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REVIEWS

Regulation of Stem Cell Technology in Malaysia: Current Status and Recommendations

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Abstract

Stem cell technology is an emerging science field; it is the unique regenerative ability of the pluripotent stem cell which scientists hope would be effective in treating various medical conditions. While it has gained significant advances in research, it is a sensitive subject involving human embryo destruction and human experimentation, which compel governments worldwide to ensure that the related procedures and experiments are conducted ethically. Based on face-to-face interviews with selected Malaysian ethicists, scientists and policymakers, the objectives and effectiveness of the current Guideline for Stem Cell Research and Therapy (2009) are examined. The study's findings show that the guideline is rather ineffective in ensuring good ethical governance of the technology. A greater extent of unethical conduct is likely present in the private medical clinics or laboratories offering stem cell therapies compared with the public medical institutions providing similar services, as the latter are closely monitored by the governmental agencies enforcing the relevant policies and laws. To address concerns over malpractices or unethical conduct, this paper recommends a comprehensive revision of the current stem cell guideline so that adequate provisions exist to regulate the explicit practices of the private and public stem cell sectors, including false advertising and accountability. The newly revised Malaysian stem cell guideline will align with the Guidelines for Stem Cell Research and Clinical Translation (2016) of the International Society for Stem Cell Research (ISSCR) containing secular but universal moral rules. However, a regulatory policy formulated to govern the technology remains the main thrust of empowering the guideline for compliance among the stakeholders.

Keywords Stem cell technology · Regulatory policy · Regulation · Guideline · Exploitation · ELSI

Abbreviations

ART	Assisted reproductive technology
ASM	Academy Science Malaysia

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BAC	Bioethics Advisory Committee
ELSI	Ethical, legal and social implication
GMP	Good manufacturing practice
HESC	Human embryonic stem cell
ISSCR	International Society for Stem Cell Research
IEC	Institutional Ethics Committee
IRB	Institutional review board
IVF	In vitro fertilization
MOH	Ministry of Health
MoU	Memorandum of understanding
MREC	Medical Research and Ethics Committee
NGOs	Non-governmental organizations
NKEA	National Key Economic Area
NMRR	National Medical Research Registry
NPRA	National Pharmaceutical Regulatory Agency
NSCERT	National Stem Cell Research and Ethics Subcommittee
OECD	Organisation for Economic Co-Operation and Development
PHFS	Private Healthcare Facilities and Services
SCNT	Somatic cell nuclear transfer
UK	United Kingdom
US	United States of America
USD	US Dollar
WoS	Web of Science

Introduction

In Malaysia, stem cell research started in 1987 with its first bone marrow transplant and since then, Malaysia has moved on with a robust programme of stem cell research and transplantation (Table 1). Currently, there are four guidelines that govern the implementation of stem cell research, clinical trial (transplantation) and stem cell banking (all of which hereon will be referred to as 'stem cell technology') in Malaysia as presented in Table 2 (National Transplant Registry 2004; Ministry of Health (MOH) 2018). These guidelines are used to manage different derivatives of stem cells such as haematopoietic (i.e. cord blood and bone marrow) and non-haematopoietic (i.e. embryonic SC), and for different purposes such as research, transplantation or banking.

As the above table shows, Malaysia relies on guidelines alone to regulate stem cell technology. While guidelines are important to help ensure the ethical conduct of everyone involved in the technology at every level, one cannot be certain of full compliance of the stakeholders to the guidelines nor do the guidelines have the force of law to hold unethical practitioners accountable (McHugh 2018; Tiwari and Raman 2014). However, the Minister of Health seems to believe that the present regulatory regime for stem cell technology is sufficient and no effort has been taken to introduce any legal framework (Ministry of Health 2012). This is in contrast to developing countries, like Thailand and Indonesia, which have initiated efforts to effectively

Table 1 Top 10 countries and their stem cell publications (1916–2017)

Countries	Number of articles
United States	26,916
China	18,111
Japan	7400
Germany	6712
United Kingdom	5619
South Korea	4468
Italy	4142
France	3352
Canada	2873
Spain	2332
Total	81,925

regulate their respective stem cell technology implementation, which includes both research and transplantation, with legislation similar to those of the developed countries (Velasco et al. 2013; Utomo 2012). The effectiveness of guidelines alone is questionable as far as oversight of products and governance for stem cell technology are concerned (Pepper and Slabbert 2015; Utomo 2012; Dajani 2014; Thai Law Forum 2014; Ministry of Health 2012), especially given rising ethical issues such as advertising and offering unproven stem cell therapies by the private healthcare providers, and indiscriminate promotion of stem cell tourism (Ung 2012).

Studies have documented many unethical practices by stem cell technology practitioners, including the use of therapeutic and reproductive cloning, unsafe clinical application of stem cell-based products on patients without assessing the risk and safety aspects, inadequate informed consent, and stem cell tourism in countries such as China, Mexico, South Africa, India and Thailand, where regulations are either liberal or weak (Huang et al. 2017; Lamb 2017; Pandya 2016; Thai Law Forum 2014). It might be argued that stem cell regulatory deficiencies in these countries are the leading cause of the unethical practices, which suggests warranting the enacting of effective regulation within a legal framework instead of relying on mere guidelines (Arellano 2012; Slabbert and Pepper 2015; Tiwari and Raman 2014). Studies such as those of Bianco et al. (2013), Then (2009), Lovell-Badge (2008), O'Neill (2003) and Robertson (1999) have clearly highlighted the ethical issues of stem cell technology and the need for stringent regulations. While some researchers focused on the implication of no regulations like Perrone (2015) and Higgins (2015), others identified the loopholes that existed within the regulations such as Roy (2016), Harvey et al. (2015) and Elder (2015). The majority of these studies were initiated and written by scholars and ethicists from the Western developed countries such as United States (US), United Kingdom (UK), and Canada, where stem cell research has been actively pursued. There is limited documentation of regulation in developing countries like Malaysia, which highlights the challenges of a small developing country with limited funding, resources, and diverse religious backgrounds in stem cell decision-making and policymaking.

Table 2 The guidelines governing the stem cell technology in Malaysia National Transplant Registry (2004) and Ministry of Health (MOH) (2018)

Guideline	Year	Purpose and focus
Guideline for Haematopoietic Stem Cell Therapy	2009	To oversee the transplantation of haematopoietic stem cell
National Standard for Cord Blood Banking and Transplantation	2008	To oversee the private & public collection and banking of cord blood for transplantation
National Standards for Stem Cell Transplantation	2009	To oversee the collection of cord blood, its processing and cryopreservation and transplantation of SC extracted from peripheral/placental blood, bone marrow and others
Guideline for Stem Cell Research and Therapy ("stem cell guideline")	2009	To oversee the haematopoietic & non-haematopoietic stem cell research & transplantation

Presently, the majority of Malaysian scholars have discussed the topic from the religious perspective, reviewing human embryonic stem cell (HESC) research based on the diverse religions in Malaysia; these researchers include Foong (2011), Sivaraman and Noor (2014, 2015) and Rahman (2015). Only Foong (2012) addressed the regulation of stem cell technology purely from the legal perspective, focusing on the deficiency of the stem cell guideline. Foong proposed a new law based on Braithwaite's Theory,[1] also known as the responsive regulatory theory, which was first conceptualised by Ian Ayers and John Braithwaite in 1992. Following Braithwaite, the proposed law "suggests that governance should be responsive to the regulatory environment and to the conduct of the regulated in deciding whether a more or less interventionist response is needed" (Ayres and Braithwaite 1992, pp. 117–132). On the other hand, Olawale (2013) argues that Islamic law alone is adequate to govern stem cell technology, similar to the regulation practiced in Iran. The study by Bin Abdul Aziz et al. (2018) presented a multitude of global regulatory practices that Malaysia could adopt to effectively regulate stem cell technology in Malaysia. The ethical controversies that surround stem cell technology, such as the destruction of embryos during HESC extraction, the use of cloning to create more cells, and unproven clinical trials, demand regulation for effective oversight to prevent unethical conduct or exploitation. A clear set of laws and policies that is appropriate to regulate stem cell technology will minimise the ethical issues, and transparent rules will facilitate scientific progress, as pointed out by many scholars previously (Caulfield et al. 2009; Mintrom and Bollard 2009; Staunton 2013).

With the foregoing discussions in mind, this study aims to develop a comprehensive documentation of the ethical, legal, and social implications, or ELSI, of stem cell technology in Malaysia by reviewing the current regulatory processes and discussing the ethical and legal implications; this attempt is quite similar to the efforts of Ishii et al. (2013), Zarzeczny and Caulfield (2009) on stem cell investigation and those of Callier et al. (2016) and Clayton (2003) on genomic medicine research. The broad analysis will provide clarification for the stakeholders regarding standard protocols and ethical conduct and will help cultivate the practice of informed decision-making among stem cell policymakers.

Methodology

This study employs a literature review and in-depth interviews of experts to understand the development, regulation, and implications of stem cell technology in Malaysia. The literature review proves helpful in identifying previous studies conducted on the topic, which enable the researcher to understand a broad area of the subject (Webster and Watson 2002). The interviews of experts such as scientists, ethicists and policymakers, are especially appropriate in exploring the many unknown aspects of stem cell technology, its ethics and regulation in Malaysia, which cannot be attained without speaking to the experts (Boyce and Neale 2006). Internet

[1] For more information on Braithwaite's Theory please see Ayres and Braithwaite (1992).

searches using keywords like "stem cell*" and "ethic*", with appropriate Boolean operators such as AND, were repetitively conducted through Google and Web of Science (WoS) to retrieve Malaysian and international journal articles, books, and book chapters written on stem cell technology, regulation and other related topics. These include government circulars, annual reports, and press releases retrieved from the Malaysian Ministry of Health. These documents were reviewed and analysed qualitatively focusing on specific keywords in context, which is a common practice in empirical study among social science researchers (Webster and Watson 2002; Onwuegbuzie et al. 2012).

In carrying out the interviews, the researcher used a semi-structured, open-ended questionnaire containing key questions formulated on stem cell ethics and related regulations in Malaysia, which permit some divergence to elicit specific responses in detail (Berry 1999). Using the purposeful sampling technique, eight Malaysian experts involved in stem cell-related inquiries were identified, including three scientists, one ethicist, and four policymakers who are familiar with stem cell developments, regulations and implications based on their respective positions and experience (Patton 1990; Boyce and Neale 2006). After securing a valid ethics approval, face-to-face interviews were carried out starting from 1 August 2016, with each session lasting between 30 and 60 min. The data were transcribed and analysed inductively, the results of which were utilised in the discussion and in drawing the conclusions of this study (Bogdan and Biklen 1982; Gill et al. 2008; Bailey 2008). Finally, the triangulation process was undertaken to assure the convergence and consistency of the data gathered from literature review and the results of the interviews (Migiro and Magangi 2011; Johnson and Onwuegbuzie 2004).

Results and Findings

Stem Cell Regulation and Policymaking in Malaysia

Figure 1 presents firstly that stem cell technology in Malaysia remains generally unregulated, implicating the private sector with the most ethical issues.

Secondly, as indicated earlier, there is no legal framework such as laws or legislation that can be enforced to effectively regulate the stem cell technology, leaving room for exploitation, as the experts have acknowledged.

> There are no legal laws or acts in Malaysia for stem cell. There is only the guideline that is meant to guide scientists and researchers, meaning when someone violates the ethical or moral conduct stipulated in the guideline, actions are not taken against them. (Scientist 1)
>
> No. We do not have any law yet. But personally, I think we need one. However, in order to come up with one appropriate law, it needs to be formulated by the right authority. (Scientist 3)

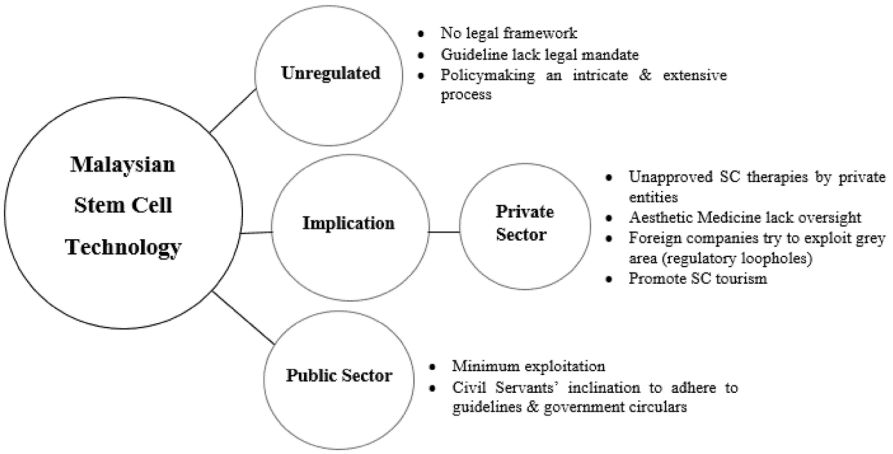

Fig. 1 Malaysian stem cell technology

> Still unregulated. We do not have any law. Stem cell regulation in Malaysia needs an act or law. (Policymaker 1)
> There is no specific law yet. (Ethicist 1)

Thirdly, in the absence of a legal framework, the four guidelines (Guideline for Haematopoietic Stem Cell Therapy, National Standard for Cord Blood Banking and Transplantation, National Standards for Stem Cell Transplantation, Guideline for Stem Cell Research and Therapy, or Stem Cell Guideline) do not have any legal standing; they overlap with one another with unclear jurisdiction and cause confusion among scientists and physicians. As a result, stem cell research and development are hindered (Carvalho and Ramalho-Santos 2013). The Guideline for Stem Cell Research and Therapy, formerly referred to as the Guideline for Stem Cell Research, was initially formulated in 2006 (revised in 2009) when the Ministry of Health was approached for the approval of Malaysia's first cardiovascular stem cell transplant, a collaboration between Kansai Medical University and Kuala Lumpur Hospital in 2003 (Lee 2003).

> Ministry of Health received a proposal from UKM,[2] as they had a professor with a heart problem who went to IJN.[3] They needed Ministry of Health's endorsement and therefore were allowed, but only as a clinical trial. Ministry of Health needed to make that clear. That in the case of death of the patient, the healthcare providers are not held responsible. (Policymaker 1)

The stem cell guideline was formulated by the Drafting Committee within the Technical Committee of Stem Cell Research, established as part of the National Committee on Human Cloning to deal with the ethical conduct of the rising number of

[2] UKM is *Universiti Kebangsaan Malaysia* also known as Malaysia's National University.
[3] IJN is *Institut Jantung Negara* also known as National Heart Institute.

stem cell transplantations and their approvals. The policy experts verified that it was meant as an interim measure while a permanent solution was being devised.

> As for the stem cell guideline, it is still deemed adequate and up-to-date. Not to mention the formulation of an act that often takes very long. Hence, the ministry voted that the guideline was still accounted for as adequate to oversee everything. (Policymaker1)

Malaysia's regular policy deliberations in the last decade faced several key challenges that had delayed the stem cell policymaking considerably. The lack of consensus among the policymakers, who were mostly physicians and scientists from different areas of the Ministry of Health, such as healthcare and research, was identified as one of the most significant challenges. Their disagreement centred mostly on the issue of whether solid organ and stem cell transplants need to be dealt with together or separately. While some are supportive of solid organ transplant, their uncertainty of the nature of stem cell transplant creates reservation. Others found combining the two categories of transplants under one piece of legislation challenging. With overlapping provisions, it is clearly a difficult process.

> There was a lot of discussion about separating the solid organ transplant and stem cell transplant. The group favouring solid organ said it would be easier to get the act passed if they did not include the hemotherapy. (Policymaker 2)

There were several other factors that complicated the legislating process: inconsistent instructions given by the current and former Deputy Directors of Health and the Attorney General, and the considerations of the diverse religions in Malaysia. The entire process is very intricate, requiring an extensive review of many aspects that are unique to Malaysia.

> I have been deliberating a lot, working with many policies and proposing a transplant act but it is still not ready. It has been so, for the past many years. During our discussion, the Deputy Director said we must combine the solid organ and stem cell transplantation together. Once combined and presented to the Attorney General, he offered a different opinion. (Policymaker 2)

While the policymakers have conflicting views, it is relevant to note that the committee of policymakers deliberating stem cell regulation consists of scientific and medical experts alone. They are knowledgeable about the stem cell research, clinical trials, and transplantation, but it is pertinent to note that no ethicists or philosophers were recruited for their insights concerning the ethics of stem cell technology (Ministry of Health 2009).

Some Implications Due to the Current Regulations

In 2008, a Malaysian state government signed a memorandum of understanding (MoU) with a foreign stem cell company to establish the world's largest rabbit breeding farm in Janda Baik, Malaysia, with the purpose of extracting stem cells

from the rabbits for human treatment (Mohamad 2008).[4] The company was said to be US-based with an office in Orange County, California; its founder was a Czechoslovakian physician who began his early medical career in plastic surgery but then pursued foetal precursor transplant with offices around the world (Coker 2018). He was convinced that by using animal foetal precursors, such as live stem cells extracted from rabbits, he could treat many incurable diseases. Despite the signing of the MoU and the official press release in Malaysia, the Ministry of Health was only consulted concerning the land lease for rabbit breeding at the very end to legalise the deal. Although the stem cell company claimed that their rabbit stem cell therapy could treat Down's syndrome, they did not comply with a sample request made by the Ministry of Health, which created doubts among the policymakers. The company is said to have fled to Indonesia to seek new business ventures, corroborating the Ministry of Health's suspicion (Hasballah 2015).

> All the claims made were never verified by any authority or theory. Basically, the claim that …. their foetal precursor xenotransplantation could polarise the patient's body from rejecting the injected rabbit's embryonic stem cell seemed far-fetched. When asked to send in sample for testing, they made excuses with more claims such as the cells would die, or the ministry experts would not know what to look for and others. (Policymaker 2)

There were several advertisements for stem cell therapy in the newspapers, social media, and websites placed by Malaysian private healthcare providers, aesthetic clinics, and various stem cell entities (whose names are withheld for ethical reasons). In 2013, the Academy of Sciences Malaysia (ASM) reported that there were eight private stem cell entities operating in Malaysia, including research companies as well as cord blood and tissue banks (Academy of Sciences Malaysia (ASM) 2013). Out of the eight, only five stem cell entities were included (as of 31 December 2017) in the 'List of Licensed Private Healthcare Facilities and Services' available in the Medical Practicing Division of the Ministry of Health. They are Stempeutic Research Malaysia (a stem cell research entity); NISCELL, CryoCord, Stem Life, and CellSafe (four cord blood and tissue banks) (Medical Practice Division (MOH) 2017a). The policymakers interviewed for this study indicated that only four entities have obtained approval from the Ministry of Health. This inconsistency of different agencies giving out contrasting data confuses the stem cell treatment seekers regarding the legitimacy of the entity providing the service. The lack of coherency highlighted two more ethical issues associated with stem cell technology in Malaysia: firstly, the unlicensed entities operated without restriction; and secondly stem cell related products and services were offered without going through the necessary risk assessment.

> But when Dr Chua was the Health Minister, he only allowed or licensed four companies under the cord blood banking, which are Stem Life, CryoCord,

[4] The Official Portal of 'Invest in Pahang', developed by the Pahang State Development Corporation (2012), has a section on Stem Cell within its opportunity section mentioning the project. There is also a write-up on the Czechoslovakian physician by Coker (2018) in OC Weekly Magazine.

> Niscell and Stempeutics. Reasons were that there were way too many. Initially, these entities at the point of entering the market, did not follow the standard ethical protocols although they eventually acquired the necessary licensing. (Policymaker 3)

The stem cell policymakers did not elaborate further on the nature of these private stem cell entities established; some of these companies operated their business while simultaneously applying to acquire a licence, but the remaining entities operating without license as previously listed by ASM (2013) raised concerns. The conduct itself is unethical as the standard protocols for licensing demand the necessity of product testing for safety and efficacy. These entities may eventually obtain their licences, but with the limited scope of this study, it is difficult to verify and justify this kind of practice, because any attempt to gain details of the processes may violate the rules of intellectual property or confidential information that protect these entities.

Arguably, the power of regulating stem cell therapy should come under the purview of the National Pharmaceutical Regulatory Agency (NPRA) but it has yet to assume the responsibility as verified by the policymakers during the interviews.

> The NPRA has yet to take on the duties of regulating SC therapies as a common therapy. The majority of them are still overseen by the National Stem Cell Research and Ethics (NSCERT) subcommittee as clinical trials. (Policymaker 4)

Currently, NPRA only handles the listing of a wide range of marketable stem cell products in its database, and the public can access the information for verification purposes (National Pharmaceutical Regulatory Agency (NPRA) 2017). This study reveals that the inconsistency of the existing stem cell entities could be due to the overlapping jurisdiction of several agencies that oversee stem cell technology. The National Stem Cell Research and Ethics Subcommittee (NSCERT) reviews clinical trials and research involving stem cells; the Medical Practicing Division of Ministry of Health regulates the private medical sector; and NPRA is expected to assume the duties of regulating stem cell therapies and other related products but it is unclear when. With several agencies overseeing the stem cell industry, there will definitely be many overlapping functions that complicate the regulative process. Some entities are licensed as a facility, based on the 'List of Licensed Private Healthcare Facilities and Services' (as of 31 December 2017), but their stem cell therapies or clinical trials are not, and hence the safety and efficacy are questionable.

The Medical Practicing Division within the Ministry of Health is in charge of registering and licensing the private healthcare providers' facilities and services (i.e. medical clinics and hospitals), conforming to the Private Healthcare Facilities and Services (PHFS) Act (1998) and the Good Manufacturing Practice (GMP) regulation. These private entities, both clinics and hospitals, are required to register their clinical trials and therapies with the National Medical Research Registry or NMRR The registry is accessible to any individual of the public who wishes to seek verification. Therefore, in order to verify the legitimacy of a particular establishment, the public can access the NMRR and the Ministry of Health databases for further

information (MREC 2012). The practice of these entities in offering treatments, while still in the process of applying for a licence, is morally and ethically reckless, and it is difficult to determine the potential extent of harm. However, this does not mean that only unlicensed entities are carrying out unethical practices (Kelland 2010; Habermann et al. 2010).

According to the PHFS Act 1998, and Allied Health Profession Act 2016, entities advertising false claims of stem cell therapy infringe the law and are punishable by a fine and imprisonment. Despite these regulations, a renowned licensed medical centre in Malaysia openly publicises its stem cell therapy for various sports-related injuries on its website (Ung 2012). The medical centre also owns a stem cell company established in 2005, which pursues research in regenerative therapy. The lead surgeon holds a US patent but the clinical trials were never registered in Malaysia prior to 2017 (National Medical Research Register (NMRR) 2017). The policymakers verified that the entity's stem cell therapy was never licensed.

> They are not actually licensed for stem cell therapy. The licence which we issue looks into what kind of services these entities are offering and what type of facilities they are getting the licence for. (Policymaker 3)

Similarly, aesthetic clinics in Malaysia are licensed and registered but their treatments and procedures involving stem cells are not (Medical Practice Division (MOH) 2017b). As a new field, aesthetic medicine is also overlooked by the Guidelines on Aesthetic Medical Practice, which do not mention stem cell therapy or treatment. The practices are based on the decisions of three credential and privilege committees that review the experts, their facilities and services (Ministry of Health 2013).

> There is even a beauty salon that offers stem cell based facial treatment, but it is not directly under the Ministry of Health's oversight. When these entities register as a company despite offering some health-based treatment and services, it comes within other ministries for monitoring. (Policymaker 1)
> If you want to open up an aesthetic establishment, even then you need to have some 'aesthetic' within your licence for every kind of service. So, they (aesthetic clinics) cannot simply put up stem cell in their licence without asking the ministry. This is because the private healthcare act is quite binding to control practices that come within its jurisdiction. (Policymaker 2)

The NSCERT subcommittee was never approached by the aesthetic clinics although the clinics offered stem cell-based treatments, live cell or otherwise.

Regulatory Loopholes Promote Stem Cell Tourism

The policymakers who participated in this study verified that the providers of aesthetic medicine and private entities that offer unproven stem cell therapy exploited the existing loopholes of the standard regulation. This is a clear regulatory deficiency that requires immediate attention.

> The healthcare facilities and services are licensed under the Medical Practicing Division. So now when they are licensed under us (Medical Practicing Division), they are licensed for certain things, especially the facilities and their medical practice. So, if they offer extra services than the approved ones, they are considered to be exploiting the act. (Policymaker 3)

However, despite the policymakers' verification of the obvious non-compliance with the PHFS act and stem cell guidelines by the aesthetic clinics in Malaysia, actions have not been taken against them. Separately, according to the Health Ministry's parliament secretary, about 100,000 foreign tourists generated total revenue of USD 36 million in 2001, compared with only USD 2 million in 1998 with about 39,000 tourists. Clearly, there are efforts to promote Malaysia as a health tourism destination with an allocated budget (TheStar 2003). Both the Ministry of Health and the Ministry of Tourism Malaysia are working towards promoting healthcare as an international commodity to boost medical tourism; they hope to rake in revenue exceeding the target of USD 535 million by the year 2022. In 2017, the Health Minister said that due to its huge potential, healthcare tourism was included as part of the National Key Economic Area (NKEA)[5] and had a potential spending of about USD 359 million for the year 2018 (TheStar 2017). This could easily include stem cell tourism, especially with the unclear or flexible regulations and weak enforcement that are quite common in countries like Mexico, India and Thailand (Sipp 2017). The favourable currency exchange rate and the affordable stem cell therapies bring in many tourists to Malaysia in search of various treatment options. Studies have identified Malaysia as one of the favourite medical tourism destinations (Bin Abdul Aziz et al. 2018; Wong et al. 2014).

The Malaysian government's effort in promoting medical and healthcare tourism will benefit the segment of stem cell tourism; unproven stem cell treatments will continue to thrive in the absence of clear regulation and oversight, and attract not only local residents but tourists too. Patients who have exhausted all available options within their country are willing to travel abroad to seek experimental stem cell treatment that is widely advertised on the official websites of private healthcare providers, and through the news and social media, although these treatments have yet to be proven safe or effective (Murdoch and Scott 2010; Sipp 2017). It is unethical for profit-seeking private healthcare providers to offer unproven stem cell treatments that have not undergone a thorough risk assessment and efficacy testing; at the same time, it is unscrupulous to charge patients a big sum of money for an experiment that could have an adverse effect on them (Sipp 2011, 2017). It is also difficult to verify if any of these therapies actually deliver what they advertise; the use of artificial cells or non-human cells cannot be ruled out (Sipp 2011). Although stem cell tourism is a major concern, the key issue is the advertisement and direct marketing of unproven stem cell treatments to the consumer in countries where regulation is non-existent or lax, like Malaysia. This not only affects Malaysians,

[5] NKEA is described as 'an important driver of economic activities towards Malaysian Economic Growth measured by the National Gross Income (CNI)'.

but also tourists coming to Malaysia from countries with more stringent regulations, proving that regulation, oversight and effective enforcement is essential (Turner and Knoepfler 2016; Lau et al. 2008).

Malaysian Stem Cell Guideline

Among the four guidelines, the stem cell guideline (2009) is the most relevant to stem cell research and therapy, including all stem cell derivatives from somatic cells to embryonic stem cells; the rest of the guidelines focus on cord blood banking and bone marrow transplant, also known as haematopoietic stem cell therapy, which is conducted regularly in Malaysia since the first case in 1987 (Gan et al. 2008). The haematopoietic therapy and non-haematopoietic therapy each have a separate guideline, but only the stem cell guideline (2009) covers both research and therapy, while the others focus on therapy alone. The stem cell guideline was originally formulated in 2006 and subsequently revised in 2009; the guideline initially included the practice of xenotransplantation but forbade it after the controversial rabbit farm incident. One of the new stipulations is to permit non-human stem cell research for all species (previously restricted to only mice and primates) and the use of embryonic stem cells for research purposes. It prohibits all forms of human embryo production for research purpose (not just assisted reproductive technology ART and somatic cell nuclear transfer SCNT) (Ministry of Health 2006, 2009). With these provisions, all future innovative techniques are accounted for.

In the initial stage of formulating the stem cell guideline, the *Fatwa*, the formal Consultative Committee of Islamic Law in Malaysia, was consulted to review if stem cell technology, especially research on human embryos, contradicts religious practice:

> We tried to get the religious authority on board. Malaysia being an Islamic country, we needed to get the *Fatwa* sorted out. The use of ESC for research before the *alaqah*[6] stage is religiously tolerable. However, to use them beyond the *alaqah* stage leaves a lot of room for religious manipulations that could be against the Islamic practice. (Policymaker 2)

The religious consideration of HESC was well studied and documented by many Malaysian and international scholars such as Sivaraman and Noor (2014), Foong (2011) and Saniei and Baharvand (2018). The review concluded that based on Islamic scripture, the process of ensoulment of an embryo, similar to the context of 'when life begins', occurs around the 40th day after fertilisation. Thus, the use of human embryos in HESC research is justified, especially with the 14th day rule as adopted by many countries around the world, including Malaysia. In 2005, the *Fatwa* approved the practice but requested that the use of sample or excess from in vitro fertilisation (IVF) embryos be further reviewed by other religious authorities

[6] *Alaqah* marks the ensoulment stage of an embryo in Islamic belief. Refer to Saniei and Baharvand (2018).

in Malaysia, taking into consideration the many diverse religious backgrounds (Ministry of Health 2006). Consequently, the policymakers approached other bodies to seek their views and comments, which included the Department of Islamic Development Malaysia (JAKIM), the Medical Association of Malaysia, and Malaysia's Consultative Council of Buddhism, Christianity, Hinduism, Sikhism, and Taoism. The outcome was neither practical nor constructive, as verified by the policymakers (Ministry of Health 2009).

> Yes, we had engaged them prior to the launch of the guideline but the feedback was not that positive. There are some who opposed HESC such as the Buddhist but the 14th-day rule justification only reflects the Muslims' view. (Policymaker 1)

The revision was also said to include constructive comments of non-governmental organisations (NGOs) and inputs of a public forum on stem cell research that comprised mainly doctors and physicians, with only one lawyer and an Islamic expert (Ministry of Health 2009). Neither ethicists nor philosophers were approached. Based on the present guidelines, there is no explicit difference between the public and private stem cell regulation, but research and therapy are dealt with separately. The guidelines state that all research and therapy are required to obtain approval from the institutional review board (IRB), institutional ethics committee (IEC), and NSCERT subcommittee. Neither versions of the guidelines address or highlight the issue of non-compliance or accountability. There is no stipulation that invokes the civic duty of the general public as whistle blowers, despite policymakers' statement that it is an essential step for the enforcers to act against any wrongdoers.

> Without any formal complaints, there is nothing the NSCERT can do regarding wrongdoing. The regulators need whistle-blowers to initiate course of action. (Policymaker 1)
> If people know that something is wrong ethically or legally, they need to make a complaint to the ministry and to the right department. (Policymaker 3)
> Right now, only guideline is available. This means, if there are any people or scientists who are doing something against the ethical or moral perspective, we cannot prosecute or cannot charge them. (Scientist 3)

Since 2009, there have been no revisions or amendments, which would seem to imply that the regulation is considered up-to-date and valid.

Discussion

Without a legal framework, stem cell technology in Malaysia remains generally unregulated, and the unclear regulation has to some extent hindered Malaysian stem cell scientists from undertaking research and development in the field, especially investigative work involving human embryos, and thus stifled growth in that area. This is not surprising, as a study by Sleeboom-Faulkner et al. (2018) related to governance of stem cell transplants in China reported a similar predicament. The

internal challenges of red tape and inconsistent instructions given by the former and current administrators have complicated stem cell policymaking. A mission statement with clear objectives and the goal of stem cell regulation will be helpful in mitigating the conflicts as well as reducing the discrepancies of decisions among the current and future policymakers and their administrators, without jeopardising the ongoing process (Tulchinsky and Varavikova 2014). However, even a clear mission statement can still be interpreted based on the policy officials' subjective level of knowledge and understanding (Huang 1999; Fischer and Gottweis 2012). Hence, discrepancies are inevitable and the process will be extended without leading to anything useful (Monaghan 2011; Uraiwan 1984).

It is clear from this study that there should be more concerns about the operation of the private sector than the public sector. The public sector is bound by the government services act, and civil servants have an inclination to adhere strictly to the stem cell guideline and a number of official circulars issued by the director general of health, dated 14 November 2011 (Ref: KKM87/P1/26/10Jld/13(39)) and 2nd April 2015 (Ref: KKM87/P1/26/10Jld18(41)). These circulars are legally binding as far as public servants are concerned. Public servants are expected to be open in their documentation of the research, clinical trials, government funding and grants, and to maintain professional integrity in the public service. Since the public sector's primary goal is not driven by sales or profits, there is less probability of exploiting the consumer or patient (Halvorsen et al. 2005).

The Stem Cell Guideline and Its Deficiency

Religion was a primary consideration with *Fatwa*'s initial feedback. As noted above, other religions' inputs on embryonic research were also considered during the revision of the guideline (Ministry of Health 2009). However, the effort proved futile as the responses were directed towards religious goals without much influence on the regulative query.

> When we had the feedback session, those from the religious bodies/group tend to speak a lot about their own religion, going into detail, for example, what is Buddhism etc. Similarly, with the Christians, so who shall we listen to? It was difficult. (Policymaker 2)

Although the aspect of religion should not pertain to the matter of clinical translation, it does however receive significant focus among Malaysian policymakers. Religious consideration will always be an integral part of law and policymaking in Malaysia as religious identity and freedom are embedded in the constitution of Malaysia (Malaysian Parliament 2010). Such preparatory efforts are prudent in anticipation of not only the possibility of future clinical trials involving HESC, but all other technologies that may emerge, especially in a multi-religious country. However, this would delay the deliberation pertaining to stem cell technology considerably.

Apart from the religious considerations, the stem cell guideline suffers from insufficiency in several other aspects. Firstly, the lack of definition between the

regulatory protocols of public and private stem cell sectors. Since most cases of exploitation and ethical issues come from the private sector, the guideline must contain distinctively exclusive stipulations. In the absence of the private healthcare providers' own IRB and IEC, only clinical trials are reviewed by the NSCERT subcommittee, while aesthetic procedures and other unconventional practices slip through the loopholes. Secondly, it is evident that NMRR registration is not provided for in the guideline despite being the only database that records stem cell research and therapy; the NSCERT reviews are not disclosed to the public, making the verification process difficult. Thirdly, the guideline does not address the non-compliance issue nor does it disclose the need for formal complaints for proper execution of the expected regulation. This hampers the whistleblowing action expected of the general public, as the people are not well-informed. According to the policymakers, the general public needs to file formal complaints against wrongdoers who breach the guidelines so that the appointed enforcement officers can take appropriate action.

> "…without any formal complaints there's nothing the NSCERT can do about it. They need whistle-blowers to take action…" (Policymaker 1); "… before the ministry can do anything or take action against any malpractice, there needs to be a complaint." (Policymaker 2) "If you know people doing things unethically, then you have to report." (Policymaker 3)

The ineffective implementation and execution of the stem cell guideline to achieve its objective is a secondary matter; the primary concern is the absence of a transparent regulatory policy or legislation which allows the guidelines to have enforcement authority to deal with the unethical practices of stem cell technology. The guideline alone is ineffective in raising awareness among the stakeholders nor does it help in identifying exploitations and curbing them, since there are so many overlapping jurisdictions (Lye et al. 2015). While the guideline has many provisions to improve the stem cell industry, the policymakers verified that the stem cell guideline contains only recommendations with general statements that do not carry any legal authority. With the non-binding nature of the guideline, the industry is compelled to act out of a sense of duty, and to self-regulate without enforcement. Generally, enforcement is a process of compelling observance or compliance with the provisions of the law or legally binding policy, the absence of which will lead to weak or no enforcement at all (König et al. 2007).

> That the guideline is deemed as merely a recommended practice, yes we agree. (Policymaker 1)
> Guideline is not binding. (Policymaker 2)
> Because if you prepare guidelines, and are not linked to an act, then people do not follow it. (Policymaker 3)

Preventing a Catastrophic Aftermath

Reports of mishaps, fraud, or death of patients can constitute proof of wrongdoing or foul play (National Academy of Sciences (US) et al. 1992). Although in Malaysia such reports of misconduct involving stem cell technology have yet to reach that magnitude, one cannot rule out the possibility entirely based on the axiom, 'absence of evidence is not evidence of absence' attributed to astrophysicist Martin Rees in his book, 'On the Future: Prospects for Humanity' (2018, p. 162). Most cases of misconducts are resolved discreetly and amicably, avoiding press and defamation (Titus et al. 2008; Ben-Yehuda and Oliver-Lumerman 2017). Since aesthetic medicine and stem cell treatments are only overseen by a guideline, unethical cases involving either of them are a likely scenario that could have catastrophic consequences. For instance, an Australian online news outlet reported that a 31-year-old man died as a result of some extreme aesthetic procedures he underwent in Malaysia in 2014 (Killalea 2016). Several local Malaysian newspapers highlighted the incident but did not emphasise the gravity of the issue in the absence of legislation to protect the stakeholders. While the surgeon involved stated that the man received the best care, it was impossible to determine if the patient knew the risk involved or if a proper informed consent was ever obtained.

Aesthetic medicine is very popular as a component of medical tourism in Malaysia and it could indirectly be used to promote stem cell treatments to would-be tourists; none of the guidelines will be able to protect those involved in the sector (Khan 2017). A broadly defined regulatory policy would prove valuable to regulate stem cell technology and other areas within the healthcare jurisdiction, including aesthetic medicine (Tipton and Krause 2006).

> Yes, I think it's important to have a law…research on stem cell is going to continue then there are already so many claims of usage and its potential use, so we should be thinking about regulating it with a proper act. (Ethicist 1)

While a regulatory policy can be definitive, dynamic, and reliable to keep a country free from corrupt practices, it can be equally beneficial to all parties concerned in the healthcare industry as presented by Noll (1985) and adopted by others.

Recommendations for Improving Current Regulation

As this study indicates, the present regulatory framework is weak and contains many loopholes that can be abused by private stem cell entities in Malaysia; this situation exists due to the lack of standardisation of instructions between the public and private sectors, which contributes to the state of confusion, discrimination, and ultimately exploitation (Organisation for Economic Co-Operation and Development (OECD) 2012). Although formulation of a regulatory policy and legislation is considered as the main solution, improving the current stem cell guideline should also be explored. Therefore, in order to strengthen the effectiveness of the regulation, these recommendations will be useful and efficacious. A clear objective concerning the roles of the

public and private sectors will encourage caution in the formulation of regulation, especially as the former serves the public and the latter is profit-seeking. The policymakers have a duty to revise the stem cell guideline and amend several noticeable shortcomings (Shekelle et al. 2012; Winker et al. 2000).

First, explicitly address the public and private stem cell regulation separately by outlining transparent stipulations to prevent unclear and overlapping provisions. A clear guideline that has well-defined conditions will appear authoritative and transparent as well as spelling out the coherent functions of the Ministry of Health (Organisation for Economic Co-Operation and Development (OECD) 2012). This includes the licensing of facilities, laboratory requirements, research and therapy approvals, and the registration of research and therapy within the NMRR registry and NPRA. A carefully crafted regulatory document will significantly reduce overlapping jurisdiction between the guidelines. There are many international stem cell guidelines formulated thus far, but the US based International Society for Stem Cell Research's (ISSCR) Guidelines for Stem Cell Research and Clinical Translation (2016) appear to be the most transparent and broad. The guidelines highlight many areas and topics of stem cell research and clinical trials; Malaysia can either adopt them or have their current guidelines revised to incorporate the currently unaddressed aspects like regulatory stages, public communication, and recommendations.

Unlike the Malaysian stem cell guideline, the ISSCR guidelines explicitly describe the different stages of stem cell research, namely laboratory research, and preclinical and clinical experimentation involving animal and human subjects. The ISSCR guideline also clearly explains the responsible conduct of the stem cell treatments and research with specific recommendations such as sourcing of stem cells, international collaborations, regulatory oversight, and consideration of social justice. In describing the practices, the ISSCR guidelines outline the prohibited practices similar to what Malaysia has adopted such as the 14th day rule and therapeutic and reproductive cloning. What is more important and satisfying is that ISSCR also considers the ethics and welfare of the animals used as research subjects. The final aspect of the ISSCR guidelines is regulatory, which entails the regulatory protocols and includes communication that addresses the issues of public information and awareness of stem cell research and its clinical trials. These two very distinct aspects are both important and necessary, but are disregarded in the Malaysian stem cell guideline. By incorporating these aspects as well as recommendations of the public and private sectors, a guideline will be thorough and well thought out, covering all the concerns raised and all the relevant subject areas (ISSCR 2016).

Secondly, resolve the non-compliance and accountability issue by adding specific stipulations to curb the following professional misconduct: misleading advertising, mislabelling of stem cell transplant, and offering of unproven stem cell therapies. At the same time, disclose the penalties for the above-mentioned issues to prevent the rising number of exploitations. Currently, the guideline has a list of prohibited research, but there is no disclosure of consequences of specific non-compliance (Foong 2012). The guideline should also address the process for formal complaints to be lodged by the general public so that appropriate action can be taken by the enforcing agents against the wrongdoers. It ought to mention the practice of aesthetic medicine and have stipulations concerning the stem cell protocols that

correspond with the aesthetic medicine guidelines, which incidentally also need to be revised. The original ISSCR guidelines do not address these matters; therefore, it is recommended that the Malaysian stem cell guidelines be revised to incorporate them and other matters relevant to the Malaysian population and practices.

A bioethical advisory committee within the Ministry of Health would prove useful; it is similar to Singapore's Bioethics Advisory Committee (BAC) or the President's Council on Bioethics in the US that comprises a broad range of experts, such as scientists, ethicist, philosophers, clinicians, lawyers, and even theologians (Turner 2004). The advisory committee will evaluate the ELSI of the various technologies, and from time to time give necessary recommendations to assist the appropriate administration in handling the various evidence-based decision-making processes. The role of the NSCERT subcommittee is inappropriate in this instance, as the members are only assigned to review stem cell research and therapy proposals; its functions are very different from those of a bioethical advisory committee. While the stem cell policymakers may have a working committee to deliberate on the laws and policies, their focus is on the legal aspects without realising what an ELSI report could offer, which is similar to the Warnock Report 1984 and Belmont Report 1979 (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research 1979; Warnock Committee 1984). These reports were instrumental in convincing the ruling governments to adopt some of the effective regulatory recommendations made. The BAC also published many ELSI reports on various subjects considered important by the Singapore government. In 2002, the BAC presented an article entitled 'Ethical, legal, and Social Issues in Human Stem Cell Research, Reproductive and Therapeutic Cloning' to provide comprehensive information on the subject of cloning, and gave the necessary recommendations to the government (BAC 2002). This study's broad presentation of the various ethical and legal implications of stem cell technology in Malaysia, serves as an ELSI report that the policymakers can use to guide them to make informed and wise decisions.

Finally, formulating a regulatory policy that has comprehensive provisions to deal with the exploitations mentioned earlier will provide all of the stem cell-related guidelines in Malaysia with the much-needed legal authority and power. Since guidelines are easier to devise and execute, the compliance is considered optional; any revision of the guidelines is incomplete without a regulatory policy (Hare 2009). The overlapping stipulations of the four guidelines will also be acceptable as long as they coincide with the main objectives of the formal regulatory policy that governs the ethical conduct of all types of stem cell technology. Since execution of a policy involves implementation, monitoring, and enforcement, it will also deal with accountability and non-compliance issues through penalties, which the guidelines have thus far neglected to address and hence they are deemed incomplete (Livesey and Noon 2007; Howard 2003).

Specific or individual provisions or prohibitions can be easily devised in the policy to effectively regulate the many areas of healthcare and biomedical research. Currently, the only aspect that reflects a universal principle incorporated in the stem

cell guidelines is the 14th day rule in HESC research.[7] Studies that have reviewed the laws and policies of stem cell technology around the world, like that of Dhar and Hsi-en Ho (2009) state that the majority of them are country-specific. However, the use of only 14-day old or younger embryos for embryonic research is significant and facilitates international research collaboration, as any procurement of embryos from the countries is lawful. The policymakers' efforts in consulting other religions in Malaysia proved unproductive, as the religious leaders were side-tracked with religiously concerned motives, but this multi-cultural and multi-religious position is a unique Malaysian heritage. It is a factor that requires significant attention and delicate handling in any policymaking process.

Currently the absence of ethical experts in the deliberation committee with a broad knowledge of ethics, legal, and social aspects involving stem cell technology, needs to be resolved. The presence of ethical experts in the stem cell deliberation committee can be valuable in clarifying the stem cell controversies and providing justifications from a multi-perspective angle such as ethical, social, religious, and legal, that scientists and physicians are not proficient in Resnik (2015).

> To tell you the truth, I don't think we have any ethicists in this country, fully trained from undergraduate and postgraduate totally in bioethics, a person who can give an overall view on ethics from philosophy practice. (Ethicist 1)

Therefore, recognising this limitation, the government and local institutions of higher learning should consider allocating grants and research fund to persuade experts to conduct inquiries into ethical principles and universal theories of various biomedical technologies, including the social and regulatory implications; such efforts will facilitate comprehensive understanding of the stem cell industry, and the investigators can also serve as experts when necessary (Finn 1999).

Conclusion

Malaysian policymakers' ongoing deliberations on stem cell regulation in the last decade have not produced anything significant. It is common knowledge that discrepancies exist among policy officials and administrators, and there are disagreements among policymakers due to conflicts between those who are in support of stem cell technology and those who are not; these are inevitable challenges that cause an extended and lengthy deliberation process. Despite the hurdle, the policymakers are convinced that with concerted efforts from all concerned parties, a comprehensive regulatory framework will materialise in the near future. The new policy or law will possibly place both solid and stem cell transplants under one regulatory

[7] It is based on the justification and opinions of many scholars (theologians, ethicists and philosophers), that any act that leads to the destruction of an embryo after the formation of primitive streak (that occurs after the 14th day) which marks the onset of a sentient-being as unethical. Embryos at blastocyst (prior to the 14th day) stage are not rational beings, and therefore the 14th day rule inspired by Immanuel Kant is a concept of universalisability, which has been adopted by many countries around the world (Potter and Timmons 2012; Cummiskey 1996; Pera 2017).

umbrella, but the exact timing of the outcome is uncertain. ELSI reviews and studies are valuable and have contributed towards providing evidence to aid the process of policy and law-making. Wide and comprehensive multi-perspective analyses are necessary for any interested party to understand an innovative technology such as stem-cell engineering and research. It is essential to document the controversies that surround a particular technology, the impact of that technology to the society, and the implication of the long-term research without restriction. Therefore, an ELSI report on the stem cell technology would definitely prove valuable in Malaysia as the policymakers attempt to conclude the policy deliberation.

This review touches the following areas and aspects: stem cell regulation, the insufficient mandate of the stem cell guideline, the implications of unregulated stem cell technology, and the loopholes that exist based on the current legal practices. The recommendations put forward in this study are valuable, and could help the policymakers make the necessary decisions in regulating stem cell technology effectively. The timing of this study could not be any better; the newly installed government is keen to mend the administrative flaws of the previous regime, and therefore can now utilise the findings of this study to improve the regulation of stem cell technology. It would be ideal if all countries in the world could adopt a universal law to promote global peace and harmony, which would prevent conflicting values and visions. Currently, the enactments of various country-specific laws, with some universal stipulations, are a step in the right direction in regulating stem cell technology.

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