SYSTEMATIC REVIEW

# Ethical Issues in Tissue Engineering: A Systematic Review

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## ABSTRACT

This study examines, classifies and discusses the ethical issues of tissue engineering published in selected online databases from the year 2015 to 2020. In overview, the published literature could be classified according to the type of ethical issues discussed, the phase in development in which the ethical issues are prominently existing and into the type of journal they are published. It proceeds with in-depth discussions on selected relevant issues that deemed to be needing further attention and clarification. It will give the readers a broad mapping of ethical issues currently existing and discussed in the context of tissue engineering and highlights the conventional responses on the issues.

**Keywords:** Ethics, Moral, Regenerative medicine, Systematic review, Tissue engineering

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## INTRODUCTION

Tissue engineering is an emerging scientific field; an intersection and combination of multidisciplinary subjects, most prominently life sciences and engineering. Ideally, it aims to overcome the problems of organ shortage resulting from a decrease in organ donors for damaged or end-stage organ failures. Like any other new science and technology, tissue engineering is not free of ethical conundrums, not only at the downstream level of application in the actual, therapeutical deployment of its techniques or results of clinical trials but also at the midstream and upstream levels of their design, fabrication and deployment in research. In this review, we display the ethical issues pertaining to tissue engineering documented in academic literature.

## METHODOLOGY

This systematic review adopted and adapted the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (1,2). The PubMed and Scopus databases were searched for papers highlighting the ethical issues concerning tissue engineering. The search utilized the following terms combinations: ''tissue engineering'' & ethic*, ''tissue engineered'' & ethic*, ''regenerative medicine'' & ethic*, ''tissue engineering'' & moral, ''tissue engineered'' & moral, and ''regenerative medicine'' & moral. The search was confined by date (published within the year 2015 to 2020) and language (English). Papers containing one of the combinations of search terms and discussing ethical issues that did not relate directly or indirectly to tissue engineering or regenerative medicine were not included.

Additionally, prominent journals in tissue engineering and regenerative medicine field—Tissue Engineering Part B, Biomaterials, Journal of Tissue Engineering, Regenerative Medicine and Tissue Engineering and Regenerative Medicine—were searched using the keywords ethic* and moral. The combination of these searches yielded 3968 papers. 355 of the resulting yields met the inclusion criteria. These papers were screened for duplicates which further yielded to 294. The selection flow was summarized in Figure 1. The papers were then classified based on the ethical issues of tissue engineering discussed, phase in the development and to the type of journal in which they were published. Additional materials not included in the systematic search were added to supplement the discussions.

## RESULTS

### Papers Classified According to Issues

The most dominant ethical question found (Table I) is

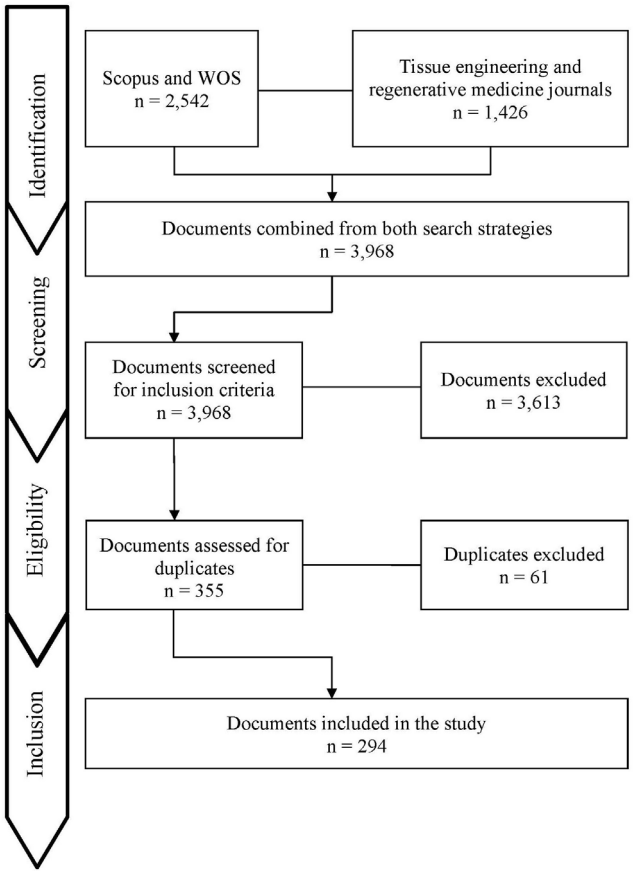


**Figure 1: The flow of papers selection process**

**Table I: Papers classified according to ethical issues**

| Ethical issues | Number of papers |
|---|---|
| Stem cells and gene editing | 43 |
| Cell donation | 15 |
| Animal experimentation | 26 |
| Ethical aspects of clinical trials | 33 |
| Biobanking | 14 |
| Public education and engagement | 29 |
| Laws and regulation | 116 |
| Resource allocation | 19 |
| Medical tourism and unproven clinical interventions | 44 |
| Scientific misconduct | 13 |

the issue of ongoing development and implementation of regulation and legislation concerning tissue engineering products, practices and researches. About 39% of the selected studies are concerned with the developmental and practical aspects raised by various attempts to regulate tissue engineering. These papers contain discussions on lax regulation causing growths of unproven interventions (3–5) and not limited to direct-to-consumer stem cell therapies (5–11). There are also studies analysing aspects of and differences in legislation systems between countries such as Australia, United States of America, Japan and European Union (12,13) and regulatory frameworks imposed by different governmental bodies and their potential commercial implications and ambiguities (14), to deliberation on an international standard for stem cell research and translation guidelines (15).

Another closely related issues frequently mentioned or discussed are the issues of medical tourism and unproven clinical practices. These issues are, for the most part, intertwined; hence they are grouped under the same category. Most of the papers discussed are on the issue of increasing direct-to-consumer advertising of stem cell treatments (5–7,10,11) with the majority being scientifically unproven interventions (3,4,8,16,17). Consequently, the effects of this malpractice are also discussed, including the adverse effects in patients obtaining unproven stem cell-based interventions (18). Matters such as the quality, methods and platforms in which the marketing take place are also discussed (19,20), including the use of social media to provide testimonials of the unproven treatments as one of the marketing strategies (21).

Another ethical issue dominating is the use of stem cells, mainly those of human embryonic stem cells (hESCs). The morally problematic nature of hESCs use in therapy and research posed as one of the disadvantages of using these cells (22–40). Besides, some papers discuss on the use of fetal stem cells for therapy and research and its associated ethical issues raised (26,39,41) as well as the ethical concerns on genetic engineering and modification of stem cells (42–52), including those of human germline (23,27,33,38,53–57). Some papers present induced pluripotent stem cells (iPSCs) as the most recent alternative source to hESCs (35,37,40,58,59). Another issue discussed is on the use of human artificial gametes produced from human pluripotent stem cells and its associated ethical considerations (28,44,60,61).

Besides the abovementioned issues, other diverse ethical issues are discussed concerning different phases in tissue engineering development.

**Papers Classified According to Phase in Developments**

The following ethical issues discussed are classified based on the development phase of tissue engineering to which they seem most relevant (Table II).

**Fundamental and Pre-clinical Research**

In this early phase of tissue engineering development, four clusters of associated ethical issues identified include: (1) the cell sources utilized in tissue engineering products, (2) the cell donation, (3) the animal use, and (4) the morally questionable ''techniques.''

(1) The first cluster deals with the source of cells used in tissue engineering. Materials coming from xenogeneic cells for tissue engineering use is a controversial issue. The concern includes mainly on the fundamental question surrounding humanization and the blurry line between species boundaries. Inter-species chimaera involves the multi- or pluripotent stem cells

**Table II: Papers classified according to phase in development**

| Phase in development | Number of papers |
|---|---|
| Pre-clinical/basic/fundamental research | 45 |
| Clinical trials | 24 |
| Clinical practice | 75 |
| Advanced clinical application | 148 |

transplantation from the human donor into an animal recipient. However, this may in some way impart ethically important human characteristic on animal hosts which inevitably violates human dignity and animal moral status (62–64). These include the concern on the chimeric animal having human thought, the prohibition of chimeric animal reproduction and the necessity to control the contribution of human stem cells to the chimaera (65). It also raises additional concern on using human pluripotent stem cells for chimaera research for their potential of developing fetus that remains controversial (66). In 2006, the United States of America Congress passed 'Human Chimaera Prohibition Act' (63) which in turns provide restrictions to the National Institutes of Health (NIH) on chimaera research. It was deemed to pose a threat to scientific progress and development; thus, lifting of the restrictions was urged by the scientific community (67). Another related issue that could delay progress is public acceptance. Despite the high potential of chimaera research with a particular emphasis on producing organs for transplantation, the general population of Japan has noticeably less support for human-animal chimaera research than scientists in Japan, in spite of generally high levels of support for regenerative medicine research in general (68). The next consideration involves animal welfare, the use of non-human animals that are considered to have moral worth and not be treated as 're-designable systems' to be manipulated for human use. The proper treatment and conduct in handling animals during research to minimize pain and suffering are considered essential (62,63). Some also raise concerns regarding the risks both to patients; the immune rejection risk, and to public health mainly on the transfer of infectious agents from animal tissues and organs to human recipients (62). There is also a small but similarly important concern regarding the use of living tissues in a machine, mainly known as the bio-hybrid machine. Utilizing living materials for application in human-made systems produces worry about emergent behaviour; a behaviour exhibited by a complex multi-component system that is not exhibited by the individual part. Research implementation of this kind in regulated environments is necessary to provide control over the bio-hybrid machine performance and lifetime (69).

(2) The second cluster is concerning cell donation. The obtainment of required informed consent from the donor is emphasized. Donors should be well-informed about the details of the future use of their cells or tissues, and the samples should not be used and should be discarded when the consent is not given. Research that uses tissues or cells without any consent from donors could raise profound moral issues (22,49,70–72). Concerning informed consent, questions are raised on how much details should be informed to donors before consenting and what is the baseline of information adequacy in a written consent form. The "key information" summary which is the new required component in a research consent form could provide essential information to facilitate informed decision-making (73). There is also a discussion on the consent of potential use of participants' data after the withdrawal from research (74). Likewise, the importance of protecting donor privacy and confidentiality is pointed out (33,72,75,76) such as through samples anonymization utilized in research. However, in the case of iPSCs, for instance, cells derived from any individual will inherently hold a large amount of private information (DNA) which deemed useless the anonymization of samples. The genetic information in iPSCs might be adequate to identify the donor or the donor's relatives. This is made possible through the growing availability of human genome sequencing data across both public and private platforms (77). There is also a concern on the sharing of research participants' data between research groups and how the findings of research may be communicated to the participants and public in general without compromising the privacy of donors (71,72). Another closely raised issue is on identity and ownership of tissues and cells, particularly of autologous type. Questions raised include the issue of autologous equates autonomous; whether donors have rights over donated cells that have undergone changes in biological properties and whether in reality, we do 'own' our body and cells (78). Additionally, the most preferable mode of umbilical cord banking has been the subject of ethical dispute. As stem cells originated from this blood might be used for regenerative purposes in the future, some ethical justifications are put forward for favouring public banks over private, commercial banks (79).

(3) The third cluster focuses on papers that highlight the ethical implications of animal use in experimentations. These include the use of animal either as a source of cells or for tissue engineering research (63,80–85). Among the uses of laboratory animals include the use as models of human diseases for drug and product testing and development, and the use to examine fundamental processes of tissue engineering. As stressed by some authors (81,84), due considerations must be given when choosing the most appropriate translational animal models to validate their utilities, which include anatomical, physiological and functional considerations. Animals could suffer pain or disability that may be hard to predict during experimentations. Thus, humane treatments of the animals by researchers are essential to minimize harms caused to the animals (63,83). Some papers proposed alternatives to animal experimentations including the use of mathematical

modelling as a primary design tool for tissue engineering (85) and the use of tissue engineering construct itself as substitutes of laboratory animals (80). Other emerging alternatives discussed include human-derived three-dimensional tissue models, organs on chips, computer modelling of various hues, micro-dosing, and human blood derivates (82) to reduce, or else to avoid the use of animal in experimentation.

(4) The fourth cluster concerns with ethical reservations on techniques deemed problematic and controversial including the mixing of human and animal cells in chimaera research (62–68) and genetic engineering of cells for tissue engineering research involving mainly CRISPR technique (45,53,54,62). Other concerns mentioned are regarding the development of synthetic human entities with embryo-like features (SHEEFs) and the associated Warnock rule (14-day rule) in embryo research (28,31,33,34) as well as the ethical discussion of brain organoids highlighting consciousness as a moral limit of brain organoid research (72).

**Clinical Trials**

Among the issues discussed are the challenges to obtain informed consent due to uncertainties in the interventions, the difficulty to achieve a proportional risk-benefit balance and the complexities in a trial design concerning follow-up and sample size (86–88). These ethical challenges surround but not limited to the issue of the participation of individuals at risk in clinical trials (87). A closely related issue is a therapeutic misconception in which participants should be made known of the distinctions between participating in research and getting treatment before consenting to participate. The duty of researchers to clarify the clinical and ethical details of unproven interventions is highlighted (73,88–91). Other issues discussed in the literature include the need to establish safety and efficacy standards before any trial is conducted, and to provide evidence-based answers prior approval of proposed clinical trials (12,29,88,89,92–95), the emphasis of transparency in conducting clinical trials, particularly in reporting results that should be guided by certain guidelines (96), the ethics of introducing sham procedures as controls in clinical trials (97,98), the regulatory challenges in multi-centre clinical trials (94), the informal professionalization of healthy participants repeatedly participating in clinical trials as a main source of income (99), the unproven and 'pay-to-participate' interventions promoted in the NIH-administered website, ClinicalTrials.gov or/and conducted by private clinics (89,100,101) and the slow ethics review process of the clinical trial proposal due to overtly bureaucratic system (102). Despite the success of xenotransplantation in pre-clinical research, its implementation in clinical research has raised several ethical questions. These include the risk of infection both for the study participant and the surrounding community. Issues such as the right of the study participant to be removed from a clinical trial that involves long-term monitoring of infectious diseases as well as the right to privacy and informed consent are also addressed (103).

**Clinical Practice (Short-term)**

The following topics are particularly appropriate to be placed in discussions regarding the introduction of tissue engineering application in clinical practices. This includes the marketing and advertisement of unproven and direct-to-consumer therapies, interventions or treatments (3, 4, 6–11, 14, 16, 17, 19–21, 104–116) underlying reported adverse events in patients receiving them (18,117), which also includes the ones claiming 'treatments' as research, thus require patients to pay to participate (118), and that gives rise to medical tourism; the practice of seeking therapies overseas, and the challenges to regulating such practices beyond national boundaries of different jurisdictions (119) and in cases of patients with threatening diseases or conditions as well as the discussions on the Right To Try laws (120). This issue is not limited to human medicine but also expands to veterinary medicine, particularly in small animal therapies (121). Another related issue discussed includes the detailed case of Paolo Macchiarini (122–128). A closely associated issue is the inaccurate narratives of treatments portrayed in mass media and its ethical implications (24,129,130). Consequently, this gives rise to initiatives to engage with patients to provide trusted information on stem cell research and treatment options available (130). These initiatives aim to address the challenges of inadequate and conflicting information, responses and advices of and from health professionals, particularly on possible risks of treatments (131). Another related topics discussed include the ethics of biobanking consisting of the recruitment of donor, informed consent and adequacy of information detailed out to the potential donor, marketing practices, commodification, the right of the donor to privacy, data protection and ownership, the access equality to healthcare with respect to private and public biobank (71,76,79,104,132–135), the distributive justice and patient access concerning high-cost treatments (104,136) that inevitably co-exist with the challenge to obtain and to retain funding for product development and market authorization without compromising the quality and benefit of treatments within the healthcare system (106,137–139), the requirement to conform to the regulations of Good Manufacturing Practice and several approaches in marketing regulations (140,141). Another associated issue is regarding the ethical aspects of bioprinting which comprise of control and confidentiality of patients' data and its economic landscape (142).

**Advanced Clinical Application (Long-term)**

This phase concerns with more complex issues extending beyond the pre-clinical and clinical research and practices, and which have long-term and diverse applications that include issues existing in almost all

previous phases. The issues include the intersection between religious perspectives and tissue engineering practices (143), particularly pertaining to the use of human embryos in research and practices (39), cloning (144) and the use of porcine as a biomaterial for Muslim patients (145). Another issue highlighted is on chimaera research and xenotransplantation (146,147) that gives rise to more philosophical and delicate inquiries and discussions concerning the risk of host animal humanization through the development of human consciousness, features and gamete production as well as the associated public discomfort on playing god issue and demoralization of human dignity (148–154). Another related issue is the complicated procedure of transplanting head and brain which poses both ethical and existential questions on intricate matters such as the clinical and psychosocial impacts this produced, including the question of personhood and identity, risk-benefit and distributive justice (155). Concerning distributive justice, Gardner (156) discusses the underlying aspect of initiatives provided by some countries that may impact the egalitarian notion and affect resource distributions in the healthcare ecosystem. A quite number of studies discuss on the pathways to regulate and to translate tissue engineering research and products into clinical markets including various complicated issues surrounding its ecosystem involving various stakeholders as a whole and at large (15,37,56,113,157–204). Other issues discussed are the moral status of cerebral organoids which include the questions of human origin and procreation potential (205) and the moral justifiability of using tissue engineering to enhance human capabilities and longevity (41,206). Some authors present on the issue of ownership and patenting of human bodies with questions related to human rights and commodification taking place (207,208).

### Papers Classified According to Type of Journal

Most of the selected papers are published in biomedical or scientific journals. In contrast, only a few minorities are published in journals of the ethics, humanities or social science domains (Table III). Nonetheless, most authors are affiliated with scientific or biomedical institutions.

## DISCUSSION

### Ethics and Laws

Even though the topics related to laws and regulations and their associated topics dominate the scientific literature concerning the ethical issues of tissue engineering, it does not imply that laws and ethics are synonymous nor co-extensive. As Benatar (209) put it, the laws could be defective ethically and morally, and ethical and moral aspects could either inadequately be incorporated into laws or fail to be all together. The outcome of this is that laws could not resolve some moral dilemmas or rectifying the ethical defects of medical and research practices. However, laws and ethics are indispensable to each other as portrayed in most literature combining discussions on both legal and ethical aspects of tissue engineering (58,77,116,200,201,210–213). Both subjects are inter-related to deliver prospective engagement to promote the development of tissue engineering. One of the occasions that could be seen in how these two subjects are interwoven with each other is in respect to the rise of commercial, unproven and direct-to-consumer therapies in the market (107), particularly the stem cell therapies (3–7,10,11,14,16,20,214) caused by lax regulations which consequently breached some ethical boundaries, most notably the ethos of medical ethics to "do no harm" to patients; primum non nocere (215). Majority of the therapies provided and advertised do not meet the required safety and efficacy standards set by the regulatory bodies. Most of the advertised treatments make claims that are not based upon data from carefully designed and conducted randomized controlled trials. Martinho and Turner (214) found several lawsuits in the U.S. prompted by claims that businesses or individuals engaged in false advertising related to stem cells. These cases are related to stem-cell-based cosmetic products for skincare or 'anti-ageing' purposes and the clinical uses of stem cells for the purported treatment of diseases or injuries.

**Table III: Papers classified according to type of journal**

| Type of journal | Number of papers |
|---|---|
| Biomedical/clinical journal | 248 |
| Other (ethics, social science, and humanities) | 46 |

While lax regulations breed unproven therapies in the market, it is also worthwhile to note that perhaps this occasion is caused by strict regulatory hurdles faced by stakeholders in bringing tissue engineering research into translation. Tissue engineering medical products could not be said to have had success in the mainstream clinical marketplace currently. Many, if not all, have entered the "valley of death"; a gap between benchtop and clinical practices hence causing scientific and economic burdens. In 1994, it was estimated that a quarter of a billion dollars were invested for the field. However, it was yet to produce a revenue-generating, commercial product. The cumulative investment grew exceeding $3.5 billion in 2000. It decreased as of 2002 due to unsuccessful regulatory trials, discouraging product launches, and the overall investment pullback in the wake of the dot-com crash hence raising alarms about the validity of its promise. It sparked questions concerning whether the technology had missed its window of opportunity. However, in mid-2007, approximately 50 firms or business units offered commercial tissue-regenerative products or services with generally profitable annual sales over $1.3 billion, a recovery for the downfall from previous years (216–220). O'Donnell et al. (200) proposed bedside to bench and back again approach to be utilized by

researchers to increase the odds of making their products available clinically. This alternative approach allows salient translational questions or issues to be defined and reconciled early in the research process, and for researchers to make informed decisions concerning the designated pathways of tissue engineering products.

**Animal Experimentation**

In 2015, it was estimated that more than 192 million animals (221) are utilized globally in experimentations or to supply the biomedical industry per year; an increase from 115 million animals used annually in 2005 (222). It is no surprise then that the concerns towards animal experimentations are growing both in public and scientific communities, questioning the relevance of increasing availability of alternative methods, including those of tissue engineering. The two main concerns generally arisen throughout the discourses are the questions on reliability and animal welfare. Akhtar (223) provides critical assessments on the reliability of animal experimentation. These include its low prediction of human outcomes, unreliability throughout a broad disease areas category and unreliability of animal experimentation that hence undermine scientific justifications in its favour. It is further argued that unreliable data from animal experimentation could cause harms to patients by generating ambiguous safety and efficacy data. It could also cause misdirection of resources away from more effective testing methods and the potential abandonment of better therapeutic options. Although we may argue that a priori ethical attitude towards animal welfare would preclude them from being subjects of life experimentation that distress, harm or kill them, the fact that animal trials have no relevance for human healthcare makes these experiments both unscientific and unethical. Striking a balanced conversation between two extremes; the first being to necessitate animal use for the sake of scientific progress, and the second being to halt animal use for the many ethical conundrums posed by it is a daunting but required task needed to be taken by all stakeholders prospectively. It is intellectually, morally and legally imperative to pursue and to opt for viable options to reduce or to replace animal use. Due to the growing concern on the ethical limitations of animal experimentation, many researchers seem to acknowledge the need to find alternatives to using animals in tissue engineering research, or to using tissue engineering approach in creating models replacing the traditional method of using animal models. For instance, Sarkiri et al. (224) reported on the expanded application of engineered skin in disease modelling and drug screening areas. These skin models are suggested to represent the anatomical and physiological traits of native skin for the efficient replication of normal and pathological skin conditions. Tissue engineering research should be geared more towards developing models to replace or to at least minimize the use of animals as models for medical research, refining the relevancy of the field as an alternative towards animal use.

Another recent topic emerged concerning animal experimentation are the questions of xenogeneic transplantation and chimaera. The responses to these issues vary, depending on the religious, ethical and cultural systems involved. For example, the proponents of chimaera research argue that inter-species chimaeras are great experimental models for investigating stem-cell potential, organismal homeostasis, and disease. The developmental niche(s) of the host animal could serve donor cells exclusively through genetic manipulation thus generating tissue- or organ-enriched chimaeras. At some point, it could assist in supplying organs for transplant. Additionally, interspecies chimaeras serving as platforms for drug screening and disease modelling could provide in vivo data with relevant clinical value concerning drug toxicity and efficacy alongside disease onset and progression (63).

**Iatrogenesis**

Iatrogenesis is a term derived from Greek which means "brought forth by the healer" (iatros means "healer" and genesis means "brought forth by"). Technically, iatrogenesis means adverse outcomes or illnesses caused to patients by medical interventions or lack thereof. They are caused either due to random individual mistakes of the healthcare providers or due to the systematic error introduced and practised in medicine, which also referred to as iatroepidemics (225,226). In the context of this discussion, this issue is related to the incident involving the implantation of the tissue-engineered trachea into patients by Paolo Macchiarini; an incident that revealed layering issues surrounding causes that lead to iatrogenic accidents. Once deemed to be a pioneer of regenerative surgery, Macchiarini intended to give patients with damaged tracheas a new windpipe. Initially, a donor trachea was used, which was then switched to an artificial scaffold. Seeded with stem cells, the engineered trachea was expected to grow into a completely functional new organ. However, out of the eight artificial trachea recipients, six of them have died post-surgery. He had then been alleged to depict a false picture of his patients in scientific papers in which some have been retracted. He was also accused of operating without ethical approval and lying on his curriculum vitae (CV). The case has thrown science into a predicament in Sweden where investigations are followed by allegations involving involuntary manslaughter (128).

Another related situation involves the direct-to-consumer marketing of and access to unproven stem cell treatments and therapies. Although it is in broad accord with tissue engineering, stem cell treatments hold a considerable promise of restoring damaged tissue and organ functions. Nevertheless, the indications that the therapies might be useful, efficacious and safe may pose some limits. In the scientific and medical community,

innovative therapies implementation works within the norm of regulatory boundaries and controlled clinical trials. To minimize patient risk, clear and adequate safety and efficacy profiles for new therapeutics are set before marketing authorization is granted. This thorough clinical validation approach every so often consumes time, which patients experiencing debilitating or terminal diseases do not have. Unproven stem cell interventions promising a cure or a working treatment for severe diseases have thus found ways into the patient community. Every now and then, providers of such treatments exploit the public's willingness to pay large amounts of money for the misguided and often lacking in the scientific evidence in hoping to achieve reliable recovery from their illnesses. This phenomenon gives rise also to the emergence of medical tourism and/or stem cell tourism. Although there are a lot of slight differences and categorization in its definition (227,228), medical tourism could generally be defined as a practice by which patients travel abroad to seek for treatments. The main drivers for this practice include the availability of advanced medical technology, a better quality of medical care, quicker and cheaper access to otherwise long waiting time and expensive treatments and regulatory hurdles in the country of residence (229). Furthermore, National Commission on Macroeconomics and Health of India (230) reported that the emerging private sector services serves as a huge potential for the country to be a hub for medical tourism. Nevertheless, this could create pressures for increased budgetary allocations for government hospitals in staying competitive due the increased overall cost of healthcare in the country.

**Ethics and Tissue Engineering**

Even though a vast majority of the selected papers are published in biomedical or scientific journals and a fraction of minority in the humanities domain, some particular concerns should be noted. The growing focus on ethical issues pertaining to tissue engineering by numerous papers in biomedical or scientific journals is indicative of increasing interest paid to ethical reflections by tissue engineering researchers. Moreover, most authors have scientific or biomedical affiliations, suggestive that ethical dialogues have reached and worked on various institutions, not necessarily those of the humanities domain alone. While these may appear as a complimentary direction tissue engineering research is moving towards, they are on the other hand running risks of "disciplinary slip" problem (209); where one slips from working in one's discipline, in which one is trained, to working in another, in which one is not. This problem may lead to a few consequent problems with the first one being namely confirmation bias. Tissue engineering researchers may be tempted to justify and validate their scientific works through ethical deliberations, whether or not they are ethically and morally right nor wrong. In the broader context of Islamic sphere concerning tissue engineering, for example, Setia (231) provided a concise argument on how the notion of "*maqāṣid*" and "*maṣlaḥa*" which were originally belonged to the worldview of Islam have been cooptated and conflated to serve the Western secular utilitarian framework discourses. He argued that "concerns that are in vogue seem to be simply assumed to be good and useful in the name of science, technology, and development, with no serious conceptual or even factual scrutiny. They are then too quickly labelled and qualified as *maqāṣidī* and *maṣlaḥawī*, and legitimized as good or beneficial in Islamic law and projected to the gullible public as "*Sharīʿa*-compliant" (already a problematic term)" (231 p. 154). Secondly, tissue engineering researchers who may not formally and adequately be trained to construct and to produce works of ethical reasoning and reflections may exacerbate the issue of poor-quality bioethics publications, for instance (209). It is therefore imperative for those qualified in each respective fields of tissue engineering and ethics to prospectively engage and work in close collaboration to accommodate the conversations revolving the ethical conundrums that may pose as threats to tissue engineering development.

## CONCLUSION

The above analysis of ethical challenges surrounding tissue engineering provides a preliminary overview of the contemporary discussions as the field is growing throughout the years. All the challenges are relevant from the ethical point of views. They are, however, differing in terms of the urgency to respond and the weight it bears. Most of the responses examined were at the pragmatic level of ethico-moral conduct and legal praxis, and less on conceptual and scientific level of first principles, theories and methodology. These ethical challenges which are primarily generated by the current biomedical hegemony (232) need to be systematically engaged for the sake of tissue engineering progress and development.

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