values clash, principles are available that can guide the decision making. The paper comments on two such principles with implications for the particular issue of patient access to experimental treatments: the precautionary principle and the principle of proportionality. The paper ends with some conclusions for the future. Keywords: Ethics; Precautionary principle; Principle of proportionality; Regenerative medicine; Value conflicts. As a library, NLM provides access to scientific literature. Inclusion in an NLM database does not imply endorsement of, or agreement with, the contents by NLM or the National Institutes of Health. Learn more: PMC Disclaimer | PMC Copyright Notice Tissue Engineering (TE) is a branch of Regenerative Medicine (RM) that combines stem cells and biomaterial scaffolds to create living tissue constructs to restore patients' organs after injury or disease. Over the last decade, emerging technologies such as 3D bioprinting, biofabrication, supramolecular materials, induced pluripotent stem cells, and organoids have entered the field. While this rapidly evolving field is expected to have great therapeutic potential, its development from bench to bedside presents several ethical and societal challenges. To make sure TE will reach its ultimate goal of improving patient welfare, these challenges should be mapped out and evaluated. Therefore, we performed a systematic review of the ethical implications of the development and application of TE for regenerative purposes, as mentioned in the academic literature. A search query in PubMed, Embase, Scopus, and PhilPapers yielded 2451 unique articles. After systematic screening, 237 relevant ethical and biomedical articles published between 2008 and 2021 were included in our review. We identified a broad range of ethical implications that could be categorized under 10 themes. Seven themes trace the development from bench to bedside: (1) animal experimentation, (2) handling human tissue, (3) informed consent, (4) therapeutic potential, (5) risk and safety, (6) clinical translation, and (7) societal impact. Three themes represent ethical safeguards relevant to all developmental phases: (8) scientific integrity, (9) regulation, and (10) patient and public involvement. This review reveals that since 2008 a significant body of literature has emerged on how to design clinical trials for TE in a responsible manner. However, several topics remain in need of more attention. These include the acceptability of alternative translational pathways outside clinical trials, soft impacts on society and questions of ownership over engineered tissues. Overall, this overview of the ethical and societal implications of the field will help promote responsible development of new interventions in TE and RM. It can also serve as a valuable resource and educational tool for scientists, engineers, and clinicians in the field by providing an overview of the ethical considerations relevant to their work.To our knowledge, this is the first time that the ethical implications of Tissue Engineering (TE) have been reviewed systematically. By gathering existing scholarly work and identifying knowledge gaps, this review facilitates further research into the ethical and societal implications of TE and Regenerative Medicine (RM) and other emerging biomedical technologies. Moreover, it will serve as a valuable resource and educational tool for scientists, engineers, and clinicians in the field by providing an overview of the ethical considerations relevant to their work. As such, our review may promote successful and responsible development of new strategies in TE and RM.Keywords: tissue engineering, regenerative medicine, bioethics, responsible innovation, social impact, scientific integrityTissue Engineering (TE) uses biomaterials, (stem) cells and bioactive molecules to construct functional, living three-dimensional (3D) tissues in a laboratory environment (in vitro) or directly in a patient's body (in situ). Examples include tissue engineered skin, 3D bioprinted bone, and liver organoids for transplantation. TE is one of three pillars of the broader field of Regenerative Medicine (RM), which aims to replace or regenerate human cells, tissue, or organs to restore or establish normal function.1 Stem cell (SC) transplantation and gene transfer (GT) constitute the other two pillars.As a rapidly evolving medical technology that has been argued to be potentially disruptive2 and even paradigm-changing,3 TE holds great promise for novel cures, but also requires attention to the ethical implications of its development, clinical translation, and future impact on individuals and society. Addressing such ethical implications early on and embedding societal values into the design of TE products will help TE to reach its ultimate goal of improving patient welfare.4The TE field has been maturing over the last two decades and ethical issues have received attention of ethicists, social scientists, and ethics-minded biomedical scientists and engineers. This body of literature has last been reviewed comprehensively in 2008, at which time the field was still in its infancy.5 Since then, the first applications have reached the stage of clinical application.6,7 Emerging technologies such as 3D bioprinting, biofabrication, supramolecular materials, induced pluripotent stem cells (iPSCs), and organoids have entered the TE field, and a shift has taken place toward strategies that mobilize the inherent regenerative capacity of the human bodyand its endogenous cell populationsto a greater extent than before (in situ TE).2,8Therefore, we have performed a systematic review (SR) of the ethical implications of the development and application of TE for regenerative purposes, as mentioned in the academic literature. While TE might have applications outside RM (e.g., as a drug screening platform or for in vitro meat production), we have focused on the clinical application of TE for tissue regeneration. To our knowledge, this is the first time that the ethical implications of this field have been reviewed in a systematic manner. An SR has the advantage of being comprehensive, methodologically rigorous and transparent, and of reducing (selection) bias.9We performed an SR to identify the ethical implications of the development and application of TE for regenerative purposes. The reviewing process was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for SRs10 and the adapted PRISMA ethics guidelines by Kahrass et al.9Ethical implications were broadly understood to be expressions of an ethical or societal issue or consideration, which may but need not take the form of a fully argument-based reason.11Four databases (Embase, PubMed, Scopus, and PhilPapers) were searched for relevant English language articles using a search string combining search terms for (a) TE, RM, or bioprinting with (b) ethics or human rights, covering the period January 01, 2008 until October 05, 2021. An experienced librarian was consulted regarding the design of the search strings and choice of databases to ensure that relevant keywords were included, and that a comprehensive area of biomedical, bioengineering, and ethics literature was covered. The original search was performed on March 30, 2020 and updated on October 05, 2021. See Supplementary Data S1 for the complete search strategy of all databases.Articles were screened for eligibility by A.J.K based on title, abstract, and keywords, and next, if applicable, based on the full text, using Rayyan software (Fig. 1). Inconclusive screening decisions were resolved through consultation with K.R.J. and A.L.B. Overview of the number of articles identified and included throughout the several phases of the screening process, depicted according to the PRISMA guidelines.Articles (e.g., original research, editorials, opinion articles, letters) published in English in a peer-reviewed academic journal in the period January 01, 2008 to October 05, 2021, which discussed an ethical implication of the development or application of TE for regenerative purposes, were eligible for inclusion. Also included were articles that discussed as their main topic ethical or societal implications of RM more generally, provided that these implications were applicable to TE as well.Excluded were book chapters, conference articles, and news articles, in addition to articles on RM that discussed SC transplantation/research or GT instead of TE. Also excluded were ethical implications related to the source of (stem) cells and the use of embryonic tissues, which have been discussed in depth elsewhere.1214Supplementary Data S1 for a more detailed description of the inclusion and exclusion criteria.As a minimal standard for quality assessment, articles had to be published in a peer-reviewed journal.Full texts of the included articles were analyzed systematically using a data extraction sheet (Supplementary Data S1) (A.J.K.). For each article, information was extracted about publication type, publication year, and about the topic and aim, substantiated by relevant quotes. Moreover, one-sentence descriptions of the relevant ethical implications mentioned in each article were extracted (referred to as an implication mention), substantiated by one or more quotes. Quote lengths diverged from one sentence up to page-length. Additional quotes were extracted to preserve contextual information relevant to the ethical implications where necessary.A thematic analysis was conducted to synthesize the data, using data synthesis sheets (Supplementary Data S1).15 Implication mentions were compared across articles, and combined into implication types based on close similarity (compare reason mention and reason type as described by Strech and Sofaer)16 (A.J.K.). Implication types were then thematized using a coding tree of four hierarchical levels (i.e., with primary, secondary, and tertiary sub themes under each main theme) (A.J.K.). Each implication type was assigned to one sub theme. If more than one sub theme was applicable, the most suitable one was selected. The formulation of the implication types and the coding tree was then evaluated by all authors and optimized through an iterative process of discussion and adaptation until agreement on a meaningful thematization was reached between all authors (A.J.K., K.R.J., M.C.V., and A.L.B.).The database search resulted in the identification of 2451 unique articles. Of these, 237 articles were considered eligible and were included in this review (Fig. 1).The included articles encompassed reviews in natural sciences (n=61/237) and humanities (n=19/237), original research in natural sciences (n=13/237) and humanities (n=56/237, of which were 8 empirical and 48 theoretical studies), perspectives (n=68/237), and other publication types (n=20/237, of which were 10 workgroup and project reports, 5 interviews, 3 methods articles, 1 case report, and 1 book review) (see Supplementary Data S2). The articles discussed TE for regenerative purposes as a main topic (n=115/237, including 21 on bioprinted implants and 4 on organoid transplantation) or subtopic (n=65/237, including as a main topic: 9 on Advanced Therapy Medicinal Products (ATMP), 8 on SC transplantation, 6 on RM, and 6 on in vitro TE), or discussed RM, broadly yet in a manner relevant to TE, as their main topic (n=51/237) or subtopic (n=6/237) (Supplementary Data S2). The articles were published in 2008 (n=10), 2009 (n=17), 2010 (n=13), 2011(n=9), 2012 (n=10), 2013 (n=18), 2014 (n=22), 2015 (n=33), 2016 (n=16), 2017 (n=23), 2018 (n=14), 2019 (n=24), 2020 (n=21), and 2021 (n=18).A range of ethical implications of TE for regenerative purposes was identified in the included literature. These were categorized into 10 main themes. The first seven themes cluster phases of TE development from bench to bedside:(1)animal welfare(2)handling human tissue(3)informed consent(4)therapeutic potential(5)risk and safety(6)clinical translation(7)societal impact.The remaining three themes group overarching ethical domains for safeguarding responsible development:(8)scientific integrity(9)regulation(10)patient and public involvement.The ethical implications (as implication types) identified in the literature are discussed below per main theme and sub theme, and are also summarized in Tables 110. Supplementary Data S3 for one-sentence descriptions of the implication mentions per article corresponding to each aggregated implication type.Overview of the Ethical Implications of Tissue Engineering for Regenerative Purposes, as Identified in Relation to Animal WelfareAnimal welfareFor tissue engineering for regenerative purposes Sub themeEthical implicationsReferencesAnimal experimentation animal welfare should be balanced with scientific need and reliability of animal models1729 in vitro, ex vivo and in silico models should be applied to (partially) replace the use of animals3048 methods should be applied to reduce the number of animals per experiment4953 the use of non-human primates or companion animals should be avoided, or experiments should be refined to minimize suffering18,27,50,5458Animal-derived TE components animal-free TE scaffold and culture components are preferred22,38,5969Overview of the Ethical Implications of Tissue Engineering for Regenerative Purposes, as Identified in Relation to Handling Human TissueHandling human tissueTissue engineering for regenerative purposes Sub themeEthical implicationsReferencesTissue collection, storage, and use requires tissue collection methods that are not harmful to the donor17,22 requires consent of (the family of) the donor for the collection, storage, and use of their tissues17,19,20,22,23,58,7076 requires that donors be fully informed on future use and possible financial interests, before collection, storage, and use of their tissues7,7786 requires protection of donor privacy when storing and using their tissues and data7,17,19,22,23,58,73,75,77,78,80,82,8690 raises the question under what conditions private, public, or hybrid model biobanks are acceptable73,74,84,85,88,9196 should be composed of non-human-derived scaffold components72,97100Ownership and commodification raises the question who has ownership over tissue engineered products7,17,22,23,75,79,88,101104 raises the question if tissue engineered products should be patentable17,73,74,82,101,105109 reinforces commercialization of human tissues, which is at odds with altruistic donation and risks donor exploitation7174,80,84,88,93,110115Overview of the Ethical Implications of Tissue Engineering for Regenerative Purposes, as Identified in Relation to Informed ConsentInformed consentFor tissue engineering for regenerative purposes Sub themeEthical implicationsReferencesChallenges to informed consent consent might be challenged by the participant's capacity to consent75,116 informed consent might be challenged by therapeutic misconception19,23,37,74,115,117119 the voluntariness of consent might be challenged by pressure from family or researchers22,120 informed consent for innovative therapies might be challenged by positive bias of the physician119,121123 informed consent is challenged by the inherent uncertainty involved in risk assessment20,22,23,71,81,88,104,112,118,119,124,125Conditions for informed consent well-considered informed consent requires that patients receive relevant information, e.g., on risk-benefit ratio, cell source, and alternative treatment options37,74,119,126128 well-considered informed consent requires that patients receive support and information in understandable language17,119,129131Overview of the Ethical Implications of Tissue Engineering for Regenerative Purposes, as Identified in Relation to Therapeutic PotentialTherapeutic potentialTissue engineering for regenerative purposes Sub themeEthical implicationsReferencesTherapeutic promise has the potential to provide a cure for diseases where currently non is available or where side effects are high75,82,106,116,132135 may provide an alternative to donor organ transplantation, removing the need for immunosuppression and solving organ shortages17,23,60,74,75,78,79,81,88,89,101103,112,117,125,128,133,136152 is excisable, which is a benefit compared to other RM strategies81,125Objectives for wellbeing should aim to improve the quality of life of patients20,153Overview of the Ethical Implications of Tissue Engineering for Regenerative Purposes, as Identified in Relation to Risk and SafetyRisk and safetyTissue engineering for regenerative purposes Sub themeEthical implicationsReferencesSafety risks bears risks related to the presence of living cells, such as immunogenicity, mutagenesis, and tumorigenicity22,23,70,75,79,81,86,88,89,101,124,125,141,154156 bears risks related to the scaffold components, such as contamination, immunogenicity, and cytotoxicity22,23,72,79,81,116,124,125,155158 bears safety risks related to the complexity of TE constructs in terms of variability, dynamic interaction, and irreversibility3,25,70,75,7881,102,115,119,122,124,132 involves inherent uncertainties related to the complexity of TE and to the limited predictive value of animal models3,23,71,80,88,104,153,159161Safety measures requires that risks are minimized and are proportional to benefits to the individual and society3,23,37,73,126,131,132,158,161,162 requires appropriate preclinical testing before first-in-human trials26,29,37,120,124,126,129,131,154,161,163 requires long-term follow-up of trial participants37,58,120,124,154,164166 requires that TE implants are detectable in case of emergency situations102 requires that safety measures are not unnecessarily burdensome131,132,165,167Overview of the Ethical Implications of Tissue Engineering for Regenerative Purposes, as Identified in Relation to Clinical TranslationClinical translationFor tissue engineering for regenerative purposes Sub themeEthical implicationsReferencesClinical trial design randomized controlled trials might be challenging if no standard of care is available and if sham surgery would be required as a control131,161,167173 first-in-human clinical trials should include patients with mid- or end-stage disease3,19,23,37,70,73,74,81,124,161,168,174,175 first-in-human clinical trials should include efficacy endpoints and capture both objective and subjective outcomes21,37,70,73,75,81,125,126,131,155,156,160,164,167,168,176 registries are needed to collect long-term safety and efficacy data3,17,37,74,86,101,117,120,126,131,167,177 clinical trials should be designed carefully, and results should be published transparently, to avoid bias and promote reproducibility71,74,125,127,163,164,178,179Innovative therapy pathway innovative therapy as alternative to clinical trials may promote patient access to experimental treatments23,37,74,122,180 innovative therapy as alternative to clinical trials is at tension with the need to protect patients from risks and with the need for evidence collection7,19,121,123,131,166,178,181183Unproven commercial interventions unproven interventions expose patients to the risk of physical harm and financial exploitation19,74,120,122,123,156,178,180,184186 researchers and physicians should protect patients against the risks of unproven interventions7,18,120,183,187,188Overview of the Ethical Implications of Tissue Engineering for Regenerative Purposes, as Identified in Relation to Societal ImpactSocietal impactTissue engineering for regenerative purposes Sub themeEthical implicationsReferencesDistributive justice could exacerbate local and global socioeconomic health disparities17,19,22,23,70,75,79,88,102,104,107,140,158,180,189195 should be developed to be cost effective to improve accessibility25,37,74,89,90,112,124,155,166,170,196198 poses a value trade-off between the future fruits of innovation and current patient demands71,74,88,104,137,146,158,169,199202 should be reimbursed based on clinical effectiveness, costs, and patient preferences19,102,123,154,167,178,182Impact on health care and markets might provide an alternative to ethically contentious health care practices like organ donation, xenotransplantation, and gestational motherhood133,140,149,203205 could help ending illegal organ trade79,90,140,141,206Biosecurity bears risks of bioterrorism related to unregulated home-use17,81,107,125,190,207Longevity and enhancement raises the question whether we should pursue longevity or accept ageing as a normal part of life88,103,110,192,193,208211 might change social acceptability of life organ donation and unhealthy lifestyles17,88,101,108,192,212 raises opportunities and concerns related to the possibility of enhancement20,23,70,75,88,108,110,112,158,180,190,213,214Human experience and identity raises presents the body as malleable and challenges our conception of what it means to be human17,88,101,104,110,115,180,189,210,215223 blurs the boundaries between the natural and the artificial17,88,140,223225Overview of the Ethical Implications of Tissue Engineering for Regenerative Purposes, as Identified in Relation to Scientific IntegrityScientific integrityFor tissue engineering for regenerative purposes Sub themeEthical implicationsReferencesResponsible conduct researchers and media should refrain from overstated promises to prevent hype23,85,88,112,137,140,146,156,169,178,180,191,194,226 a benign research environment and better oversight mechanisms are needed to prevent fraud129,169,227,228 scientists should (be trained to) be aware of the societal and ethical implications of their work3,25,37,74,102,107,168,192,229231Transdisciplinary collaboration successful development co-depends on transdisciplinary and international collaborations between scientists, clinicians, regulators, and industry37,92,102,106,121,125,131,137,177,182,232236 commercial pressure might lead to premature testing and commercialization, so that government sponsored trials are preferable17,20,67,80,89,106,115,118,131,162,168,174,177,178,180,194,237 responsible development is fostered by involvement of ethics and social science scholars in the innovation process17,38,106,140,181,238,239Overview of the Ethical Implications of Tissue Engineering for Regenerative Purposes, as Identified in Relation to RegulationRegulationFor tissue engineering for regenerative purposes Sub themeEthical implicationsReferencesGuidelines and oversight adequate regulatory frameworks should be established and be harmonized internationally70,103,120,154,157,178,180,181,234,240 uniform guidelines and oversight for the use of human tissues should be established84,85,93,128,136,162,165,241 uniform safety, quality and efficacy standards, and controls for TE products and processes should be established23,25,75,106,108,120,124,126,127,132,171,174,179,195,242245 regulation of innovative therapies offered outside clinical trials is needed19,122,153 regulation should foster a balance between safety requirements and speed of innovation, to promote patient access3,20,22,74,80,102,111,135,144,246 clarification or revision of the current regulatory classification of TE products is needed17,78,79,81,89,101,126,217,224Liability it should be determined who is responsible for quality control and maintenance and who should be held liable if complications arise20,75,83,101,102,112,121,126,217Overview of the Ethical Implications of Tissue Engineering for Regenerative Purposes, as Identified in Relation to Patient and Public InvolvementPatient and public involvementFor tissue engineering for regenerative purposes Sub themeEthical implicationsReferencesPublic engagement the public should be educated on the opportunities, hurdles, and ethical aspects23,82,88,108,131,147,158,180,181,185,245,247 patients and the public should be consulted to include their values and needs20,71,74,82,88,107,175,181,195,230,233,237,248,249 (bio)art may pose critical questions and provide new spaces for public dialog38,215,222,250,251The literature discusses ethical implications related to animal welfare that can be subdivided between conditions for preclinical testing on animals and concerns related to animal-derived TE components (Table 1 and Supplementary Data S3).Animal welfare should be balanced with the scientific need and expected human benefit of animal models.17,18 The design should therefore take the predictive value of a particular animal model for humans into account1924 and the experiments should be performed in accordance with the 3R principles (replace, reduce, and refine).2529To replace animals for biomaterial testing or to study regenerative processes, the use of computational modeling30 or in vitro models3133 are advocated. These include SCs,34 organoids,35 decellularized tissue,36 and organs-on-a-chip.37,38Ex vivo tissue culture systems3944 and the chorioallantoic membrane assay4548 are proposed as means of partial replacement. To reduce the number of animals per experiment, continuous monitoring of each animal,4951 testing of multiple biomaterials per animal,52 and skipping small animal models in favor of one large animal model53 are suggested. Last, a preference is expressed not to use companion animals,18,27,50,54,55 such as dogs, or primates56 as large animal models, and, if primates have to be used, to refine the experiments by minimizing the suffering caused.57,58Animal-derived decellularized scaffolds and culture medium components might raise religious and moral objections related to xenotransplantation and animal welfare, especially among religious or vegan patients.22,5962 Autologous,63 allogeneic,6466 or plant-based components6769 are proposed as alternatives.The literature identifies ethical considerations regarding how to handle human tissues. These can be grouped in two sub themes: first, the collection, storage, and use of cells and tissues from human donors for research and clinical applications, and second, ownership over and commodification of donated and engineered tissues (Table 2 and Supplementary Data S3).Tissues should be collected through non-invasive methods that do not cause harm or pain to the donor.17,22 Consent of the donor or their family is required for collection and storage of tissues,22,23,58,7072 which should be explicit19,73 and voluntary.74,75 Some suggest that consent should be specific to the intended use17 while others argue that broad consent suffices.20,76 As a prerequisite for consent, donors should be provided relevant information, including information on present and foreseeable use of the collected tissues,7,7781 on the need to forego financial rights over the tissue,82 and on policies outlining the return of findings83,84 and the possibility to withdraw.85,86To safeguard the confidentiality and privacy of the donor of collected and stored samples,19,22,58,80,82,86,87 some suggest that sample anonymization is desirable,7,17,77 while others point out that this would limit clinical value73 and the possibility of return of findings23 and of dynamic (ongoing) consent.88 Particularly, safeguarding privacy and confidentiality of the (medical) data and digital models required to create personalized 3D bioprinted tissues is warranted.75,78,89,90A dispute exists whether private (commercial) biobanking is acceptable91 or that public banking should be preferred74 for tissue storage. Specifically, private banking is said to be based on a (false) promise of yet-to-be-developed RM treatments,88,92 which could erode public trust.85,93 Yet public banks would fail in providing a supply that is inclusive to all.84 A hybrid model of public-private biobanking is therefore advocated that allows privately stored tissues to become publicly available, increasing the publicly available supplies9496 and accelerating research.73Finally, moral and religious objections could be raised to the use of (decellularized) human tissues, especially cadaveric tissues, as scaffold components. Synthetic scaffolds,97 animal-derived scaffolds,72,98 or (decellularized) tissues from living donors99,100 would therefore be preferred.The question is raised which parties may claim ownership over donated7,22,23 and engineered17,75,79,88,90,101104 tissues: the tissue donor, the patient receiving the implant, or the parties involved in producing the organ? Moreover, it is debated whether and under what conditions intellectual property rights over TE, for example, by patenting the technology or the product, is desirable. While patenting could foster innovation,105 ensure quality control, and prevent misuse,17,101 it might also hinder open science and research82,106 and equal access to the fruits of the technology.74,107,108 According to some, notwithstanding property interests of other parties, patients should retain a right to control certain uses and access to the organ.73,109 Finally, TE creates a paradoxical and potentially undesirable situation in which altruistically donated tissues are turned into profitable materials for which donors have no right to financial gain.7174,80,84,93,110 This appears at odds with human dignity111 and the ban on the commodification of human body parts,112 and might lead to donor exploitation or coercion.88,113115The literature mentions informed consent as a necessary precondition for several phases of TE development: for tissue donation (as discussed under Tissue collection, storage, and use), participation in clinical trials, and clinical application, whether as innovative therapy, compassionate use, or routine treatment. A distinction can be made between challenges and conditions for obtaining valid, informed consent (Table 3 and Supplementary Data S3).Consent might be challenged if the patient's capacity to consent is impaired, for example, in emergency situations116 or when treated for brain conditions.75 Second, patients' hope or desperation for a cure might lead them to misunderstand the risky and experimental nature of a TE trial (therapeutic misconception) and affect the validity of their consent.19,23,37,74,115,117119 Third, patients might feel pressured to participate by family members or researchers.22,120 Fourth, possible positive bias and conflicting financial or professional interest of the physician-researcher involved in an experimental TE treatment might affect the neutrality of the information provided.119,121123 And last, uncertainty about possible complications due to the novel,81 complex,22,119,124 invasive,20,118 and irreversible125 nature of TE makes it difficult to provide accurate information about the risk-benefit ratio of the intervention.23,71,88,104,112Due to these challenges, medical professionals should provide, and carefully explain, all relevant information, including information on the characteristics of the TE intervention itself, the source of cells and other components, foreseeable risks and benefits, safety measures, alternative treatment options, and a disclosure of interests.37,119,126128 Yet, even if high quality information is provided, consent should always be accompanied by oversight mechanisms to prevent patients from unacceptable risks.74 Moreover, information should be provided in understandable language,17,129 and may be supported by the use of educational materials119 and consultation of an independent medical professional.130,131One of the main ethical opportunities and key drivers of TE is its therapeutic potential. The literature elaborately discusses its therapeutic promise, and briefly its objectives related to broader wellbeing (Table 4 and Supplementary Data S3).TE is proposed to address an unmet clinical need, having the potential to treat diseases for which currently no curative therapy is available75,106,116,132134 or for which current therapies have risky side effects,135 and to improve the quality of life of elderly patients.82 Most often, TE is presented as an alternative to donor organ transplantation. As such it would remove the need for immunosuppression,133,136 improve length and quality of life60,74,79,88,103,128,137 and psychosocial outcomes (for face TE),138,139 provide patient-tailored75,81,89,125,140 and/or off-the-shelf available78,141,142 treatment options, and reduce the cost of care.23,143 In the long run it might solve organ shortages,102,117,144148 thus saving lives and avoiding complexities related to organ donation, including the surgical risks for donors,149,150 the need for (prior or proxy) consent,112,151,152 and the acceptability of directed donation.17,101 Moreover, compared to other RM strategies such as SC injections or GT, cell scaffolding provides TE the benefit of excision if needed, thus allowing partial reversibility.81,125Finally, TE should not merely be aimed at treating disease, but also at improving overall quality of life20 and promoting human flourishing.153Notwithstanding the therapeutic potential of TE, the literature discusses several risks of harm for the patients or trial participants, along with safety measures (Table 5 and Supplementary Data S3).Risks are associated with different aspects of TE constructs: The presence of living cells poses risks of immunogenicity,70,88,154 mutagenesis (especially for bioprinting),89,101,124,155 undirected differentiation,81,125,156 and teratoma and tumor formation,22,23,75,79,86,141 which are compounded by bioprinting forces. TE components such as scaffolds and bioactive factors pose risks of contamination and introduction of pathogens,22,23,79,124,155,157 potential immunogenicity,72,158 and cytotoxicity (especially of degradation products).81,116,125,156The complexity of the TE constructs themselves pose risks that are foreseeable but hard to quantify, that is, risks associated with inherent variability of the constructs,78,79,119 unpredictable dynamic interactions with the bodily environment,25,80,124,132 and the irreversibility of the surgical implantation and regeneration process.3,102,115,122 The latter particularly impedes patient's opportunity to withdraw from the trial.70,75,81 In addition to the known risks, TE involves inherent uncertainties, because of the complexity and manufacturing variability of the construct,23,71,159 and because the predictive value of preclinical animal studies is limited.3,153 As a result it is challenging to provide a realistic risk-benefit analysis,88,104,160 and to decide when evidence suffices to start first-in-human trials.80,161Trials might be justified if adequate safety measures are taken to minimize risks131,132,162 and if the benefits to the individual (compared to available therapies)3,126,161 and society (in terms of scientific value)23,37,73,158 are maximized. The following safety measures are described: To understand the biological mechanisms underlying TE126,154 and to evaluate safety and efficacy of the technology, thorough in vitro163 and in vivo26,129,131,161 preclinical research is required and must be optimized to minimize translational distance.29,37,120,124 To monitor adverse events and the success of regeneration, there is a need for long-term follow-up of trial participants,37,58,154,164166 and pediatric patients in particular.120,124 Artificial organs should be identifiable in case emergency situations arise.102 However, safety measures should not be unnecessarily burdensome131,132 or hamper patient access.165,167The pathway of TE treatments from experimental design toward clinical application can roughly take three routes: through clinical trials (i.e., traditional pathway, aimed at evidence collection for research), as innovative therapy (i.e., non-research pathways aimed at improving patient access, including off-label use, compassionate use, and hospital exemption), or interventions can simply reach the market before evidence of efficacy and safety is complete (i.e., unproven commercial interventions). The literature discusses ethical implications related to each of these pathways (Table 6 and Supplementary Data S3).Several suggestions are provided on how to optimize the design of clinical trials for TE. First, while randomized controlled trials (RCT's) should be used where possible,168,169 this might be ethically challenging, especially if no standard of care is available.167,170172 Sham surgery may be required as a comparator, but is justifiable only if surgery is minimally invasive and if anticipated social value outweighs harm to the control group.131,161,173 Moreover, adequate and fair participant selection is challenging,19,73 because fewer patients can be enrolled than are eligible,74 little is known about comorbidities,174 and end-stage patients are especially vulnerable to therapeutic misconception.23,37Still, consensus seems to exist that for high-risk TE, performing first-in-human phase I trials on healthy volunteers or stable patients is unacceptable.3 Patients with mid- or end-stage disease should be included instead,70,81,124,161,168,175 because they might benefit most and risk losing least. Regarding outcome measures, first-in-human trials may involve efficacy endpoints in addition to safety endpoints,73,81 to maximize the scientific value. Efficacy endpoints should include objective outcomes, such as overall survival167 and success of tissue regeneration,126,164 evaluation of which should preferably not rely on invasive biopsies,21,176 and subjective outcomes related to patient wellbeing.37,131,160,168 For personalized (3D bioprinted) implants, heterogeneous outcomes are to be expected and limit the possibility to extrapolate the results.70,75,125,155,156Finally, curated registries should be set up and used to collect long-term data from clinical trials and follow-up studies regarding safety and efficacy of TE interventions.3,17,37,74,86,101,120,126,167 This would allow to trace adverse events,177 help build a solid evidence-base, and allow to evaluate when the intervention needs no longer be considered experimental.117,131 Moreover, in combination with general non-biased and transparent publishing practices and the use of scientifically valid and rigorous research methods,71,74,125,127,163,164,178,179 this could promote reproducibility and foster translation of TE products to the clinic.Because the use of traditional clinical trials for TE is faced by several challenges, alternatives are needed. One option is to allow patients to access experimental RM and TE treatments as innovative therapy outside clinical trials. This would improve patients access74,122,180 and circumvent the need for sham surgery.23,37 However, such access might be at tension with the need to protect patients from considerable risk,7,121,178 and the need to generate conclusive evidence regarding safety and efficacy of the product123,181,182 and could therefore harm public trust. Publishing outcomes and adverse events in open registries might partially overcome these concerns.19,131,166,183Commercial clinics also offer SC-based RM interventions (which could include TE interventions) without sufficient proof of efficacy and safety. Authors warn that such unproven interventions operate outside existing regulations and are based on false promises,123,180,184,185 thus exposing vulnerable patients to the risk of physical harm and financial exploitation,19,74,156,178,186 and harming public trust in the RM field.120,122 Both researchers and physicians are responsible to inform patients and protect them against these risks.7,18,120,183,187,188The literature discusses several societal impacts of TE and RM development. These include so-called soft impacts related to human values, experiences, identity, relations, and perceptions. The literature covers challenges to distributive justice, the impact on health care and market, biosecurity, longevity and enhancement, and human experience and identity (Table 7 and Supplementary Data S3).Concern exists that the expected high costs of TE interventions will limit its accessibility. If only those who can afford to pay will benefit in terms of quality and length of life,17,75,140,189191 this may exacerbate socioeconomic health disparities19,22,23,70,107,158,192,193 both locally102 and globally.79,88,104,180,194,195 However, if, in the long run, the costs of TE will decrease, treatments could become cost effective.89,112,166,196 Efforts should be made toward that end so as to improve accessibility.25,37,74,90,124,155,170,197,198 Additionally, to ensure equal access to TE treatments, reimbursement will be necessary154,182 and reimbursement decisions should be based on evidence of clinical benefit,123 patient preferences,167 and initial and lifetime costs102,167,178 compared to current treatments options.Moreover, while there is an imperative to fund RM and TE research,199,200 this might draw resources away from existing health care solutions, exposing a value trade-off between the future fruits of innovation and the demand of patients in need today.71,74,88,104 Resources should therefore be allocated based on good science rather than hype137,146,169 and arrangements for benefit-sharing (such as price limits or revenue sharing) should be put in place.158,201,202TE might provide an alternative to several ethically contentious health care practices: TE organs might circumvent personal identity issues related to organ donation,203 and naturalness objections against xenotransplantation.140 Transplantable bioartificial uteri might provide an alternative to gestational surrogate motherhood149,204,205 and could possibly contribute to the realization of human ectogenesis on the long run.133 TE organs could also help ending illegal organ trade,79,141,206 provided that regulations are adopted to prevent new black markets in TE organs.90,140Concern is raised that TE technology, and particularly 3D bioprinting because of its relative accessibility and affordability, might lead to unregulated home-use, which could facilitate bioterrorism.17,81,107,125,190,207TE might help to prolong the average human life span or even cure aging, which raises the question whether longevity is socially desirable193,208,209 or that ageing should be viewed as a normal part of life.88,103,192 In particular, an expanded life span might impact the retirement system210 and could decrease solidarity with older generations.110,211 If TE tissues and organs would become widely available, this could also affect social norms: unhealthy and reckless lifestyles might be normalizsed17,88,101,108,192 and support for organ donation might decrease.212 Moreover, TE could be used for cosmetic purposes or potentially to enhance physical or cognitive abilities. While the pursuit of enhancement is deeply embedded in human culture23,75,112 and could help to pursue the good life,88 it raises concerns about potential harm,108 increasing inequalities,70,158 fair resource distribution,20,110 and the legitimate goals of medicine.180,190,213,214TE presents the body as malleable110,189,215 or machine-like.104 This raises the question whether the human body or life itself is something that should be engineered,17,115,180,216 and might challenge our understanding of what it means to be human,210,217,218 and our perception of the self219,220 and of others.101 The engineering ideal driving TE might obscure

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