

Beyond Hopes, Beyond Cures: A Proposed Malaysian Regulatory Framework for Somatic Gene Therapy in Human

Zakiah Samori¹ and Fadilah Abd Rahman²

Abstract

After serious side effects 20 years ago, somatic gene therapy (SGT) is gaining traction again. The pipeline for somatic gene therapy has expanded rapidly. Although SGT has shown remarkable efficacy for cancer and genetic diseases, it also carries risks, ethical challenges, and legal concerns. This study intends to (i) present Malaysia's experience with SGT clinical trials (ii) evaluate the adequacy of existing regulatory frameworks and (iii) propose future legislation. The study employs a qualitative approach by utilizing both primary and secondary data. Statutory provisions are referred to for doctrinal legal analysis. Primary data was collected through a purposeful sampling of experts. Interviews were conducted with government representatives, medical experts with experience in SGT, and Shariah experts. The findings indicate that in establishing Malaysian law on SGT, customary beliefs, especially Shariah perspective, must be taken into account, as well as adopting best practices from other developed countries and improving Malaysia's existing law.

Keywords: Somatic Gene Therapy (SGT), Gene Therapy Products, Clinical Application, Malaysian Regulatory Framework, Legal Issues.

INTRODUCTION

Over the last several decades, gene therapy in humans has made significant advances and most exciting discoveries towards its potentiality in treating previously incurable human genetic disease. Using gene editing as a treatment for genetic diseases has the advantage of its simplicity: instead of treating symptoms, it can cure the underlying cause (Bittlinger et al., 2022; Cring & Sheffield, 2020). High expectations are raised for therapeutic breakthroughs with advances in gene therapy and genome editing. This is evident where a series of clinical trials have been conducted in Europe and the United States involving somatic gene editing (e.g., CRISPR–Cas9) that may provide safe and effective treatment and cure for various cancers, some monogenic conditions that result in cancers as well as other genetic diseases (Cornel et al., 2019).

Currently, it is considered an important medical treatment technique that eliminates some of the challenges that hindered early success (Asher et al., 2020; Bulaklak & Gersbach, 2020; Garcia-Perez et al., 2020; Giacca & Zacchigna, 2012; Mitani, 2020). Recent technology has shown that clinical trials using CRISPR/Cas technology, are frequently conducted, which offers many potentials uses beyond classical gene therapy. Through the end of the first quarter of 2023, there were more than 100 different approved gene, cell, and RNA therapies throughout the world, with over 3,700 more in clinical and preclinical development (Chancellor D, Barrett D, Nguyen-Jatkoe L, Millington S, 2023).

As Somatic Gene Therapy is applied clinically in humans, it is common that the application of this new technology will entail its own set of benefits, risks, ethical and societal implications (ELSI) which are subject to legal ruling to govern such application. To ensure the expected risks and benefits of using gene transfer technologies are ethically balanced, the expected risks and benefits of such trials must be properly regulated and governed by the legal provision. As far as Malaysian situation is concerned, the clinical application of Somatic Gene Therapy is still at the infancy level and expected to be implemented in future. Nonetheless, the Malaysian regulatory framework overarching Somatic Gene Therapy is not comprehensive and inadequate. The existing legal provisions and guidelines for Somatic Gene Therapy were seen to have several loopholes, and the

¹ Department of Halal Industry Management, Academy of Contemporary Islamic Studies (ACIS), Universiti Teknologi MARA (UiTM), 40450 Shah Alam, Selangor, Malaysia, +60173107270, Email: zakiahsamori@uitm.edu.my, (Corresponding Author)

² Head Halal Supply Chain, Malaysia Institute of Transport (MITRANS), Universiti Teknologi MARA (UiTM), Department of Halal Industry Management, Academy of Contemporary Islamic Studies (ACIS), Universiti Teknologi MARA (UiTM), 40450 Shah Alam, Selangor, Malaysia, Email: dilah091@uitm.edu.my

monitoring is not adequate and effective. Thus, this study is conducted to describe Malaysia experience on conducting SGT clinical application (ii) examine the adequacy of existing regulatory framework for somatic gene therapy in human (iii) proposes the legal framework governing Somatic Gene Therapy (SGT). The proposal of comprehensive regulatory framework is vital to ensure adequate legal protection of this therapy may become first-line treatments and have a profound impact on the lives of patients with genetic disorders. In order for SGT to become a standard medical practice, many technical issues must still be resolved. Therefore, it is imperative that the relevant bodies address the ethical issues that this novel medical therapy raises. Regulation can only be necessary to develop based on relevant and flexible parameters after discussing the ethical issues.

Problem Statement

This study is conducted on the basis of the inadequacy of the Malaysian Legal Provision regarding the legal position of Somatic Gene Therapy in Human. In the context of Malaysia's current biotechnology scenario, a study conducted by Malaysian scholars Mustafa et al., (2017) strongly suggests that advances in biotechnology have great potential for gene therapy and Somatic gene editing has demonstrated its potential *in vivo* by treating genetic diseases, infectious diseases, and acquired diseases. Ethical issues related to Somatic Gene Therapy have been highlighted in numerous research papers, for example, in (Babak Arjmand, Bagher Larijani, Motahareh Sheikh Hosseini, Moloud Payab, Kambiz Gilany, Parisa Goodarzi, Peyvand Parhizkar Roudsari, 2019; Koonrungsomboon et al., 2016; Moradi et al., 2019; Salzman et al., 2018; Tang & Xu, 2020). The majority of research has concentrated on the moral and ethical implications of manipulating the human genome, as well as the possible social consequences (Ayanoglu et al., 2020; Cornetta et al., 2018; Hidayati Husainy Hasbullah & Marhaini Musa, 2021). Despite the fact that Malaysia lacks theoretical publications and research papers in gene therapy, legal and regulatory issues have also received less attention. No study has been conducted so far to examine the legal situation of somatic gene therapy.

To be more specific, it has never been examined whether Malaysian legal frameworks are suitable and adequate for facilitating Somatic Gene Therapy. Hassan et al., (2016) indicates that human gene therapy is not governed by specific laws or regulations in Asia as a whole, and the absence of a legal framework in Malaysia confirms that gene testing, screening, and treatment are not regulated. A very general guideline on medical genetics and services can only be found in the "Medical Genetic and Genetic Services Guideline 2006" by Malaysia Medical Council. It appears that clause 19 of the said guideline reinforces the fact that gene therapy will likely be associated with ethical dilemmas (Malaysian Medical Council, 2006), even though it mentions gene therapy and cloning. There seems to be some general requirements for gene therapy products in the Guidance Document for Gene Therapy Products (CGTP) (2015), another general

guidance document applicable to gene therapy products. Neither this guidance document nor the Malaysian Medical Council Code of Professional Conduct contain legal requirements for human use of Somatic Gene Therapy.

There is a lacuna in the current legislation with scattered guidelines and guidance documents to govern Somatic Gene Therapy's use in humans. This implies that Malaysia's national legislation has not addressed genetic information access issues, genetic discrimination, or genetic manipulation of human cells. The issues have not been raised elsewhere so far. It is expected that gene therapy and its technologies would reach Malaysia within the next 5-10 years, once enough evidence on their efficacy and safety are shown.

From this point of departure, a comprehensive proposed legal framework with key recommendations that puts ethical issues at the forefront is essential to address the lack of a national genetic policy and regulation in Malaysia. It is necessarily crucial for Malaysia to consider three important dimensions in developing a legal and regulatory framework that appropriately governs the use of Somatic Gene Therapy, namely; the shari'ah perspective, customary beliefs, which are currently available in Malaysia, and the legislation from developed countries such as UK, EU and USA whenever possible for adoption. Existing laws and customary practices must be considered when developing such legislation¹ while ethical standards must be agreed upon by medical and scientific professionals when developing future legislation of SGT in humans to ensure that the technologies will not be abused, used or performed unethically or only available to certain privileged people.

There has also been emphasis on the importance of a regulatory framework, despite the fact that laws differ from country to country.

OBJECTIVES OF RESEARCH

The aim of this study are as follows:

To describe Malaysia experience on conducting Somatic Gene Therapy.

To examine the adequacy of existing regulatory framework for somatic gene therapy in human.

To proposes a legal framework relating to the application of Somatic Gene Therapy in Malaysia.

LITERATURE REVIEW

Clinical Application of Somatic Gene Therapy: Potential and Ethical Issues

One of the most important technologies in modern medicine is gene therapy, which allows therapeutic genes to be introduced into cells of the body. The approach involves genetics and recombinant DNA techniques that allow manipulating vectors for delivery of exogenous material to target cells. The efficacy and safety of the delivery system are a key step towards the success of gene therapy. SGT is the easiest in terms of technology and the least problematic in terms of ethics. In recent academic research, SGT has shown promising results and encouraging outcomes for treating common and diverse early-stage genetic diseases. Among these diseases are Duchenne muscular dystrophy (DMD), B-thalassemia, Cystic Fibrosis (CF), heart, anaemia, sickle cell diseases, lysosomal storage diseases, haemophilia, and haemoglobin diseases. (Gollomp et al., 2019; Greenberg, 2017; Makris, 2020; Nathwani et al., 2017; Rashid & Ankathil, 2020; Zittersteijn et al., 2020).

Since then, numerous types of somatic cell gene therapy have been investigated for the treatment of diseases that are not primarily caused by inherited genes, including: acquired diseases like AIDS and most cancers, thromboembolic cardiovascular diseases and neurological disorders, upper gastrointestinal tract infections, autoimmune diseases, and systemic protein deficiency (Chellappan et al., 2018; Greely, 2015; O'Connor & Boulis, 2015; Wang et al., 2017) and novel treatments for Huntington's disease and achondroplasia are being actively pursued (Rashid & Ankathil, 2020).

In addition, Somatic Gene Therapy is also being used for ADA deficiency, X linked severe combined immunodeficiency (SCID-X)1 (Goswami et al., 2019; Liu et al., 2020) Primary Severe Combined Immunodeficiency (XSCID) and other immunodeficiency diseases, namely Chronic granulomatous diseases and Wiskott-Aldrich (Bulaklak & Gersbach, 2020; Dorsey et al., 2017; Goswami et al., 2019). Gene therapy is being demonstrated in an increasing number of clinical trials, and, more recently, cancer is by far the most commonly treated disease with gene therapy. According to Delhove et al., (2020) and Zittersteijn et al., (2020), over 60% of all clinical gene therapy trials worldwide are focused on cancer (Hidayati Husainy Hasbullah & Marhaini Musa, 2021).

Previous academic research has shown that SGT has a number of promising results providing new hope to patients. These hopes, however, are tempered by ethical issues. The ethical, technical, economic, and legal implications of these issues transcend health and safety since the advent of gene therapy in humans, and especially with its expansion in scope and application. Given that gene therapy in humans has different aims and purposes, the question of its purpose is one of the most important ethical issues. In order to justify the justifiability of each purpose, it is important to know which purposes are ethical (Delhove et al, 2020; Koonrungsesomboon et al, 2016).

Among the ethical concerns surrounding somatic gene therapy are those regarding informed consent, privacy, and confidentiality, balancing potential harms and benefits, and safety and accuracy. (Almeida & Ranisch, 2022; Debin Zhang, Amjad Hussain, Hakim Manghwar, Kabin Xie, Shengsong Xie, Shuhong Zhao, Robert M. Larkin, Ping Qing, Shuangxia Jin, 2020; Gollomp et al., 2019). Some studies expressed concern about the inherent significant risks which quite high associated with this procedure performed (Aiyegbusi et al., 2020; Riva & Petrini, 2019). Some cases may result in a tension between harm and benefit (Alnasser, 2021; Sari et al.,

2021). The potential risks to the affected patients need to be well defined, considering that some risks may be manageable, while others may be irreversible (Koonrungsesomboon et.al., 2016). Few studies further highlighted (Cring & Sheffield, 2020; Riva & Petrini, 2019), the potential risks of using these procedures far outweigh the potential benefits for humans. Misuse has caused high levels of uncertainty of this novel technology, which may also affect society as a whole. In addition, the failure to communicate the risks along with the benefits has caused this technology to be viewed with fear (Kohn et al., 2016; Kuo & Kohn, 2020). In some cases, desperate patients are not consenting to a greater extent, and that the potential benefits of the treatment are exaggerated by the public's perception of genetics.

Technical limitations also include benefit-risk assessment, direct toxicity, specificity of delivery and side effects. The effects associated with gene therapy would affect the target tissue as well as other cells (Bittlinger et al., 2022) along with some unexpected complications (Delhove et al., 2020; Zittersteijn et al., 2020). Gene therapy with Somatic cells is therefore in the same position as most experimental therapies because of its adverse effects such as leukaemia, immune reactivity, and serious health risks including toxicity, inflammation and insertional mutagenesis, unexpected clinical findings, production difficulties, efficient delivery (Assaf & Whiteley, 2018; Carvalho et al., 2021; Landfeldt, 2022), possible adverse effects of vector or transgene expression throughout the whole process. retroviruses may inadvertently cause mutagenesis and cancer through accidental insertion. There are indeed viral vectors that can cause mutagenesis and cancer inadvertently (Gollomp et al., 2019; Goswami et al., 2019; Alnasser, 2021; Sari et al., 2021). Some of the risks may be unpredictable, however for example the increasing number of defective genes. On top of that, it is an expensive treatment that is beyond the reach of many health care systems and lay societies.

Somatic Gene Therapy in Malaysia: Present Development

In order to stay on top of this modern world landscape and technological wave, Malaysia has also placed science and technology at the top of its agenda. In order to accomplish this, Malaysia has spent the past eight years strengthening its biotechnology ecosystem, developing its local industry, and carving out its niche as one of Asia's prestigious biotechnology hubs (International Business Review Asia Group, 2019), as outlined in Vision 2020 and the National Biotechnology Policy (hereinafter referred to as NBP).

The National Biotechnology Division of the Ministry of Science, Technology and Innovation (MOSTI) has therefore led the national agenda by developing strong intellectual property and protection to facilitate research and development, technology development, and promotion of biotechnology programs based on global standards and best practices (International Business Review Asia Group, 2019; Rozhan Abu Dardak, 2019). As part of its efforts to become an industrial nation and knowledge-based economy, the government has acknowledged medical technological advances and has demonstrated a serious commitment to making biotechnology a key component of economic growth by its vigorous involvement and commitment to biotechnology development. New technologies contribute to a sustainable economy, improved quality of life, and improved physical and mental health, which is consistent with Industrial Revolution 4.0's primary objective.

Based on prior literature reviews, the theoretical publications and research papers on Somatic Gene Therapy clinical application are underdeveloped. It is difficult to find theoretical publications and research papers in Malaysia related to somatic gene therapy. Neither the Malaysian regulatory framework nor the shari'ah perspective have been studied specifically for its legal position so far. There have been very few studies discussing the general issue of regulation and emphasizing the need for it. In Mohd Firdaus Raih, (2017) for instance, the researcher stresses the need to prepare for gene therapy's implementation in Malaysia even though it has not yet taken place. A number of issues were raised by him, including the socio-economic implications of such revolutionary therapies as well as how they will impact our health system and adequate regulations to protect patients and institutions. It is also alarming that legislation must be put in place to protect patients and provide a code of conduct for institutions, clinicians, and researchers in the face of the challenges involved. Among the promising success stories of gene therapy and its potential to flourish in the near future, another Malaysian study offers an updated overview. As a result of the rarity of most diseases that can benefit from its benefits (Rashid & Ankathil, 2020), resources and finances are limited in its development because of the high cost of gene therapy. Since most prominent potential advocates of gene therapy are pharmaceutical companies,

which are highly profit-driven, funding and profit are important considerations. The commercial availability of the product is another concern. Although cancers are common, most of the time, the patient needs an individualised gene therapy for better efficacy. The scholars however, believe that these challenges motivate scientists to advance this technology so it can be used more efficiently while making its limitations and side effects as minimal as possible.

In a similar study by Mustafa et al., (2017) the researchers assert that gene therapy could be the last therapy humans will ever need because it is associated with risks. The study also discusses some of the pitfalls and challenges associated with gene therapy for example vector selection and gene expression control. There are a lot of uncertainties surrounding the very expensive therapies, as well as questions of ethics and practicality. Additionally, the scholars briefly discussed the available guidelines for human gene therapy and research, including those from the International Guideline and FDA regulatory requirements, without discussing Malaysia's regulatory framework. Another Malaysian study ((Bannur et al., 2014) found that most respondents had poor to fair knowledge, and nearly half had no pharmacogenomics education. These results point to the need for better strategies and guidelines for enlightening HCPs on gene therapy. Meanwhile, a very recent Malaysia study emphasizes the legal and regulatory provision concerning human genetics and genomics.

According to Kalidasan & Theva Das, (2021), the existing legal and regulatory framework is still insufficient, and it is important to highlight the shortcomings. At present, guidelines describe merely how ethical can be applied to medical genetics, such as genetic counselling, informed consent, genetic testing, and disclosure and confidentiality. It is obvious that in Malaysia, Somatic Gene Therapy is still under developmental phase. Nonetheless, the cutting edge of the clinical application in the biotechnology industry should be adequately addressed and framed in accordance with the key guiding principles: Values, Cultures and Ethics, Tolerance and Respect to Genuine Caring and Compassion, as clearly highlighted in Industrial Revolution (IR).

Regulatory Authority Oversight and Primary Legislation on Somatic Gene Therapy in Malaysia

The regulatory authority in Malaysia that regulates clinical trials and the licensing scheme for clinical trials is the NPRA, an agency under Ministry of Health (MOH) which was formerly known as National Pharmaceutical Control Bureau (NPCB) and the Drug Control Authority (hereinafter referred to as "DCA") and reviewed by IRBs, including the Medical Research & Ethics Committee (MREC) for trials using the MOH Malaysia facilities; or the MREC committee may act as an independent ethics committee for non-governmental institution or private company.

The NPRA acts as the secretariat of the DCA. NPRA also licenses clinical trials conducted in Malaysia, registers and licenses medicines, pharmaceutical products, and cosmetics, and enforces quality control systems for drugs. Through the implementation of relevant legislation by competent personnel, Malaysians can ensure the quality, efficacy and safety of these products (NPRA, 2018; Trial Expert, 2018). It supervises the pharmaceutical recall scheme for substandard or dangerous products. This authority is also responsible for the implementation of Good Clinical Practice (GCP), an international ethical and scientific quality standard for the design, conduct, recording and reporting of trials involving human subjects. In the meantime, the DCA has the power to review matters relating to product registration and to approve or reject the application for a license to import medicinal products for Clinical Trials Import Licence (hereinafter referred to as "CTIL") or Clinical Trial Exemption (hereinafter referred to as "CTX"). The CTIL is required for the importation of medicinal products into Malaysia for the purpose of clinical trials. If the medicinal product is to be manufactured in Malaysia, a manufacturing authorization is required solely for the purpose of manufacturing samples for clinical trials or registration, a Clinical Trial Exemption ("CTX") is required. In addition to the NPRA and DCA, there is a joint responsibility of various authoritative bodies and relevant stakeholders, namely the National Committee for Clinical Research (hereafter referred to as the NCCR). The NCCR is a policy making body focused on policy making and reports to the Department of Health.

Among the primary laws and regulations that govern clinical trials in Malaysia are the Sale of Drugs Act 1952 (Revised 1989) and the Control of Drugs and Cosmetics Regulations 1984 (Revised 2009), which regulate the

importation and licensing of drugs used in clinical trials. In both regulations, the MOH is empowered to impose regulations related to drugs, including the regulation of clinical trials, as provided by Section 26 of the Sale of Drugs Act 1952. With regard to clinical trial, these shall be read in conjunction with **Malaysian Guideline for Independent Ethics Committee Registration and Inspection** (Malaysian Guideline for Independent Ethics Committee Registration and Inspection, 2016) which specifically layouts the registration process for a new ethical committee, inspection procedure involved and administrative maintenance of ethical committee with DCA. Other than that, it shall be read together with the Malaysian **Guideline for Phase I Unit Inspection & Accreditation Programme** (National Pharmaceutical Regulatory Agency (NPRA) MOH, 2018).

It is demonstrated from the above that there is still no single law in Malaysia that regulates and determines the conduct of Somatic Gene Therapy. The only existing legislation that can be relied upon in this matter falls under the Sale and Drug Act 1952 (Revised 1989) and the Control of Drugs and Cosmetics Regulations 1984 (Revised 2009). In spite of the fact that these provisions are relevant, they do not specifically regulate Somatic Gene Therapy in any way. However, several existing Guidelines and Standard relevant, directly or indirectly to Somatic Gene Therapy were in place. Analysis on this statutory legal provision is essential to see whether the legal policy impose were adequate and sufficient to govern the use of Somatic Gene Therapy in human. Table 1 briefly describes the available statutory legal provision and Guidelines.

No.	Legal Provision	Remarks
1.	MMC Guidelines for Stem Cell Research and Therapy (2009)	<ul style="list-style-type: none"> Regulates stem cell research in Malaysia Most of stem cell research being conducted involves haematopoietic including stem cells including bone marrow, cord blood and peripheral blood and Malaysian Emphasize that all experiments and clinical trials must be based on a sound foundation of basic science and animal research and must meet the highest medical and ethical standards; Ethical Guidelines for Stem Cell Therapy: As for the therapy or clinical trial of cell or tissue transplantation, stem cell and tissue treatment are still in the experimental stage and should not be used as a commercial product. Further highlights in Article 2: (e) <i>“Gene therapy to correct genetic disorders e.g., subacute combined immune deficiency disorders (SCID) and thalassaemia is still in developmental phase.</i>
2.	National Standards for Stem Cell Transplantation (2009),	<ul style="list-style-type: none"> Regulates on Stem Cell Transplantation in Malaysia
	National Guidelines for Hematopoietic Stem Cell Therapy (2009)	<ul style="list-style-type: none"> Provides guidelines and standards for Hematopoietic Stem Cell Therapy
	Checklist for Research on Stem Cell and Cell-Based Therapies (NSCERT 2009).	<ul style="list-style-type: none"> Dedicated specifically for stem cell research
	Guidance Document and Guidelines for	<ul style="list-style-type: none"> To govern and oversee on Gene Therapy Medicinal products (GTMP).

<p>Registration of Cell and Gene Therapy Products (CGTPs) in Malaysia (2015).</p>	<ul style="list-style-type: none"> • Issued by the Director of Pharmaceutical Services under Regulation 29, Control of Drugs and Cosmetics Regulations 1984 • <i>CGTPs are covered under the Sale of Drugs Act 1952: Control of Drugs and Cosmetic Regulations 1984 [P.U.(A) 223/84] as it fits within the meaning of medicinal products. CGTPs are presented as having properties for medical purposes – treating or preventing diseases in human beings, or that they may be used in or administered to human beings with a view of restoring, correcting or modifying physiological functions by exerting principally pharmacological, immunological or metabolic action, hence, they are classified as biological medicinal products”</i> • Specifically intended to cell and gene therapy products (CGTPs), which establish some of the principles and, like all other biologics, are subject to the investigational new drug (IND) process and product registration or approval • Through the formation of a Technical Working Group (TWG-CGTPs) chaired by NPRA, Ministry of Health Malaysia, relevant stakeholders from various government agencies, research, academic and treatment institutions, pharmaceutical industry, manufacturers and importers were involved. • (CGTPs) 2015 was developed based on similar fundamental concepts and scientific principles of established international regulatory framework e.g., US FDA, EMA, TGA, ICH & WHO. • Covers cell therapy products, tissue engineered products, gene therapy products, and xenograft products. It focuses primarily on human stem cells, human tissue therapy products (e.g., skin, cardiovascular, ocular, musculoskeletal), human cellular therapy products (e.g., cartilage cells, pancreatic islet cells, cultured skin cells, peripheral blood and cord blood hematopoietic stem/progenitor cells), genetically engineered cellular products, cell-based cancer vaccines, cell-based immunotherapies and dendritic cells, lymphocyte-based therapies, cell-based therapies for cancer, peptides and proteins
<p>MMC Guidelines on Medical Genetic and Genetic Services 010/2006.</p>	<ul style="list-style-type: none"> • Addresses various issues such as genetic counselling, consent for genetic testing, genetic registries, prenatal diagnosis, Assisted Reproduction and medical genetics and other related aspects. • The main goal: To help people and their families who have to live with a genetic impairment to live as normally as possible, to enable them to make informed decisions in reproductive and health matters, to help people to access relevant medical services (diagnostic, therapeutic, rehabilitative or preventive) or social support systems, to help them to adapt to new conditions and to familiarise themselves with the current new developments in the field of medical genetic services. • Article 12 MMC Guideline 2006 highlights: <i>the importance of consideration of not only the cultural traditions and beliefs of the country, but also with overall respect for the autonomy of individuals and families while conducting such procedures.</i>

	<p>MMC Guideline on Clinical Trials and Biomedical Research 009/2006.</p>	<ul style="list-style-type: none"> • Emphasizes that <i>reproductive cloning (the creation of foetus whose genome is exclusively derived from another individual) has been opposed by many international bodies as this technique and method are against currently accepted International ethical standards.</i> • Thus, Malaysia has taken the same stance of prohibiting reproductive cloning from being conducted in this country. • Article 19 of the MMC Guideline 2006 directly highlights on the gene therapy and cloning stating that: <i>“Issues likely to present health professionals with ethical dilemmas are gene therapy and cloning”.</i> • Govern any trial and medical products involving human beings and is directed towards the pharmaceutical industry. It outlines the role and functions of an Institutional Ethical Committee in handling the research. • Excerpts from the Declaration of Helsinki (drawn up by the World Medical Association in 1964) along with the Nuremberg Code and its basic principles are adopted from the International Committee on Harmonisation of Good Clinical Practice (ICH-GCP) subject to certain modification to suit with local conditions. • Article 7 (2) of MMC Guideline: <i>“All proposals on biomedical research including clinical trials involving human participants have to be cleared by the ethics committee before the project begins. Besides, all studies that require additional investigative testing, invasive procedures, or medication above normal standard practice of medicine also have to be reviewed.</i> • Article 5 of the Guideline, provides three guiding principles namely, Respect for persons, Beneficence and Justice. • Article 8 of the MMC Guideline provides specific Guidelines for the ethical conduct of the research involving humans. This includes Care and protection of patients/ healthy volunteers should be given. • Article 8.5: “Risks to subjects should be minimized. There should be no unnecessary exposure to risk. There should be supervision and support for research subjects, available rescue mechanisms, and means for the research subjects to contact the investigator(s) whenever necessary. Patient/healthy volunteers taking part in a clinical trial should be satisfactorily insured against any possible injury caused by the trial. The research plan documentation should also include provisions for privacy of subjects and confidentiality of data. Personal medical information must be respected and protected, in accordance with the MMC Code of Professional Conduct, Good Medical Practice and Confidentiality”
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From the above, it is demonstrated that, Guideline 2009 made significant advances to the regulation of HESC research in Malaysia. It also reflects the Fatwa (Islamic Verdict) on Cloning and ART (Assisted Reproductive Technology)- Ruling on Therapeutic Cloning and Stem Cell Research has been released following the 66th National Council Fatwa Meeting on 22nd February 2005 and later on has been also included in the Stem Cell Research and Therapy Guideline 2009 by MOH with the incorporation of additional guidelines. Two legal provisions in pursuant of the above guideline (Article 2 and Article 6 MMC 2009) specifically stated on the application of gene therapy. In particular, gene therapy to correct genetic disorders e.g., subacute combined immune deficiency disorders (SCID) and thalassaemia is considered at the developmental phase while the use of lentiviral shall be carried out in a P3 laboratory. On the other hand, conducting *gene therapy research using viral vectors should* comply with the Biosafety Level 3.

Based on the above analysis, The development of CGTP guidelines in Malaysia is critical for enhancing safety and control, promoting sound science and its practical application in cell therapy. Given that, through the interview session with a representative (R) from National Pharmaceutical Regulatory Agencies (NPRAs) the Ministry of Health, (RPD 1) denotes that:

“...the boundary-crossing nature of many of the CGTPs and applications are subject to a wide variety of regulatory oversight. Thus, the following Ministry of Health (MOH), Malaysia Acts and Guidelines are also applicable and complement the CGTP regulatory framework:

Private Healthcare Facilities and Services Act 1998 (Act 586)

Guidelines for Stem Cell Research and Therapy 2009 MOH/P/PAK/177.08(GU)

National Standards for Stem Transplantation 2009

MOH/P/PAK/188.09(BP)

National Guidelines for Hematopoietic Stem Cell Therapy 2009 MOH/P/PAK/179.09(GU)

National standards for Cord Blood Banking and Transplantation 2008 MOH/P/PAK/131.07(BP)

Checklist for Research on Stem Cells and cell-based Therapies (NSCERT 2009)

Guidelines on Importation and Exportation of Human Tissue And/or Body parts (CDC 2006)

Medical Device Act (2012) (Act 737).

She further adds that the regulation of CGTPs involves a multidisciplinary approach; *“Therefore, its full control will be subjected to various authorities, such as: the clinical use/medical procedure of the product will be under the ambit of Medical Development Division and Medical Practice Division of the Ministry of Health, Malaysia. The device element of such products must comply with the Medical Device Act and regulations under the ambit of Medical Device Authority (MDA) of Malaysia, and NPRAs will ensure the medicinal product’s quality, efficacy and safety”*.

It appears that the principle embedded in MMC Guidelines on Medical Genetic and Genetic Services 010/2006 postulates the right to access to genetic services: *“Genetic services for the prevention, diagnosis and treatment of disease should be available to all, without regard to ability to pay and should be provided first to those whose needs are greatest”*. In addition, Article 19 merely reaffirms that gene therapy is likely to present ethical dilemmas. This demonstrates that such a concise and comprehensive legal framework for handling Somatic Gene Therapy shall be developed. Legal and ethical framework concerning Somatic Gene Therapy and needed to govern such practices from being misused. Although genetic services are still in their infancy in Malaysia, it is time that ethical considerations are duly taken into account in genetic services thus the population can benefit from the advances in genetic knowledge from the outset and without harm. In developing such legislation, it shall consider customary practices along with the existing legislation. However, such establishment should be read in conjunction with, the Medical Act Regulations, Code of Professional Conduct of the Malaysian Medical Council and other Guidelines issued by the Council or any related organization as well as any statute or statutory provisions in force and all related statutory instruments or orders made pursuant thereto.

On the other hand, MMC Guideline on Clinical Trials and Biomedical Research 009/2006 clearly specifies that only minimum risks are allowed and any unneeded and unwarranted exposure to risk are not permitted. Also, the patient who is voluntarily involved in the procedure should be insured and well informed on any possible injury that might be expected during the trial. The information includes all aspects of trial and the purpose of trial. The decision should be voluntarily adduced and officially documented. They have to be informed on their right to retract their consent from participating in the trial without retribution. The element of informed consent and confidentiality are also being highlighted promoting that all the documentation and personal medical information of the patients should be kept secret

and confidential.

RESEARCH METHODOLOGY

Research Design

The research design of this study is based on ADDIE's *Design and Developmental Research* (DDR) approach which has been modified to suit the objectives and research questions. As proposed by Rita Richey and James Klein (Richey, R. C., & Klein, 2007; Richey & Klein, 2005; Yusof et al., 2020) the DDR approach focuses on a systematic investigation of the design, development, and evaluation of processes with the goal of empirically determining the development and enhancement of existing models and the developers behind them, and it is considered flexible in answering research questions (Y. M. Yusof, Ayob, Md Saad, Affandi, & Hussain, 2020). It consists of three phases: 1) *need analysis*, 2) *design and development*, and 3) *evaluation*. Through this phase, it would guide the researcher to develop a proposed guidelines or standard.

For this study, DDR approach has been employed with slight modification to be tailored with the nature of legal study. Hence, Figure 1 depicts the general and overall picture on how this study is being conducted.

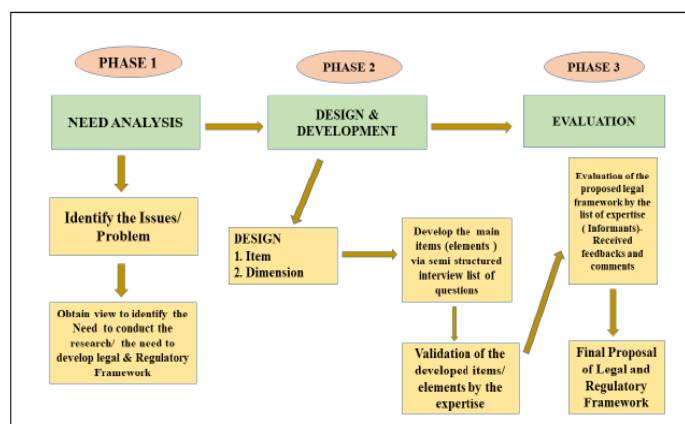


Figure 1: Phase of Design and Development Research as proposed by Richey & Klein (2007) with slight modification by the researcher to suit for the purpose of this study.

Phase 1: Need Analysis Phase. An interview instrument with a short list of questions has been developed by the researcher and distributed to THREE (3) genetics and genomics experts from three different institutions. To determine to what extent a legal and regulatory framework to govern Somatic Gene Therapy is necessary, the Need Phase Analysis must first obtain their views and opinions of the need for conducting the study. Furthermore, this stage provides a brief overview of the current state of this medical novel therapy in Malaysia, as well as the advantages and risks associated with this clinical application. In this phase, this study employed Qualitative Techniques using library research. The main elements/dimensions that have been identified to be used to develop this framework have been used in *Phase II: Design and Development Phase*.

The researcher has examined in detail the requirements for creating future legal and regulatory frameworks in Malaysia regarding SGT and the legal indicators that should be considered when establishing such frameworks. The procedure and process of conducting the *Need Analysis Phase* is presented in Figure 2 and the list of designated experts biodata involved in this Phase is depicted in Table 2.

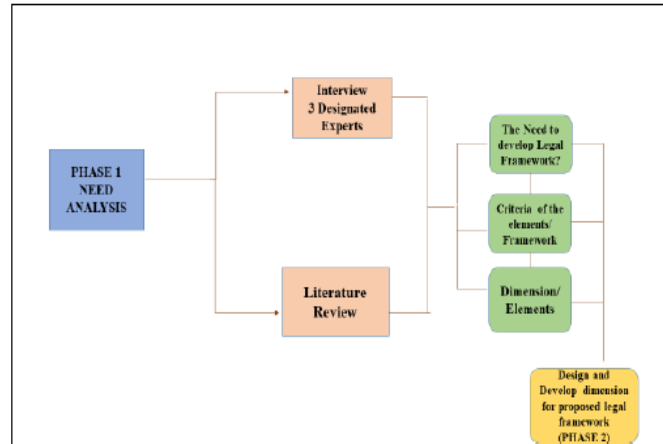


Figure 2: Phase I: The Design Procedure in Need Analysis

Table 2List and Biodata of Three (3) Designated Experts for Interview Session During Need Phase Analysis

No.	Name (Informant)	Institution
1.	[RPA1]	Institute of Bioscience, Head of a Research Centre (genetics and regenerative medicine), Faculty of Medicine & Health Sciences, Universiti Putra Malaysia (UPM) Serdang, Selangor.
2.	[RPA2]	Faculty of Medicine and Health Sciences Internal Medicine (General Medicine), Rheumatology, Clinical Immunology Universiti Sultan Zainal Abidin, Kuala Terengganu.
3.	[RPA3]	Consultant Paediatrician (Haematologist and Oncologist) Head, Paediatric Department Hospital Kuala Lumpur

Data Collection

Qualitative Technique

Since this is a legal research study, the qualitative techniques have combined several types of approaches, such as legal doctrinal research, which take a critical, analytical and comparative approach to obtain data. Reference has been made to numerous statutory provisions, legislation, and judicial opinions as a source of data. The current state of regulation and statutory provision in Malaysia includes a number of Acts that have direct relevance to genomics and genetics have been reviewed. Heavy reliance has been made to the academic journals, key academic works, books, relevant documents, guidelines, standards, and primary Islamic authorities and have been comprehensively reviewed and analysed.

Interview Session

Various professional backgrounds were selected as informants for this study. Semi structured in-dept interviews were employed in this study to collect qualitative data. key informants have been interviewed in a semi structured manner. Several semi-structured interview instruments have been prepared, and their content has been validated by two experts from two panels. The questions have guided the researcher when conducting interviews. Among the potential participants are some experts in bioethics and genetics, a medical doctor, representatives from the National Pharmaceutical Regulatory Agency (NPRA), Ministry of Health (MOH), Malaysian Medical Association (MMA), Malaysia Medical Council (MMC) & National Fatwa Committee of Islamic Religious Affairs Malaysia (JAKIM). This has been conducted during Phase II DDR- *Design and Development Phase*.

Data Sampling

To choose a sample of subjects/units from a population, this study used expert sampling, a non-probability sampling technique. In this process, the expert or known expert in the area of study consents to the study and the information was collected

directly from them. Expert sampling involves selecting people who are knowledgeable about a topic and willing to share their knowledge and demonstrate their experience (Frey, 2018; Khan, 2020; Omona, 2013; Sharma, 2017). The informants selected were from Malaysia, and they are key players who can potentially shape and influence the policy-making process and governance for emerging biotechnologies. Informants were selected based on a range of backgrounds. A total of eight (8) informants have been selected by the researcher for interviewing, based on their expertise in the field associated with this study. In Table 2, the informants relevant to this study are listed with their informant's expertise background.

Table 3:List of Eight (8) expertise selected as Informant Relevant to this study during Phase II- Design & Development Phase

No.	Informant	Ministry/ Academic Centre/ Government Agencies/ Private Institution
1.	[RPD1]	National Pharmaceutical Regulatory Agency (NPRA), Ministry of Health Malaysia (MOH)
2.	[RPD2]	Malaysian Society for Human Genetics (MHSG), Malaysia. Paediatrics Department School of Medical Sciences, Universiti Sains Malaysia (USM), Kubang Kerian, Kelantan, Malaysia
3.	[RPD3]	Genetics/ Metabolic Paediatrics Department, School of Medical Sciences, Health Campus, Universiti Sains Malaysia (USM), Kubang Kerian, Kelantan, Malaysia
4.	[RPD4]	Genetic Pathology Department of Genetics, Hospital Kuala Lumpur (HKL), Malaysia
5.	[RPD5]	Allergy and Immunology Research Centre (AIRC), Institute for Medical Research (IMR) Immunodeficiency Primer Unit, National Institute of Health (NIH), Ministry of Health, (MOH) Malaysia.
6.	[RPD6]	Informatics Cluster, Advanced Medical and Dental Institute, Universiti Sains Malaysia (USM), Kepala Batas, Pulau Pinang, Malaysia
7.	[RPD7]	Minister's Department (Religious Affairs). Former Malaysian Mufti of Federal Territories (Wilayah Persekutuan), Islamic Complex, Putrajaya, Malaysia
8.	[RPD8]	Centre of Research for

		Fiqh Science & Technology (CFiRST), Universiti Teknologi Malaysia Skudai Fatwa Fellow (Research Unit)- Islamic Development Department (JAKIM)
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FINDINGS AND DISCUSSION

Result of Interviews: Perspectives from Medical practitioners, Scientists and Clinical Geneticists

This following section would further analyse the findings received from the eyes of medical practitioners, scientists and geneticists. These experts on the relevant field have been selected to be interviewed to seek their feedback and opinions on the issue concerned. In conducting the interview, the author is guided by a set of questions designed with the objective to obtain their views on: 1) Malaysia experience on conducting Somatic Gene Therapy clinical application and whether it should be implemented in future? 2) The adequacy of current regulatory framework in the sense do Malaysia need to develop comprehensive regulatory framework governing SGT based on the ethical based on ethical standards agreed upon by the scientific and medical experts as well as authoritative body in Malaysia; 3) The feasibility to take into consideration shari'ah perspective in legislating future Act; 4) The viability and the possibility of adopting foreign legal provision from developed countries (such as UK, EU and USA) in enacting such law (whenever possible therein). The findings would assist achieving the objectives of this present study.

Malaysia Experience on Somatic Gene Therapy in Human: Should it Be Implemented in the Future?

With respect to the experience of Malaysia in conducting Somatic Gene Therapy in Malaysia so far, based on the series of interviews conducted with industry players, Somatic Gene Therapy has begun to conduct in Malaysia though it is still at early phase or development phase.

In the interview conducted with [RPD 6], one of the expertise in genome editing who has ample experienced in conducting genome editing in pioneer lab in USA and has spent more than ten years working on various genome editing tools, when being asked how far Somatic Gene Therapy technique has been conducted in Malaysia, based on her experience and current practices, she reflects that:

“There has been some preliminary work conducted on gene therapy and its application in Malaysia, but further testing needs to be done to ensure efficacy and safety before it can be applied to humans. There is also a huge push for personalized medicine (which is related to gene therapy) in Malaysia in the past few years, especially related to genetic diseases and for cancer”

Based on the above, this technique has been at the preliminary work and has been tested incrementally by various agencies to date, and further testing is still needed. Every crucial aspect in the clinical application of gene therapy needs to be optimized before its effective implementation to ensure its efficacy and safety for human beings. [RPD 6] further asserts that:

“Different institutes/ agencies have made progress in different aspects of gene therapy work. A lot of the fundamental and in vitro work has been done in public universities. Private hospitals have been championing more personalized medicine types of techniques. Private stem cell companies have been making progress on the GMP/ GLP techniques needed for gene therapy. Each aspect would need to be optimized before the technique can be successfully implemented”

When asked whether SGT should be used in Malaysia to cure genetic diseases, she replied that this clinical application for medical treatment is only possible if certain conditions are met. These include that the technique used is optimized, the benefits outweigh the risks, all stakeholders agree and all implications are fully and properly considered. She considers that:

“Human gene therapy practices require highly skilled personnel and knowledge. Even at a global level, it has only been done successfully in a handful of people. If the technique has already been optimized, can ensure that the benefits outweigh the risks, has obtained the approvals by all related parties, and all repercussions are fully understood, then yes, it can be implemented in Malaysia to cure genetic diseases”.

This study further sought views of [RPD 5] a representative from the Institute for Medical Research (IMR) Malaysia and directly conduct research in the laboratory. According to her, Malaysia is taking a safe position with regards to Gene Therapy practices. She expresses her concern stating that.

“Gene Therapy is now still in the discovery phase and experimental in a way it is to further evaluate whether it is effective enough to be applied or not. Therefore, we are still observing other developed countries' practices for example the UK on this application. This is because gene therapy could cause other adverse effects and cause regulation in the human body. It might also cause mutation resulting from such treatment in which such mutation would result in another disease for example leukaemia or lymphoma”.

Another view has also been obtained from [RPD 3], Clinical Genetics and Paediatrics expert, who specialist in Genetics/ metabolic, when although she agrees that this technique to be implemented very near future, she however expresses her concern that limitation shall be imposed as to the need for such medical treatment practices. Only gene therapy which has undergone clinical trials and proven to be safe and effective, then it could be used for this country.

“If it is proven to be effective and safe, I think we should also be using gene therapy to treat patients”. We cannot do things like give therapy to the patient without proven effectiveness or without any based on theoretical background, without any examples from others colleague or reasonable examples”.

According to the above account, feedback indicates that this innovative treatment may be implemented in the future as it has a huge potential for addressing existing unmet medical needs that are substantially different from traditional therapeutic agents and provides a significant impact on the health system for its curative approaches. Hence, this study strongly believes that SGT treatment via gene therapy product could to a certain extent be applied to treat most common cancers affecting Malaysian male and female, Colon cancer, lung cancer, breast cancer, prostate cancer and ovarian cancer. However, the application of Somatic Gene Therapy for cancer treatment is still dependent on the case by case.

However, in order to avoid misuse of this technique and its application, issues of safety and efficacy, the expected high price, the hurdles in manufacturing and the ethical conflicts that pose a challenge in its application need to be considered. This new medical technology should be properly governed and comprehensively regulated by statutory legislation and regulatory control. The existing regulatory control of biomedical research has merely encompassed a guideline without any legal support. Therefore, the following section shall then obtain the opinion from industry players as to;

The adequacy of current regulatory framework and the need to have future comprehensive legislation for SGT.

From the above analysis, this study submits that there are overlapping guidance documents (i.e., Guidelines for Stem Cell Research and Therapy, National Standards for Stem Cell Transplantation, National Guidelines for Hematopoietic Stem Cell Therapy), causing confusion among clinicians and researchers. Even though MOH released a ‘Checklist for Research on Stem Cell and Cell-Based Therapies,’ the document fails to address the issue of non-compliance and accountability (Gopalan et al., 2017). Activities related to stem cells are mainly guided by the documents discussed above, which suggest good

practices and guidelines, but are not legally binding. In the absence of such regulations, there are no legal consequences when a person violates the practices recommended in the instruction (Nishakanthi, 2019).

Despite the difficulties surrounding stem cell research in Malaysia, (Kalidasan & Theva Das, 2021) finds that it is unclear whether gene editing, which includes gene therapy, is governed by any standards or guidelines. Accordingly, the scholars suggest Malaysia adopt some aspects of the current international proposal, while adding its own historical, economic, social, and cultural perspective Kalidasan & Theva Das (2021) also emphasise that regulation and legislation are crucial to manage new technologies for the benefit of the public. Nevertheless, the existing Malaysian guidelines were variable and limited, and there was a discrepancy between the written regulations and the daily practice of clinical laboratories and scientists. Gopalan et al. (2017) further adds that the guideline

is only a general statement without any mandatory controls. The parameters of a policy, standard, or procedure are defined in it. It is only a support document which is optional and not rigid.

It is envisaged that based on the current scenario, the recent technology which is being developed has led many policymakers and stakeholders to express concern about whether appropriate systems are in place to govern this technology and how and when the public should be engaged in these decisions? This study contends further that certain peremptory norms and legal framework are needed to govern and properly guide Somatic Gene Therapy application. MOH should consider adopting an effective regulatory framework to govern the Malaysian scientists and clinicians within ethical guidelines.

Feedbacks received from the interview conducted with [RPD 2], the scholar opined that the existing Guideline for Stem Cell Research and Therapy (2009) is not adequately enough to be relied upon as the main reference in developing Malaysia legal provision for Somatic Gene Therapy in humans. The reason given:

“The implication of stem cell therapy and gene therapy to humans is different. Cell therapy involves the transfer of cells with the relevant function into the patient while gene therapy involves the transfer of genetic material. With the advancement of genetic study, involving gene editing in which both cell and gene therapy are applied simultaneously, the legal provision must be free from any legal loophole that may be taken advantage of by scientist and medical practitioner”

In this effect, [RPD 3] in her feedbacks views that although the purpose of conducting Somatic Gene Therapy for therapeutic purposes, it is still masked with a range of legal and ethical considerations which warrant for a specific legislation. While being asked about the adequacy of very recent Guidance Document and Guidelines for Registration of Cell and Gene Therapy Products (CGTPs) in Malaysia (2015) developed by NPRA, she further asserts that this available guideline governed by NPRA, MOH is merely for drugs used which refers to GTMP products but not the practice itself. She views that it should be another body or division under MOH that is having control and concern with Somatic Gene Therapy clinical practice and the respective body should comprise of people with clinical experience. According to her, the MMC guideline 2009 which only provides very general provision on gene therapy is also not adequate and there is a need to expand it so that we could prevent misuses of gene therapy for one medical purpose.

Another feedback has also been sought from [RPA 3], a Senior Consultant Paediatric Haematologist & Oncologist (Paediatric Department) Hospital Kuala Lumpur. From the interview conducted, he agrees that this therapy should be allowed for therapeutic purposes thus comprehensive legislation is needed. Similarly, [RPA 1] therapy is further adding that although SGT still a relatively new procedure, he cautions that scientist's, geneticist as well as medical practitioner enthusiasm must be governed. Regulatory policy should be of paramount concern in order to ensure that this future acceptable method is properly guided and to avoid any misuse of medical treatment to human subjects. To achieve this, he agrees with the opinion that a comprehensive legislation needs to be enacted in order to monitor and the ethical issues surrounded this technique

The study on the needs for implementation of Somatic Gene Therapy and the call for regulating future legislation of this therapy would not be complete without seeking opinion from Muslim Fiqh experts. This is because future legislation shall also adopt Islamic perspective in the formation of legal framework as Islam has been given special place in the Federal Constitution as the official religion of the federation. Therefore, this study further sought views from [RPD 7], former Mufti of the Federal Territory) (Malaysia) pertaining his opinion on the need to have future legislation of SGT in Malaysia. He strongly agrees to develop specific comprehensive legislation to govern Somatic Gene Therapy. He asserts that formation of fatwa is important to determine the status of many scientific discoveries including on this gene therapy. Therefore, the main authoritative bodies under the (MOH) Malaysia are the responsible body on this matter shall then embark and develop a set of legal provision and they (JAKIM) will give cooperation to enhance and refine the proposed draft of such framework in accordance with Islamic perspective.

Another feedback also received from [RPD 8] a representative from Fatwa fellow (*Istinbat* Unit), Research Department, Malaysia Fatwa National Committee Council, Malaysia, Malaysian Islamic Development Department (JAKIM) on this matter. He asserts that, if the need of conducting SGT is an extreme need nowadays in particular for cancer treatment and has ample scientific evidence for its high effectiveness, then, when it comes to application to patient suffering, one specific legislation shall develop. Otherwise, this practice will be abused by other nontherapeutic purposes that contradict the legitimate purpose of SGT. So far as fatwa

is concern, the only fatwa which in place at present is only fatwa concerning Stem Cell research and therapy perse embedded in MMC Guidelines for Stem Cell Research and Therapy (2009) which does not specifically dedicate for gene therapy.

Unlike the rest, different feedback received from [RPD 1], a representative from Centre for Product Registration, National Pharmaceutical Regulatory Agencies (NPRA) the Ministry of Health), while being asked on the need to construct comprehensive legislative framework for future implementation of SGT. In the interview conducted, she disagrees with the idea of enacting a law for Somatic Gene Therapy. The reason given is that because the legal framework is already existing. (Refer to the CGTP document 2015). She recommends that the existing Malaysia Acts and Guidelines are also applicable and complement the CGTP Guidance document. To her, what needs to be done is:

“To strengthen communication, collaboration and joint responsibilities between different authorities so that the gaps in the field of CGTPs can be covered”

In lieu of the above account, this study prefers to adopt majority industry players’ opinion, feedback and views on the need to govern Somatic Gene Therapy in humans comprehensively with one single legal provision. The medical treatment should not be left alone to professional bodies and cannot be effectively singled out for regulation but should legitimately be controlled by the statutory regulation.

It is clearly shown that the laws regulating gene editing technology particularly gene therapy have not yet been updated to reflect developments and might not be sufficiently comprehensive. Furthermore, the legislation does not mention any specific consequences for violating the regulations. This is where this study finds lacuna. This includes

the absence of provisions which thoroughly addresses the ethical consideration, legal requirements and parameters to conduct Somatic Gene Therapy, weightage of risk benefit, patient rights and safety, and other related ethical issues

The viability and the possibility of adopting foreign legal provision from developed countries (such as UK, EU and USA) in enacting such law (whenever possible therein).

In response to the questions if we were to learn a lesson from other countries legislation and provision, to what extent such importation should be limited in accordance with our law of nation, valuable feedback has also been obtained from [RPD 6] who has been more familiar with US practices in gene therapy, the feedback received is based solely on her own experiences. She expresses her agreement for such importation but further stating that;

“Sure, since gene therapy is new in Malaysia, I do think learning from US (or UK)’s policies would be a good stepping stone. We can then adapt the policies according to other country’s practices (where suitable), without compromising the safety to our patients. But I do want to emphasize that the policy makers should really understand each component prior to implementation. For example, in the absence of certain equipment or facilities (which is not available in Malaysia), can those components be substituted with something else. That would be the best way to move gene therapy forward”

Responding to the question as to what other elements or dimensions that should be included in the future legislation of Somatic Gene Therapy in human, majority of the above major key players and expertise suggest that future legislation should not miss out some important provisions which include among others: the adequacy of equipment and facilities involved, setting up the monitoring body and licensing body that should be carried out by the Ministry of Health Malaysia, the provisions on Consent, balancing risk and benefits, the ethical guidelines in conducting research, the do and don’t and the formation of patient organization. [RPD 3] sharing the same view asserting that attempts could be made to actually follow review the legal provision from other countries whether it is UK or somewhere else, but we cannot just copy and paste:

“We have to look into the suitability of the provision for our population. We can look at their guidelines. That will increase our understanding on issues that are probably important when you want to create the guideline for human gene therapy. But to relies on it solely, I don’t think so”

Emphasizing on the need to develop our best future legislation on Somatic Gene Therapy, she further suggests learning from other countries provisions such as USA, UK, Japan and Australia in the formation of our own future legislation as long as the adoption is suitable for our multiracial and multi-religious population and for our existing law and the medical practices in the country. From her own perspective, she adds:

“This is my own perspective that nowadays, the USA is the one who introduces laws or whatever when you talk about law, it starts in the US rather than in Europe. So, they are a leading country in gene therapy products. That’s why we can follow the FDA regulations rather than the UK. I think it is okay to look at the provision from other countries like the UK or you want to look at Japan, Australia. It doesn’t matter. We try to create the best legislation that is suitable for our populations”

While being asked on the elements that should be included or highlighted in the future legal framework for Somatic Gene Therapy in human, [RPD 4], genetic pathology expert, Hospital Kuala Lumpur (HKL) recommends few essential provisions to be included and cannot be ignored; 1) Objective and scope of the gene therapy need to be

specify and have certain limit; 2) Setting up monitoring bodies that should be responsible for such practices 3) Administration of this gene therapy, who would be the appropriate person or appropriate bodies involved; 4) Patient safety protection in in the sense that patient should be protected from medical fraternity from doing something beyond the field; 5) The right of the patient to receive therapy for whatever illness. 6) Who should be the person financing those patients receiving the clinical trial who is not capable of bearing the cost of therapy. In this effect, the legislation should be clear that the treatment is for everybody and there must be the body who covers the finance for this therapy. She emphasized that gene therapy involves treatment for disease that is without any other alternative, and severe diseases. Thus, when it involves severe diseases, then there is a right for every patient to receive treatment. 7) legislation and consideration to control the safety of the child who suffers disease and opt for gene therapy. There must be a certain limit for what a patient can undertake. For example, you have a gene therapy which is not proven, and then you have the parent of the child, the parent might want the child to be subjected to this unproven gene therapy.

In another feedback received, [RPA 3] agrees but highlights on certain point:

“You would need to consider how the regulatory authorities in developed and not-so-developed countries handle the Human Gene Therapy issues to understand the differences on over-arching oversights (read restrictive) in some versus no oversight (read free for all) and reasons for such scenarios”

The scholar recommends that in implementing Somatic Gene Therapy in humans, we shall learn from other well experienced countries' experiences especially from other developed countries such as the UK and the USA, but total importation is not possible since there exists difference oversight. He agrees with the opinion that comprehensive legislation needs to be enacted to monitor the application. In doing so, reference and many could also be learnt from other developed existing guidelines in medical technology but with certain limitations, conditions and restrictions should be in place to avoid any devastating consequences for such practice.

“We can draw insights from experiences in many other areas of advances in medical technology whereby advances have out-paced guidelines and led on to practices in uncharted territories without full knowledge of the potential consequences which can be devastating. The wisdom of caution and not allowing the opening the door for more harm applies in this particular case of experimenting on human embryos beyond a certain stage of its development...”

The Feasibility to Take into Consideration Shari’ah Perspective in Legislating Future Act

In response to the question whether the proposed legal and regulatory framework governing Somatic Gene Therapy should receive high validity and reliability by taking into account the feasibility to adopt shari’ah perspective in legislating future legal provision, [RPA 2] further asserts that in developing such legislation, it shall consider customary practices, international ethical standards along with the existing legislation. She agrees in the sense that:

“The validation should also be in concordance with international ethics on gene therapy as to embrace our holistic Islamic ethic globally. The validation to develop comprehensive legislation should also take into account the International ethical standards as well as Islamic ethics holistically”.

She further recommends that the proposed legal framework and future legislation shall develop after all comply with our shari’ah law. In addition, she

highlights that in order to have stronger justification as to the proposed stipulated law governing Somatic Gene Therapy application, the law shall also in line with scientific evidence on the successful treatment being offered to and the high probability of the effectiveness of such therapy.

To ensure that Malaysia's ethical, spiritual and cultural concerns are adequately safeguarded, it is not possible to fully adopt the legal frameworks of other developed countries. Since Malaysia and the UK, the EU, and the USA do not share the same culture, beliefs, or jurisprudence, a definite line must be drawn between implementing the laws of those countries that regulate gene therapy. Malaysian political and social landscapes are different from those countries so the extent of adoption of this legislation should be limited. The extent to which such importation is possible has also been highlighted by [RPD 2].

The law of the nation shall then be interpreted by this study as Islamic customary practices, since Islam is our official religion under Article 3 of Malaysia Federal Constitution. On this note, [RPD 2] again further adds that; *“The UK, EU and US legislation is adaptable as long as the Islamic principles are not violated. Gene research and Gene therapy may have positive uses to restore health, however care must be taken to ensure Islamic principles are not violated. Only somatic cell lines should be used in transplantation of genetic material since parental integrity is then not compromised and there is no question of hereditary characteristics being influenced”.*

This indicates that such importation of other legislation should be limited and adaptable as long as the Islamic principles are not violated. Results from interview sessions with key industry players and genetics experts further reveal the medical genetics should be governed by Statutory Regulation (law) instead of Professional Self-Regulation. Unlike Professional Self-Regulation which in most cases depends ultimately on the common sense and decency of the medical community, “legal regulation” is capable to protect clinicians and scientists not only from legal action for malpractice but also to give them a shield against accusations of ethical malpractice. As emphasizes by [RPD 6] *“The term medical genetics is quite broad and encompasses all areas of diagnosis and management of hereditary disorders, including genetic counselling, gene therapy and personalized medicine. As all those areas mentioned are highly tied to ethics, regulation, and in some ways, even religion, it would be challenging to draw the line if self-regulation were allowed”.*

Recommendation: A Way Forwards for Future Legislation of Somatic Gen Therapy

From the above findings, it is clear that despite the existence of specific legislation that regulates all activities related to human clinical trials and provides sufficient powers to the respective medical regulatory authorities in Malaysia in relation to professional medical acts, none of the legislation addresses the issue of Somatic Gene Therapy in Malaysia. To date, it appears that Malaysia prefers the 'professional self-regulation' approach to 'statutory regulation' in regulating the practice of human clinical trials and biomedical research. SGT is surrounded by ethics, bound by regulation and even culture and religion. Thus, to govern this, the dynamic and comprehensive “statutory regulation” shall develop compared to Self-Regulation. It would be difficult and challenging to draw a line of reliance to “Self-Regulation” per se to monitor such activities which involved many aspects.

Analysis of the feedback and comments from the interviews with key professionals in the field revealed that all key stakeholders confirmed that Somatic Gene Therapy clinical use is not yet regulated in Malaysia. The majority of key stakeholders agreed that there should be a uniform legal and guaranteed procedure regarding Somatic

Gene Therapy in Humans. This study further suggests that those involved in providing treatment using Somatic Gene Therapy should observe the standards and requirements of good clinical and scientific practice. It is recommended that references to other guidance provided by other international documents authorities or professional bodies on particular points are needed. As shown in Table 3,

the following International Guidelines and Laws are relevant to this study.

Table 4: International Declaration and Convention on Human Genetics Research and Application.

GUIDELINE AND LAWS	YEARS	SOURCE
Nuremberg Code	1947	first generally accepted code of ethics in medical research
Declaration of Helsinki	2013	Guidelines by the World Medical Association
European Convention (EU) on Human Rights and Biomedicine (Oviedo convention)	1997	Council of Europe
Universal Declaration on the Human Genome and Human Rights	1997	UNESCO's 29 th General Conference
Universal Declaration on Bioethics and Human Rights	2005	UNESCO 33 rd General Conference
International Declaration on Human Genetic Data	2003	UNESCO
International Ethical Guidelines for Biomedical Research Involving Human Subjects	2002	Council for International Organizations of Medical Sciences (CIOMS)

Source: Base on Researcher's Analysis

On the other hand, the total adoption from other foreign developed countries is not possible although they might serve as the best practice as it involves different jurisdictions adopting different cultures, values and religion. There are certain provisions of the foreign regulation and directives

may not suitably be imported into Malaysia.

In lieu of this, this study proposes that in

legislating Somatic Gene Therapy in this country, certain modifications shall be made to meet the Malaysia local culture and religious belief. The limit shall be drawn and thus further recommends that the shari'ah framework be adopted as a harmonisation tool to measure the limitation should adoption and adaptation be made. The customary traditions and beliefs of the country must also be taken into account in accordance with our law of nation. Such fundamental issues and questions are appropriately guided by the principles of shari'ah. Specific fatwas (Islamic rulings) should be included in the proposed legal framework to achieve harmonization. It is expected that great strides will be made in the field of gene therapy in Malaysia in the coming years, especially based on a number of Somatic Gene Therapy clinical trials that have proliferated in other developed countries. The study further recommends that key components of the different regulatory landscapes and policies from developed countries (i.e: UK, US and EU) relating to gene therapy clinical trials and gene therapy products should be identified further. Hence, the common ground for future regulatory convergence related to Somatic Gene Therapy in humans which involves the use of Gene Therapy products shall then list down. Table 5 summarise a few key aspects that should be incorporated derived from a number of legal provisions that pertain to somatic gene therapy and the use of gene therapy products.

Table 5: Key Components for SGT and Gene Therapy Products. Based on Researcher's Analysis

No.	Somatic Gene Therapy Application	Gene Therapy Products
1.	Setting Up and Formation of Multidisciplinary Expert Committee for Approval	Marketing Authorisation of Gene Therapy Medicinal Product
2.	Qualification of Multidisciplinary Expert Committee- Licensing Authority	Centralised Marketing Authorisation Application- Roles and Responsibilities of Specialist Expert Committee
3.	Observance of Good Clinical Practices (GCP) during Clinical Trial- Patient Safety: Assessment of	Technical Requirements of Manufacturing Process – Quality, Safety and Efficacy

	predictable risks with foreseeable benefits	
4.	Ethical Principles Involved- Patient Free-Informed Consent, Privacy and Confidentiality of Patient Clinical Trial Data.	Compliance with Good Manufacturing Practices (GMP)- Safety Measures and Risks- Benefit balanced
5.	Patient Follow Up	

Through the entire discussion, analysis and feedback received from a major player, the proposed model of shari’ah Framework is designed and developed to fulfil the lacuna of shari’ah framework governing Somatic Gene Therapy in humans. In formulating the proposed legal framework, some underlying Islamic ethical principles should be applied in permitting the use of Somatic Gene Therapy to the patients. Figure 3 outlined the proposed shari’ah framework for SGT.

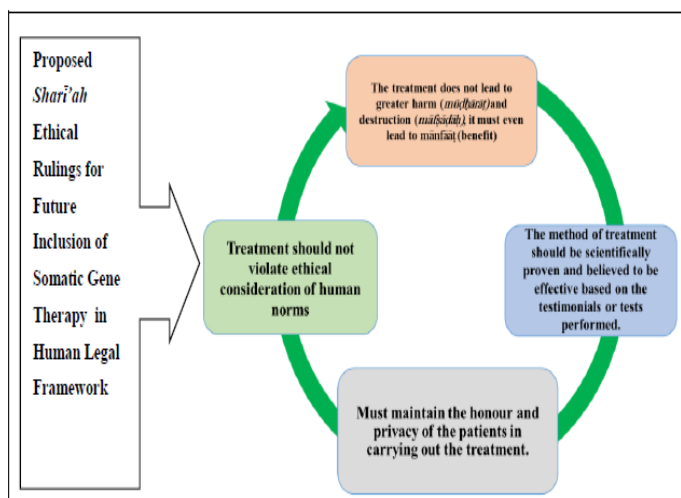


Figure 3: Proposed Key shari’ah Ethical Ruling and Principles for future legal framework for Somatic Gene Therapy in Malaysia. Based on Researcher’s analysis.

Further to that, the harmonization amongst those two perspectives (Common law as well as shariah Perspective) enabled the study to further proposed an agenda for a way forward suggesting some crucial aspects and legal requirements to be included in the proposed Malaysian legal and regulatory framework for Somatic Gene Therapy in humans. Figure 4 thus summarized and depicted the proposed aspect to be included for future legislation of Somatic Gene Therapy in Malaysia

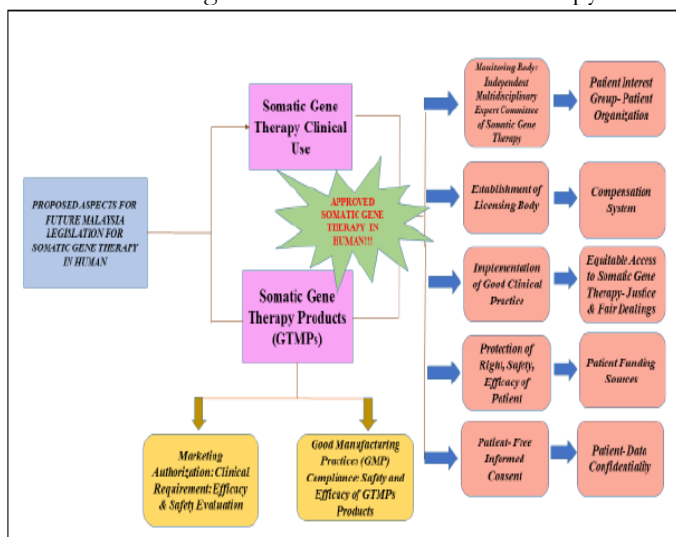


Figure 4: The Proposed Key Aspects to be Included for future legislation of SGT in Malaysia. Based on Researcher's analysis.

CONCLUSION

It is believed that the harmonization and confluence of international agreements and the adoption of common Shariah principles will pave the way to national legislation of Somatic Gene Therapy. Based on the above recommendation., legislation must be in place to protect and provide a code of conduct for patients as well as the institutions, clinicians and researchers involved. We must make the necessary preparations to provide the best outcomes. For this reason, this proposed legal framework which received constructive comments and valuable input from that expertise in the medical and scientific field as well as Muslim religious organization are advantageous in the regulation of human Somatic Gene Therapy in Malaysia.

It is believed that to further translate technique and products from the laboratory to bedside and to adopt suitable policy in this country, it is therefore crucially important to involve serious discussion between the researcher, clinician and regulatory bodies to ensure a way reform for Somatic Gene Therapy is achievable.

In conjunction with the above, this study believed that this framework would serve as the ethical basis for the application of Somatic Gene Therapy in Malaysia and beyond (particularly Muslim countries) especially for Muslim doctors, scientists and Muslims at large.

The compliance with regulatory requirements is essential to any study or treatment that involves ethical and safety considerations. Without a legal mechanism, such activities can be irresponsible, merely for enhancement purposes and not for medical purposes. It is also important to note that the safety and lives of patients and subjects may be at risk without a legal mechanism. A combination of effective legal measures and international cooperation is essential to prevent misuse of these new technologies.

As a conclusion, this is the first study conducted in Malaysia from a regulatory framework and the shari'ah perspective to examine Somatic Gene Therapy in humans. Further research will be possible in the future in the following areas:

Researchers could conduct a more comprehensive study of stakeholders' perceptions and intentions concerning somatic gene therapy adoption. It may focus on the attitudes and behaviour of the relevant stakeholders to the acceptance towards gene editing technology with special concentration on gene therapy in human medical treatment. The stakeholders could be from the healthcare providers as well as the patient. Surveys and Questionnaires. Distribution methods could be applied in this kind of study.

A detailed examination of the limitations and challenges on the implementation of Somatic Gene Therapy should be further evaluated by future research. This would include technical hindrance and scientific challenges. How to address each and every aspect of limitation should also be provided by future research.

As this study focussed on the legal framework of Somatic Gene Therapy in

humans, future research could be conducted with special reference to another type of human gene therapy i.e. Germline Gene Therapy application and practices. Focus could be given to the applicability and its legal position from shari'ah perspective. Comparative study of this kind of gene therapy could also be carried out with other countries

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