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ARTICLE

AN INSIGHT INTO THE LEGAL FRAMEWORK ON HUMAN GENE THERAPY IN SELECTED COUNTRIES

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ABSTRACT

Background: *Recently, the fields of biotechnology and genetic engineering have been given great emphasis by most of the countries from all over the world. It is proven that genetic living organism could be successfully manipulated and redesigned using various applications of biotechnological sciences. Similarly, this overwhelming advancement of science has also encouraged the government of Malaysia to put great emphasis to this biotechnology evolvement. Given that this industry is believed to be the prominent key areas in generating economic growth, various incentives, investments, effective research and medical devices have been successfully conducted and developed. While the use of this novel technology is increasingly tremendous, so does the field of human gene therapy. Current trends signify that gene therapy technique has been widely used as it has been proven to be a successful treatment for cures of epidemic diseases in human at the molecular level. It has nevertheless been found that this technique has been associated with a wide range of ethical and legal issues. In view of this point, this study seeks to examine the legal issues surrounding human gene therapy. On this, special concentration would also be paid to the legal provision and regulation currently enforced in few selected countries governing human gene therapy. Considering that there has been absence of legislative regulation to regulate gene therapy treatment and activities in Malaysia, this study further recommends that it is essentially indispensible for Malaysia to also having a set of legal and regulatory framework in place. To achieve this, this study proposes that the relevant regulatory framework in selected countries could be considered in developing the legal framework for Malaysia. However, this study further submits that the extent of importation of the relevant legislation into Malaysia should be limited in order to safeguard Malaysians' ethical, spiritual and cultural concerns.*

KEY WORDS

Biotechnology,Human Gene Therapy, Legal Provision on

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INTRODUCTION

The advancement of genetics and genomics have taken place world widely especially in the developed countries. Like in other countries, even though the development of biotechnology in Malaysia is rather slower, initiative has been taken by the Malaysian government specifically in making collaboration with other biotech partners such as Thailand, New Zealand, Hungary, Japan and Korea [1]. This collaboration has successfully assisted Malaysia in developing biotechnology field with special concentration given to the medical aspect.

The field of genetics and genomics have becoming a vast major field targeting to envisage potential benefits for chronic diseases such as breast cancer, colon cancer, cystic fibrosis and diabetes [2], [3]. The scientific discovery reveals that the genetic basis of the diseases might be caused by the changes (mutations) in the DNA, [4] on which it could be cured using genomics medicine. The similar view has also been pointed out as in [5] where the genomics and biotechnology were heralded as a successful tool to elucidate health problem in developing countries. Considering that this promising field has great potential [1] to resolve issues associating with human, this major contribution is therefore vital. Following these, various novel techniques associated with human genome have been used. These include; cloning (DNA cloning, reproductive cloning, and therapeutic cloning); somatic and germline therapy.

In view of the above, current trends signify that human gene therapy is efficacious to treat certain genetic diseases at the molecular level. Reviews of literatures demonstrate its benefits and successful treatment to cure epidemic diseases in human. [6], [7]. Therefore, the successful of this clinical trial has provoked an excitement amongst scientist and clinicians in this promising therapy for curing many genetic disorders. Nonetheless, despite the prospect of clinical trial obtained from gene therapy, it has been encountered with a wide range of ethical and legal controversies. [8], [9], [10]. This technology has been used irresponsibly with high level of uncertainty which consequently caused fears to the society at large. Besides, significant risks involved in this technique could possibly outweigh the

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potential benefits [11], [4], [12], [13]. On top of that, debates on gene therapy activities among scientists and Muslim scholars have also taken place. Although the ethical issues have been discussed extensively, less attention has been given to address the legal issues. Hence, this paper highlights the legal issues surrounding this technique. The existing legal and regulatory provision relating to human gene therapy in few selected countries shall then be appraised so as to establish whether it is able to adequately regulate the human gene therapy technique and activities

DEFINING HUMAN GENE THERAPY

There are vast array of literature representing the work that ultimately brought about the meaning of gene therapy, the procedure and techniques accomplished within, the application method and the vector system used in human gene therapy. Essentially, gene therapy is a medical technique that seeks to transfer genetic material to a cell to generate a therapeutic effect by correcting an abnormality that exists within the host cell [14]. The principle of human gene therapy as in [15], [16] is replacing the defective genes by a new functional gene that corrects the defects. New genetic instructions will be introduced into the patients' tissue for the treatment of disease or to compensate for an abnormal or missing gene by conveying a new function [17]. The procedure and techniques could be carried out either ex *vivo* or in *vivo* [18], [19]. Originally, certain diseases are caused by a defective gene or by the absence of a functioning gene. Therefore, this preventive approach involved the identification and cloning of the genes associated with many human diseases, including, B - thalassemia, Gaucher's disease, adenosine deaminase deficiency, cystic fibrosis, AIDS, and cancer [18], [19].

Types of Gene therapy

Practically, human gene therapy involves changes in either somatic cells or germ cells. As in [9], [26] human gene therapy comprises of i) Somatic gene therapy which involves an insertion of the gene directly into the host's tissue. This gene therapy enables to further correcting a genetic defect in the somatic (i.e., body) cells of a patient. Likewise, somatic gene therapy procedure is similar with other more conventional forms of pharmacological intervention as it involves the manipulation of gene expression in somatic cells that has been corrected, but not inherited by subsequent generations; [17], [22] ii) Whereas in Germ line gene therapy, it requires the insertion of the gene into the reproductive tissue of the patient (ovaries or sperm) which entails modification over the subjects' germline the disorder in his or her offspring and future progeny would also be corrected. Apart from that iii) Enhancement genetic engineering [9] is another type of gene therapy which involves the insertion of a gene to 'enhance' a known characteristic; for example, the placing of an additional growth hormone gene into a normal child ; and iv) Eugenic genetic engineering is a therapy which manage to alter or 'improve' complex human traits, each of which is coded by a large number of genes; for example, personality, intelligence, character, formation of body organs, and so on. Above all, performing of somatic gene therapy are the prevalent efforts and a novel approach to gene therapy for genetic disease taken in clinical trial rather than germline gene therapy. The primary concept of this therapy is that the application of gene therapy vectors to the targeted tissue may avoid or delay the development of early disease related organ damage and may allow targeting of inaccessible organs and tissues.

Potential applications of Gene therapy

Scientific discovery reveals that certain pediatric hereditary disorders are due to definite genes and defects in specific proteins. Thus, this scenario would eventually lead to the initial evolution of the gene therapy concept [4], [26]. Essentially, numerous potential applications of gene therapy could possibly extending from monogenic hereditary disorders such as Duchenne muscular dystrophy, lysosomal storage diseases or cystic fibrosis to acquired disorders like AIDS, cancer, thrombo-embolic cardiovascular diseases and neurological disorders, upper gastrointestinal tract infection, autoimmune disease, and systemic protein deficiency [26], [16]. These disease interact with genetic factors by which scientist have further found it could be treated using the genomic medicine. Additionally, the promising of this preventive approach in producing tremendous good and reducing the suffering and death caused by genetic diseases has been proven in many clinical trials. Studies with special attention discussing on the scientific aspects, elaborating its potential benefits and successful treatment to cure epidemic diseases using human gene therapy technique are enormous; [27], [16], [28], [29], [30], [31], [19], [23], [32], [33],[34]. Hence, it is further believed that gene therapy will certainly represent, a major therapeutic option applying in particular disorders with no available alternative treatment [27]. This new method for example has been successfully act as a preventive intervention against cancer targeted by utilizing genes to destroy cancer cell [29], [30],[18]. Also, gene therapy approach is currently being pursued in primary severe combined immunodeficiency (XSCID) and other immunodeficiency disorders, including chronic granulomatous disease and Wiskott-Aldrich syndrome [28], [35] and the active pursuit of gene therapy for inherited single-gene defects have also been sought in Cystic Fibrosis (CF) [36], [24] Despite the absence of curative treatment

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available, other candidates severe genetic disease such as phenylketonuria (PKU), Duchene muscular dystrophies (DMD) which caused by mutations in the X-chromosomal dystrophy gene, hemophilia IX, and orthine transcarba- mylase deficiency (OTC) may also be amenable using gene therapy [26], [23]

LEGAL ISSUES SURROUNDING HUMAN GENE THERAPY

In view point of the above discussion, it brought to our attention that both types of gene therapy are surrounded by ethical and legal concerns [9]. Debates surrounding the human genome have focused primarily on the moral and ethical propriety of manipulating the human genome, as well as on the potential social harms. Amongst the studies which primarily examine the ethical issues of human gene therapy are as in [37], [38], [39], [40]. Reviews from these academic literatures reveal that ethical issues must remain a paramount consideration in conducting gene therapy. Unlike somatic gene therapy experiments, germline gene therapy appears to be more controversial and has been surrounded by a wide range of unresolved issues. Hence, this advent requires such a comprehensive policy and legal and provision to govern the scientific progress. However, in deriving legal solution, further scrutiny of the underlying ethical issues surrounded the human gene therapy is needed.

Since the goals and objectives of gene therapy in human are varied, the purposes of gene therapy in human would be a major issue that needs to be addressed upon. It is important to know as to what purposes would be considered as ethically acceptable, and in justifying the acceptability of each purpose, what mechanism should be applied. On the other hand, the question of human dignity is another pertinent issue that needs to be overcome as highlighted in [41]. Therapeutic interventions on human embryo might be affected while human cells could be amenable to treatment or alteration. Non-therapeutic interventions which alter the genetic of an individual are another concern which stems from the fear that human is considered as a mechanism to achieve certain aims.

Besides, issues regarding safety and regulatory aspects of gene therapy have been outlined as in [27].Three significant areas have been identified and need to be overcome include i) experimental and pre- clinical research; ii) manufacturing of gene therapy products; iii) clinical trials and development. The author further concludes the essential issues in each of these areas remain unresolved particularly in terms of the efficiency and safety of gene therapy clinical trial. Concentration has been given on the ethical issues as in [7], [42], [43]; i) the process of establishing safety and efficacy of therapeutic gene manipulation. ii) Weighing potential harms and benefits, iii) establishment of procedural fairness in the selection of patients for research, iv) assurance that consent to experimental treatments is informed and voluntary, and v) protection of privacy and confidentiality of medical information. On this point, it is further submitted that the specific issue of informed consent is among crucial issue that should be given special attention in both type of gene therapy. In Germline gene therapy, since the therapy implies a patient who may give informed consent and subsequently being treated, the question would then arise; Who is the subject of therapy?; who did give the consent and if the clinical trial is successfully conducted, the resulting child and future generation never will have such disease, then, it is accurate to say that the child was treated? [44].

Conversely, despite the extremely potential applications of gene therapy, this may however causes risk which involves insufficient therapeutic efficacy. As a result, like any other new treatment, proper assessment of safety and effectiveness and informed consent are crucially needed in conducting somatic gene therapy [11]. Few studies indicate that many fear that the risks inherent in using these procedures in humans far outweigh the potential benefits [12], [13]. Similarly, failure to communicate on the potential risks along with the benefits has then establishing fears to this technique so attained [45], [27]. As in all cases of research, it is imperative to balance the value of knowledge to be gained, with the risk of harm that has incurred. Therefore, gene therapy in human brings into tension two fundamental moral principles: the duty to prevent or alleviate suffering, and the duty to respect the value of human life. The question then is which principle should be given precedence in the event of a conflict? Should be given the first priority over the second by permitting human gene therapy and allow its destruction? Or should we totally ban such therapy without considering the potential benefits it could offer? Also, taking into account on the potential benefits and the risks of a gene therapy, the potential benefits may be outweighed by the risks involved. As a consequence, it is pertinent to further consider an appropriate mechanism to protect the rights and welfare of gene therapy patients participating in clinical research.

LEGAL PROVISION ON HUMAN GENE THERAPY IN SELECTED COUNTRIES

Given the above, having a statutory legal provision to govern gene therapy is therefore vital. This is to ensure that research and applications are done for the benefit of human welfare and the rights of others are not infringed. In addition, to avoid misuses of these new technologies, effective responses

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from legal perspective coupled with international cooperation are indispensably crucial. The harmonization of appropriate regulation [27] is essential to facilitate the scientific evolvement. This is evident by significant efforts which are being made towards harmonization and the establishment of international guidelines to govern gene therapy activities.

Among the notable international declarations and guidelines issued by non- governmental organizations such as the World Medical Association (WMA), the Council for International Organizations of Medical Sciences and other academic or professional institutions. Other documents which merely cover on specific bioethical issues is the UN Declaration on Human Cloning of 2005 and the UNESCO Universal Declaration on the Human Genome and Human Rights of 1997. Another regional instrument is the European Convention on Human Rights and Biomedicine of 1997. Despite the great number of existing international guidelines, statements and declarations relating to bioethics, the new Universal Declaration on Bioethics and Human Rights adopted by the United Nations Educational, Scientific, and Cultural Organisation (UNESCO) which put in place on 19 October 2005 is another international declaration, though non-binding that comprehensively deals with the linkage between human rights and bioethics in particular which involve biomedical research and clinical practice [46].

Considering that the moral conviction and domestic regulation for each countries differ because of socio cultural, historical, philosophical and religious background associated with human gene therapy, as in [47], he proposes that international cooperation is needed to not only harmonize the existing legal standards but also to ensure that such standards are effectively implemented by establishing appropriate mechanism.

European countries

In discussing on medical genetics technique, juridical questions are among the issue that avail apart of ethical issues. Few authors have discussed on ethical issues with special reference to the international regulation [48], [49]. According to [50], recent advances in stem-cell research have also been accompanied by social, political, economic, legal, religious, and ethical questions. Current European legislation has been enforced among various European countries ie; Sweden, Norway, Germany, Belgium and United Kingdom upon the acceptance of therapeutic and reproductive cloning. While it appears the acceptance is on the ground that medical benefits outweigh the risk, it has nevertheless opposed by Europe Convention on Human Rights and Biomedicine (adopted by the Council's Committee of Ministers on November 19, 1996) which involved 29 European countries except Germany, Belgium and the United Kingdom. It seems that numerous laws and regulations have been implemented or are being considered in order to control the use and spread of this new technology.

On the other hand, as in [51] comparison studies on "Gene Therapy in Germany and in Europe: Regulatory Issues with special concentration on Germany Regulation" reveals that there is a considerable body of regulations including the German Drug Law protecting the patients during clinical trials. Amongst the regulation is that the requirement of marketing authorization prior treatment towards patients. German gen Law is another regulation governing the requirements of experiments, storage and inactivation in gene therapy involving the use of genetically modified organisms (GMOs). As for Germany, gene therapy drugs can be constructed and analyzed in laboratories approved according to the German Gene Technology Law ('GenTG') by the competent authorities in each federal German state. Aside from that, there appears to exist a considerable body of regulations including the German Drug Law ('Arzneimit- telgesetz') protecting the patients during clinical trials. Likewise, in experiments of gene therapy using genetically modified organisms (GMOs), they have to be adhered to German Gene Law (which is a transformation of Council Directives 90/219/EEC and 90/220/EEC) where such trial have to be performed in gene laboratories of safety levels 1–3 used for research, which have been approved of by the competent authority of the federal German state where the laboratory is located. This has been made clear that Gene Law regulations will ensure that necessary precautions are taken into account during the use of viral vectors and genetically modified cells. Safety of human beings other than the patient and the environment will be put at the utmost consideration.

The implementation of a gene therapy clinical trial in France however is under the responsibility of the French Medicines Agency. Documents for guidance in conducting clinical trials shall be released by the expert working group in French Medicines Agency. This documents contain such a comprehensive safety and efficacy issues relating to gene therapy clinical trials in humans: information on the GMOs and risk for deliberate release; pharmaceutical and biological information, a comprehensive approach to strategy, gene construct and gene delivery system, manufacture and control, intended product use ex viva or in vivo, storage and destruction; the delivery system and the full therapeutic product and clinical trial data. Final decisions must be given by coordination of several departments inside the Medicines Agency [27]. Further to that, as in [51] under this agency, it involves the independent advisory body known as The National Advisory Committee on Ethics (CCNE). As an independent body,

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the CCNE may decide to release comments or questions on any subject of its choice. On the other hand, the 'Commission de Genie Genetique' (CGG) and the 'Commission de Genie Biomoleculaire' (CGBM) are two bodies which connected directly with French Ministry of University-Education and Research and French Ministry of Environment. Their function is to review of the clinical trials protocols before giving an approval for gene therapy for human is being permissible to be conducted. Ultimately, the protections of human beings which participate in biomedical research are controlled by the Research Ethics Committees. This include, certain protocol have to be followed to before an approval being vested by the Local Research Ethics Committee.

These denote the rules in particular; have been extended to be applied to the use of products derived from biotechnology form the basis for gene therapy. In terms of the clinical trials, approval of the competent national authorities is required by most of the EU countries before they can be conducted. Meanwhile, Ethics Committee approval is a requirement prior to the trial being conducted at the hospitals and centers. [52], [7], [35] however further claims that besides its complex treatment strategy, gene therapy is considered as more expensive compared to conventional drug treatments.

United States of America

[53], [54] highlight on the regulation of gene therapy in USA. Currently gene therapeutic products and gene therapy research in human subjects' therapy in the United States administered primarily under the auspices of National Institute of Health (NIH) and Food and Drug Administration (FDA). The FDA regulates the clinical application of gene therapy and acts as deliberative body that oversees and reviews the safety and control measures associated with gene therapy. FDA's approval is required for all gene therapy protocols. On the other hand, in terms of regulation to govern the gene therapy activities, NIH carries primary oversight role [55].Within NIH, the subcommittee composed of professionals in the science, medical, and law fields together with The Special consultative group known as Recombinant DNA Advisory Committee (RAC) will be formed and will then review gene therapy protocols. These three bodies should actively control and monitor the gene therapy activities. However, besides the formation of regulation as a necessary component of gene therapy research and applications, extra caution and modification should further be imposed by the government regulation to also govern the germ line gene therapy which possesses much more controversies which may affect future generation [56].

Similarly, as in [13], current regulation governing these technologies with special reference to Food and Drug Administration (FDA) has been discussed. Seemingly, the FDA's authority and jurisdictions has also been extended to both public and privately funded agencies. FDA seems to be the appropriate regulatory agency to oversee federal regulations since the federal government has very little legislation or guidelines regulating this activity. As a consequence, those attempting to use the techniques as reproductive technologies or medical therapies would firstly answerable to the FDA for applications of germline gene therapy used clinically in humans. The same approach as in European countries, the FDA regulation requires the institution to submit a research proposal and obtain authorization before the trials in human subjects is being implemented. On this, the FDA has a full discretion to obviate certain procedures or assays when it is felt there is no impact on safety. The element of informed consent of human subjects is also another vital element required by virtue of FDA and hence subject to enforcement and sanctions.

However, flexible approach [35] has been brought by the Food and Drug Administration (FDA) with regard to an early clinical trial of cell and gene therapy which does not require full cGMP manufacturing. All in all, the FDA framework is flexible and subject to modifications in the light of scientific advances as with the RAC 'Points to Consider documents' which present pertinent issue in a given area of product development [27] . Center for Biologics Evaluation and Research (CBER) has been appointed for being responsible to reviewing gene therapy protocols as well as the new biological by adopting the principles already established.

United Kingdom

Review of the literatures demonstrates that a vast array of works being done on human gene therapy with special focus on the UK legislation. Among the scholars are [52], [4], [51], [57]. As far as UK legislation is concerned, germline gene therapy is totally illegal in the UK and many other jurisdictions because the risks of unintended harm would be harder to predict and control [4] compared to somatic cell therapies. The relevant provision could be referred to in Part 3, Regulation 19 (3) of The Medicine for Human Use (Clinical Trials) Regulations 2004.
Reg 19- Authorisation procedure for ethical trials involving medicinal products for gene therapy
Reg 19 (3)- The licensing authority shall not authorize a clinical trial involving products for gene therapy if the use of those in the trial would result in modification to any subject's germ line genetic identity (The Medicines for Human Use (Clinical Trials) Regulations 2004, 2004 No.1031)

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Thus, the above regulation has made clear that germline gene therapy is illegal and would not be permitted to be conducted. Other than that, Article 24 of the Universal Declaration on the Human Genome and Human Rights states that the International Bioethics Committee of UNESCO should disseminate the principles set out in the Declaration and should further proposes that germ line gene therapy activities could be contradictory to human dignity [58].

However, this is likely to be affected by virtue of Human Fertilisation and Embryology Act, (2008) for the possibility and permissibility of making changes to mitochondrial genomes that could be inherited by future generations in order to treat or prevent mitochondrial disease. Also, Article 13 of the European Convention on Human Rights and Biomedicine further states that; An intervention seeking to modify the human genome may only be undertaken for preventive, diagnostic or therapeutic purposes and only if its aim is not to introduce any modification in the genome of any descendants.

As in [4], he again claims even mitochondrial disease could be inherited in the maternal line but it is not part of germline genetic modification. Having reviewed the protocol in UK, few literatures [51], [57], [59] elaborate on the regulatory body involves in human gene therapy activities. Gene Therapy Advisory Committee (GTAC) which was created in November 1993 is the authoritative body to govern, to oversee, review and monitor gene therapy activities in UK. This GTAC has replaced the former Committee on the Ethics of Gene Therapy (CEGT). The following tasks of the GTAC include: review of the clinical protocols for gene therapy research with respect to the scientific merit and the potential benefits and risks; cooperate with other agencies which have responsibilities in this field including local ethics committees and agencies with statutory responsibilities, i.e. the Medicines Control Agency, the Health and Safety Executive and the Department of the Environment; and advice of the UK Health Ministers on trends and development in gene therapy research. A case-by-case review is performed by the GTAC and approval of the protocol must be obtained before starting the clinical trial. In addition, the final statement of GTAC is always transmitted to the local research ethics committees and to the applicant. Any clinical study must be referred to and gain the approval of a Local Research Ethics Committee (LREC) as it is also required for other clinical trials. With regard to the licensing authority in the UK, the Medicines Control Agency (MCA), operates the national scheme for clinical trial certificates under the provision of the Medicines Act 1969 [7]

In addition, [60] further notes that gene therapy which involves a research and recruitment of patients into research trials should be governed under strict rules set out by the GTAC. Even so, GTAC approval can only be obtained in the case of somatic cell gene therapy (i.e. on any cell other than the sperm or egg cells) proposal. As such, consideration would not be given for any proposals for germ line cell (egg or sperm) gene therapy. Among the primary consideration that would be assessed by this Committee include; i) whether the research proposal meets accepted ethical criteria for research on human subjects. ii) GTAC reviews would strictly examine the scientific merits of the research and evaluating its potential benefits and risks. On top of that, the safety and welfare of patients is of paramount importance. Annual report as well as guidelines on submitting protocols [54] to carry out gene therapy and on writing information for patients has also been established by the GTAC. The special reports contain an examination of the use of adenovirus in human clinical trials, and the potential use of in utero gene therapy.

CONCLUSION

The above review demonstrates that there have been different approaches taken by countries in regulating gene therapy research. In certain countries gene therapy is regulated as an experimental therapeutic and therefore subject to general medical legislation. On the contrary, given the ethical issues surrounding Gene Therapy, in some other countries the regulatory mechanism developed was only non-statutory advice by the creation of specific monitoring body; national ethics committees and advisory boards such as the US Recombinant DNA Advisory Committee (RAC) and the UK Gene Therapy Advisory Committee (GTAC).

Meanwhile, in the Malaysian context, there has been absence of legislative regulation to regulate gene therapy treatment and activities [61]. The only guideline is the “Medical Genetic and Genetics Services 2006” by Malaysia Medical Council. The Guideline however 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. This guideline merely provides a very general guideline on medical genetics and services. On top of that, by virtue of Clause 19 of the said guideline which addresses on the gene therapy and cloning, appears to merely reaffirm that gene therapy is likely to present with ethical dilemmas (Malaysian Medical Council, 2006).

With the many ethical issues surrounding Gene Therapy and the dynamic progress that it shows, the existence of a comprehensive legal and regulatory framework emphasizing on the ethics is vital. In the

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absence of a legal mechanism, such activities may take place irresponsibly, merely for enhancement rather than medical purposes. Most importantly, without a statutory regulation, the safety and life of patients and research subjects may also be at risk too. On top of that, by having a statutory regulation over self-regulation public confidence and trust could possibly be retained if greatest attention is given in protecting the rights of patients participating in the therapies.

However, considering the different approach among law of nation, this study further propose that those principles outlined by the international instrument and declaration could be integrated and be adopted as a basic standard to help countries to develop proper legal and regulatory framework on gene therapy clinical trial without repugnant with the principles of international human rights law.

CONFLICT OF INTEREST

There is no conflict of interest

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None

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