



A Preliminary Review on Moral Challenges in Tissue Engineering

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Abstract

Tissue Engineering and Regenerative Medicine (henceforth TERM) research and development (R&D) is driven by substantial and growing medical needs. The ultimate goal of TERM is to reconstruct biological spare parts or living tissue graft which also known as Tissue Engineered Medical Products (henceforth TEMPs) for the human body. The emergence of this biomedical field has created numerous treatment approaches as well as prospects to manage tissue/organ loss worldwide. This advancing technology offers unique insights into its potential to customize functional human tissue/organ based on the specific needs of an individual patient. The demands for TEMPs have been increasing over time. However, other than certain technical ambiguity, its scientific progress is shrouded by several moral challenges which have yet to be addressed systematically. At present, there are only few literatures addressing the moral challenges of TERM principles and practice from the Islamic perspective. This paper attempts to bridge the gap. The discussion will try to harmonise and seek balance between the empirical aspects and the social dimensions of the technology. This paper perhaps could enlighten the stakeholders to reach answers to certain questions which may bring the best out of TERM technology.

Keyword: *Tissue engineering, regenerative medicine, moral challenges, personalized medicine, Islamic perspective*

Abstrak

Aktiviti penyelidikan dan pembangunan (R&D) dalam bidang Kejuruteraan Tisu dan Perubatan Regeneratif (TERM) didorong oleh keperluan perubatan yang semakin meningkat. Matlamat utama TERM adalah untuk membina semula alat ganti biologi atau graf tisu yang dikenali sebagai produk perubatan yang dihasilkan melalui kaedah kejuruteraan tisu (TEMPs) untuk tubuh manusia. Kemunculan bidang bioperubatan ini telah menghasilkan pelbagai pendekatan dalam kaedah rawatan dan juga prospek bagi menangani keperluan penggantian tisu/organ yang rosak di seluruh dunia. Kemajuan teknologi ini menawarkan suatu kaedah unik yang berupaya untuk menyesuaikan fungsi tisu/organ yang dibina semula berdasarkan keperluan khusus pesakit secara individu. Permintaan terhadap TEMPs semakin meningkat dari semasa ke semasa. Namun, selain daripada wujudnya kekaburan tertentu dari aspek teknikal, perkembangan saintifik teknologi ini diselubungi oleh beberapa cabaran moral yang masih belum ditangani secara sistematik. Pada masa ini, hasil penulisan sedia ada tidak banyak membincangkan isu moral dan cabaran berkaitan prinsip dan amalan TERM dari perspektif Islam. Kertas kerja ini cuba untuk merapatkan jurang tersebut. Perbincangan untuk kertas kerja ini akan cuba mengharmonikan dan mencari keseimbangan dalam teknologi ini dari aspek empirikal dan dimensi sosial. Kertas kerja ini diharapkan dapat membantu pihak berkepentingan untuk mendapat jawapan kepada soalan tertentu dan meraih resolusi yang terbaik untuk teknologi ini.

Kata kunci: *Kejuruteraan tisu, perubatan regeneratif, cabaran moral, perubatan peribadi, perspektif Islam*

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Introduction

According to World Health Organization (2010), "...transplantation of human cells, tissues or organs saves many lives and restores essential functions where no alternatives of comparable effectiveness exist...". The authors would start this paper by a problem statement on the current status of organ donation and transplantation, particularly from Malaysia

standpoints. A good problem statement, in this aspect, signifies an effort to give Tissue Engineering and Regenerative Medicine (TERM) research projects a direction. Perhaps, the questions are worthy and could be helpful to reach an answer to the multifaceted moral challenges of tissue engineering, particularly from the Islamic perspective. The paper distances itself from providing an ultimate Islamic decree in the application of TERM in healthcare. It neither meant to invoke legal maxims and protection of five human interests based on Maqasid al-Shar'iah to promote commodification of human tissue/organ through medicalization. The Maqasid al-Shar'iah primarily addresses five purposes of Islamic law that include protection of life, religion, progeny, intellect and wealth.

Based on recent updates provided by the Transplant Unit, Medical Development Division and National

Transplant Resource Centre, Ministry of Health (MOH) Malaysia, there are more than 17,000 patients awaiting the chance to benefit from a transplant. However, from the latest actual donor statistics which has been updated on 6th July 2015, the total available organ donors are 537 individuals (Chinese=314; Indian=147; Malay=35; others=30; unknown=11) (Medical Development Division, 2007; Transplantation Unit & National Transplant Resource Centre, n.d.; World Health Organization, 2010). From these recent numbers, one can tell that the in-need transplant patients are approximately 31 times higher than the actual organ donors. The distribution or, the percentages of the actual donors based on the ethnicity are represented in Figure 1.

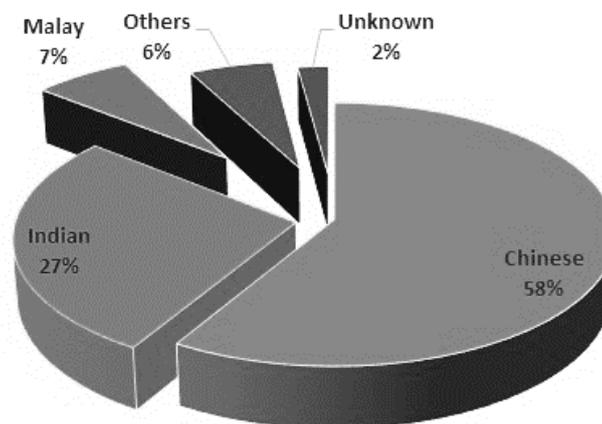


Figure 1: The latest actual donor statistics in Malaysia based on ethnicity, as of 6th July 2015

It is indicated in the Article 1.5: The National Organ, Tissue and Cell Transplantation Policy (Medical Development Division, 2007), MOH Malaysia that, “...Historically there has always been a shortfall in the supply of organs and tissues. The success of transplantation has increased demand, thus increasing the gap even more. The shortage of organs for transplantation has led to greater use of organs from living donors...” Adding to this, at a TED conference in 2011 (Atala, 2011), one of the renowned scientists of the TERM field, Anthony Atala, reasserting that there is a major public health crisis nowadays, in terms of the shortage of organs. This crisis, perhaps is due to the fact that the remarkable achievement in the field of medicine, science and biomedical technology has dramatically increased the average life expectancy. Research shows a surprising and continuing

improvement in life expectancy among those aged 80 or above (National Institute on Aging, 2015). However, one should understand that the more we age, the more our organs tend to fail. Based on United States (US) data (1991 – 2013), the number of patients on the transplant lists continues to increase, but the number of transplants remains unchanged (Figure 2).

A brief online search using Google database and “organ donation and transplantation” as the keywords indicates that there is a dire need for organs transplants worldwide. The existing trend shows that there will be inadequate organs to be offered to the patients, as time goes on. To a large extent, this is where a unique field of biomedical research i.e. TERM comes in and paves the way for an alternative treatment modality in medicine.

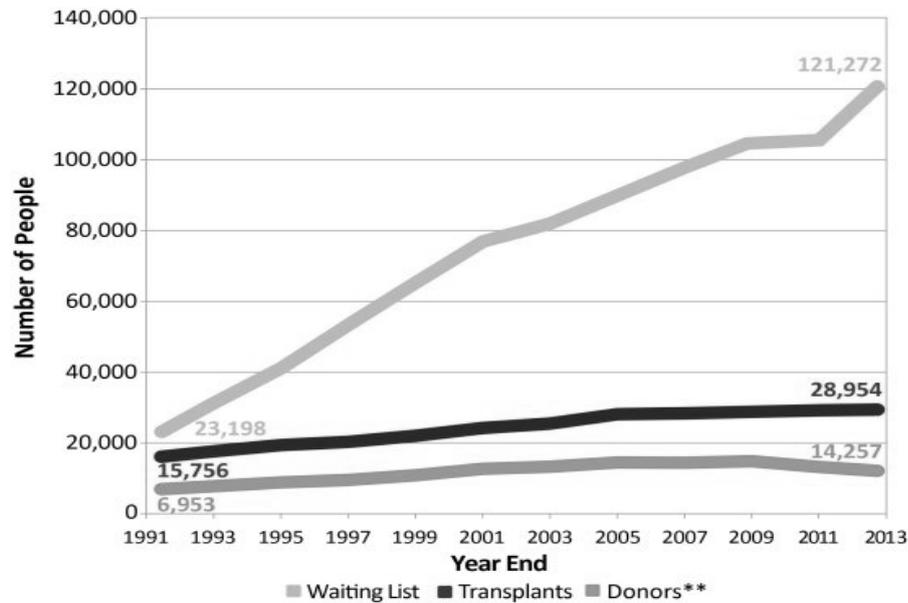


Figure 2: The number of waiting list, transplants, and donors over the year in US (U.S. Government Information on Organ and Tissue Donation and Transplantation (n.d.).

**The data include deceased and living donors

Definition of Term: Scope and History

The concept of reengineering or, reconstructing or, building body part sounds amazing; implying science fiction more than the actual medical and engineering practices. Despite the reservations, the authors are certain that TERM, is a concept which time has come. Although it is difficult to define, TERM has indicated within its embrace, the real possibility of new modality for restoration and repair of tissues/organs. This biomedical technology aims at reconstructing an autologous tissue and/or organ using the patient's own cells. Ideally, the autologous approach will help bypass multitude shortcomings and ethical issues surrounding the conventional organ donation and transplantation. For a record, inadequate supply of cells/tissues/organs, immunoreactivity between donor cells/tissues/organs and recipient's body that lead to rejection and life-long immunosuppression requirement are among the persistent problems in the organ donation and transplantation. It is hoped that the success of TERM may change the quality of life of many individuals in the coming decades.

Tissue Engineering and Regenerative Medicine (TERM) is not truly a new field. There are few versions of the historical aspect concerning TERM. However, perhaps, in the modern views, some concepts relating to TERM can be traced back in the 1937's articles (Carrel, 1937; Okkels, 1937a, 1937b) and the 1938's books (Carrel & Lindbergh, 1938; Parker, 1938). Interestingly, the three 1937's articles and the book entitled "The Culture of Organs" present an infinite detail of the equipment and the methods for in vitro

maintenance of organs. Alexis Carrel (a Nobel Prize Winner) and Charles A. Lindbergh, the authors of the book wrote, "... Anatomical specimens are nothing but useful artefacts; ... structure and function have no separate existence; and ... cells and medium are one. ." These brief ideas, later facilitate proper understanding of organs. Both Alexis and Charles spent their entire life working at the Rockefeller Institute in New York in the area of the culture of organs. The authors believed that the factors which influence the organs, are attainable only when they are studied under conditions of survival and under the influence of the fluids which regulate function. As for the author of "Methods of Tissue Culture", Raymond C. Parker, other than presenting a laboratory manual on procedures essential for in vitro tissue culture and offering a new approach to various biological problems, also discusses the applications of tissue culture to experimental biology and medicine. It was 80 years ago that he had already outlined, the significance of tissue culture technique in the study of experimental morphology, tumours, viruses, hypersensitivity, and immunity states.

In the past, 'tissue engineering' term was applied loosely in such cases of manipulation of tissues and organs in surgery. The term was also used to describe surgical approaches that involve prosthetic devices or biomaterials. A key point in tissue engineering was signified in an article written by Robert Langer and Joseph Vacanti. As it is nowadays understood, they defined tissue engineering as ... "the application of the principles and methods of engineering and life sciences toward the fundamental understanding of structure-

function relationships in normal and pathologic mammalian tissue and the development of biological substitutes to restore, maintain, or improve function.” (Langer & Vacanti, 1993). Meanwhile, for ‘regenerative medicine’, the term was not well-defined when compared to tissue engineering, although, it was used earlier in the literature. However, regenerative medicine is now seen as a field that focus primarily on the use of stem cells to regenerate tissue and aim at remodelling damaged tissues/organs in humans (Freitag, 2016).

Practically, tissue engineering can be regarded as a valuable tool to achieve regenerative medicine. This is probably one of the reasons why both “Tissue Engineering” and “Regenerative Medicine” terms have been used interchangeably in the literatures. Based on the present trend, both terms have been combined and referred to as one dedicated, productive scientific field, known as “Tissue Engineering and Regenerative Medicine (TERM)”. This field brings together experts ranging from basic science researchers to the following professionals namely materials science engineers and chemists (to design and construct scaffolds for new tissues or organs); physicists and mathematicians (to model tissue growth), biologists (to monitor and control cell growth), pharmacologists, surgeons, and other clinical staff as part of the team. From the said descriptions, it is evident that TERM is an

interdisciplinary field encompassing principles from various area of expertise.

Discussion

Principles and Practices of TERM

Tissue Engineering and Regenerative Medicine (TERM) is driven in part by a substantial and growing medical needs. The ultimate goal of TERM is to reconstruct biological spare parts or living tissue graft (which also known as TEMPs) for the human body. After decades of these mind-boggling research activities, researchers eventually realize that the conceptual approaches of TERM can be summarized and visualized as in Figure 3. The application of TERM is governed by the following three main ‘elements’ (or, sometimes known as ‘principles’),

- I. *Cell sources*: either differentiated or undifferentiated cells (adult versus embryonic stem cells);
- II. *Scaffolds materials*: either naturally-derived or synthetically-derived three-dimensional porous matrix;
- III. *Signalling factors or, ‘regulators’ or, ‘bioactive agents’*: either physical stimulus such as mechanical loading, culture conditions and flow condition *in vitro* (bioreactors), and/or chemical such as cytokines or growth factors.

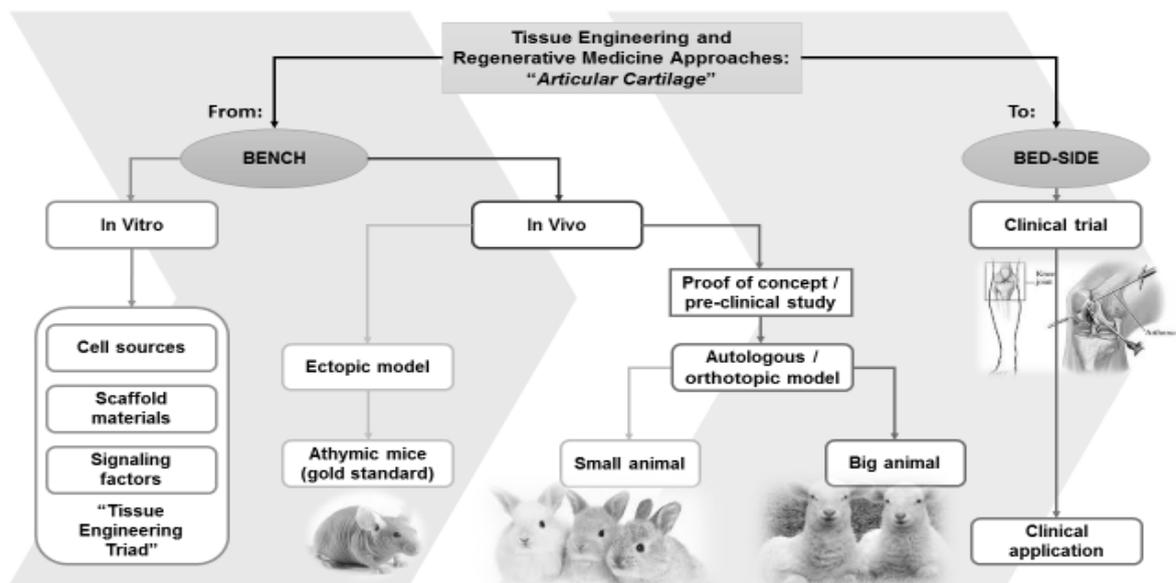


Figure 3: Conceptual approaches of TERM from bench to bedside. Cell sources, scaffolds materials and signalling factors are the three governing principles for successful reconstruction of 3D tissue in TERM

The above three elements, commonly known as ‘tissue engineering triad’ may be used individually or in combination to engineer TEMPs for transplantation purposes. The macro- and micro-architecture of a tissue is determined by adhesion mechanisms that

involve “cell to cell” interactions as well as “cell to matrix” interactions. To achieve the mechanisms, cells can be seeded and cultured into porous, 3D absorbable biomaterial scaffolds capable of supporting new tissue formation. The scaffolds and signalling factors serve to

regulate cell growth and proliferation. A biomimicry internal affairs simulation, range from a simple carbon dioxide (CO₂) incubator to a high-end bioreactor, shall provide an optimum *in vitro* microenvironment for cells/tissues survival.

Successful application of TERM principles hypothetically involves at least four distinct technical stages from bench (laboratory research) to bedside (clinical trial/application) as below,

- Stage I: *In vitro*, non-clinical experiment in the laboratory.
- Stage II: *In vivo*, pre-clinical / animal study for proof of concept.
- Stage III: Clinical trial involving human subjects.
- Stage IV: Regenerative medicine; the actual clinical application.

To further broaden approaches in Figure 3, the above technical stages can be elaborated in the following diagram (Figure 4) to facilitate better understanding. Other than underlining the empirical aspect of TERM in a concise manner, the authors intend and aim at building capacity within the relevant stakeholders in order to help all interested parties develop a broad understanding of the social and ethical implications of TERM. These aspects are important and have to be addressed properly in order to bridge the gap between bench and bedside. The social and ethical implications of TERM will be discussed in the next section of this paper.

Various TEMPs such as tissue-engineered cartilage, bone, skin, bladders, small arteries and even a full trachea have been implanted in patients. However, those are still considered at experimental stages and not cost effective. It can be appreciated that at the moment, TERM plays a relatively small role in the actual healthcare settings. Although more complex tissues or organs have been successfully reconstructed to certain extent by some researchers from the Wake Forest Institute for Regenerative Medicine (Wake Forest Baptist Medical Center, n.d.), the organs are still far from being fully reproducible and ready to be implanted into a patient.

At present, the three governing principles for successful reconstruction of 3D tissue in TERM are yet to be tackled, entirely. Despite all these challenges and uncertainties, the field continues to expand. Until the outcome of TERM is proven, the researchers will continue to be hastened by various stakeholders and the field will continue to be shrouded with scepticism and question... "Will we ever grow complete organ in the laboratory?". While certain clinical procedures routinely apply TERM concept without realizing it,

there are an array of basic laboratory researches in the design of TEMPs that must be followed for proper clinical trials and application in the near future. Despite having few clinical advances thus far, the goals of TERM are increasingly achievable. Even a small step towards the progress of TERM is worthy of effort and sacrifice. It is a rapidly changing prospect, hence the opportunities for the use of TERM will definitely vary year by year. Coupled with this, it is anticipated that the moral challenges of TERM will also be different and must be reviewed from time to time. It is hoped that TERM will become accessible to anyone interested in the alternative personalised medicine in the near future.

Ethical Issues Related to TERM

It is true that modern scientist and surgeon have made a remarkable breakthrough in the field of TERM. However, the practices of this promising biomedical technology carry with it significant moral and ethical obligations as well as legal concerns. The applications of TERM have raised a number of concerns which are multilevel in nature, similarly to many other medical biotechnology applications and the conventional organ donation and transplantation. Some concerns are related to the experimentation aspects of TERM in the laboratory, while the other concerns are besieged with scepticism on the consequences of its application onto patients. As the TERM processes are mostly related to organ, tissue and cell donation and transplantation, it can be appreciated that the concerns are very much connected to the necessity to preserve life, the sanctity of the human body, and also the protection of human rights and dignity (Hashi, 2015).

Issues raised in relation to the technical aspects in TERM experimentation can be categorized and deliberated based on the processes of TERM; "from bench to bedside". As depicted in Figure 4, the stratified procedures begin with the *in vitro* and the *in vivo* experimentations. If the outcomes are conclusively and completely proven to be safe, these laborious *ex vivo* reconstruction of TEMPs subsequently will lead to the clinical trial in humans. A successful practice-based clinical trials will ultimately be a thriving factor in gaining approval for clinical application in the actual patients. Once again, this complexity and the multilevel nature of TERM have always been the challenges which mainly drive the ethical concerns in its practices thus far (Sha'ban et al., 2014; Gelhaus, 2009). With these in mind, the authors would like to explore and to take a closer look at the issues and challenges in TERM.

Tissue Engineering Pathway (for regenerative medicine)			
Empirical Aspect			Social Science Aspects
Stage I	Stage II	Stage III	Exploring the hidden social dimension from bench to bedside: Socio-technical systems; Knowledge, idea, and value or belief system; Science, technology, and governance; Infrastructure needs (Note: Points adopted from the National Science Foundation Supported Workshop Report in 2008 (Miller, Sarewitz, & Light, 2008) with minor modification)
Laboratory / non-clinical experiment	Pre-clinical / animal study / proof of concept	Clinical trial / human subject	
Cell sources: Tissue harvest and cells isolation; to perform under aseptic condition			
Cell sources + signalling factors: Monolayer (2D) cell culture and expansion; to obtain sufficient cells for 3D tissue reconstruction			
Cell sources + scaffold materials + signalling factors: Construct formation in vitro / 3D culture			
Implantation in nude mice, ectopic xenotransplantation model	Autologous implantation, orthotopic model	Autologous implantation based	
Evaluation and validation analysis		Clinical evaluation	
Determining Biosafety and Biocompatibility (GMP, GLP, GTP, ISO)			
Stage IV			
Clinical application			

Figure 4: Common stages or pathway in technical approaches of TERM. Note: Good Manufacturing Practices (GMP), Good Laboratory Practices (GLP), Good Tissue Practices (GTP) and International Organization for Standardization (ISO) are among the international standards that must be followed and adhered by the relevant practitioners to ensure the safety and efficacy of service delivery.

The *in vitro* setting has brought up few basic questions on “what is the most suitable type of cells can be used?” and “what is the best conditions to maintain the cells quality *in vitro*?” These questions have led to further discussion of benefits and risks of the method used. Are the cells readily available from patients and reliable for *in vitro* culture? The question must be given due consideration because in the autologous approach (using patient’s own committed/differentiated cells or, also known as, adult progenitor cells), due to the morbidity at the donor site, there are increasing trends in TERM research whereby cells are taken from any of the autologous pluripotent stem cells (patient’s own uncommitted/undifferentiated cells), allogeneic (other human donor cells) or xenogeneic (interspecies; animal) cells sources. Since these alternative cells sources are not the cells of the intended lineage and have yet to exhibit the actual committed cells characteristics, do the cells

need further modifications? If yes, will it increase the risk of adverse events? Furthermore, there are instances in TERM researches wherein cell therapy may be annexed with gene therapy to enhance the cells function and growth. Do they pose the risk of inducing cancerous cells lineage due to the uncontrollable cells growth? In light of this, the criterion of the cells source selection has to be done in a very attentive way. There is lack of necessity to discuss and emphasize on the embryonic stem cells (ESCs) as one of the cell sources in this paper since Malaysian government has a strict policy on the ESCs related to transplantation procedure. It is clearly stated that this type of cell source is not allowed to be used (World Health Organization, 2010).

Human body may react to latent degradation implants, residues and additives in unexpected manner. Being unique or different, it is generally believed that there is no two identical people. It is evident as in the

organ donation and transplantation procedure, where the so-called biocompatible organ recipients require life-long immunosuppressive drugs to prevent post-implantation rejection. Thus, what is the finest materials to be used to fabricate or engineer the scaffold? The affinity of *in vivo* implantation depends on the biocompatibility of the materials used. Hence, it is necessary for any materials to undergo biocompatibility and biosafety tests to assess the possible harms and complications after the implantation. The assessments done must adhere to the FDA (U.S. Food and Drug Administration) guidelines. But, will these risk-benefits analysis and biosecurity aspects give an impact or, increase the cost of TERM application significantly?

Cell growth requires optimum physiological conditions from different aspects such as signalling molecules or soluble factors as well as mechanical stimulation. Dynamic culture system may improve cell seeding and functional tissue development when compared to the static culture condition. The question is, what are the signalling factors required to stimulate cells function by mimicking nearly the same as human body? Does the use of the signalling factors further cause unnecessary interaction that influence the degree of invasiveness? Mechanical or physical stimuli usually involve mechanical loading or flow condition in a bioreactor; which can directly or indirectly in-contact with the cultured cells. However, for signalling molecules or soluble factors, the chemical stimuli or the reagents/substances used (for example, growth factors and/or its genes) are supplied to the cells through culture media which has direct contact with the cultured cells. As for the genes, they are usually transferred or transfected into the cells to genetically enhance cells properties. The techniques, either way, introduce substantial cells manipulation. Although the outcomes have been reported as positive, the long term effects remain unknown. Therefore, the safety issue shall be addressed thoroughly in this aspect by all TERM researchers.

Subsequent to *in vitro* experimentation, pre-clinical or animal study has long been debated as the animal models are inflicted with pain and trauma. Although numerous data obtained from the animal testing has led to novel research findings and discovery for us to better understand the systemic treatment mechanisms, the ethical aspects of the animal experimentation need to be considered in the TERM practices (Abdul Rahman et al., 2014). Among the major questions are: What is best animal model to be utilized for specific TEMPs? Do all researchers adhered to 3R concept to optimize the animal usage? (National Centre for the Replacement, Refinement & Reduction of Animals in Research, n.d.). Besides that, the implantation of

human or animal cell-scaffold constructs into the athymic nude mice also raised a number of ethical questions as the process involves chimera production (Jielin, n.d.). Thus, how far this ectopic *in vivo* implantation procedure degrades or diminishes human dignity? Will it compromise animal rights? Will it transform the chimera into a beast? Does it give any benefit to human kind?

While in the clinical setting, cell harvesting and implantation surgery may imply the risk of infection, contamination, inaccuracy and incompatibilities. But still, do the benefit outweigh the risk? In addition, the researchers must adhere to the biomedical ethics which govern the safety of the clinical trial participants. Even if the rational patients have given informed consent, the aspects of beneficence, non-maleficence, and justice still need to be critically considered. It is a well-accepted principle that the opinion of an expert should be sought in decision making process. However, the decision should not be based simply on the basis of the opinion of an expert without a proper corroboration. The opinion should be taken with caution for it may be unsafe otherwise. As mentioned earlier, at present, the cost to realize the TERM application in the clinical setting is very expensive. Thus, who is exactly may benefit from the application of TERM? Will the insurance company cover for the surgical procedures involving TERM? Is it only for the affluent people? How about the poverty-stricken and indigent individuals? Does everyone have the access to the treatment using this technology?

It can be inferred that the ethical issues in TERM practices are mainly driven by the technical complexities with addition to that of socio-economical and anthropological aspects. The issue, which is often criticized as “playing God” is still being debated until now. It is worth to emphasize that all the ethical issues are perceived differently by diverse worldviews. The concerns mentioned here are commonly raised with regard to TERM practices. However, these ethical issues and more to come, may be addressed in various manners by global communities.

Islamic Input Related to TERM

Many medical scientists and practitioners from *Muslim* counterpart have embraced TERM technology. They have been contributing and expanding the knowledge of the technology to be practiced in their local society. *Islam* encourages its followers to use their contemplate faculties to find and seek for cure and treatment. It is better-known that in Islamic tradition, the first *ayah* revealed to Prophet Muhammad (ﷺ) is about the importance of seeking knowledge (*The Qur'an* 96:1-5). The advancement in TERM is in fact a manifestation of knowledge from *Allah Subhanahu Wa*

Taa'la (henceforth *SWT*) resulted from the utilization of the intellect by individuals. Briefly, the tradition promotes the seeking of knowledge in the spirit of *tawhid* to eventually recognize *Allah SWT* as the Lord of the universe (*rabbal 'alamin*). Muslim researchers and physicians are carrying out their duties on the basis that only *Allah SWT* cures any illness (*The Qur'an* 26:80). Indeed, Muslims are encouraged to explore technology in medical context (As-Sijistani, n.d.) as one of the obligations on the earth. Moreover, Imam Al-Shafi'i expressed, ... "After the knowledge of what is lawful (*halal*) and what is unlawful (*haram*), I do not know of any type of knowledge more noble for a Muslim to acquire than that of medicine..." (Al-Dhahabi, 1961).

Bioethical contemplation based on the Islamic worldview cannot be separated from the religion itself that holds the relation between body and mind, material and spiritual realms, and also, jurisprudence and ethics (AFI-Faruqi, 1982; Daar & Al Khitamy, 2001). Islamic bioethics which is being discussed in TERM principles and practices is an extension of *shari'ah*, based on the two major sources in *Islam*; the Holy *Qur'an* (*The Qur'an* 41:44) and the *Sunnah* - Prophet Muhammad (ﷺ) way of life.

Other than the *Qur'an* and the *Sunnah*, there is a prime guideline in *Islam* for medical researchers to ensure that no harm is meant to be introduced in TERM application (Al-Qazwīnī, n.d.). The use of permissible materials should be in conformity with the two sources (*The Qur'an* 7:157) and not to be violated. Thus, Islamic principles has clearly stated that, a medical practitioner has no right to administer or prescribe any harmful material and/or substances to his or her patients. If a certain action ends in both benefits and harm, then it is advocated to first prevent the harm. This can be understood from the Islamic jurisprudence of "avoiding harms takes precedence over bringing good" (Hashi, 2015). However, if the good is much greater than the harm, then such action could be applied. The concept can be used in TERM experimentation as to optimize the benefit as well as to reduce or prevent the harm.

As indicated in the previous section, numerous potential effects encompassing "tissue engineering triad" may not be manifested within a short time

duration. Based on the principle "to go for a lesser harm", the possible effects must be examined and followed up carefully in the long run. If TERM can be realized, it can reduce (if not replace) the dependency on the organ donation which in line with jurisprudential maxims of "yuzal al-darar al-ashaddu bi al-darar al-akhaff" – a greater harm is eliminated by means of a lesser harm, as in the harm reduction approach. Thus, there is a need to apply TERM application in the public health setting but the procedures must strictly follow the *shari'ah*. It is important to note that, TERM is practically applicable in the current healthcare scenario (Mohamad et al., 2014). Therefore, it is an appropriate time for the researchers to present to the public an integrated and holistic approach of TERM in accordance to the *Maqasid al-Shar'iah* to further examine this advanced application (Figure 5).

Interestingly, the advancement in TERM practices and applications may offer specific cell-lines customization for medical industry to test on which can reduce the use of animal in pre-clinical setting. *Islam* has emphasized on the use of everything created by *Allah SWT* on the earth (*The Qur'an* 2:29) but human beings need to observe the limitations. Given these points, stakeholders in this field should look forward to offer a holistic approach in diseases management and ultimately reduce the socioeconomic burden on healthcare system.

Conclusion

The potential of TERM technology is yet to be fully uncovered. Based on the current progress, TERM is indeed, a promising biomedical innovation that will help in attending the necessity of the end-stage organ failure treatment due to the tissues/organs donor deficiency worldwide. This biomedical technology is worth to be explored by Muslims considering the growing number of Muslims population that will benefit from its application. If properly studied, it is anticipated that a great balancing acts of the "tissue engineering triad" namely quality cells source, biomaterial scaffolds and signalling factors will allow the success of TEMPs reconstruction and regeneration.

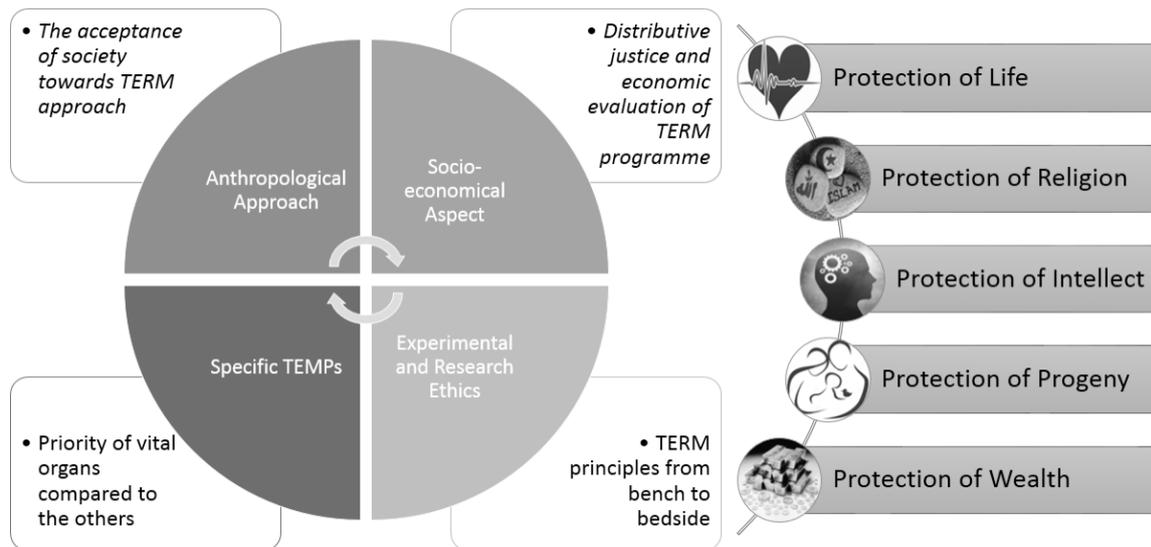


Figure 5: Holistic approach of TERM (adapted from Trommelmans et al., 2007) can be examined in accordance with the *Maqasid al-Shar'iah* principles.

Taking advantage of the autologous approach, ideally the application of TEMPs will minimize the risk of infection and the issues of rejection in patients. In view of the complexities of TERM from bench to bedside, it could be difficult to answer all questions in the current TERM state. However, at some point, continuous deliberation and the effort to harmonise between the empirical aspects and the social dimensions could help us to reach some solid answers to some questions that would bring the best out of TERM technology. Based on the situation as the authors have described, it seems that there are certain options in seeking the best treatment patients could choose from. Everyone is responsible for their own decisions and should bear the consequences. Any Muslims who intend to undertake any matters is encouraged to pray two supererogatory units of prayer and, after which he or she should supplicate and ask *Allah SWT* to guide him or herself to the right sort of action (Al-Bukhārī, n.d.). The decisions and options in life would have either positive or negative consequences. Hence, it is important for the patients to stay alert so that they will be able to cope with those difficulties and accept them from a positive, strong and responsible stand point. Our future works will discuss further on the relevancy of the objectives of *al-Shariah* in TERM. The discussion shall include thorough debate on the technology from the conventional and Islamic ethical perspectives.

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