

Creative regulatory practices to develop stem-cell technology: the way forward for Malaysia

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Malaysia aspires to develop regenerative medicine through stem-cell technology. It needs a regulatory system that could facilitate development and prevent unethical practices. A comparative legal analysis on the regulation of stem-cell technology, with a focus on stem-cell research in Malaysia and selected Commonwealth countries that are experienced in regulating this complex technology, demonstrates that the selected Commonwealth countries have adopted a hybrid of different regulatory mechanisms. This paper argues that Malaysia should consider adopting a similar approach to equip relevant authorities with different regulatory mechanisms that are able to promote innovation in stem-cell research activities and cultivate a successful and profitable regenerative medicine industry in the future. Such a strategic action can produce an optimal regulatory outcome and help Malaysia to realize its aspiration.

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Malaysia has identified stem-cell technology as a vital technology to develop regenerative medicine to address chronic diseases that are prevalent among its population [1]. The country also aspires to be the hub for medical tourism in the region. Many countries are also competing to cultivate a successful and profitable regenerative medicine industry based on stem-cell technology. Both developed countries such as the UK, Germany, Japan, Canada and the USA as well as emerging economies such as Brazil, China and India recognized its economic potential and have heavily invested in this sector to compete in seeking economic advantage [2–6]. For instance, in the UK, the former Minister of Business, Innovation and Skills, David Willetts listed regenerative medicine as one of the ‘eight great technologies’ for having the potential to drive the country’s economic growth and benefit the public if the area is given appropriate state investment and support. The UK government has announced £25 million in funding for the regenerative medicine industry [7]. This is an example of a state’s involvement and commitment, and it can be seen as a strategic action taken by the UK. The UK National Stem Cell Bank and the UK Regenerative Medicine Platform have also been established as initiatives to support stem-cell technology, not only to underpin research work but also to facilitate research to be translated into safe clinical and viable commercial applications. Currently, Malaysia is said to be at the disadvantage given the lack of funding allocated for stem-cell technology as well as its less permissive approach toward stem-cell research involving human embryos. Nonetheless, it is not the focus of this article to discuss the funding issues in Malaysia as it will require a separate study with an in-depth analysis.

As has been widely discussed, this promising technology poses ethical challenges. Malaysia lacks regulation for this promising area, both in the realm of stem-cell research and therapy (SCRT), and this has raised some concerns among key stakeholders in the country as to whether or not its existing regulation is adequate and responsive [8]. This paper recognizes the importance of establishing legislation to address the challenges. However, besides legislation, it is vital for Malaysia to have a regulatory system that is suitable to regulate this rapidly evolving technology. The UK, for instance, is actively taking action to ensure their regulatory system keeps pace with the rapid and complex technological change. It has been consistent in its approach to the emergence of technological innovation. The

UK also determined to maintain its reputation as the global leader in science and research as well as its quality of regulatory practices that support innovation while protecting environment and the public. Therefore, the UK continues to develop a more agile approach to regulation. In 2019, a White Paper was published to set out the plan to ensure UK's continuous regulatory success. In so doing, it has identified key challenges that need to be addressed to enhance its regulatory oversight of technological innovations [9]. The Organisation for Economic Co-operation and Development (OECD) also recognizes the importance of good regulatory practices that able to unlock the potentials of transformative technology while protecting public safety. The OECD has produced recommendations for members of the organization and nonmembers that are designed based on four identified pillars, namely: regulatory system that fits for the future; cooperation within and between jurisdictions; agile and adaptive regulatory governance that can promote technological innovations; and adaptive enforcement strategies based on the 'new normal' posed by technological advancements [10].

One would argue that to allow a newly emerging technology to flourish in a country such as Malaysia, it would be best not to regulate due to the existing common perception toward regulation as being too restrictive and will hamper technological advancement [8]. However, the initiatives taken by the UK as the global leader in science and innovation, and the OECD as an international organization that looks into better regulatory policies, suggest otherwise. For Malaysia to realize its aspiration, the country must follow these footsteps and develop a more adaptive and agile regulatory system. This paper argues that the challenge faced by Malaysia lies in the creativity in designing a regulatory system that is neither too punitive nor too liberal and that can facilitate ethical and safe development. For instance, the UK, in general, adopts a strict but permissive approach to science advancement. Such approach is apparent in the measure taken by one of its regulatory bodies, Human Fertilisation and Embryology Authority in regulating stem-cell research activities, whereby the UK scientists are permitted to carry out many different types of research techniques that are prohibited in other countries. However, these research activities are tightly regulated to ensure ethical conduct.

It is, therefore, particularly relevant for Malaysia to learn from the UK given its track record as one of the global leaders in stem-cell technology and for its globally recognized regulatory practices. Also, Malaysia's legal system is based on the UK system and legal transplant can be an option. Nevertheless, it is also beneficial for Malaysia to look at other Commonwealth countries. A doctrinal-based study was carried out to examine the regulatory techniques and enforcement strategies adopted by selected countries of the Commonwealth: the UK, Australia, Canada and Singapore. These countries have an established regulatory system for stem-cell technology, not only in the research domain but also in the clinical and commercial applications. This paper recognizes that the regulatory spectrum for stem-cell technology encompasses research and therapy domains; however, this paper aims to demonstrate on how these countries have already been adopting a creative regulatory mechanism to regulate stem-cell research activities.

A brief overview of ethical challenges posed by stem-cell technology

The most controversial issue posed by stem-cell technology is the question on the moral and legal status of human embryos, which has been debated for many years [11–15], but it remains unresolved until today [16–18]. This issue has a significant impact on governmental policy, which has resulted in a regulatory phenomenon known as 'regulatory patchwork' [19]. While some countries support the advancement of human stem-cell research, in general, including the use of embryonic stem cells, others only encourage the use of nonembryonic stem cells. Unlike the former, the latter are universally and ethically accepted across the globe [20] and many researchers have moved to working with nonembryonic stem cells such as induced pluripotent stem cells because there are lesser ethical challenges involved. Notwithstanding, there are other pressing ethical issues such as compliance with procedures for safe and appropriate research conduct, clinical practice and its impact on public safety [21]. The Hwang case in South Korea is an example of fraudulent and unethical conduct in stem-cell research domain involving a fabrication of research data and various wrongdoings [22,23]. Due to this incident, South Korea's regulatory system, particularly its Bioethics and Biosafety Act 2005, was scrutinized and amended [24,25]. 'Stem-cell tourism' is another global phenomenon, whereby patients often travel from their home country that has a more restrictive regulation to countries with less strict or no regulation [26–31]. However, the emergence of this phenomenon is no longer due to whether or not the regulation in emerging countries is weak or poor as argued by Lysaght [6]. This is because autologous adult stem cells are also being offered in wealthy countries such as Japan, the USA and Australia as demonstrated in a study by Lysaght *et al.* [32] and many others [26,31,33–39].

Regulation of stem-cell technology in Malaysia

An advisory report published in 2013 states that Malaysia sees the potential of stem-cell therapy and aspires to develop regenerative medicine industry. The report also states that Malaysia does not have the resources to invest widely and therefore, it is important to choose certain areas that will maximize the return on research investment. A national taskforce has identified the top four chronic diseases that cause disability among the older population; dementia, musculoskeletal diseases, visual-bearing impairments and cardiovascular diseases, which creates a drain on public healthcare spending [1]. To address this issue, regenerative medicine based on stem-cell technology is seen as a potential solution that may provide treatments to reverse the conditions. Nevertheless, the taskforce pointed out that Malaysia is said to be ‘at a distinct disadvantage when competing in a knowledge intensive field such as regenerative medicine and stem-cell research’ [1] because of its relatively restrictive policies whereby only research using surplus embryos is currently allowed, the lack of sufficient funding and skills in this area.

The report explicitly states ‘research on stem cells are not covered by any legislation’ and there are also no provisions on stem cell therapy except that the practice must comply with the Private Healthcare Facilities and Services Act 1998 [1]. There is little regulation in the stem-cell area, in general – both basic research and clinical applications, and even less regulatory oversight with regard to the former. The Ministry of Health is the authority responsible for regulating this field. It has introduced the National Guidelines for Stem Cell research and Therapy in 2006, which were then revised in 2009. The Malaysian Medical Council also produced guidelines to regulate SCRT. When comparing them with other countries’ guidelines, the Malaysian guidelines appear outdated, for instance, the use of induced pluripotent stem cells is not included [8]. There are other agencies established under the Ministry of Health’s patronage, namely, the Medical Research and Ethics Committee and the National Stem Cell Research Ethics subcommittee. The former was established to protect the safety and welfare of human participants in research in general and the latter was established specifically to govern SCRT. It is worth noting that the ambit of the Medical Research and Ethics Committee and guidelines is only limited to research that involves staff members of the ministry, its facilities and human subjects, which means private sector may not fall within its purview.

Basic research is only governed by the guidelines, which are not legally binding. In view of this, one could extrapolate; current research activities are not comprehensively regulated. The term ‘regulatory vacuum’ can also be used to describe the current scenario in Malaysia to demonstrate a regulatory system that is lacking of important measures, in other words, legally binding rules, licensing and monitoring system to secure compliance and ethical conducts [40–45]. Sithole reaffirmed this argument in his study on the regulation of stem-cell research in South Africa by stating that the government needed to ‘provide a proper regulatory framework in order for private, and in time, for public health establishments to advance the use of stem cells in the health industry’ [46]. This article maintains that a similar argument can be applied to Malaysia, particularly basic research activities in the private sector that are not governed by the national Guidelines. This suggests that the regulatory strategies for stem-cell research in Malaysia is fragmented and underdeveloped. An empirical study conducted in 2012 involving key stakeholders in the country shows that there are no appropriate measures to ensure ethical conduct and provide protection for research subjects. It was reported that research activities are being conducted in a climate of uncertainty and there are concerns about the safety of the public and the reputation of this technology if it is continued to be in the status quo [8]. This may not only put members of the public in a risky position of being misled or manipulated but also raises the possibility of the area being tainted by unethical conduct, which might affect public confidence and jeopardizing the commercialization prospects.

The role of regulation & its application in stem-cell technology

Regulation is adopted to control social behavior, whether to permit or prohibit certain types of behavior or activities [47–51]. Central to its role, in the context of stem-cell technology, the regulation introduced for this area is designed to regulate research activities by emphasizing certain boundaries. More specifically, its introduction is primarily a result of the need to address the ethical challenges surrounding this technology. There are two prominent views as to how regulation could function to influence desired behavior and to achieve regulatory aims or goals. The first view is a narrower view. It involves state-sanctioned actions, whereby legal rules are established and enforced with a monitoring system in place. The second view is a broader one, which does not necessarily require legal sanctions, but involves different forms of social control and it can be either imposed by the state or other social institutions [52]. Instead of separating these different views, this article demonstrates in the following sections that both views are significant, and they complement each other, at least in the area of stem-cell technology. Isasi and Knoppers state, ‘... South Korean scandal regarding fraud and gross ethical violations in stem-cell research

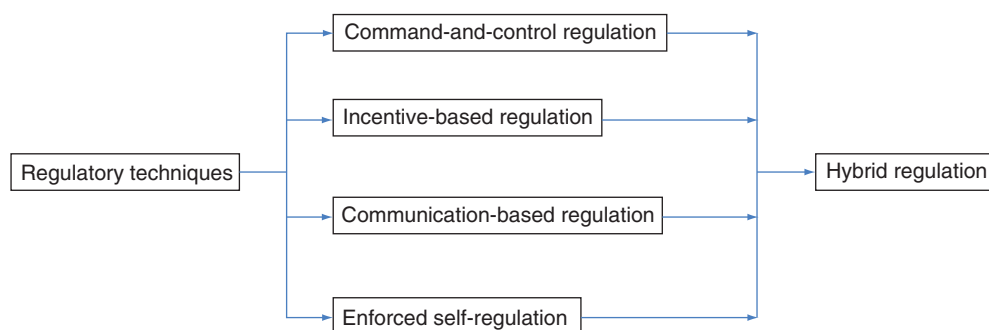


Figure 1. An example of a composition of a hybrid regulation.

illustrates that legislative responses are neither necessary nor sufficient. What are needed are authoritative regulatory oversight, scientific integrity, transparency and accountability' [53]. This leads to the discussion on the different types of regulatory techniques that can be employed to creatively regulate stem-cell technology without having to solely rely on legislation.

Hybrid regulation is a combination of different types of regulatory techniques, as shown in Figure 1. Instead of focusing on one regulatory technique, government could employ different types of techniques depending on the suitability [54]. For instance, government could introduce laws to regulate activities that are permitted and prohibited to achieve statutory goals. However, relying solely on command-and-control regulation through legislation and the threats of criminal and civil sanctions does not guarantee compliance. Sanctions are enforced once the harm is done and may not be the best approach particularly for a highly sensitive and ethically complex area. Better results could be achieved if communication-based regulation is adopted to increase awareness and understanding of the statutory rules to ensure compliance among the regulatees with the purpose to avoid any harm. Since legal rules can be too broad and complex, this issue can be addressed by adopting communication approach. Regulators can also adopt incentive-based regulation to tone down the restrictiveness of the regulation that often portrayed by legislation. States with resources such as public funding could adopt this approach instead of resorting only to legislation. In addition, enforced self-regulation can also be employed to allow highly complex sector to formulate more specific and less complex rules and for the government to delegate the regulating task to self-regulators particularly for an area that is rapidly progressing. This measure would be desirable for government that has the resources instead of relying on legislative measures.

As highlighted by Hutter, 'enforcement of the law did not refer simply to legal action but to a wide array of informal enforcement techniques including education, advice, persuasion and negotiation. These were used by all law enforcement officials, but came into particular prominence in the regulatory arena' [55]. The employment of the different techniques both formal and informal enforcement techniques are the features of smart regulation proposed by Gunningham and Grabosky, as shown in Figure 2 below [48]. With a smart regulation, regulators can deploy a strategy or a mixture of different strategies to achieve a desired outcome on the ground [55–57]. It does not mean, legal action such as sanctioning will not be engaged in the enforcement process, but it is a matter of last resort to guarantee protection and to discourage violations or unethical conducts.

Methods

This study was conducted mainly based on a document review. It involves the collection and a detailed review of national legislations, ethics guidelines and regulations to examine their regulatory strategies. It only aims to examine the general regulatory framework for stem-cell technology without making specific distinctions between the sources of stem cells as well as the specific domains of the technology. However, it is worth mentioning that the examination in this paper is leaning more toward research domain because the scope of the regulation of clinical applications is rather broad and complex. It deserves a legal analysis on its own and a study is under way with regulation of clinical application in Malaysia as its focus.

Themes established in the review and analysis are based on the regulatory theories identified from the literature. This article discusses the adoption of the different regulatory techniques by the selected countries in turn with the employed compliance strategies. A comparison is made between Malaysia's current regulatory framework and the regulatory techniques adopted by the UK, Australia and Canada. These countries are selected due to their

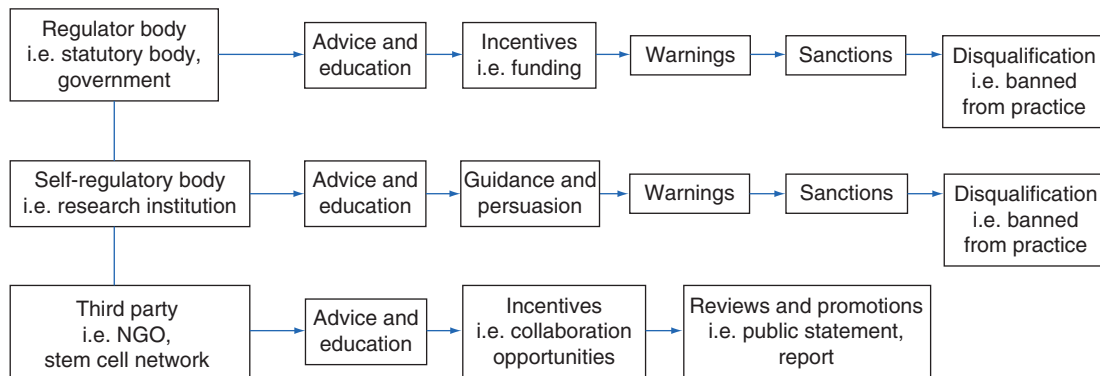


Figure 2. An illustration of a smart regulation based on the theory proposed by Gunningham and Grabosky. It involves different regulators and different types of enforcement measures. NGO: Non-governmental organization.

Table 1. Legal provisions on sanctions.

Country	Law	Sanction provisions	Prohibited activities
Australia	Prohibition of Human Cloning for Reproduction and the Regulation of Human Embryo Research Amendment Act 2006	Schedule 2 – Research Involving Human Embryos Act 2002	Section 9 – placing a human embryo clone in human body or animal; export and import of human embryo clone; create human embryo for purpose other than pregnancy; create human embryo other than by fertilization without a license; create embryo that contains genetic material of more than two persons without license; develop human embryo outside woman's body for more than 14 days; alter genome that is heritable; collect a viable embryo from a woman's body; create a chimeric embryo; develop a hybrid embryo for more than 14 days and without license; commercial trading in gametes and embryos
Canada	Act Respecting Assisted Human Reproduction and Related Research 2004	Sections 60 and 61 – fine (not exceeding CAN\$100,000–\$500,000) or imprisonment term (from 2 to 10 years) or both	Sections 5–7: for example, creation of human clone, creation of IVF embryos other than for assisted reproduction purposes, maintain embryo outside human body for more than 14 days; alter genome that can be transmitted to descendants; creation of a chimera, creation of a hybrid for reproduction, purchase of gametes, purchase or sale of embryos IVF embryos
Singapore	Human Cloning and Other Prohibited Practices Act 2004 (Revised 2005)	Section 18 – fine (not exceeding SGD\$10,000) or imprisonment (not exceeding 10 years) or both	Sections 5–13: for example, creation of human clone, creation of embryo other than by fertilization of egg and sperm, developing embryo outside human body for more than 14 days, collect viable embryo from human body, importing and exporting prohibited embryos, commercial trading in gametes and embryos
UK	Human Fertilisation and Embryology Act 1990 (as amended in 2008)	Section 41 – fine or imprisonment (not exceeding 10 years) or both Imprisonment term varies under Section 41, subsection 4, 4A, 4B, 5, 9	Sections 3–4: for example, create embryo without a license; place other than permitted gametes or embryo in a woman, place embryo in animal; place a human admixed embryo in a woman, mix human and animal gametes, keep or use embryo after 14 days; alter genome of embryo

IVF: *In vitro* fertilization.

experience in regulating stem-cell technology and given the fact that they share a common root of a British colonial legal system (Commonwealth) with Malaysia. However, emphasis is given to the approach adopted by the UK due to the reasons highlighted in the introduction.

Results

Regulatory techniques adopted by the Commonwealth countries

Command-and-control regulation

Australia, Canada, Singapore and the UK have introduced legislation that is directly or indirectly regulate this technology. This means that regulators in these jurisdictions have the legal power to impose sanctions for non-compliance. Such a measure is clearly embodied in the legislation introduced in the respective jurisdictions, as shown in Table 1 below.

Statutory provisions backed by legal force would be more efficacious since any offense will have legal repercussions. Regulated parties would feel 'threatened' and therefore, they would be likely to conform to the rules. However,

Table 2. Provisions on funding scheme and requirement for compliance.		
Country	Law/guidelines	Relevant provision
Canada	Updated Guidelines for Human Pluripotent Stem Cell Research 2010	Para 7.0 – “These guidelines apply to all research involving human pluripotent stem cells that is funded by the Agencies, or is conducted under the auspices of an Institution that receives any Agency funding.” (paragraph 7.0)
UK	No specific provisions in the law and code of practice. There are certain requirements set by funding agencies	In other words, requirements for grant holders, Wellcome Trust: “As with all scientific research funded by the Wellcome Trust, stem-cell research will be funded on merit and scientific excellence after rigorous peer review and in line with the current legal and regulatory framework.”; (text from website) Terms and Conditions of Research Councils Grant, Medical Research Council's: “The Research Organisation is responsible for ensuring that ethical issues relating to the research project are identified and brought to the attention of the relevant approval or regulatory body. Approval to undertake the research must be granted before any work requiring approval begins.” (text from website)

‘classical’ regulation might not be the most appropriate technique to solely rely on, given the intricacies of the system. In particular, the establishment of law often involves a complex procedure where it takes a long time to develop, and it is problematic for the law to keep pace with technology. The development of the UK legal system would probably be the best representative of such a complex process. When the Human Fertilisation and Embryology (HFE) Act 1990 was introduced, it was not anticipated that the derivation of stem cells from human embryos would one day be possible for research. The discovery of the cell nuclear replacement technique [58] and the success of deriving stem cells from a human blastocyst, a technique that could be used for therapeutic cloning [59], which were not within the list of the permitted research purposes have raised questions about the scope of the Act [60], resulting in a new regulation being introduced [61]. Eventually, the HFE Act 1990 was amended in 2008 to reflect these changes including the creation of human-admixed embryos for research purposes [62]. Having to solely rely on legislation would not be the most convenient and effective means for making changes to the legislation is time consuming. Contrastingly, it would be easier to amend and update guiding rules. For instance, the UK has clearly indicated that the Human Fertilisation and Embryology Authority (HFEA) Code of Practice is an evolving or living document. With this system, the stipulated rules can be continuously revised and updated as and when necessary. An example of the application of guiding rules is discussed in the next section.

Incentive-based regulation

Mintrom points out that ‘the primary predictor of a country hosting stem-cell research is not the religious mix of the population but the wealth of the country and the commitments that successive governments have made to the funding of their research universities’ [63]. This means funding (or public wealth) can be deployed by some jurisdictions that have the resources as the ‘incentive’ by regulators to secure compliance in SCRT. This shows that guiding rules complemented by funding schemes can be used as an alternative regulatory technique and could be particularly compelling in jurisdictions whereby researchers are mainly depending on government funding. This technique is also being practiced in jurisdictions that have legislation in place, such as the UK and Canada, as shown in Table 2 below.

Unlike legislation, the establishment of guiding rules does not need to go through parliament. This is an advantage, especially in terms of its ability to accommodate changes in policy and its implementation. Additionally, incentive-based regulation would encourage compliance without having to rely solely on sanctions. Nevertheless, it can be argued that guiding rules for funding could only be imposed on firms or individuals that receive the funding. In view of this, one could maintain that legally binding rules are therefore, still important. This argument is accurate to some extent, but it is worth highlighting that first, the binding effect that law has, can be extended to the enforcement of guiding rules. For instance, such approach can be found in Australian system whereby its statutorily established body is required to regard relevant guiding rules before granting license [64]. Despite the existence of the HFE Act 1990, the regulatory body in the UK is also required to establish guiding rules, the HFEA’s Code of Practice to complement the enforcement of the law. Second, provisions on funding can also be extended to nonfunded parties. For instance, Canada requires its updated guidelines to be applicable not only on parties that receive funding directly from the Agencies but also to those who do not receive the funding directly but conduct a research work under the auspices of any funded firms.

Communication-based regulation

Once promulgated, statutory rules are not self-enforcing. Due to this limitation, it is important to establish a regulatory body to communicate with regulatees to ensure understanding on the rules' meaning, application and implication. The countries under study adopt this regulatory technique. First, there are regulatory bodies established in respective jurisdictions, namely, HFEA (UK) and Human Tissue Authority (UK); National Health and Medical Research Council (Australia); and Stem Cell Oversight Committee under the purview of the Canadian Institutes of Health. Singapore has its Bioethics Advisory Committee, but as its name implies, it is not a regulatory body and it only makes recommendations to the government on the regulation of human biomedical research. Apart from enforcing the rules in place, the regulatory bodies in the UK, Australia and Canada also communicate and disseminate any relevant matters and information pertaining to SCRT. Besides communicating with relevant stakeholders, especially the public and researchers through websites, they also utilize other social media platforms such as Twitter. For instance, the UK HFEA with its website: www.hfea.co.uk and Twitter: @HFEA; Canadian CIRM; website: <http://www.cihr-irsc.gc.ca>, Twitter: @CIHR_IRSC; Australian NHMRC: <https://www.nhmrc.gov.au>, Twitter: @nhmrc. Through these cyber platforms, regulatory agencies could provide necessary information and at the same time allow easy access for any queries.

In addition, these countries also have established stem cell network, such as Australian Society for Stem Cell Research, Stem Cell Network Canada, Singapore Stem Cell Consortium and London Regenerative Medicine Network, that would enable the relevant stakeholders to stay connected with each other. This network provides a platform for both researchers and regulators to keep abreast with the technology and regulatory matters. Such aspiration can be seen embedded in the objectives of the establishment of one of the networks:

'To provide all interested parties with the opportunity to access information relating to scientific, medical and ethical advances in the broad field of stem cell research. A particular emphasis of The Society will be to communicate this information to the general public.' [65].

It is widely known that stem cell providers attract patients through advertisement, especially on the internet. To tackle this marketing practices of offering unproven stem cell interventions, the Australian Therapeutic Goods Administration introduced a ban in 2018 for advertisement of stem cell intervention direct to consumers. The word 'stem cells' is also prohibited from being used in advertising stem cell interventions. This shows a proactive regulatory approach taken by the Australian authority through communication-based regulation that can be adopted by other countries facing the same issues with the increasing number of clinics leveraging on the words 'stem cells' to market their services [66].

Enforced-self regulation

Provisions on informed consent and ethical review can be seen embedded in laws that regulate research activities. Such practice is in line with enforced-self regulation, practiced at the institutional level through ethical review. Informed consent is one of the requirements for approval to conduct research. Ethical review process is vital as it requires researchers to disclose full information about their research before approval is granted by the ethics committee. Such requirement is one of the important elements included in guidelines.

Table 3 shows that the requirement of respecting informed consent through ethical review is a global practice in the regulation of SCRT to obtain approval, license, as well as funding. Researchers are required to disclose and provide further information and explain possible risks to research subjects. By fulfilling the requirements, researchers would satisfy regulators that proposed research will be conducted in an ethical way. The importance of informed consent can be further stressed particularly after the reported fraud in South Korea [24,67–69]. This case illustrates that the existence of law alone does not guarantee protection for research subjects and other measures such as informed consent is important too. Jhalani in his argument emphasizes the failure of the South Korean Bioethics and Biosafety Act 2005 because it 'does not require that the consent obtained from research participants be voluntarily' and 'does not require that research subjects understand the information presented to them before allowing them to participate in stem cell research' [69]. As with informed consent, ethical review is also adopted as a legal and ethical requirement in the jurisdictions' regulatory system. With or without legislation and legal force, this requirement has to be met by researchers before research application could be granted a license, funding or both.

Table 3. Provisions on consent and ethical review.

Country	Provision on consent	Ethical review requirement
Australia	Schedule 2, Subsection 24(1) of the Amendment Act 2006 Schedule 2, Subsection 24(1) stipulates, 'a licence is subject to the condition that before an excess ART embryo or human egg is used, or any other embryo is created or used, as authorised by the licence: (a) each responsible person in relation to the excess ART embryo, human egg or other embryo must have given proper consent to that creation or use...'; (b) 'the licence holder must have reported in writing to the NHMRC Licensing Committee that such consent has been obtained, and any restrictions to which the consent is subject.'	Section 4 of the 2007 Guidelines Section 4 dictates, 'Researchers, in the design and conduct of research, and HRECs, in their review of proposals, must apply these guidelines.'
Canada	Section 8(1) (2) (3) of the 2004 Act Section 8(1) states, 'no person shall make use of human reproductive material for the purpose of creating an embryo unless the donor of material has given written consent...'; section 8(2) states, 'no person shall remove human reproductive material from a donor's body after the donor's death...unless... has given written consent...'; section 8(3) states, 'no person shall make use of an <i>in vitro</i> embryo for any purpose unless the donor has given written consent...';	Section 1 and 5 of the Updated Guidelines Section 1 stipulates, 'no research with human pluripotent stem cells would be funded without the prior review and approval...in conformity with the CIHR guidelines,' section 5 states, '... a Stem Cell Oversight Committee (SCOC) has been created to conduct ethical review of all human pluripotent stem cell research proposals recommended for approval by the Agencies' scientific peer review panels...SCOC can also, on request, provide ethical review of... proposals submitted by other public or private granting agencies or by industrial sponsors of research.'
Singapore	Part III of the Guidelines 2015 Recommendation 6 states, 'for the derivation and use of ES cells, there must be informed consent from the donors of surplus human embryos, gametes or cells'; recommendation 9 states, 'in obtaining consent from donors of cells, gametes, tissues, foetal materials and embryos, the information provided to the donors must be comprehensive...'	Part II of the Guidelines 2015 The Bioethics Advisory Committee reports state 'there are no ethical reasons for an actual prohibition on research in advance. Individual research proposals will in any case need to be considered by ethics committees which will take into account both the details of the proposed procedures and its likely theoretical or practical benefit.'
UK	Schedule 3 of the HFE Act 1990 (as amended in 2008) Also see Section 12(1) Schedule 3(2) of the Act states 'a consent to the use of any embryo must specify one or more of the following purposes: (a) use in providing treatment services to the person giving consent, or that person and another specified person together, (b) use in providing treatment services to persons not including the person giving consent, or (c) use for the purposes of any project of research, and may specify conditions subject to which the embryo may be so used.'	Para 49–51 of the Guide to Licensing laid down by the HFEA Para 49 of the HFEA's 'Guide to Licensing' states, 'upon receipt of a complete application, the Authority commissions peer reviews of that application. The Authority normally commissions about two or three peer reviews of each application.'

CIHR: Canadian Institutes of Health Research; HFE: Human Fertilisation and Embryology; HFEA: Human Fertilisation and Embryology Authority.

Techniques in securing compliance

Sanctioning strategy

Legal prosecution through sanctioning strategy is a common approach in command-and-control regulation. Therefore, those jurisdictions that have enacted legislation to regulate SCRT shall have statutory provisions sanctioning prohibited activities (see Table 1). The forms of sanction vary from imprisonment, civil fines or both and some even constitute a criminal offense. This strategy is appropriate particularly for highly contentious regulated areas such as stem-cell technology, as this area involves human subjects. As has been argued by Isasi and Knoppers, 'good governance calls for provisions contemplating sanctions and enforcement mechanisms' [53]. However, they also emphasize the importance of other mechanisms that can be adopted to ensure compliance and secure protections for research subjects. These mechanisms can be categorized as compliance strategy as the spirit of its implementation is to deter noncompliance from the earlier stage of research activities. This is particularly relevant given the sanctioning strategy involves a high compliance cost and is not necessarily adequate and effective to deter noncompliance as has been shown in the Hwang case earlier.

Compliance strategy through licensing & monitoring

A licensing system is adopted to certify that a regulated activity is ethically acceptable and as an agreement between the regulators and regulatees that the activity will comply with the rules in place. Table 4 below shows that the UK has a specific licensing body. Similarly, Australia has reformed its regulatory regime by following the UK's approach in establishing a licensing system. Other countries do not seem to have specific licensing body except approval processes by funding or regulatory bodies, in other words, Canadian Institutes of Health Research's Stem

Table 4. Provisions on licensing and monitoring system.

Country	Licensing provision	Scope of licensing	Monitoring provision
Australia	Authority: NHMRC Licensing Committee Statute: Division 4 of the RIHE Act 2002 (as amended)	In other words, use of excess IVF embryo; creation and use of embryo other than fertilization (egg and ovum; genetic material of more than two persons); creation of embryo using precursor cells; creation of hybrid; creation and use of hybrid embryos by fertilization of animal egg and human sperm up to first mitotic division; research and training involving fertilization of human egg and embryo prior to first mitotic division	Authority: Inspectors appointed by NHMRC Licensing Committee Statute: Section 36 of the RIHE Act 2002 (as amended); Section 1.3, 1.7 of Licensing Committee Information Kit; Section 1.8 of the Guidelines 2007
Canada	Authority: No specific licensing body except approval by the federal funding Tri-Agencies	–	Authority: Inspectors appointed by Minister CIHR's Stem Cell Oversight Committee Statute: Section 46(1) of the AHR Act; Section 2 of the Updated Guidelines
Singapore	Authority: No specific provision and licensing body except Bioethics Advisory Committee's recommendation	–	Authority: Inspector appointed by Director of Medical Services Statute: Section 14 of the Prohibited Act 2004
UK	Authority: – HFEA Licensing Committee Statute: Section 5 of the HFEA 1990 (As amended) – HTA Statute: Section 13 of the HTA 2004	HFEA: Issues license for research involving human gametes and permitted embryos for activities stated in Figure 3 Human Tissue Authority: Issue license for research involving human cells (including embryonic cell lines). Exclude gamete cells and embryo (governed by HFEA).	Authority: – Research involving human embryos and gamete cells – HFEA Statute: Section 8 of the HFE Act 1990 (as amended) – Research involving human adult and embryonic stem cells lines – HTA Statute: Part 2 of the HTA 2004

AHR: Assisted Human Reproduction; CIHR: Canadian Institutes of Health Research; HFE: Human Fertilisation and Embryology; HFEA: Human Fertilisation and Embryology Authority; HTA: Human Tissue Act; IVF: *In vitro* fertilization; NHMRC: National Health and Medical Research Council; RIHE: Research Involving Human Embryos.

Cell Oversight Committee (Canada), Bioethics Advisory Committee (Singapore). This mechanism also involves a monitoring system. To ensure licensees comply with the rules, the regulatory body does not rely merely on legal force and sanctions, which usually take place only after noncompliance has occurred, but rather the regulators keep track of the licensees' activity from the beginning and ensure compliance. Unlike the UK, most of the countries do not have an established statutory body to oversee compliance. Their system, however, requires the appointment of inspectors to carry out inspections and the power of appointment is given either to a Minister (Canada); a Director of Health (Singapore); or a regulatory body established specifically for this area (Australia's NHMRC).

This compliance measure is embedded in the UK's and Australia's legislation as one of the statutory requirements, which gives the regulatory body the mandate and statutory power to monitor and oversee regulated activities. One could argue that this is an effective strategy to secure compliance. Isasi and Knoppers assert, 'the imposition of accreditation through licensing as a condition of operation is the one procedural mechanism with the greatest impact on embryonic research' and 'probably the best-known model of effective oversight and licensing is the UK's Human Fertilisation and Embryology Authority (HFEA)' [53].

The following section further discusses the advantages of adopting a hybrid regulation, as demonstrated in the regulatory approach adopted by all of the countries. It is worth noting that despite the similar approaches, there are some minor differences between them, for instance, only the UK and Australia have a specific licensing provision on the use of human stem cells backed by a legal force. Of all the countries, the UK appears to have a framework that best reflects a hybrid regulatory model. Therefore, this paper argues that Malaysia could learn from the experience of the selected Commonwealth countries, but emphasis is given to the UK, as its approach would be able to address the issues with Malaysia's existing regulatory issues and local stakeholders' concerns that have been reported in Bin Abdul Aziz *et al.* [8].

Discussion

The preceding section demonstrates that the optimal means of regulating stem-cell technology would be through establishing and maintaining a regulatory strategy that is designed from a combination of different regulatory techniques and enforcement strategies. This is in line with Mandel's argument that 'traditional one-size-fits-all command-and-control regulation will not suffice' [70]. Similarly, Brownsword and Somsen argue, 'it needs

to be appreciated that traditional command-and-control interventions... are not always an effective form or response... regulators to be aware of the range of regulatory instruments and the importance of putting in place an optimal mix' [71]. A hybrid regulation offers flexibility and alternatives, and this is particularly important when emerging technologies such as stem-cell technology are at play. The technologies are rapidly growing and developing, bringing about uncertain risks and ethical issues, which mean new regulatory issues, would also arise requiring a system that is adaptive and agile, a challenge that is already recognized by both the UK and the OECD.

The availability of different regulatory measures that can be employed by regulators in a hybrid regulatory system can be seen from the different approaches adopted by the countries under study. All of the countries provide a list of prohibited activities, and offenses involving any of the activities will be sanctioned with fine or imprisonment or both. This mostly concerns the use of human embryos and gametes for research. As mentioned earlier, this is an example of command-and-control regulation. Before they reach at the level of imposing a penalty, the UK and Australia (except Canada and Singapore, which do not have a specific licensing body) have established a licensing authority that regulates stem-cell research activities from the beginning. Also, the UK and Canada have adopted provisions on a funding scheme as a measure to ensure compliance, which reflects the incentive-based regulation. In addition, all of the countries have imposed an ethical review requirement through guiding rules and a statutorily mandatory requirement (except Singapore) for researchers to obtain consent for certain research conduct, which is also a command-and-control regulation. Similar rule is also imposed in Singapore but only through a guiding rule. Among the countries, the UK's ethical review requirement can be regarded as an enforced self-regulation in the strictest sense, because the requirement is established through a guidance document on licensing, which is an extension of its mandatory licensing requirement. Furthermore, the countries under study (except Singapore) also established a regulatory body that not only governs stem-cell research but also adopts communication-based regulation.

As has been argued earlier, among the countries examined in this paper, it can be said that the UK's regulatory approach embodies all the highlighted regulatory techniques that is consistent with the concept of hybrid regulation. This strategic action has been the key feature of the UK's long-established regulatory system and has been maintained for many years in governing this ethically complex technology. Such strategy equips a regulatory system with measures that are capable of allowing exploration and progress into new areas while securing and facilitating compliance, in line with Mandel's observation that designing a more flexible governance system that can respond to changing knowledge and information is necessary to optimally handle the benefits and risks of emerging technologies [70]. This supports the argument made in this paper that the UK has the most advantageous regulatory model for Malaysia to follow, in addition to the fact that UK is one of the world leading nations in stem-cell technology with a globally recognized regulatory framework. The UK also has set an example to the other countries by demonstrating that even though it has established relevant legislation for this area, it also recognizes the usefulness of nonlegally binding standards to act as an information guide to promote best practices among stakeholders such as scientists, industry and stem cell players. In 2006, the British Standards Institution published a standard that can be used as a guide and a starting point for the stakeholders to access to the relevant information that they need when they wish to enter this regulated area. The standard provides detailed information such as code of practice, standardized methods and regulation from basic research to clinical application [72].

By adopting the same strategy as the UK, Malaysian regulators will have options that they can employ, depending on the situations and suitability, in order to achieve their desired regulatory goals, given the fact that different regulatory techniques have their own strengths and weaknesses. As has been pointed out earlier, by implementing command-and-control regulation, this technique will provide Malaysian framework, and all regulatory measures that are necessary in this field, with legal effects. Such regime would also be able to close the regulatory gap by providing more comprehensive framework. For instance, stem cell-related activities that are governed by law will have legal effects both in public and private sectors. With law in place, the framework will provide Malaysian regulators with legal power; however, they would also benefit from other regulatory techniques such as enforced self-regulation through an independent regulatory body at the national and institutional levels. Given statutory rules are not self-enforcing and not self-explanatory, such body is crucial for rules implementation and enforcement as well as to secure compliance through communication with the regulated parties.

Also, it is important to highlight that local authority should leverage on social media to 'communicate' with the regulated parties and public. In 2019, it was reported that Malaysia was ranked top five globally for social media use and the highest in the Southeast Asia [73]. Based on a report in 2020, there are 26.69 million internet users in Malaysia and 26 million social media users [74]. The most active social media platforms in the country are,

namely: YouTube with 93% users; Facebook with 91% users; WhatsApp with 91% users; and Twitter with 44% users [75]. The unprecedented COVID-19 pandemic particularly shows the importance of communication-based regulation as an effective way to reach out to everyone in the country. The authority has since communicated with the public through WhatsApp and Twitter among other platforms to ensure that everyone is updated with the movement restriction orders and standard operating procedure to curb the outbreak. Therefore, this shows that the authority realizes and recognizes the effective role played by social media to inform and communicate with the masses, as a creative regulatory approach to ensure compliance and safeguard public health. Such approach is already in existence, and it only needs to be applied by the responsible authorities for stem-cell technology. This will be in line with one of the recommendations made by the OECD that regulators should consider develop or adapt governance and regulatory approach based on the 'new normal' and forward looking [10].

Notwithstanding, there is a need to examine how a hybrid regulation adopted by the selected countries, especially the UK, can be transplanted into Malaysia's system. Considerations need to be given whether Malaysia has the resources to have a similar approach. Also, this paper focuses more on the regulatory approach for stem-cell research. This paper recognizes that regulation of stem cell therapy is of utmost importance too, which also need to be examined in Malaysia. It involves different aspects such as the manufacturing, testing, clinical development, clinical trials and marketing authorization and pharmacovigilance. While other countries have already introduced new laws and accelerated approval process aimed at promoting the clinical translation of stem cells and regenerative medicine, there is still not much progress or discussion initiated by the relevant regulatory authorities in Malaysia.

Conclusion

Countries such as Malaysia that has the aspiration to develop regenerative medicine through stem-cell technology will benefit from a regulatory strategy that is designed based on a hybrid regulation, which is probably an appropriate regulatory strategy for such an ethically challenging area. Such strategy allows regulators some flexibility and would produce an optimal regulatory outcome that able to ensure ethically acceptable development of the technology and offer assurance for public safety. This examination also suggests that Malaysia does not need to reinvent the wheel. A legal transplant from these countries, especially the UK as a model, can be an option. However, this would require further comparative and in-depth legal examination between Malaysia and the UK as to how this creative approach can be implemented and embedded in the organizational structures of the relevant regulatory institutions to regulate the development of stem-cell technology in the country, particularly the domain of stem-cell research, which is currently only being regulated through nonbinding rules that are only applicable to the public sector. It is also important for Malaysia to have a comprehensive regulatory framework that govern research activities both in the public and private sectors.

Future perspective

In-depth research work on the governance of stem-cell technology in Malaysia is lacking. Based on a few reported studies, it suggests that regulation of this area is inadequate. There are concerns over the regulatory practice, particularly in the private sector and the operation of stem-cell providers offering unproven stem cell therapy in Malaysia. These are important issues, not just because it may put the public at risk but it also may jeopardies the reputation of this technology, and in turn would affect the aspiration of Malaysia to promote technological innovation based on stem cells. These issues must be addressed urgently. More research is needed to examine the extent of the regulatory reform that is needed to improve the existing regulation, particularly focusing on the use of human embryos and other sources of stem cells for research, as well as clinical applications in both public and private sectors.

Author contributions

M Bin Abdul Aziz was responsible for the main research work from the acquisition of literature, comparative legal analysis to drafting and revision of the manuscript after editorial decision. M Morrison and J Kaye were responsible for guiding the preparation of the manuscript.

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Executive summary

Aspiration to develop stem-cell technology in Malaysia

- To realize its aspiration in developing regenerative medicine through stem-cell technology, Malaysia could learn from the experience of the Commonwealth countries, such as the UK, Australia, Singapore and Canada, which share the same legal roots and have the experience in regulating this complex and ethically challenging technology.

Ethical & regulatory issues

- The ethical issues surrounding stem-cell technology, especially in the development of regenerative medicine, touch on issues such as compliance with procedure for safe and appropriate clinical practice, public safety and the reputation of the field.
- Stem-cell technology is under regulated in Malaysia and the existing guiding rules are outdated. This is compounded by regulatory framework that can be regarded as fragmented and the absence of legislation for regulators to legally impose rules, monitor and sanctions. Therefore, its adequacy to ensure ethical conduct and compliance is questionable.
- The challenge for Malaysia is to develop regulatory mechanism that is adaptive and flexible in addressing the complexity of challenges posed by a rapidly evolving technology such as stem-cell technology without hampering its advancement.

A creative regulatory framework for stem-cell technology

- The countries under study adopt a hybrid regulation, which consists of command-and-control regulation, communication-based regulation, incentive-based regulation and enforced-self regulation. Given each regulatory technique and compliance strategy has its own strengths and weaknesses, an optimal regulatory outcome could be achieved.
- A hybrid regulation offers flexibility and alternatives for regulators. It is particularly useful when dealing with challenges posed by a rapidly evolving and emerging technology. Such an approach represents a flexible, adaptive and agile regulatory approach, which is recommended by the Organisation for Economic Co-operation and Development and recognized by the UK in its White Paper that sets out to maintain its global presence as a leader in science and innovation.

The way forward for Malaysia

- To join the experienced countries in the global stem-cell race, Malaysia should improve its regulatory system. The country does not need to reinvent the wheel when it can learn from its counterparts in the Commonwealth realm, especially the UK due to its globally recognized regulatory practices that promote technological innovation in a safe manner.
- Further research is needed to examine whether Malaysia has the resources and capacity to implement a creative regulation similar to the strategy adopted by the UK and the other countries under study.

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