REVIEW ARTICLE

Legal Aspects of Articular Cartilage Tissue Engineering Experimentation: A Review on Malaysian Acts, Regulations and Guidelines

Muhammad Aa'zamuddin Ahmad Radzi[1], Majdah Zawawi[2], Munirah Sha'ban[3], Nur Syamimi Mohd. Azharuddin[1], Azran Azhim[1], Abdurezak Abdulahi Hashi[4]

[1] Department of Biomedical Science, Kulliyyah of Allied Health Sciences, International Islamic University Malaysia, Jalan Sultan Ahmad Shah, Bandar Indera Mahkota, 25200 Kuantan, Pahang Darul Makmur, Malaysia
[2] Islamic Law Department, Ahmad Ibrahim Kulliyyah of Laws, International Islamic University, Malaysia, P.O. Box 10, 50728 Kuala Lumpur, Malaysia
[3] Department of Physical Rehabilitation Sciences, Kulliyyah of Allied Health Sciences, International Islamic University Malaysia, Jalan Sultan Ahmad Shah, Bandar Indera Mahkota, 25200 Kuantan, Pahang Darul Makmur, Malaysia
[4] Department of Biotechnology, Kulliyyah of Science, International Islamic University Malaysia, Jalan Sultan Ahmad Shah, Bandar Indera Mahkota, 25200 Kuantan, Pahang Darul Makmur, Malaysia

ABSTRACT

Presently, there is no specific federal legislation governing articular cartilage tissue engineering (ACTE) experimentation practices in Malaysia. However, there are related regulations and guidelines provided by government agencies to oversee and guide such practices. The rules and regulations provided in the documents have the essential aim of safeguarding public health through ensuring that non-clinical studies reach a certain quality, efficient and safe for human use. There are themes identified when scrutinising relevant documents which includes, the need for authorised personnel and the establishment of facilities in conducting such experiments, the aspect of cell-scaffold construct development, the use of human materials, the aspect of biosafety, animal care and use during the experiments, and considerations on the impact on the environment. The individual laboratory or facility shall adopt and adapt these standards as deemed appropriate by the ACTE researchers to ensure that non-clinical studies are conducted in a proper and ethical manner.

Keywords: Articular cartilage, Tissue engineering, Legislation, Experimentation

Corresponding Author:
Abdurezak Abdulahi Hashi, PhD
Email: hashi@iium.edu.my
Tel: +60 9 570 5043

INTRODUCTION

Over the years, local experts of different backgrounds from various ministries, public and private institutions have drawn numerous national policies, acts, regulations, and guidelines to safeguard the function of healthcare system nationwide. Existing guidelines govern the development of new modalities, e.g., articular cartilage tissue engineering (ACTE), in treating joint diseases such as osteoarthritis. Different from other tissues, articular cartilage has limited capacity to restore itself because of its aneural, avascular and alymphatic characteristics which making the regeneration to be complex (1–3). Ever since the emerging of tissue engineering and cell therapy, the issue of regulations in translating the products from bench to the clinical setting has been debated by the researchers, clinicians and regulatory agencies (4). There are ACTE experimental procedures that have been conducted worldwide, which are also being practised in Malaysia, but there is no specific federal legislation governing the practices locally. However, there are related regulations and guidelines provided by Malaysian government agencies to oversee and guide such practices based on the stages in tissue engineering experimentation or non-clinical study. Non-clinical study in tissue engineering research may involve in vitro (cell culture) and in vivo (animal implantation) under the laboratory conditions. Other countries, e.g. the United States, Canada, Australia, Japan, South Korea, and European Nations, have also addressed the legal aspects of tissue engineering products (5). In light of the situation, this paper analyses existing local federal and subsidiary legislations that may be relevant to the practice of ACTE. The main aim of this endeavour is to see how these laws address the development of ACTE through experiments or non-clinical studies involving tissue engineering triad, namely, cell sources,

biomaterial scaffold, and signalling factors.

RELEVANT LEGISLATION ON ACTE EXPERIMENTATION

In Malaysia, cell- and tissue-based transplantation into human patients, including tissue engineering, are considered as cell and gene therapy products (CGTPs) (6). Any enhancement done on the cells or tissues to increase their ability to regenerate, repair, or replace damaged tissues through substantial manipulation is considered as 'engineered' as stated in the Guidance Document and Guidelines for Registration of Cell and Gene Therapy Products (CGTPs) in Malaysia (henceforth CGTPs Guidance Document) (6: pp.12,31). Subsequently, the CGTPs is also regulated as 'biologics' as stated in the second edition of Drug Registration Guidance Document (DRGD) (7: pp.48,216). CGTPs Guidance Document and DRGD should be read together as both documents address the regulatory framework of biologic products (7: p.216). Both documents are produced by National Pharmaceutical Regulatory Agency (NPRA), an agency accommodated with facilities which can handle the activities of testing and quality control on medical products (8).

Rules and regulations pertaining to ACTE experimentation may fall under the jurisdiction of several ministries and agencies. For example, the relevant CGTPs Guidance Document, which is applicable to tissue engineering end-products was prepared by NPRA within the scope of the Sale of Drugs Act 1952 under the Ministry of Health. On the other hand, the use of animals in ACTE pre-clinical studies may be related to the Animal Welfare Act 2015, which is under the purview of the ministry charged with the responsibility for the agriculture and agro-based industry. Various acts, regulations and guidelines need to be investigated in order to address the bioethical questions of ACTE experimentation in respect of legislation. The present authors agreed with the assertion on the regulations of CGTPs – which include tissue engineering – made by the then Head of Biologics Section, NPRA, Arpah Abas in the document foreword section (6: p.13). The most related legal document to tissue engineering is the previously mentioned CGTPs Guidance Document as tissue engineering products is considered as CGTPs (6: p.22).

The drug control authorities or Pihak Berkuasa Kawalan Dadah (PBKD) have decided that CGTPs Guidance Document and Good Tissue Practice Guidelines need to be referred to as user guides. The CGTPs which are yet to be registered with the PBKD may only be used for experimental purpose as stated in item 4 of the directive (BPFK/PPP/01/03 Jld. 3). However, the following directive (BPFK/PPP/07/25 Jld. 1) has nullified the former with some improvement. Instead of the two documents to be referred to as user guides, the PBKD (297th meeting) has enforced the implementation of the guidance documents in developing and marketing the CGTPs. The control enforcement of the CGTPs will begin on 1st January 2021.

The criteria of CGTPs fit the definition of medicinal products stipulated in the Control of Drugs and Cosmetic Regulations 1984 [P.U.(A) 223/84] under the Sale of Drugs Act 1952 in which the CGTPs would be classified as biological products (6: p.18). There are different levels of regulations that apply to the CGTPs, and the framework is formulated based on the risk-management approach associated with their applications (6: p.22). The appraisal made in this paper may complement the contents of the CGTPs Guidance Document.

The Researchers and Facilities

The researchers including healthcare personnel and scientists directly involved in ACTE experimentation are identified as surgeons including physicians, dentists, and veterinarians for the collection of the biological samples from human patients and perform the surgery on animals. Other personnel involved in developing the ACTE include biomedical scientists, material engineers, chemists, and statisticians. All the professions are bound to different acts including, but not limited to the following legislation; Medical Act 1971 (9), Dental Act 1971 (10), Veterinary Surgeon Act 1974 (11), Technologists & Technicians Act 2015 (12), and Allied Health Professions 2016 (13). The acts are functioning in consolidating and amending the provision relating to the registration and practice of the aforesaid professions with the establishment of governing councils or board. For example, the Malaysian Medical Council has the authority to 'exercise its disciplinary jurisdiction' by conducting the investigation and holding a disciplinary inquiry on its members.

On the other hand, the operation of a research laboratory is different from a pathology lab, whereby the latter is regulated by a specific Pathology Lab Act 2007 which focuses on the medical diagnostics instead of researches. In discussing ACTE experimentation, the Good Laboratory Practice (GLP) guidelines are more relevant if compared to the current Good Manufacturing Practice (cGMP) guidelines because the experimentation or the non-clinical studies does not involve human testing and the activities are still in the product development phase. In 2013, Malaysia formally became a non-member (with full adherent) to the Council Acts of Organisation for Economic Cooperation and Development. The participation means that Malaysia needs to adhere to Mutual Acceptance of Data in the Assessment of Chemicals on GLP (6: para 7).

The quality system of GLP is to promote the establishment of quality data in which the 'non-clinical health and environment safety studies are planned, performed, monitored, recorded, archived and reported' in an organised manner and condition (5: item 1,6: para 1).

The Malaysian government has designated two agencies to be the Malaysian Compliance Monitoring Authorities (CMAs), namely NPRA and Standards Malaysia. The former is responsible for 'non-clinical safety testing of test items contained in pharmaceutical products, cosmetics products, veterinary drugs and food additives' by providing relevant programme manuals on the procedures for laboratory inspections and study audits in Malaysia (5: item 7,6: para 3). Meanwhile, the latter is in charge of the non-clinical safety testing of test items contained in industrial chemicals, pesticides, feed additives, and biotechnology (non-pharmaceuticals) (5: item 7,6: para 2). However, if the experiments or studies conducted fall under the scope of both agencies, the laboratory may have to request for joint inspection by both CMAs by putting a parallel application for GLP certification (6: para 5).

The government appointed NPRA as one of the CMAs in June 2009 by issuing a directive under Regulation 29 of the Control of Drugs and Cosmetics Regulations 1984 (6: para 3). NPRA has asserted the importance of GLP in monitoring the non-clinical studies to safeguard the human and environment upon the application of particular products, starting from laboratory practices (6: para 6).

In the 1st July 2016, NPRA has issued Directive No.9/2016 (Bil. (40) BPFK/PPP/07/25) on the requirement of GLP for non-clinical safety study to register New Chemical Entity (NCE), biologics, and herbal products with high therapeutic index. The directive was issued under the same regulation and is in force starting 1st January 2018. As ACTE is considered as biologics, it is presumed that the laboratory that intends to conduct relevant non-clinical studies shall be certified with GLP. It is implied, the failure to obtain the certification may limit the reliability of data to be used for the clinical development phase.

The Development of Cell-Scaffold Construct

Tissue engineering products are regulated based on the risk factors which may be imposed on human patients or users. In the CGTPs Guidance Document, risk factors are defined as 'qualitative or quantitative characteristics that contribute to a specific risk following handling and/or administration of CGTPs' (6: p.29). There are several aspects which need to be considered in identifying the factors in the experimental setting. The aspects may include but not limited to the cell sources, the cells' ability to differentiate and proliferate, the degree of cell manipulation, cell-scaffold construction, the use of physical and chemical cues, the mode of administration, and the exposure duration. The researchers also need to consider the risk of the materials damage and contamination, should the experimentation be done in the same facilities with other cell- or tissue-based researches. The condition may pose the 'infectivity, virulence, or other biologic characteristics of adventitious agents' (6: p.30) on the engineered articular cartilage cells or tissues. Besides, the researchers also need to consider the future clinical application in identifying the risk factors such as patient-, disease-, and medical procedure-related risk factors (6: p.30).

The risk-based approach may be applied to regulate ACTE experimentation as the test results obtained from the study will be used to analyse the potential risk in the proposed final products. Moreover, tissue engineering products are classified into Class II of higher risk cell therapy products. Different from Class II products, regulation for Class I products are not subjected to the premarket review approval or requirements. Tissue engineering products are included in the category of Class II because it does not meet all the requirements of Class I (6: p.32).

Thus, ACTE experiments can be classified in the same level of high-risk CGTPs that is categorized as Class II, which are regulated as biological products. Engineered articular cartilage produced during the non-clinical phase in the laboratory is considered as 'highly processed' whereby the tissue may be either used for other than normal function, is combined with non-tissue components, or is used for metabolic purposes (7: p.216). Both current Good Tissue Practice Guideline (GTPG) and cGMP are required before the products can be tested in human (6: p.33). Thus, the researches done for ACTE development need to demonstrate, 'sufficient data demonstrating the product is safe and effective' whereby the 'quality and scientific evaluation must be adequate to permit an evaluation of the product's effectiveness and safety' which are characterised by the manufacturing description and the pre-clinical pharmacology and toxicology data (6: p.33). However, NPRA reserves its full jurisdiction in assigning the product classes in which 'product presumed to present the highest level of risk until demonstrated otherwise' (6: pp.30-31). The diversity of tissue engineering triad used in ACTE experimentation may influence the classification of the final product. Thus, it is essential for the researchers to identify each and every raw material used to develop their prototype of articular cartilage.

The Use of Human Biological Samples

Human biological cells, organs, or tissues discarded after the medical procedures or diagnostic investigation are valuable resources for biomedical research to develop a new treatment for the particular disease. Nevertheless, there is hardly any public awareness of what happens to the samples if they are not being used for research as mentioned in the second edition of Malaysian Guidelines on the Use of Human Biological Samples for Research (16: p.6). Some proponents, e.g. biomedical researchers, may support the idea of using discarded human biological materials for the right course instead of merely being disposed of (17). However, the idea itself is not all-embracing as 'it is recommended that wherever

practicable individual consent should be obtained for the use for research of human material surplus to clinical requirements' (16: p.6).

It is noted that there are international ACTE researchers who have utilised the human biological samples while conducting the experiments in efforts to produce functional articular cartilage tissue in the laboratory. The samples taken from the human donor include discarded tissues or cells from medical treatment, such as total knee replacement (18–22). Besides taking the tissues from the living donor, the samples were also taken from the human cadaver from different parts of the body such as knee (23–30), femur (31–38) and nasal septum (39).

The Ministry of Health Malaysia has provided several guidelines which can be adopted and adapted for ACTE experimentation in using human biological materials. The guidelines include but not limited to:

1. Malaysian Guidelines on the Use of Human Biological Samples for Research, second edition, December 2015 (Human Biological Samples Guidance Document) (16),
2. Guidelines on Importation and Exportation of Human Tissues and/or any Body Part, August 2006 (GIEHTBP) (40),
3. Good Tissue Practices Guideline, second edition, December 2015 (GTPG) (41),
4. National Standards for Cord Blood Banking Transplantation, January 2008 (NSCBBT) (42),
5. Malaysian Guidelines for Stem Cell Research and Therapy, 2009 (MGSCRT) (43),
6. National Guidelines for Haemopoietic Stem Cell Therapy, July 2009 (NGHSCT) (44),
7. National Standards for Stem Cell Transplantation: Collection, Processing, Storage and Infusion of Haemopoietic Stem Cells and Therapeutic Cells, second edition, September 2018 (NSSCT) (45).

Even though most of the guidelines mentioned above are focusing on clinical applications, they may be used by relevant parties in conducting and approving ACTE studies involving human biological samples. The parties may include clinical researchers, biomedical scientists, tissue engineers, ethics committees, sponsors and research laboratories in conducting ACTE experimentation. GTPG, for example, is focusing on the aspect of manufacturing the final product of cells and tissues for human applications. There are specific requirements can be adopted for ACTE researchers such as 'requirements for facilities, environmental control, equipment, supplies and reagents, recovery, processing and process controls, labelling controls, storage, receipt and distribution' of the cells and tissues used in the experiments (41: p.3). The adoption of GTPG may facilitate ACTE researcher to prevent contamination of cell and tissues samples and ensure the integrity and functions of the samples.

The use of these guidelines is essential as the patients undergoing medical treatment usually are not informed, and their consent is not being sought prior to the use or handling of their biological materials for non-clinical studies. Hence, to protect the human patients' right, there is a need for a standardised framework to govern the collection, storage and use of human biological samples – across this country and its borders – for research purposes. These guidelines can be used by the Institutional Review Board or Independent Ethics Committee (IRB/IEC) at the national level.

For researchers who intend to export or import human cadaver or its parts for research purpose, they need to adhere to provisions stipulated in the Prevention and Control of Infectious Diseases (Importation & Exportation of Human Remains, Human Tissues and Pathogenic Organisms & Substances) Regulations 2006. The regulation is promulgated under the Prevention and Control of Infectious Diseases Act 1988, as stated in Guideline on Importation and Exportation of Human Tissue and Parts (40: p.ii).

Meanwhile, Human Biological Samples Guidance Document (16) is formulated based on the ethical principles of:

'beneficence (doing good), non-maleficence (preventing or mitigating harm), justice, fidelity and trust within the investigator/participant relationship, personal dignity of study participants or subjects, and autonomy pertaining to both informed, voluntary, competent decision-making (informed consent) privacy of personal information'. (p.6)

The document mentions its objective explicitly to direct the attention to essential ethical issues that should be taken into account when conducting researches. The point can be seen through the assertion made on the requirement to obtain informed consent from the potential donor. Different types of research in using human tissue materials result in specific terms and conditions to obtain informed consent (40: pp.6-8).

Human Biological Samples Guidance Document may serve as a standard for IRB/IEC on the fundamentals and strategies to address the issue of utilising human biological samples for research, including those in ACTE experimentation. Even though the ethics committees are expected to adhere to these documents; the committees may need to adjust or modify the content based on the particular institution or research conditions and requirements. For instance, the guideline stated that the researcher needs to handle the human biological samples based on the specified bio-banking standards (16: p.11), which may differ in ACTE research methodology of tissues harvesting and cells isolation. On the other hand, Human Biological Samples Guidance Document is 'not

intended to cover the use of such biological tissues for medical diagnostic purposes, disease surveillance, teaching or stem cell research' (16: p.5).

Other aspects which are being discussed in the document pertaining to the use of human biological samples include the patient information sheet, confidentiality and anonymity, and custodianship. The guidance document also advises the researcher to keep and handle collected human biological samples based on bio-banking standards. Aside from that, the analysis should be conducted in the current best practice of laboratory. It is considered unethical for a researcher to collect or process the samples without adherence to proper standards, which may affect the reliability and validity of the analyses resulting in unsound scientific findings. Thus, a complete series of Standard Operating Procedures should be made available anywhere in the laboratory, e.g. 'samples acquisition, transport, processing, archiving, disposal, (and) safety' documents (16: p.11).

In ACTE experimentation, the samples taken from the human donor also include various types of stem cells such as embryonic cartilage stem cells (46), adipose-derived stem cells (47,48), bone marrow mesenchymal stem cells (49,50), placenta-derived mesenchymal stem cells (51,52), synovium-derived mesenchymal stem cells (53,54), tooth germs stem cells (55,56), and umbilical cord blood-derived mesenchymal stem cells (57,58) whereby the range of donors' age varied from eight weeks old embryo (46) to 90 years old (59).

As the experimentation of ACTE employs various types of stem cells, the researchers may also need to refer to the NSCBBT – which produced by the experts in National Stem Cell Committee set up under the National Transplantation Council (42: p.3). The guidance document is essential to ensure the production of stem cells from cord blood is up to the quality standard (42: p.4). Thus, necessary conditions such as 'organisation, personnel, facility, equipment, supplies and reagent, process control, safety, testing, inspection, documents and records' are being explicitly scrutinised in the document (42: p.5). The guidance document, however, did not attend to the matters of the 'collection, processing and administration of erythrocytes, mature granulocytes, platelets, plasma or plasma-derived products intended for transfusion support' (42: p.15). The primary purpose of the document is to ensure the quality of cord blood banking through good medical and laboratory practices. In 2009, the Ministry of Health had published the MGSCRT whereby the ministry will support the research and development of stem cell therapy in Malaysia. Thus, all applications for stem cell research must be reviewed by IRB/IEB of the respective institution for approval to safeguard the ethical aspect of research and use of stem cells. It is clearly stated that:

'all experiments and clinical trials involving stem cells must be based on a solid foundation of basic scientific and animal experimentation and carried out with the highest medical and ethical standards'. (43: p.9)

On top of the above-mentioned requirements of the stem cells researches, it is interesting to note that the researchers are advised to refer to the fatwā (Muslim jurist's opinion), which is exclusive to Muslim subjects, on the ruling of therapeutic cloning and stem cell research issued by Consultative Committee of National Council for Islamic Religious Affairs Malaysia (60) in its 67th conference on 22nd February 2005 (43: p.31).

Nevertheless, it is prohibited for any stem cell researches to be conducted if the study generates human embryos for the purpose of research through any technique including assisted reproductive technology or somatic cell nuclear transfer (43: p.31). Moreover, the researcher of human embryonic stem cells and the physician for infertility treatment should not be the same individual. This condition is to avoid conflict of interest and enable the autonomous choice to the patients who are free from any influence from the researchers. There should be no payment or honorarium provided for donating clinical excess of blastocysts for research purposes. The informed consent should be obtained before any retrieval of the blastocyst from the donor. Even if the donor may indicate the intent to donate their excess blastocyst after the clinical treatment for research purpose, new consent should be sought beforehand. The donor also has a right to withdraw from the research until the blastocysts are actually utilised for deriving cell line. On the other hand, the working group of the guidance document has outlined the stem cell researches that are prohibited from being conducted in Malaysia at the moment include a few types of studies. For examples, '[r]esearch involving in vitro culture of any intact human embryo, regardless of derivation method' and '[r]esearch in which [human embryonic stem] cells are introduced into nonhuman primate blastocysts or in which any [embryonic stem] cells are introduced into human blastocyst' (43: p.35).

To conduct the above-mentioned studies which prior to the clinical trial, the researchers may want to make sure that facility and laboratory are conformed to the GLP requirement. The researchers are also advised to conduct internal and external audits to safeguard the 'quality, viability, purity, safety, reproducibility and efficacy' of the samples (43: p.14). Therefore, the handling of stem cells should conform to the national standard on stem cell procurement and processing. The researchers also need to be trained, proficient and acknowledged by their institutions to be able to conduct stem cell research. Subsequently, any employment of gene therapy technique on cell sources using viral gene delivery shall comply with the requirement of Biosafety Level 3 (43: p.36). Besides, the conformity

to the national standards of stem cell procurement, storage and allocation is also being highlighted in the NGHSCT. It is also essential for the laboratory to have proper support with the 'availability of microbiological tests, monitoring of drug levels, chimerism study and histopathology services' (44: p.14).

In addition to the facilities requirement – as the number of government and private healthcare institutions providing the service for haemopoietic stem cells and therapeutic cells transplantation is increasing – Ministry of Health has come out with the second edition of NSSCT published in September 2018. The publication of NSSCT is in line with the National Organ, Tissue and Cell Transplantation Policy, as stated in Chapter 9 (Cell Transplantation) of the policy (45: p.2). The guidance document has outlined the updated laboratory framework to enhance the stem cell therapy technology starting from the 'point of collection, processing, storage, handling and infusion' in developing the end-product of stem cells. With the publication of this second edition of NSSCT, the outdated first edition (July 2009) shall no longer be referred to and annulled with immediate effect (45: p.iii).

NSSCT acknowledges the importance of laboratory roles in stem cell therapy, whereby the proper quality standards of laboratory practices should be implemented in accordance with national and local regulations (45: p.iv). NSSCT is not only limited to the haemopoietic stem cells and lymphocyte infusion, whereas, other therapeutic cells therapy, e.g. mesenchymal stem cell may also adopt the requirement of the document (45: p.3). Similar to other guidelines, the NSSCT also advises all laboratory users to comply with additional relevant regulatory requirements, e.g. GTPG and CGTPs Guidance Document as provided by NPRA.

Conclusively, it is important to highlight that not all of these guidelines are legally binding and has little or no legal consequences. This is mainly due to the fact that these guidelines are not supported by specific tissue engineering legislation. The effect of this lacunae may cause the ACTE researchers to not strictly follow the guidelines properly.

Biosafety Concerns

The procedure in some ACTE experimentation may involve the manipulation of articular cartilage cells or tissues. The manipulation can be divided into two categories, which are minimal and substantial manipulations. Minimal manipulations can be applied to either tissues or cells in a particular stage of ACTE. The minimal manipulation of the articular cartilage tissue denotes, 'processing that does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair or replacement'(6: p.30). The minimal manipulation of the articular cartilage cells can be defined as 'processing that does not alter the relevant biological characteristics of cells' (6: p.30).

Meanwhile, substantial manipulation may include but is not limited to, 'cell expansion (culture [for more than 48 hours]), genetic modification of cells, and differentiation with growth factors' (6: p.30). A process will be considered to be a substantial manipulation if there is insufficient information to show that the particular process meets the criteria of minimal manipulation.

In ACTE experimentation, chemical and physical stimulations can be applied to test the potential effect of particular stimulation in developing functional tissues of articular cartilage. The stimulations may include the employment of gene delivery or transfer technique, which is considered to be modifying the chondrocytes (articular cartilage cells) to express the desired characteristics, which affect the functions of the final products. Moreover, the genetic materials used to express the desired characteristics can be amplified through culturing the transfected bacteria, i.e. Escherichia coli. The transfection may involve either transformation (non-viral gene delivery) or transduction (viral gene delivery).

For instance, viral gene delivery was used to enhance the production of the hormones of insulin-like growth factor 1 (61), bone morphogenetic protein 2 (62), bone morphogenetic protein 7 (63), transforming growth factor beta-2 (64), transforming growth factor beta-3 (65,66), Bone morphogenetic protein 6 (67), and sex-determining region Y-box transcription factor 9 (68,69). Meanwhile, the production of hormones was also be enhanced by using non-viral gene delivery such as insulin-like growth factor 1 (70,71), transforming growth factor beta-1 (72,73), transforming growth factor beta-2 (74), transforming growth factor beta-3 (75) and sex-determining region Y-box transcription factor 9 (76,77). Thus, the technique of gene transfer in ACTE experimentation may be regulated by legislation and regulations addressing the issue of biosafety. In 2003, the Malaysian government ratified the Cartagena Protocol on Biosafety, which resulted in the enactment of the Biosafety Act 2007, which is in line with the 1998 National Biological Diversity Policy and NBP. The legislation led to the formation of the National Biosafety Board in order, 'to regulate the release, importation, exportation and contained use of living modified organisms, and the release of products of such organisms' (78: p.7). The legislation is under the purview of the Ministry of Water, Land and Natural Resources. Any research that involves the modification of cells should be monitored by the institutional biosafety committee (IBC), which is registered with the National Safety Board under the Department of Biosafety as stated in Section 12(1) of the act:

'12. (1) No person shall undertake any release activity,

or any importation of living modified organisms, or both without the prior approval of the Board.' (78: p.16)

Failure to comply with Section 12(1) may result in the penalty of fine or imprisonment or both, as stated in Section 12(2) of the Biosafety Act 2007. As of July 2019, there are 50 institutional biosafety committees comprised of public and private institutions, e.g. universities, research facilities, and biotechnology companies, all of which are registered with the Department of Biosafety.

The Use of Animal in the ACTE Experimentation

Prior to the application of CGTPs, i.e. tissue engineering such as ACTE in a national clinical trial, the researchers must file an application which reports the data obtained from the pre-clinical studies in terms of safety and the efficacy of the product (6: p.29). It is expected that the manufacturing control and testing process will be stricter as the product transitions from one level to another, e.g. pre-clinical to clinical phase (6: p.41). However, the data generated from the pre-clinical studies of CGTPs, including ACTE, may not always be informative as compared to other pharmaceuticals due to various issues, including the specificity and the immunogenicity of the animal species chosen. Thus, the extrapolation of the ACTE dose administered in animals to the dose to be applied in human patients can be less reliable than the customary allometric scaling of the pharmaceuticals. Subsequently, these issues can restrict the reliability of pre-clinical data to guide in designing the early phase of the clinical trial (6: p.58).

Nevertheless, the ACTE researchers need to address the safety issues arising during the pre-clinical development, especially tumourigenicity (producing or tending to produce tumours), cell persistence (the tendency of a cell to continue moving in one direction) and trafficking (the ability of the cell to migrate throughout the body). In addressing these issues, choosing appropriate models, analytical methods and non-invasive imaging techniques need to be given high priority. Notably, the absence of a suitable animal model for the disease, e.g. osteoarthritis or in the absence of physiologic similarity may limit the predictive value of homologous animal model (6: p.62). Notwithstanding the above, it will not be appropriate to use traditional and available standardised approaches to preclinical safety testing in the case of ACTE experimentation. The diversity and complexity of ACTE development may lead to individualised, pre-clinical testing strategies. For instances, the analysis conducted on stem cells may differ to that of chondrocytes even though both of the cell sources were to be implanted in the same animal models (6: pp.55-56). ACTE researchers need to be aware of the additional pre-clinical requirements if gene therapy techniques were to be used in developing the articular cartilage tissue. The use of gene therapy techniques also varies in their complexity and heterogeneity, which may give different risk profiles of each final product (6: p.75).

On the other hand, NPRA highlights the responsibility of the CGTPs researchers to adhere to the 3R's principles (Reduce numbers, Refine protocols, and Replace animals) in conducting animal research. Animal models may not be able to replicate the exact range of human toxicities. Thus, extra precautions must be applied in conducting pre-clinical toxicity testing on ACTE samples. Moreover, ACTE researchers also need to ensure that the 'comparability of the product used in pre-clinical experiments to that intended to be used as clinical material' (6: pp.55-56).

There were various types of animals that were used in ACTE in vivo experimentation. These include small and big animals, either ectopic or orthotopic models, for instances, canine (80,81), caprine (82,83), equine (84,85), laprine (86,87), murine (88,89), ovine (90,91), porcine (92,93), and primate (94). The use of animals in non-clinical studies in ACTE need to comply with several acts including but not limited to Animals Act 1953, Wildlife Conservation Act 2010, and Animal Welfare Act 2015.

As the animal research and testing have been strictly regulated in Animal Welfare Act 2015, ACTE researchers need to ensure the welfare or husbandry of the laboratory animals in their studies were being taken care of properly. The welfare of animals' needs is specified in Section 24 of the act. The researchers that commit the offence will be 'liable to a fine of not less than fifteen thousand ringgit and not more than seventy-five thousand ringgit or to imprisonment for a term not more than two years or to both' (95: p.21).

Moreover, it was stated in Subsection (1) until (3) of Section 26 that only licensed person or educational institutions may use and breed animals for the purpose of research, testing, and teaching in accordance with the guidelines provided by the Animal Welfare Board – chaired by the Director-General of the Department of Veterinary Services. Sections 26 also describes 'all reasonable steps are taken to ensure that the physical, health and behavioral needs of those animals' (95: p.22). Any ACTE researcher who contravenes any provision under Section 26 will, 'be liable to a fine of not less than twenty thousand ringgit and not more than one hundred thousand ringgit or to imprisonment for a term not more than three years or to both' (95: p.22).

At the end of the studies, ACTE researchers need to sacrifice or kill the animals in a humane manner, and such sacrifices must be approved by the animal ethics committee established by the particular institution. Any researcher that is found to be non-compliance in killing the animals, without a sound justification will be subjected to 'a fine of not less than twenty thousand ringgit and not more than one hundred thousand ringgit or to imprisonment for a term not more than three years or to both' (95: p.27).

Consequently, the use of various biological samples, biomaterials, signalling factors and animals in ACTE experiments will lead to the production of research wastes. Next part of the section continues to discuss the legal and regulatory requirements in dealing with research waste management.

Research Waste Management

The Guidelines on the Handling and Management of Clinical Waste in Malaysia (GHMCW) (96) has categorised wastes from hospital and healthcare facilities into five types, namely, clinical waste, radioactive waste, chemical waste, pressurised containers, and general waste (96: p.8). It is interesting to point out that the waste produced in developing ACTE in the laboratory is very much similar to those produced in hospital and healthcare facilities. Even though ACTE experimentation is regarded as non-clinical studies, the waste produced may fall under any one of the types mentioned above because of the nature of tissue engineering itself that employs various biological materials and physicochemical substances to generate the articular cartilage tissue.

In Malaysia, clinical waste is classified as scheduled waste which regulated under the Environmental Quality (Scheduled Wastes) Regulations 2005 which is in accordance with the international standard of classifying clinical and related waste produced through 'medical, nursing, dental, veterinary, or similar practices' (96: p.3). The GHMCW was produced by cooperation between the Department of Environment and the Engineering Division of the Ministry of Health Malaysia to help the healthcare providers to comply with the requirement set by the particular regulation (96: p.3). The guidance document provides details of considerations in handling and managing clinical waste from both public and private healthcare facilities which are in line with the requirements of waste management stipulated in Environmental Quality Act 1974 (96: p.5).

Furthermore, there are specific instructions provided by NSSCT in disposing of haemopoietic progenitor cells and therapeutic cells – including mesenchymal stem cells, which are no longer required for transplantation or therapy. Likewise, the guidelines may be applied for the proper disposal of human cells and tissues used in ACTE experimentation, as stated in Section 10.1. The guidance document further specifies the steps – required documentation as well as approval, method, and recording of disposal – to be taken into consideration while disposing of the cells in Section 10.2.

Even though the method of the disposal did not clearly mention specific rules and regulations, it can be presumed that the method is to be based on the requirements provided in the GHMCW. Appropriate handling and disposal of wastes generated through ACTE non-clinical studies is vital to prevent any contamination which may affect the experimental results, and also, the public health and environment as a whole.

CONCLUSION

It can be appreciated that NPRA has been given the most authority to regulate tissue engineering practices in Malaysia. However, the establishment of tissue engineering experimentation in Malaysia has prompted the debates on the need for a more comprehensive legislative provision among the key holders nationwide. Not all existing guidelines are legally binding and thus may result in little or no legal consequences. This is mainly due to the fact that these guidelines are not supported by specific tissue engineering legislation. The effect of this lacunae may cause the ACTE researchers to not strictly follow the guidelines. Therefore, there is a need for a more comprehensive legal regime, including the enactment of specific legislation on tissue engineering experimentation and future clinical trial.

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