

## REVIEW ARTICLE

# An Islamic Ethico-legal Framework for Articular Cartilage Tissue Engineering Research

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## ABSTRACT

The available studies showed a connection between mental health features of anxiety, depression, and stress with osteoarthritic patients. The joint disease can be treated with articular cartilage tissue engineering (ACTE), which has undergone various research and development. However, the ethical and legal concerns of such practices, including cell sources, biomaterials, signalling factors, and animal study, have yet to be addressed systematically. The study aims to formulate an Islamic ethical and legal framework to facilitate both the scientific and social progress of ACTE research in the Malaysian context. The present work used content analysis of relevant journal articles obtained through systematic online searches. The study then utilised the existing documents on Malaysian laws, regulations, and guidelines; and *fatwā* related to the ACTE research to build a framework. Based on the documents, the ethical and legal framework was formulated. The framework was proposed to include six steps in handling the ethical and legal issues in ACTE research. There are (1) to select research design and strategy, (2) to identify the potential issues, (3) to review relevant laws, regulations and guidelines, (4) to review the relevant *shari'ah* rulings and opinions, (5) to consider possible alternatives and its consequences, and (6) to decide and implement the best course of action. These six steps are aligned based on the concept of *Maqāsid al-Shari'ah* (the objectives of Islamic law) and *al-Qawā'id al-Fiqhiyyah* (Islamic Legal Maxim). The framework can serve as a guide to conduct safe and sound ACTE research based on the Islamic perspective.

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## INTRODUCTION

Injury to the articular cartilage by acute physical trauma can cause disabling symptoms such as effusion, pain and locking of the affected joint (1). Articular cartilage damage mostly occurs at knee joints and may happen to other synovial joints such as hip, shoulder, ankle, wrist and elbow. According to Christian (2017) (2), patients with damage to the articular cartilage will experience inflammation, stiffness, and range limitation at the site of injury. The condition is also known as osteoarthritis. The pain experienced by osteoarthritic patients has been linked to an increased risk of mental health (3–5), including depression and anxiety (6–9).

Moreover, the pain may induce other mental disorders such as stress perception and suicidal ideation among the affected patients (10). The standard in treating articular cartilage disease is to regenerate the joint surface with cartilage matter produced by chondrocytes. As articular cartilage has a limited capacity to regenerate itself, there is still no definitive solution to mimic the native cartilage based on its structure and functions (11).

The treatment can be achieved through the articular cartilage tissue engineering (ACTE) technique by producing viable articular cartilage constructs for autologous implantation. The tissue constructs must be reliable regarding structure and function. To realise the autologous approach, the cells that are taken from the patients will be cultured and expanded in vitro. The cells may be derived from varieties of cell sources but trained or maintained to be chondrocytes. When the cells numbers are enough, the cells will be harvested

and incorporated into 3D scaffold materials for tissue construct formation. The 'cell-scaffold' constructs will be implanted back into the same patient in the affected region of the articular cartilage. However, the ethical and legal concerns of such practices, including cell sources, biomaterials, signalling factors, and animal study, have yet to be addressed systematically (12–15).

The availability of various ACTE research procedures has raised several issues, mainly the scattered of relevant legal documents that have allowed biomedical laboratories to operate without specific non-clinical guidelines in Muslim countries. This lacuna has resulted in the biomedical laboratories which have conducted ACTE research modelled after foreign practices that are legally and ethically questionable (16). The issues may include the materials and methods of utilising tissue engineering triad to regenerate articular cartilage for research purposes. Thus, the question remains, which model should the authorities adopt when legislating ACTE research in the country?

This study summarises the flow and steps on how the articular cartilage tissue engineering (ACTE) researchers should handle bioethical issues considering ethico-legal aspects with an Islamic approach. This study denotes a doctoral thesis's main product and conclusion showing numerous findings. The ACTE technology holds great promises and potential for humankind, including Muslims. However, literature searches showed that there had 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, especially the objectives of Islamic Law (*Maqāṣid al-Sharī'ah*), is evident.

Muslim academicians suggest that the authority should draft an Islamic ethical framework to govern the development of ACTE research, which may serve tissue engineering as a whole (12–15). Thus, based on the discussion in the thesis, an Islamic ethico-legal framework was formulated as a comprehensive approach in educating the stakeholders of ACTE research. The practicality of Islamic Law in accepting the application of ACTE can be seen from this proposed framework. The audience may appreciate the integration of Islamic values into ACTE research. A relevant conclusion based on what is discussed was inferred. Hopefully, this study can be a reference for Malaysian authorities and biomedical scientists to work together to derive a new ruling on TERM issues by thoroughly analysing relevant documents. Due to the word limit set for this article, only the main points were elaborated and discussed.

## MATERIALS AND METHODS

This study employed a systematic search and content analysis to examine the scopes and approaches of ACTE

research. In brief, the study was done by searching and extracting data in relevant articles published in journals indexed in two international online databases, namely Scopus and Web of Science. The terms used in the search query are 'articular cartilage' and 'tissue engineering' to obtain the relevant articles. The systematic search is adapted from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Meanwhile, the refined version of content analysis is adapted from a study done by Lunny, Shearer, Cruikshank, Thomas, and Smith (2011) (17). The data extracted from the articles were coded based on the tissue engineering triad category, including cell sources, biomaterial scaffold and signalling factors (11,16,18,19).

The analysis on the local legislation (20) and Muslim jurists' opinions (*fatwā*) (21,22) related to ACTE research was done through library research method by utilising the secondary analysis of historical documents as well as available contemporary materials that include a perusal of journals, newspaper, magazines and books. Subsequently, the flow and steps on how the ACTE researchers should handle bioethical issues, considering ethico-legal aspects with the Islamic approach, were organised and rearranged in an ethico-legal framework, which modelled after a study done by Ismail (2018) (23).

## RESULT

This study screened 5,464 search results related to ACTE research, with 2,838 from Scopus and 2,626 from Web of Science. After removing the documents with exclusion criteria, 1,644 full-text articles were analysed. Meanwhile, more than 30 related documents, including acts, regulations, and guidelines provided by the local government agencies, can be referred to oversee and guide tissue engineering practices. After screening the existing Malaysian *fatwās*, similar to local laws, no specific ruling has been given on the permissibility of ACTE research. However, there are more than 130 *fatwās* given by local Mufti (*fatwā* committee) on specific issues which can be linked to practices of tissue engineering experimentation.

Based on the findings, the framework was proposed to include six steps in handling the ethical and legal issues in ACTE research. These six steps are aligned based on the concept of *Maqāṣid al-Sharī'ah* (the objectives of Islamic law) and al-Qawā'id al-Fiqhiyyah (Islamic Legal Maxim). The steps are (1) to select research design and strategy, (2) to identify the potential issues, (3) to review relevant laws, regulations and guidelines, (4) to review the relevant *sharī'ah* rulings and opinions, (5) to consider possible alternatives and its consequences, and (6) to decide and implement the best course of action.

## DISCUSSION: DECISION-MAKING PROCESS IN CONDUCTING ACTE RESEARCH

The current and the upcoming acts, regulations, guidelines, and *fatwā* can be continuously rearranged and reorganised according to the ACTE research mapping, and the updated framework can be comprehensive and able to help the decision-making in conducting the research. Nevertheless, this ethico-legal framework with the relevant Islamic input can be used as the primary reference for responsible bodies such as governments, legislators, and scientific organisations to draft relevant guidelines and legislation for ACTE research.

### Step 1: Select Research Design and Strategy

Referring to this “Islamic Ethico-legal Framework of Handling Bioethical Issues in ACTE Research” is beneficial if only ACTE researchers understand and recognise that the situation they are facing is an ethico-legal problem.

When ACTE researchers talk about ethical issues, the circumstance usually denotes a problem in the research laboratory. The matter is that, occasionally, the researchers are unaware that the scenario they face is related to ethico-legal situations. In this condition, the researchers either feel a dilemma in making decisions or are uncertain about choosing the best option. Moreover, the researcher may not know what is right and wrong for each decision made.

Perhaps, the situation is due to the poor awareness about ethico-legal requirements whereby some of the researchers would not recognise the issues in the laboratory. The condition may affect the researchers’ ability to solve the issue as the role of the decision-making process has ceased to exist. Therefore, the research design and strategy selection have been placed as the first step in this framework.

### Step 2: Identify the Possible Issues

Once the proper research design is selected, the researchers may proceed to the next step. The researchers are required to identify the potential issues involved. Identifying the possible issues requires some critical thinking process steps to analyse whether the matter might be affected by the issue or perhaps the matter was causing the issue. Islam teaches its adherents to seek treatment, and the action includes the research involving a systematic investigation into disease and study of materials and sources to establish facts and reach new conclusions. The instructions given by Islam imply the researcher needs to consider the objectives of Islamic law or *maqāṣid al-sharī‘ah* of how the disease may affect the five essentials of human well-being, namely faith, life, intellect, lineage, and wealth. As Muslim researchers, these five basic essentials should be present in their minds when the process of decision-making is taking place. It is presented that every legal

ruling in Islam has a function to benefit human beings or protect against harm.

The degenerative joint disease, i.e. osteoarthritis, may cause harm in terms of disability, mortality, mental and economic instability, and affect sexual activity (12). ACTE, being one of the solutions in treating osteoarthritis, complements the currently available treatments in managing the disease. It offers benefits if the technology can be conducted in a systematic order. However, there are still scientific and ethical challenges that surround the application of ACTE. The application of *maqāṣid al-sharī‘ah* in ACTE can serve as a practical framework to safeguard the five essentials of osteoarthritic patients. Thus, the endeavour to seek treatment of osteoarthritis is considered as *ḍarūriyyah* as the disease directly affects the patients’ well-being. These concerns are of few inquiries that should be present in the mind of ACTE researchers. However, “the ends do not justify the means” whereby seeking the best treatment for osteoarthritis does not make any prohibited things become lawful in the research, just like that. Materials and methods identified in the previous step may involve things that are not in line with the ethico-legal aspect either from the conventional or Islamic approach. Since ACTE researchers’ conducts are likely to involve the concept of *maqāṣid al-sharī‘ah*, the condition fulfils the basic requirement to proceed to the next step.

### Step 3: Review Relevant Laws, Regulations, and Guidelines

By successfully identifying the potential issues involved, the process of decision-making needs to move on to this step. ACTE researchers come from different backgrounds and work in various entities such as public or private organisations, institutions, or hospitals, whereby the legislation, regulations, and guidelines could not be ignored. Therefore, in Step 3, ACTE researchers are required to review these relevant legal documents to make the decision in the non-clinical setting.

These legal documents were prepared by local experts from different agencies and entities. Malaysia itself adopts international legal systems; thus, the legal documents may be influenced by the conventional ethico-legal principles. The majority of the guidelines provided by the healthcare agencies related to ACTE research are adopted and adapted from international sources. However, a guidance document, for example, includes the decision of local *fatwā* in its content, such as on page 31 of Malaysian Guidelines for Stem Cell Research and Therapy (24). Thus, in this Islamic ethico-legal framework, the legal documents are appreciated as long as the contents are in line with Islamic teaching. However, the concern is that the approach or application of these laws, regulations, and guidelines in the Islamic ethico-legal system might contradict each other.

As the process of developing ACTE through non-

clinical studies is legally bound to Malaysian law, then ACTE researchers are required to review relevant laws, regulations, and guidelines throughout their study. It is presumed that not all ACTE researchers have the competent legal knowledge and how to integrate them into ACTE practices. Thus, in this step of decision-making in this framework, it is suggested that researchers consult relevant agencies to get suggestions or opinions on the legal status of their experiments. Likewise, seeking opinions from other authorities such as senior researchers and ethics committees are highly suggested if their opinion would provide a solution.

**Step 4: Review Relevant *Shari'ah* Rulings and Opinions**  
After relevant laws, regulations, and guidelines have been reviewed, the next step requires ACTE researchers to review relevant local *shari'ah* rulings and opinions, or *fatwā*. The *fatwā* may not be related explicitly to ACTE research; however, the researchers can relate the *fatwā* with the particular conduct in their study.

The researchers may adopt and adapt the opinions given by the *Mufti* departments. It can be seen that the concept of *maqāsid al-shari'ah* and *al-qawā'id al-fiqhiyyah* are the core components used by Muslim scholars to come out with the *fatwā* on the issues. The endeavour does not end here; ACTE researchers are not immune from having a misconception on specific issues, which would lead to unfair judgements on the experiments. Thus, ACTE researchers are advised to consult with the *Mufti* departments if they want further clarification. The researchers may provide details of their materials and methodology, which they found as a *shari'ah*-related problem to be used in their experiments and discuss the problem with the *Mufti* department of a particular state.

**Step 5: Consider Possible Alternatives Course of Actions and Their Consequences**

After reviewing Steps 1 to 4, at least ACTE researchers would have a few strategies or possible courses of action in dealing with the issues. Reviewing relevant legal documents and *atwāin* Step 3 and Step 4 are regarded as the best medium for ACTE researchers to collect as much as possible the ideas towards decision making. To reach this step, ACTE researchers have to list down all the possible alternative course of action regardless of whether the results of each strategy is favourable or not.

For example, when using trypsin, an enzyme to dissociate the adherent cells from culture plate, which may be produced using *haram* sources, ACTE researchers have to list down the possible course of action and its consequences that they might face. First, the researchers have an option to use the trypsin produced from porcine – *najāsah mughallaḥah* – to be used in the experiment without any excuse. Second, they might opt for trypsin produced from bovine. The enzyme might be produced using *halāl-to-be-eaten* animals, but not slaughtered according to *shari'ah* Third, ACTE researchers might use

plant-derived bovine trypsin. The trypsin may be free of the animal pathogen; however, is the performance the same as the animal-derived trypsin as has been claimed by the manufacturer? Fourth, the researchers change their research without using any cells, thus not utilising any enzyme. However, the efficacy of their research may be questioned to exclude cell study. Fifth, they can abandon the whole project and focus on other fields that do not involve enzymes and cells, leading to other researchers – unknown of their moral principles – to conduct ACTE research. The various possible course of action and consequences could be listed for this single ethical issue.

In this step, ACTE researchers have to decide on what appears to be the best course of option. It is suggested to use the principle of *al-qawā'id al-fiqhiyyah*, as described below, to analyse and decide which one is the best action. There is no doubt that the principle is in line with the Islamic teachings; thus, ACTE researchers should consider the principle as a reasoning tool in making judgments for solving conflict and ethical issues. As the *Qur'an* and the *Sunnah* do not explicitly mention the ways of the solution; thus, this reasoning tool will be beneficial to find the answer. ACTE researchers have to think critically about whether each option could conform to the tools. If yes, perhaps the option could be considered as the right solution. The reasoning tools are:

- 1- *al-umūr* bi maqāsidihā (acts are judged by the intention behind them) and its subsidiaries: conduct that is done with good intentions are morally worthy even though the outcome is not favourable.
- 2- *al-yaqīn* la yazūl bi al-shakk (certainty is not overruled by doubt) and its subsidiaries: doubt or the suspicious of mind does not always ensure the top end of conduct.
- 3- *al-mashaqqah tajlib al-taysīr* (hardship begets facility) and its subsidiaries: hardship is a problem that should be overcome because the difficulty will prevent the moral agent from doing things accordingly.
- 4- *al-Ḍarar yuzāl* (harm must be eliminated) and its subsidiaries: harmful things should be eliminated in any practice.
- 5- *al-Ādah* muḥakkamah (customary usage is the basis of judgement) and its subsidiaries: standard practices in handling the problem sometimes are considered reasonable and applicable to conduct.

**Step 6: Decide and Implement the Best Course of Action**  
Step 6 denotes the final step of the framework. In this step, ACTE researchers have to decide and implement the best course of action.

Based on the long list of possible courses of action in Step 5, if any item is not aligned with this rule, then the item can be removed from the list. Thus, the best option would be identified. Here and now, ACTE researchers may implement the best course of action. For example,

on the issue of choosing the enzyme for cell culture trypsinisation, the researchers may want to use the trypsin derived from a plant, based on the tool of ‘harm must be eliminated’. However, the researchers need to make sure that the use of plant-based enzymes will not affect the efficacy of the study in generating articular cartilage, which may be used in a human patient in the future based on the tool of ‘certainty is not overruled by doubt’. Besides, the researchers also need to ensure that the use of plant-based enzymes is in line with the federal legislation, regulations and guidelines based on the tool of ‘customary usage as the basis of judgement’. However, if there is an obstacle to using plant-based enzyme due to its cost or availability, the researchers may need to use animal-derived enzyme temporarily until it is feasible to use the former as in line with the tool of ‘hardship begets facility’. Importantly, their practices must be in accordance with good intention as ‘acts are judged by the intention behind them’.

## ISLAMIC ETHICAL AND LEGAL FRAMEWORK OF ACTE RESEARCH

The ethico-legal framework can also be applied in another scenario. For example, ACTE researchers want to utilise animals for in vivo studies. Firstly, they need to identify the best animal models based on their research

design. The researchers must be aware of the need for ethical approval for animal study as described in Animal Welfare Act 2015. If the researchers plan to use wildlife animals such as macaque, other acts must be consulted, including Wildlife Conservative Act 2010 and Animal Act 1953. Besides, ACTE researchers need to study the specification for animal study, which has been outlined in Guidance Document and Guidelines for Registration of Cell and Gene Therapy Products, authorised by National Pharmaceutical Regulatory Agency, Ministry of Health Malaysia.. At the same time, relevant *fatwā* have to be reviewed before conducting the animal study, such as *fatwā* of utilising dog, issued by Jawatankuasa Fatwa Negeri Terengganu (1995), Jawatankuasa Fatwa Negeri Pulau Pinang (2017), Jawatankuasa Fatwa Negeri Johor (2003, 2008), and Jawatankuasa Fatwa Negeri Selangor (2016), which are based on *Maqāṣid al-Sharīʿah* and *al-Qawāʿid al-Fiqhiyyah*. However, the limitation of the framework is that it is mainly formulated based on the local laws and *fatwā*. Thus, the Muslim researchers in other countries may need to improvise the framework’s application based on their respective local laws and regulation. Nevertheless, the framework will be further improved to include the elements of international laws and *fatwā*. In general, any scenario in ACTE research can still be assessed through the framework summarised or mapped into a systematic Islamic ethico-legal

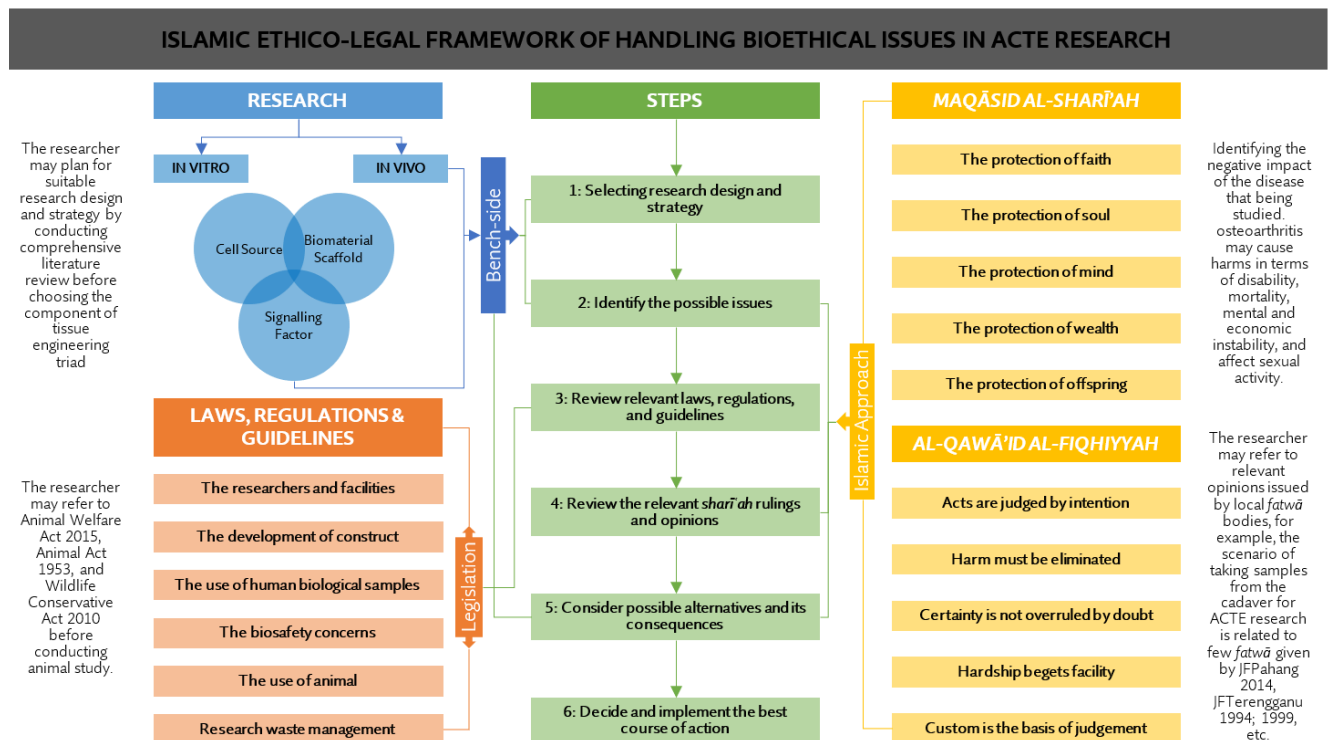


Fig. 1 Islamic Ethico-legal Framework of ACTE Research

framework as visualised in Fig. 1 below.

## CONCLUSION

The study attempts to integrate the Islamic essence into the ethico-legal framework in conducting ACTE research. Integrating bioethics and the Islamic ethico-

legal paradigm in this framework could be a better alternative in dealing with and solving ethical issues as ACTE research involves multidisciplinary fields. The relevant ethico-legal documents are scattered in different places and sources. For Muslim ACTE researchers in Malaysia, this ethico-legal framework could be the right option to guide them in searching for a solution

while referring to the ultimate goal of the *sharī'ah*. Without a doubt, the technology itself has the potential to overcome the issues brought upon by osteoarthritis on five important aspects (faith, life, progeny, intellect and wealth) of human lives, which is given high priority by the *sharī'ah*. However, bearing in mind, medical technology is constantly being applied or brought into the Muslim world without looking thoroughly at the experimental part. The concept and intention of the modality seem good, but to achieve the application part, we need to go through the experimental part, which we often overlook. Even though the technology has been brought into the Muslim countries, it is still not too late to check the bench-side or laboratory aspects of the technology. A simple and general risk assessment is not possible in ACTE as each TERM level's purposes, procedures, and applications are too variable. Thus, there is a need for a comprehensive review to address all the issues, respectively. Therefore, whether to consider the approach is a suitable framework for adoption to Islamic environment, the study ventures into addressing the ethico-legal aspects of the research part of ACTE to understand the practice of in vitro and in vivo of the technology. *Wallāhual'lam*.

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