

**ANALYTICAL STUDY ON ARTICULAR CARTILAGE
TISSUE ENGINEERING RESEARCH: ITS ETHICO-
LEGAL ASPECTS FROM ISLAMIC PERSPECTIVE**

BY

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degree of Doctor of Philosophy in Health Sciences**

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ABSTRACT

Degenerative joint disease has no known cure. Although this medical condition affects mostly the ageing population, joint injuries at a young age may accelerate the degeneration process. The existing pharmacological and surgical treatments alleviate symptomatic pain and help patients to remain active. Unfortunately, there is no single treatment that is able to address the root cause of the disease thoroughly. As an alternative, tissue engineering and regenerative medicine (TERM) method offer numerous options to treat joint diseases. There are growing demands for tissue-engineered medical products (TEMPs) worldwide, including Malaysia. However, based on a scoping review, scientific development and clinical translation activities for TEMP are not progressing as they should be. These multitude limitations perhaps stemmed from many challenges in TERM practices ranging from scientific and technical issues, economic recession, social perplexities, as well as ethical and legal issues. This study aims to formulate an ethical and legal framework to facilitate both scientific and social progress of articular cartilage tissue engineering (ACTE) research in Malaysian context. A survey on the worldwide trend of ACTE research was conducted using a systematic search and through content analysis in formulating the framework. This ethical and legal framework is addressed from the Islamic perspective. A framework, with the benefits being weighed up against possible risks and harmful effects, should be the basis of the practices of ACTE research. Since both ethics and scientific knowledge play a role to determine the permissibility of ACTE research, this study uses both scientific as well as ethical and legal literature, so the two disciplines are bridged. It is so because the concerns made by the bioethicists in this matter are worthy. While scientific endeavours done by the researchers to improve the scientific knowledge in ACTE is also worthy, these two concerns are thus complementary, not contradictory to each other. Although the monitoring by responsible bodies such as governments, legislators, and scientific organisations is essential, it equally is the responsibility of a competent TERM professional to be morally aware when confronted with issues related to ACTE research. More intellectual and engaging deliberation on ACTE research should enter the domain of ongoing moral, ethical and legal education. The end goal of this effort is towards establishing a holistic healthcare management model for patients in the future.

خلاصة البحث

لا يوجد علاج معروف لمرض المفصل الغضري في حتى الآن. فعلى رغم من أن هذه الحالة المرضية تأتي غالباً في المرحلة الشيخوخة، فإن من المعلوم أيضاً أن إصابات المفاصل في سن مبكر قد الإصابة بهذا المرض. إن العلاجات الدوائية الحالية تخفف من ألم الأعراض وتساعد المرضى على البقاء نشيطين. ولكن للأسف لا يوجد علاج واحد قادر على التصدي لأسباب المرض بصورة جذرية. على كل حال، فإن هندسة الأنسجة والطب التجديدي (TERM) تقدم العديد من البدائل لعلاج أمراض المفاصل. هنالك طلب متزايد على المنتجات الطبية لهندسة الأنسجة (TEMPS) بما في ذلك ماليزيا. ومع ذلك فإن المراجعة العامة تبين أنه لا توجد تقدم ملموس في النشاط العلمي لتطوير المنتجات الطبية لهندسة الأنسجة كما ينبغي. ربما هذه القيود ناشئة من العديد من التحديات التي تواجه أنشطة الهندسة الأنسجة، وهي تحديات تتراوح بين القضايا العلمية والتقنية، والركود الاقتصادي، والاضطرابات الاجتماعية، وكذلك القضايا الأخلاقية والقانونية. تهدف هذه الدراسة إلى تحديد وصياغة إطار أخلاقي وقانوني لتسهيل التقدم العلمي والاجتماعي لتجربة هندسة الأنسجة الغضروفية المفصلية (ACTE) في النطاق الماليزي. تم إجراء المسح حول الاتجاه العالمي لتجربة (ACTE) باستخدام البحث المنهجي في تحليل البحوث في هذا المجال يهتم هذا البحث بالجانب الأخلاقي والقانوني لتجربة هندسة الأنسجة الغضروفية المفصلية من منظور إسلامي. فإن الباحث على قناعة بأن هذا الموضوع، مع الفوائد التي فيها ضدالمخاطر المحتملة والآثار الجانبية، يجب يكون هنالك أساس أخلاقي وقانوني لتجربة هندسة الأنسجة الغضروفية المفصلية، لأن كلا من الأخلاق والمعرفة يلعب دوراً محورياً في تحديد مدى جواز التجربة. تعتمد هذا الدراسة على المراجع العلمية وكذلك المراجع القانونية والأخلاقية، وبالتالي يتم سد الثغرة في هذا الموضوع ويتم الإجابة على الأسئلة الأخلاقيات والقانونية التي أثارها تجارب الهندسة الحيوية. وجدير بالاهتمام أيضاً الجهود العلمية التي قام بها الباحثون لتحسين المعرفة العلمية للهندسة الحيوية. فإن الجهود العلمية ومعرفة الجوانب الألاقية والقانونية يكملان بعضهما البعض، وليس متناقضين. وعلى الرغم من أن المراقبة من قبل الهيئات المسؤولة، مثل الحكومات والمشرعين والمنظمات العلمية، أمر ضروري، إلا أن مسؤولية المختصين في هندسة الأنسجة والطب المتجدد (TERM) المداولات الفكرية المثارة حول أبحاث وتجارب هندسة الأنسجة الغضروفية المفصلية في مجال التعليم الأخلاقي والقانوني بصورة مستمرة. فالهدف النهائي لهذا الجهد هو إنشاء نموذج شامل لإدارة الرعاية الصحية للمرضى المفصل الغضروف في المستقبل.

APPROVAL PAGE

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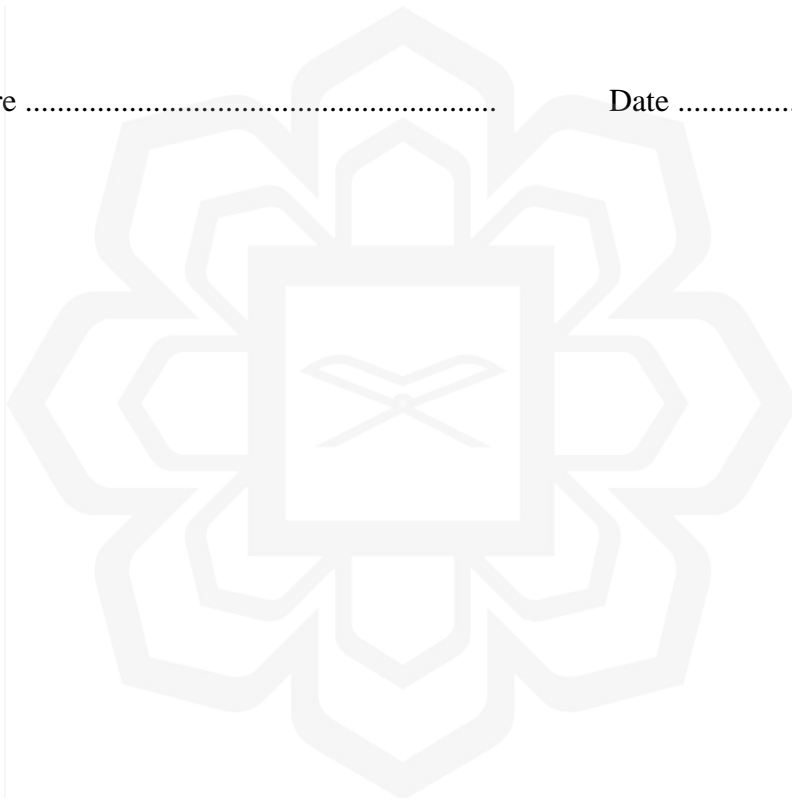
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DECLARATION

I hereby declare that this dissertation is the result of my own investigations, except where otherwise stated. I also declare that it has not been previously or concurrently submitted as a whole for any other degrees at IIUM or other institutions.

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All glory and infinite gratitude are due to Allah alone, the Almighty. Blessing of Allah upon Prophet Muhammad ﷺ and his family whom we seek intercession on the Day of Judgement.

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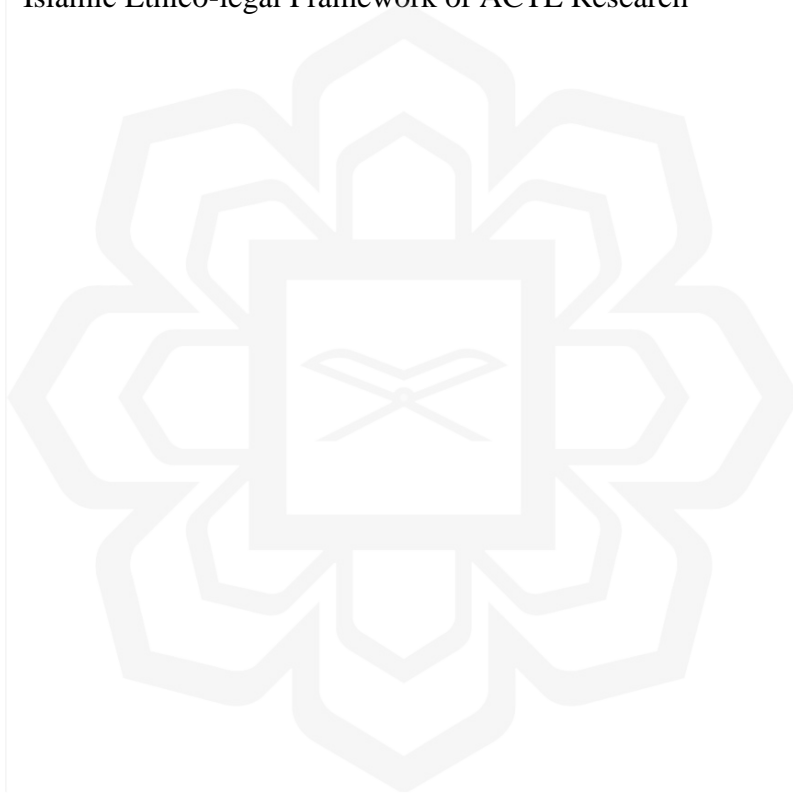
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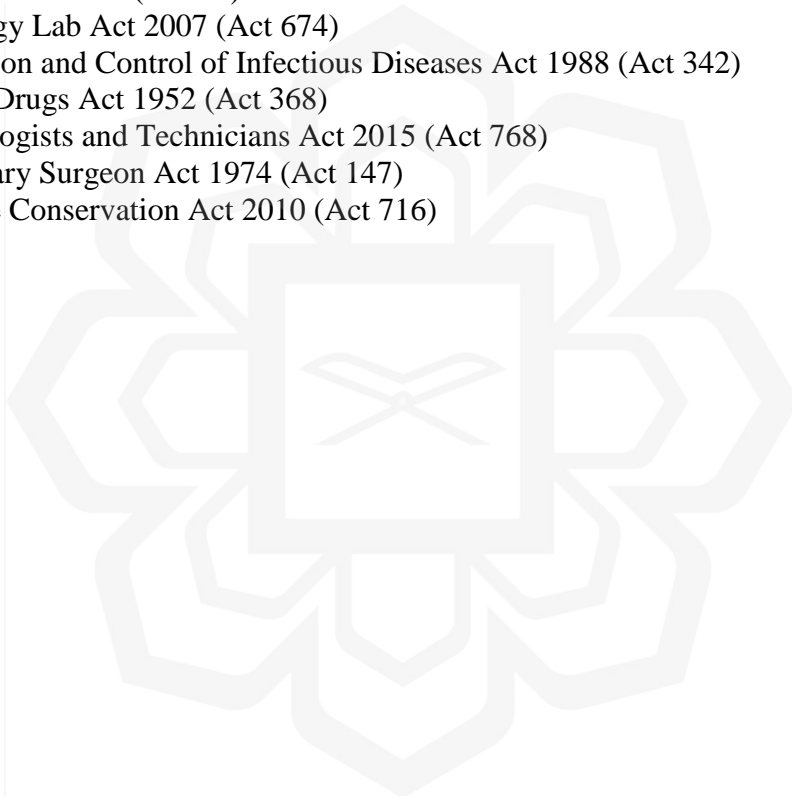
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Animal Welfare Act 2015 (Act 772)
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Biosafety Act 2007 (Act 678)
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Medical Act 1971 (Act 50)
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Prevention and Control of Infectious Diseases Act 1988 (Act 342)
Sale of Drugs Act 1952 (Act 368)
Technologists and Technicians Act 2015 (Act 768)
Veterinary Surgeon Act 1974 (Act 147)
Wildlife Conservation Act 2010 (Act 716)



LIST OF ABBREVIATIONS

3D	3-dimensional
ACTE	Articular Cartilage Tissue Engineering
ASEAN	Association of Southeast Asian Nations
BMP	Bone Morphogenetic Protein
CAGR	Compound Annual Growth Rate
cGMP	Current Good Manufacturing Practice
cGTP	Current Good Tissue Practice
CGTPs	Guidance Document and Guidelines for Registration of Cell and Gene Therapy Products
CSV	Comma Separated Value
DNA	Deoxyribonucleic Acid
DRGD	Drug Registration Guidance Document
ECM	Extracellular Matrix
ESCs	Embryonic Stem Cells
FGF	Fibroblast Growth Factor
GAG	Glycosaminoglycan
GDP	Gross Domestic Product
GHMCW	Handling and Management of Clinical Waste in Malaysia
GIEHTBP	Guidelines on Importation and Exportation of Human Tissues and/or any Body Part, August 2006
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practices
GTP	Good Tissue Practices Guidelines, second edition, December 2015
IGF	Insulin-Like Growth Factor
IIUM	International Islamic University Malaysia
IRB/IEC	Institutional Review Board or Independent Ethics Committee
ISO	International Organization for Standardization
JFJohor	Jawatankuasa Fatwa Negeri Johor
JFKedah	Jawatankuasa Fatwa Negeri Kedah
JFKelantan	Jemaah Ulama` Majlis Agama Islam Dan Adat Istiadat Melayu Kelantan
JFMelaka	Jawatankuasa Fatwa Negeri Melaka
JMMKI	Jawatankuasa Muzakarah Majlis Kebangsaan Bagi Hal Ehwal Ugama Islam Malaysia
JFN9	Jawatankuasa Fatwa Negeri Sembilan
JFPahang	Jawatankuasa Perundangan Hukum Syarak Negeri Pahang
JFPerak	Jawatankuasa Fatwa Negeri Perak
JFPerlis	Jawatankuasa Fatwa Negeri Perlis
JFPP	Jawatankuasa Fatwa Negeri Pulau Pinang
JFSabah	Majlis Fatwa Negeri Sabah
JFSarawak	Lembaga Fatwa Negeri Sarawak
JFSelangor	Jawatankuasa Fatwa Negeri Selangor
JFTerengganu	Jawatankuasa Fatwa Negeri Terengganu
JFWP	Jawatankuasa Perundangan Hukum Syarak Wilayah Persekutuan
MeSH	Medical Subject Headings

MESTECC	Ministry of Energy, Science, Technology, Environment and Climate Change
MGSCRT	Malaysian Guidelines for Stem Cell Research and Therapy, 2009
MOH	Ministry of Health
MOSTI	Ministry of Science, Technology and Innovation
n.d.	no date
NBP	National Biotechnology Policy
NCE	New Chemical Entity
NGHSCT	National Guidelines for Haemopoietic Stem Cell Therapy, July 2009
NPRA	National Pharmaceutical Regulatory Agency
NSAIDs	Non-steroidal Anti-inflammatory Drugs
NSCBBT	National Standards for Cord Blood Banking Transplantation, January 2008
NSSCT	National Standards for Stem Cell Transplantation: Collection, Processing, Storage and Infusion of Haemopoietic Stem Cells and Therapeutic Cells, second edition, September 2018
OA	Osteoarthritis
OECD	Organisation for Economic Cooperation and Development
PBKD	Pihak Berkuasa Kawalan Dadah
PEG	Poly(ethylene glycol)
PGA	Poly(glycolic acid)
pH	Potential Hydrogen
PLA	Poly(lactic acid)
PLGA	Poly(lactic-co-glycolic acid)
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QOL	Quality of Life
RM	Ringgit Malaysia
Scopus	Elsevier's Scopus
STZ	Superficial (Tangential) Zone
TED	Technology, Entertainment and Design
TEMPs	Tissue Engineering Medical Products
TERM	Tissue Engineering and Regenerative Medicine
TGF- β	Transforming Growth Factor-beta
TXT	Text File
USD	United States Dollar
WFIRM	Wake Forest Institute for Regenerative Medicine
WHO	World Health Organization
WOS	Clarivate Analytics' Web of Science™ Core Collection

TRANSLITERATION

ء	<i>hamzah</i>	`	ظ	<i>zā`</i>	z
ا	<i>alif</i>	ā	ع	<i>‘ayn</i>	‘
ب	<i>bā`</i>	b	غ	<i>ghayn</i>	gh
ت	<i>tā`</i>	t	ف	<i>fā`</i>	f
ث	<i>thā`</i>	th	ق	<i>qāf</i>	q
ج	<i>jīm</i>	j	ك	<i>kāf</i>	k
ح	<i>ḥā`</i>	ḥ	ل	<i>lām</i>	l
خ	<i>khā`</i>	kh	م	<i>mīm</i>	m
د	<i>dāl</i>	d	ن	<i>nūn</i>	n
ذ	<i>dhāl</i>	dh	ه	<i>hā`</i>	h
ر	<i>rā`</i>	r	و	<i>wāw</i>	w;ū
ز	<i>zāy</i>	z	ي	<i>yā`</i>	y;ī
س	<i>sīn</i>	s	أ	<i>alif maddah</i>	ā
ش	<i>shīn</i>	sh	ة	<i>tā` marbūtah</i>	h;t
ص	<i>ṣād</i>	ṣ	ال	<i>alif lām</i>	al-
ض	<i>ḍād</i>	ḍ	ى	<i>alif maqṣūrah</i>	ā
ط	<i>ṭā`</i>	ṭ			
ـَ	<i>fathah</i>	a	ـِ	<i>fathah yā`</i>	ay
ـِ	<i>kasrah</i>	i	ـِو	<i>fathah wāw</i>	aw
ـُ	<i>ḍammah</i>	u	ـَـ	<i>fathatān</i>	an
ـَا	<i>fathah alif</i>	ā	ـِـ	<i>kasratān</i>	in
ـِـ	<i>kasrah yā`</i>	ī	ـِـ	<i>ḍammatān</i>	un
ـِو	<i>ḍammah wāw</i>	ū			

Note: Certain terminologies which derived from Arabic words but has been applied as the Malay terms are spelt with Malay words such as Arpah Abas, Abu Bakar Abu Zaid, and etc.

CHAPTER ONE

INTRODUCTION AND LITERATURE REVIEW

1.1 BACKGROUND OF THE STUDY

Articular cartilage plays a vital role as a load-bearer in human synovial joints. It has minimal capacity to repair and restore itself because of its aneural, avascular and alymphatic nature, which make it distinctive from other tissues. Damage inflicted on articular cartilage, especially in the knee joint, is irreversible. If left untreated, it might eventually lead to osteoarthritis, a bone-joint inflammation. This disorder has affected, literally, millions of people around the world. Not only does it cause morbidity to the patients, but it also contributes to the growing financial burden of health care (Centers for Disease Control and Prevention, n.d.). The use of the medical device for walking support, conventional treatments such as medications or drug therapy and surgical interventions including drilling, microfracture, and mosaicplasty usually act as a temporary measure only (Tur, 2009). If those treatments are no longer helpful, patients may have to consider and undergo total knee replacement surgery.

Besides degenerative joint disease, other tissue losses and organ failures have also become one of the devastating results in humans. Some people are of the view that this is part of ageing. There are more than 17,000 Malaysians on the waiting list for organ transplant based on the updates provided by the Transplant Unit, Medical Development Division and National Transplant Resource Centre, Ministry of Health (MOH) Malaysia. While from an economic point of view, these tissue losses and organ failures have become a costly predicament in the health care system worldwide (Trogon et al., 2015).

Advances in organ transplantation, reconstructive surgery, and replacement with prosthetic or artificial organ have indeed improved the outcome of patients. However, these approaches have limitations and complications. These include several possible risks, namely rejection of the tissue or organ, the shortage in the supply of tissue or organ for transplantation, the morbidity of the donor site and the risk of infection. Hence, in dealing with these practical challenges, the field of tissue engineering and regenerative medicine has been established. It is a new multidisciplinary field that applies the principles of engineering and life sciences towards the development of a suitable biological substitute to restore, maintain and improve tissue or the whole organ function (Langer & Vacanti, 1993).

Scientific advances in biomaterial scaffolds, stem cells, growth factors as well as biomimetic environment have created opportunities to reconstruct a wide range of human tissues in vitro. The 3-dimensional (3D) tissue is formed and engineered using a combination of quality cell source, scaffolds and biologically active signalling molecules (Langer & Vacanti, 1993). These three main components are also known as the “tissue engineering triad”. This technology holds great promises and potential for humankind that involves Muslims as well. However, a random literature search shows that there has been a lack of Islamic ethico-legal establishment not only in this Tissue Engineering and Regenerative Medicine (TERM) technology but also in many areas of biomedicine. Thus, the need to fill this gap from the worldview of Islam is evident.

Although certain aspects of TERM give rise to highly controversial issues such as the use of embryonic stem cell, animal models and gene therapies, it also includes unsuspecting, low-risk research like basic cell culture experiment (Gelhaus, 2009). Besides, there are ongoing debates on certain aspects in TERM that indicate that man may be “playing God” (Munirah et al., 2014). Muslims accept the Islamic faith not as a

religion only, but also as the way of life. The activity of seeking the best treatment through research is as an essential part of human responsibilities as the vicegerent (*khalīfah*) in this world. To provide necessary Islamic input for new technology, the Muslims scholars (*ulamā`*) must seek first to understand the technology as well as the processes behind it. In the case of articular cartilage tissue engineering (ACTE) research, the scientists must disclose the truth and be able to make a clear explanation of the ACTE development and its advancement.

In the realm of modern science, pre-clinical studies using animals as research subjects contributed to a remarkable discovery and research findings that help the scientists to understand the way intervention works in ACTE (Munirah, 2006; Munirah, Ruszymah, et al., 2008a; Sha'ban, Kim, Idrus, & Khang, 2008). However, there are many criticisms on animal research since, these experiments in nature, often inflicted the animals with injuries (Chu, Szczodry, & Bruno, 2010). On the one hand, it is unethical to use or exploit animals in any way, but on the other hand, there may be limited answers to find new therapies for human beings without the pre-clinical experiments. Even with the advantage of experiments outweighs animal usage, researchers should reduce the number of animals used in their studies. Thus, with the advancement in ACTE, it is hoped that massive dependence on animal testing can be reduced. It is because other than the clinical application, ACTE or TERM as a whole can be developed and used as in vitro living tissue model too.

With the development of modern biomedical technology, Muslim jurists and ethicists raised some ethical concerns about the morality and the permissibility (*ibāḥah*) of applications of technology to the human body (Rozlin, Norhayati Aida, Abdurezak, Norhafizah, & Munirah, 2015). The expansion of scientific knowledge (e.g. in medical and health sciences) shall be geared to improve the health conditions of the society.

Although Muslim jurists acknowledge the importance of the above and agreed in principle on the practices, they raised some ethical and *fiqh* concerns on its methods and implications. It is because preservation or safety of human life is one of the fundamental objectives (or, *maqāṣid*) of the Islamic *sharīʿah*. Biomedical researches are primarily designed to improve human health and save lives. Therefore, this kind of actions is morally justified. The justification is so because since the safety of human life is part of *maqāṣid al-sharīʿah*, then all legitimate means of achieving such objective is also justified (*mā lā yatimmu al-wājib illā bihi fa-huwa wājib*). The means includes the researches in health sciences. Nevertheless, these researches should not risk human life or cause unnecessary harm, neither such researches should risk human dignity (*karāmah al-insāniyyah*).

Ethical and legal (henceforth referred to as “ethico-legal”) discussion, hopefully, can bridge the gap between bench and bed-side (Rozlin, Muhammad Aa’zamuddin, Norhamiza, Noorhidayah, & Munirah, 2015). These ethico-legal aspects shall not be viewed as a hindrance for TERM or other research to expand. It shall be used as a tool to promote the full potential of research as long as it is within the accepted boundaries (Amin et al., 2011; Rozlin, Azlina, & Munirah, 2013). The challenge is how to upgrade biomedical science research and its related technology, in this case, the ACTE, without breaking the ethico-legal norms. Given all the above, this study aims to address the ethico-legal principles and aspects in ACTE from the Islamic approach in the Malaysian context. Other than the *Qur’ān* and the *Sunnah* of the Prophet *Muḥammad* ﷺ, this research presents the perspective of the local Muslim jurists (*fuqāhā`*) on issues related to ACTE research.

1.2 STATEMENT OF THE PROBLEM

The research of ACTE has triggered a multitude of not only legal issues but also ethical concerns as well. The availability of various ACTE research procedures in Malaysia has arisen several issues, mainly the scattered of relevant legal documents has allowed biomedical laboratories to operate without specific non-clinical guidelines. This lacuna has resulted in the biomedical laboratories which have conducted ACTE research modelled after foreign practices that is legally and ethically questionable. The issues may include the materials and methods of utilising tissue engineering triad to regenerate articular cartilage for research purpose. The disposal of laboratory waste has also raised concerns about the ethico-legal status of the research.

There is, however, another approach, which identifies the religious and cultural differences that are apparent between Malaysia and the West. These two aspects should be taken into consideration when legislating ACTE research in this country. Due to the richness in religious and cultural diversity, Malaysian have placed very high consideration on the society, the concept of medical safety and protecting faith, life, intellect, wealth, and lineage. Thus, the question remains, which model should the government adopt when legislating ACTE research in the country? The difficulty is evident from the Government's attempt to regulate the practice related to ACTE since 2014 by producing the guidance document for product registration of cell and gene therapy in Malaysia.

This study identifies and surveys international ACTE research and development, which may have some similarities in practice in the Malaysian setting. Besides, the study analyses Islamic ethico-legal principles and examines various local legislations, regulations and guidelines in search of a model for formulating an ethico-legal framework for ACTE research and development in this country.

1.3 RESEARCH OBJECTIVES

The study aims to identify and address ACTE research and its ethico-legal concerns from an Islamic perspective in the Malaysian context. The study attempted to achieve the following research objectives:

1. To analyse the scopes and approaches of ACTE research.
2. To explain the Malaysian legislation on ACTE research.
3. To analyse relevant local Muslim jurists' opinions on the permissibility of selected issues related to ACTE research.
4. To formulate and suggest the Islamic ethico-legal framework in conducting ACTE research.

1.4 RESEARCH QUESTIONS

1. What are the scopes and approaches to ACTE research?
2. What are the relevant Malaysian legislations on ACTE research?
3. What are the Muslim jurists' opinions and their stance on the permissibility of selected issues related to ACTE research?
4. What is the Islamic ethico-legal framework in conducting ACTE research?

1.5 LITERATURE REVIEW

1.5.1 Introduction

The World Health Organization (WHO) (n.d.) indicated that “transplantation of human cells, tissues or organs saves many lives and restores essential functions where no alternatives of comparable effectiveness exist”. Adding to this, at a Technology, Entertainment and Design (TED) conference in 2011, one of the renowned scientists of the tissue engineering and regenerative medicine (henceforth “TERM”) field, Anthony