Title

Regulating Human Stem Cell Research and Therapy in Low and Middle Income Countries: Malaysian Perspectives

Abstract

Many ‘rising powers' such as India, China, Argentina, Singapore, and Brazil are investing in stem cell technology, joining the traditional leaders in the field, such as the UK, Germany, USA, and Japan. Malaysia is also entering this sector because of the potential medical and economic benefits that the use of stem cell technologies could provide. Like other countries, Malaysia faces the challenge of how to encourage scientific progress and innovation in an ethical manner while at the same time ensuring a safe and accessible market for regenerative therapies. This paper reports on the research findings of semi-structured interviews with local stakeholders to investigate how they perceived and evaluated the current regulatory framework for human stem cell research in Malaysia, and what might be at stake if the state continues with its current regulatory approach.

Keywords:

Human Stem Cell Research; Regulation; Stem Cell Ethics and Policy

Introduction

Human stem cell research (hSCR) is recognised as "one of the most high profile and promising areas of 21st-century science" (Huang He, and Wang, 2013; p. 3320). The study of stem cell technology holds considerable ‘therapeutic promise’ for producing new regenerative treatments for chronic and degenerative diseases, which are incurable by current conventional medical treatments. Concomitantly, new knowledge produced by stem cell technologies is also anticipated to open up new spheres of commercial activity and drive economic growth and prosperity for scientists, companies, and states (Perrin, 2005; Salter, 2008; 2009;

Gardener, Webster and Mittra, 2017). While stem cell research promises many benefits, it also has been controversial because of the many ethical issues that it raises, which have led to different national approaches to regulation.

To become a 'player' in this sector, a new state needs to find a suitable way to become competitive in the global marketplace for regenerative medicine while protecting public safety and maintaining international scientific legitimacy. Therefore, one can argue that *de novo* national investment in hSCR involves tensions between the aspiration to support and encourage development of new medical interventions and the need to assuage public concerns and ensuring safe, accessible, and ethical development.

Malaysia provides a case study of how the tensions between local and international demands, and between competition and legitimacy, shape the implementation of a regulatory strategy in a smaller Low and Middle Income Country (LMIC). We aim in this article to examine the Malaysian regulatory framework that has emerged to govern hSCR and to investigate the ways in which this framework is negotiated and evaluated by various local actors, including regulators, stem cell scientists, and clinicians. We review the challenges encountered by those attempting to conduct or regulate hSCR in Malaysia, providing some insights into the regulation of stem cell technologies by LMICs more generally.

This paper is based on empirical research that was carried out by the first author for a doctoral research project funded by the Malaysian Ministry of Higher Education and University of Malaya. The aim of the research was to identify an appropriate regulatory framework for hSCR in Malaysia. In so doing, a comparative legal study was carried out between Malaysia and a few chosen Commonwealth countries, namely the UK, Canada, Australia, India, South Africa, and Singapore, taking into accounts views and opinions shared by local stakeholders that were obtained from qualitative interviews. The nature of the interviews is described in more detail in the methods section of this paper.

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The Regulatory Challenges

Stem cell research is an increasingly globalised phenomenon with many 'rising powers' such as India, China, Argentina, Singapore, and Brazil investing in hSCR, alongside the traditional players such as the UK, Germany, USA, and Japan (Salter, 2008; 2009; Rosemann et al., 2016). On the one hand, this has resulted in increased transnational collaboration between stem cell scientists (Luo and Matthews, 2013), but on the other hand, states increasingly position themselves in competition to one another for a share of the prospective global market for regenerative therapies (Salter, 2008; 2009). From this perspective the role of the state is to actively facilitate and promote innovation (Salter, 2009; Gardener, Webster and Mittra, 2017). One way in which states can do this is by providing a regulatory framework. Regulation provides a means for states to alter the behaviour of relevant actors in ways that accord with desired policy goals or outcomes, through standard-setting and behaviour modification (Mandel, 2009).

Notwithstanding its potential benefits, hSCR has also been attended by its share of controversial issues. The most contentious, at least in terms of public debate, has been the use of human embryos for the derivation of human embryonic stem cell (hESC) lines, with extensive discussion over the moral status of human embryos and the ethics of their use/destruction in both research and reproductive scenarios (Zarzeczny and Caulfield, 2009). Other issues that have proven controversial include the technique of somatic cell nuclear transfer (SCNT) for both 'reproductive' and 'therapeutic cloning', the sourcing of (and trade in) human oocytes for creating new stem cell lines, intellectual property rights in stem cell lines and techniques, and unproven stem cell therapies (WHO Resolution WHA51/6; Langlois, 2017; Bahadur and Morrison, 2010; Schultz and Braun, 2013). The latter aspect, in particular, remains a source of ongoing contestation. Given the high degree of promise

associated with its medical potential and the global pool of patients with unmet medical needs, there are many individuals who have been prepared to try stem cell therapies (and things marketed as 'stem cell therapies') that have not undergone regulatory assessment or conventional clinical evaluation (Sipp et al., 2017; Servick, 2017).

One of the tasks for regulation is therefore to manage the potential dangers and hazards (including moral hazards) posed by disruptive new biotechnologies. In the case of research using human embryonic material, countries have adopted different strategies resulting in an international 'regulatory patchwork' (Caulfield et al., 2009). Broadly, three types of approach to hESC can be distinguished: restrictive; flexible or less permissive; and permissive or liberal, as some countries promote and support hSCR involving the creation of human embryos for research purposes, others only allow the use of 'surplus' human embryos, or only non-embryonic SCR (Caulfield et al., 2009). These types of approach reflect differing degrees to which the idea of hESC research is regarded as morally acceptable or not by different polities and are shaped by varying historical and social contexts, as well as specific local factors such as resources, the state of the science base, and systems of healthcare provision.

Different governance frameworks can also reflect competing national strategies to drive translation of stem cell research and stimulate a local regenerative medicine industry (Salter, 2008; 2009 Sleeboom-Faulkner et al., 2016). A similar 'regulatory patchwork' also exists regarding the stringency and extent (or even existence) of oversight of clinical application of stem cell products. This has given rise to the marketing of 'unproven' stem cell therapies (Sipp et al., 2017) and the phenomenon of so-called 'stem cell tourism', whereby patients leave their home countries where unproven or experimental 'stem cell treatment' are less accessible or strictly regulated, and travel to another country where the treatments can be easily obtained from providers operating on a for—profit basis. These practices have been the

cause of much international concern. For instance, India and China were criticised for their approach to regulating the provision of untested stem cell therapies (Tiwari and Raman, 2014; Cyranoski, 2009). Leading scientific bodies in the field such as the International Society for Stem Cell Research (ISSCR) have also publicly condemned stem cell tourism and unproven therapies.

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However, the issue is not straightforward. Whilst countries such as India and China that have often been cited for promoting stem cell tourism, have ultimately moved to clamp down on such 'rogue traders' (Tiwari and Raman, 2014), many jurisdictions that previously imposed strict rules on stem cell-based therapies, such as the UK, Japan, the European Union, and the USA have introduced 'special' regulatory provisions for stem cell based-treatments and other advanced therapies (Rosemann et al., 2016; Sleeboom-Faulkner et al., 2016; Servick, 2017). These provisions allow for access to stem cell-based therapies before they have completed the traditional three-phase randomised clinical trial regulatory approval procedures. These include hospital exemptions, 'compassionate-use' or 'right to try' exemptions, as well as fast track approval procedures for cell therapies addressing unmet clinical need. Such provisions are designed to facilitate more rapid uptake and translation of stem cell science into clinical and commercial applications. As Sleeboom-Faulkner et al (2016: 241) observe: "a very large grey area of stem cell-related activities exists in which stem cell scientists, doctors, politicians, and regulators accommodate, adjust, circumvent and alter regulatory spaces to help advance clinical research in ways that suits their circumstances".

As a new player in the field, Malaysia is also attempting to find a regulatory framework to manage these issues, while at the same time promoting innovation. In recent years the Malaysian federal government has identified hSCR as a promising platform to develop its medical technology base, address pressing healthcare issues, and to stimulate

economic growth and boost national productivity. As relatively little has been written about the governance of biotechnology in Malaysia, it will first be necessary to provide a brief introduction to some relevant aspects of Malaysian society and an overview of recent developments in the regulation of SCR in Malaysia.

Overview of Malaysian Legal System

Historically, Malaysia was a Malay Kingdom, part of the British Empire. In 1957, Malaysia gained full independence, although it has remained a member of the Commonwealth. The colonial episode has played a considerable role in shaping the legal system of Malaysia. English Common Law heavily influenced the law of Malaysia and its Constitution is based on the 'Westminster model' (Syed Ahmad, 2001). Given its population consists of predominantly Malays, who are Muslims, the country declares Islam as the official religion and at the same time, also embraces the freedom to practice other religions. The legal system also incorporates Islamic law resulting in the existence of dual legal and judicial systems of civil and sharia laws. Islamic matters fall under state jurisdiction where the state legislature has the power to make Islamic law. However, laws relating to criminal matters fall under the purview of the Federal Parliament, and therefore Islamic laws that are enforced in Malaysia today are generally non-criminal in nature – Islamic law only relates to issues such as marriage, divorce, and inheritance involving Muslim parties (Federal Constitution, 2010; Article 76 (1) (2) (3)).

Apart from Islam, there are also other religious groups that play their important role in advising the government on what is and what is not acceptable. For instance, the national fatwa[1] on human stem cell research was introduced after consultations not only with Islamic

[1] Fatwa is a legal opinion given by mufti or legal scholars in a situation where a religious ruling is needed to resolve a question posed by members of the public or a court of law on a certain issue where fiqh or Islamic jurisprudence is unclear. For instance, the emerging issues

scholars but also among other religious groups. Due to opposition largely among Catholic and Buddhist groups, the fatwa took a pragmatic approach, similar to the UK's Warnock Committee, by permitting the use of human embryos only up to 14 days after fertilisation. This is in contrast to the more commonplace Muslim interpretation that ensoulment only occurs after around 40 days of the embryo's development, which could potentially have allowed for a longer acceptable timeframe for embryo research being incorporated in regulation.

Scientific and Regulatory Development of SCR in Malaysia

Many countries have heavily invested in some or all aspects of hSCR and Malaysia aspires to be part of this highly promising area. Accordingly, the Malaysian Academy of Sciences commissioned a Task Force to prepare a report about the current state of art and capacity of SCR and therapy in Malaysia.

Led by Emeritus Professor Cheong Soon Keng together with ten other Malaysian expert members from local research institutes that are active in SCR, the Task Force's *Advisory Report on Stem Cells: Ageing and Regenerative Medicine* (2013 Advisory report), explains that Malaysia seeks to venture in this area for two main reasons: (i) the potential of cell therapy to address the diseases of a rapidly growing population of ageing citizens, and the associated increase in national healthcare costs this entails; and (ii) cell therapy has been identified as the key research field that could help to achieve the national development goals set out in Malaysia's Vision 2020 plan.[2]

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such as cloning and whether it is permissible, from the Islamic perspectives. Even though fatwa is applicable to all Muslims in the relevant community, unlike the rulings of secular courts, a fatwa is non-binding in nature unless it is incorporated into a piece of legislation

[2] The strategic plan set forth by the 5th Malaysian Prime Minister, Dr. Mahathir Mohamad, who aspires to see Malaysia becoming a 'fully developed' nation by 2020.

The report emphasised that Malaysia does not have the resources to invest widely, and its investment in this area is currently viewed as "inferior to that of India and China" (Sleeboom-Faulkner et al., 2016). Given its limited funding, the Task Force was mandated to choose certain areas that would maximise the return on research investment. The Task Force identified the top four chronic diseases that cause disability among the older population: dementia, musculoskeletal diseases, visual impairments, and cardiovascular diseases, as those placing the greatest burden public healthcare spending and therefore most in need of redress. The Task Force consider stem cell research as providing a potential solution to this problem by developing treatments to ameliorate these conditions. However, the Task Force observes (2013 Advisory report: 33) that Malaysia is "at a distinct disadvantage when competing in a knowledge intensive field such as regenerative medicine and stem cell research" due to its relatively restrictive environment for stem cell research, limited funding, and lack of human capital development.

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The report also highlights that approximately 30% of the research funding in the country comes from government grants. Funding for hSCR in Malaysia is still relatively low compared to other countries such as India and China. A few local funding sources are the Ministry of Higher Education, the Malaysian Biotechnology Corporation, the Ministry of Science, Technology and Innovation, and the Malaysian Technology Development Corporation, which was established to allow researchers who are based in the industry sector to apply for government funding.

There is limited information about the status of collaborative work between local and foreign researchers, and the flow of external funding from overseas into Malaysia in developing hSCR. In addition to an active stem cell research community based in the major national universities in the country, Malaysia also hosts a number of international companies working in the field. The best known of these is probably Stempeutics PYT Limited, which

operates facilities in Bangalore, Manipal (both in India) and Kuala Lumpur (Malaysia) and is the company with the greatest portfolio of research publications in the hSCR field in Malaysia. In terms of geography, most research activities are concentrated in the Klang Valley and some activities take place in the State of Penang situated in the north region.

As with other countries, the ethical issues surrounding hESC and embryo research have been a significant factor in Malaysia. HSCR using adult stem cells is more ethically acceptable and less contentious. According to the advisory report, "research on stem cells is not covered by any legislation" and there are also no specific statutory provisions for stem cell therapy except that practices must comply with the Private Healthcare Facilities and Services Act 1998 (2013 Advisory report: 31). Instead, there are National Guidelines for Stem Cell Research and Therapy issued by the Malaysian Ministry of Health (MOH) initially in 2006 (2006 Guidelines) and later revised in 2009 (2009 Guidelines).

A national fatwa on stem cell research issued by Malaysia National Fatwa Council was fully adopted and reflected in the 2006 Guidelines, and its incorporation remained after the revision. The 2009 Guidelines stipulates research activities that are permissible and prohibited based on the fatwa. These include: (i) adult stem cells derived from foetal tissues from a legally performed termination of pregnancies; (ii) non-human stem cells; and (iii) hESCs derived from surplus IVF embryos. The guidelines prohibit "creation of human embryos by any means including but not limited to assisted reproductive cloning (ART) or somatic cell nuclear transfer (SCNT) specifically for the purpose of scientific research" (2009 Guidelines: 31).

Based on the current system, hSCR falls under the regulatory purview of the MOH. Under its patronage, other agencies have been established such as the Medical Research and Ethics Committee (MREC) and the National Stem Cell Research and Ethics (NSCRE) sub-committee. The latter was established through the guidelines specifically to govern hSCR.

Between the two agencies, the former seems to have more authority, especially in granting licences and/or approval for research, whereas the latter has the task of reviewing research applications.

The 2009 Guidelines aim to encourage the involvement of Malaysian scientists in stem cell research within an ethical environment. In so doing, the 2009 Guidelines also set out other ethical requirements: all research activities involving stem cells derived from humans or animals must be reviewed by an institutional research body or an institutional ethics committee, adhering to the 2009 Guidelines. A copy of all research proposals must be submitted to the NSCRE Sub-committee and the committee retains the right to review any proposal.

The Guidelines call for autonomous and informed decisions in the production of human embryos for infertility treatment, prohibit the involvement of any financial or in-kind payment for embryo donation for research purposes, and emphasise that the donor has the right to "withdraw consent until the blastocysts are actually used for in cell line derivation" (2009 Guidelines: 32). In addition to the national guidelines, the Malaysian Medical Council also produced its own guidelines to regulate SCR, which are in line with the 2009 Guidelines.

Importantly the scope of the guidelines is limited to research that involves staff members of the ministry, its facilities, and work on human subjects. It is therefore not certain whether or not research activities, especially in the private sector, that do not involve ministry-employed staff are subject to MREC's and NSCRE Sub-committee's oversight and approval. This has resulted in a 'regulatory gap' between the private and public sectors, whereby the latter being regulated to some degree, perceive the former as being under-regulated, particularly given the absence of legislation applicable to all actors involved in this area. However, the rules and requirements stipulated in the guidelines can also be imposed on a private actor in a setting where there is a collaboration with a public actor in a research work

that is funded by the ministries. In addition, a regulatory gap can also be seen between clinical and non-clinical research activities. Since the involvement of human subjects is the criteria for the involvement of MREC, it is also uncertain whether non-clinical hSCR is subject to MREC's approval and oversight or not.

It can, therefore, be seen that the Malaysian state has begun to deploy a governance framework for hSCR to complement its investment in the field, but that at present some uncertainties and gaps are evident. The remainder of this paper investigates how those who are involved with stem cell science perceive the current framework, how they navigate its requirements and uncertainties, and how the emerging field of translational hSCR is being shaped as a result.

Methods

To understand how the current governance framework shapes practice in hSCR in Malaysia and how actors negotiate the tension between competing imperatives, it is essential to consider how both the regulators and regulatees perceive the current framework, what is felt to be 'at stake' if Malaysia continues with the current approach, and what alternatives might be available. Their views are also vital in facilitating policymakers to consider the complexities around stem cell research governance based on the local contexts and to allow them to evaluate possible ways to remedy the situation, which was part of the original remit of the research on which this paper is based. To achieve this, a variety of methods including literature-based research and empirical interviews with key stakeholders were employed. The latter is particularly important given that there is little information on Malaysia's stem cell research regulatory system available in the literature.

The first author conducted semi-structured interviews with open-ended questions after undergoing University of Oxford's ethical approval process, from January 2013 until March

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2013. Twenty-six interviews were conducted involving respondents from different backgrounds (medical practitioner, lawyer, stem cell scientist, non-governmental agency, ethicist, religious authority, ministry official) recruited through a 'snowball' sampling technique (Bryman, 2012). Most of the interviews lasted for about one hour and a half. During the interviews, respondents were asked about the current national governance regime for laboratory and clinical research using stem cells, including ethical oversight of human participants in research and derivation of hESC. The interviews focused on perceived challenges or benefits of this governance framework and respondents were encouraged to provide illustrative examples from their own experiences as well as to reflect on Malaysia's place in the global stem cell research field. The locations for the interviews were not significantly geographically diverse, being concentrated in the area of Kuala Lumpur and nearby districts, where most of the research and clinical activities in Malaysia are being carried out. The interviews were recorded and transcribed with the respondents' permission, and the findings were analysed using thematic analysis (Bryman, 2012; Punch, 2013).

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Awareness and adequacy of existing Regulations

It cannot be assumed that because a governance system exists – in this case, the National Guidelines and the two committees set up by the MOH - that it will produce the desired policy outcome. A first necessary step in assessing the impact of the Malaysian governance regime for hSCR was to evaluate respondents' awareness of its various provisions and mechanisms. In general, most of the interviewees were aware of the existence of the national guidelines introduced to govern stem cell research and therapy. However, this was not universally the case, nor did all respondents have the same interpretation of the guidelines. This can be illustrated using the example of the regulation of human embryonic research:

> In Malaysia...I don't know the human embryonic stem cell policy...because I don't see any kind of a very clear [regulatory provisions] against towards usage of the human embryonic stem cells. But I do believe that there is a restriction on the isolation of the human embryonic stem cells. **[Respondent 12: Stem cell scientist]**

> Well you can [create embryos to derive stem cells] actually, provided that you are not allowed after a certain number of days... **[Respondent 1: Stem Cell Scientist, Stem Cell Policy Panellist]**

Respondent 12 proffered a potential version of the rules - that hESC research was permitted although there were restrictions on the isolation of new cell lines from embryos – and presented this understanding as arising from a general perception of the field rather than being based on knowledge of a specific policy instrument. In contrast, respondent 1 appeared quite confident in their knowledge of what was permitted – that embryos could be created for the purposes of deriving new hESC lines – but expressed an interpretation that is divergent from that of respondent 12 and from the 2009 guidelines' prohibition on creating human embryos for research purposes. This suggests that not only are there different levels of engagement with the existing regulatory guidelines but, more significantly, that this is likely to result in divergent practices 'on the ground' as well.

A number of respondents who had experience with other national regulatory systems used the contrast with these other jurisdictions as a way of criticising the current Malaysian system:

> The good thing about FDA is...you can write to them and you can have an initial discussion with their officers who will guide you...so that you don't spend too much of your resources designing something that is out of the scope that can be approved by FDA... **[Respondent 5: Stem Cell Scientist]**

> Well, there [the UK HFEA] I feel...everything is clear-cut. I know where I need to go, whom I should contact, what kind of things I can do and don't, and things are actually come with a clear reasoning, why you can do this why you cannot do that...[...] once I come back...I just don't know how things work here, I don't know whom I should contact when I talked to all professors who are working on stem cells, they are not sure about the guidelines either. **[Respondent 12: Stem cell scientist]**

These accounts present other regulatory agencies (the US Food and Drug Administration and the UK's Human Fertilisation and Embryology Authority) as providing clarity and interactive guidance to scientists and clinicians, with the implication that these elements are lacking in the current Malaysian regulatory environment. Respondent 5 felt that Malaysian researchers particularly could benefit from more active engagement with regulators to offer guidance about what was and was not permissible in research and therapy. This again supports the idea that current engagement of scientists with the existing governance framework in Malaysia is patchy and limited, possibly due to limited communication from regulatory authorities and that the fact that the 2009 Guidelines were relatively new at the time of the interviews (in 2013).

The examples reported in this section suggest a disconnect between written regulation and the day-to-day experience and knowledge of laboratory and clinical scientists. It also

demonstrates how the increasing global connectivity between scientists in the stem cell field (Luo and Matthews, 2013) provides some Malaysian scientists with experience of other national regulatory frameworks that come to serve as *ad hoc* standards for evaluating the functioning of their own local governance regime.

Comparison with other jurisdictions was also discursively employed in another strand of debate about the adequacy of the current Malaysian governance framework for hSCR; this time concerning the ability of Malaysia to compete effectively with other stem cell research promoting countries:

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> The guidelines are actually fairly conservative. Compared to other countries in the world, our position on things like embryonic stem cell is actually much more restrictive compared to other countries that are active in stem cell research..**[Respondent 10: Medical Practitioner, Stem Cell Scientist, Advisory Council]**
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> I don't think we need to spend money on embryonic stem cell, we will benefit from other more matured technology or more feasible one like iPSCs is certainly good, very good area to go in. **[Respondent 18: Stem Cell Scientist, Advisory Council]**

As the above quotes demonstrate, the adequacy of Malaysian regulatory provisions is also entangled with debates about the putative advantages of different technological approaches within the field of SCR. Respondent 10 uses the current regulations on human embryonic stem cell research to locate Malaysia within the more 'restrictive' segment of the international regulatory patchwork (Caulfield et al., 2009). This argument positions hESC research as an

important and necessary aspect of hSCR, without support for which Malaysian scientists risk not being able to compete effectively with other countries that adopt a more 'liberal' approach.

Respondent 18 offers an alternative view: that hESC technology is neither 'mature' enough (by contrast to 'adult' stem cell therapies) nor 'feasible' enough (by comparison with induced pluripotent stem cell technology) to be worth investing in. Accordingly, it would be wasteful to spend time and effort updating the regulations on hESC research to make them more permissive and, in this view, Malaysia would be better served developing iPSC technology to become competitive with other states. These debates about the relative promise of different types of stem cell technology echo those that have been described in other countries, such as Italy (Beltrame, 2014) and in the wider literature on regenerative medicine (Morrison, 2012).

This section highlights two ways in which scientists evaluate the 'appropriateness' of the current Malaysian regulation of hSCR. The first involves the clarity of the regulatory framework and how easy, or otherwise, it is to conduct research under this set of rules. The second concerns the scope of the regulations, in terms of which technologies like embryonic stem cell research or therapeutic cloning are permitted and which are prohibited. In both cases, the Malaysian system is evaluated by comparison with regulations of hSCR in other countries. One likely reason is that the 2013 Advisory Report from the Malaysian Academy of Sciences identified a lack of existing expertise in hSCR in Malaysia as a potential barrier to success. The authors explicitly advocated encouraging Malaysian scientists with expertise in hSCR who were based abroad to relocate their research to Malaysia, as well as seeking to attract non-Malaysian scientists to the country.

It is therefore to be expected that at least some of the current Malaysian stem cell science base, including those who took part in this research, would have experience of

working in other regulatory environments. However, these accounts remind us that individual scientists and research groups are also in competition with each other. In fields such as stem cell science where multiple technological options exist (Morrison, 2012), different scientists and groups may back divergent and competing technologies and research agendas (Beltrame, 2014). Scientists in any given nation may be in competition for limited resources such as government funding, but they (may) also have the option of relocating between countries if it is believed that one state offers better prospects for a particular type of research than another.

In this way scientists' perspectives on the value and appropriateness of particular technologies (such as hESC) influence their attitudes to the desirability and suitability of regulatory measures and strategic state investments (e.g. if hESC are seen as outdated compared to iPSC then detailed regulations to facilitate the use of hESC are inappropriate and unnecessary, but if hESC are seen as critical to the future of regenerative medicine regulations that ensure hESC research is safeguarded are highly desirable). Scientific competition thus plays a role in state strategies for national competitiveness as well. In the next section we consider a further dimension - that of the perceived stringency or leniency of the current regulations.

Opportunities and dangers in the current regulatory regime

While some respondents presented the current regulatory framework as overly restrictive in relation to areas such as human embryonic stem cell research or therapeutic cloning, others invoked the disconnect between written guidelines and the practical enforcement of oversight to instead characterise the research environment as overly permissive:

> Yes, it's too facilitative, mainly because of the lack of monitoring, I think we do have...written regulations but a lot of it seems to me is really just I take your

word from it. And then, there is no monitoring. **[Respondent 3: Scientist, Ministry Official]**

There's no enforcement, there's nobody to come knocking on your door unless the only thing that I can think of is that… maybe because of death only then they will investigate. But if not and nobody complains, it will just go uninvestigated. **[Respondent 21: Ethics Committee Member]**

Respondents expressed the sense that there was limited practical oversight of activities in Malaysian hSCR in relation to a number of contexts. Some respondents highlighted a perceived lack of enforcement in non-clinical research, using the topic of informed consent. The 2009 Guidelines require that sample donors be recontacted to have their consent updated if their cells are to be used for new research that lies outside the scope of their original consent. However, several respondents reported that it was not clear if this requirement was actually adhered to: "so whether they actually get a new informed consent or not, we don't know... because there is no monitoring..." **[Respondent 9: Ethics Committee Member]**. Another area where the absence of effective monitoring and regulation was presented as an issue was stem cell treatments and products offered by private sector providers, especially as some of these were percieved to be of dubious or unscientific provenance:

Well, I can quote you a recent [example], which is very unfortunate. There is a company that is actually…introduced rabbit stem cells for treatment for Down syndrome…we don't agree with that…we frown upon such tactic, which has no scientific basis. **[Respondent 18: Stem Cell Scientist, Advisory Council]**

Respondents expressing concerns about lack of regulatory enforcement presented regulation as a means to prevent unethical or unscientific activities. Therefore, the focus is on what is done in practice rather than what is officially stipulated in the current guidelines, with the emphasis on enforcing the rules rather than ameliorating to encourage technology development.

Among respondents then there was a mixed set of reactions to the current framework. For some, it was presented as overly restrictive, primarily in relation to specific areas of technology such as hESC research or therapeutic cloning (SCNT), and in need of reform to bring it more into line with more countries seen as more 'permissive' such as the UK or Singapore. Others presented the current environment as overly facilitative, because of inadequate or absent monitoring of research and clinical activity, lacunae in regulatory coverage and a lack of enforcement of the rules. A few respondents actively picked up on this tension and recognised both opportunities and dangers in the situation:

> In the short run, it's good because you can do anything. In a long run, it's bad because someone eventually will do something that will cast the whole thing into disrepute. Think about the gene therapy using viruses in the late 90s. That was actually poorly regulated. And there was a number of deaths that occurred that actually stunted the entire field for the whole decade...this is the kind of thing that will happen in Malaysia. If we are lack[ing] of regulation, it's good if you want to get in and get started. It's very very bad if you got something good and someone else spoils the market for you. **[Respondent 10: Medical Practitioner, Stem Cell Scientist, Advisory Council]**

A relatively under-enforced or uncertain regulatory environment was seen as offering potential advantages to scientists and to the development of hSCR in Malaysia, in terms of constituting a low barrier to scientists and companies moving into this area. At the same time, an overly lax regulatory environment resulting in risky practices could also present a danger to the desired advancement of the field of hSCR in Malaysia. The danger was specifically located in unethical or under-regulated practices involving human participants. Respondent 10 above made explicit reference to the case of gene therapy during the 1990s. Two incidents, both involving the deaths of participants in experimental gene therapy trials, are widely held to have damaged the promise of gene therapy research and deterred further commercial investment in the technology[3] (Spink and Geddes, 2004; Friedmann, 2005).

The danger of a similar disinvestment and loss of commercial, public and/or government support for the field was evoked as a potential consequence if an under-enforced regulatory environment was allowed to persist for too long. In this way, the 'gene therapy example' becomes a cautionary tale about the appropriate management of science in a similar fashion to the way that 'GM crops in Europe' are evoked in relation to public engagement in other contexts. Another respondent made a related argument, based on a distinction between pre-clinical and clinical work as the point where greater regulatory scrutiny was warranted:

> That's actually a good thing [less strict monitoring system] but I don't think it's a good thing when you talk about having to experiment on human, and you're not

[3] In 1999, Jesse Gelsinger died after being administered with an adenoviral gene therapy vector in a study at Penn State University. In addition, other serious adverse events reported and US gene therapy trials have been accused as the outcome of the lack of independent oversight. In 2002, two young boys were announced to have died in a study of gene therapy for the treatment of X-SCID.

> very clear on how it's done...there must still be restriction but when it comes to human...before we exploit people we need to understand the science...at this point of time, they are not being very, very restrictive, but it's open to exploitation. **[Respondent 1: Medical practitioner, stem cell scientist]**

Again there is a tension between a regulatory environment that facilitates scientific research - allowing Malaysia to try to catch up with its competitor nations, and the risks of under-regulated or irresponsible experimentation on human participants, where a serious error could damage Malaysia's reputation in hSCR locally and in the international community.

Discussion

The challenge for regulators in any state is to develop appropriate standards (Baldwin, Cave and Lodge, 2012). However, as this case study shows, how 'appropriate' is configured, is subject to considerable negotiation. Low and Middle Income Countries (LMIC), like Malaysia, wishing to build a stake in the global hSCR field face a number of challenges in this regard. Regulation of biomedical science is often problematised as an undesirable curtailment of scientific freedom or as a 'burden' experienced by academic and commercial institutions compelled to meet bureaucratic requirements for ethics review of research protocols, evaluation of clinical trial data by regulatory agencies and similar processes. For states wanting to build national capacity in a particular area of (biomedical) research and attract scientists, companies and investment there is an apparent impetus to minimise regulation.

At the same time, a key function of regulation is protecting the public from unsafe or unethical scientific or medical practices. This includes prevention of physical

harms, for example by ensuring medicines go through clinical trials before being approved for marketing, but a need for regulation can also be invoked to prevent moral harms, as has been argued in some jurisdictions to result from research using human embryos. Scientific research also involves considerable collaboration, including collaboration across national boundaries (Luo and Matthews, 2013). This is particularly prominent in pre-clinical research, which still accounts for the majority of stem cell science. While commercial and academic scientists may seek to strategically collaborate with colleagues in jurisdictions that have more permissive regulatory frameworks (Sleeboom-Faulkner et al., 2016), if a jurisdiction has no regulation or is perceived as having overly lax regulation this may also dissuade collaborators, especially if they are based in countries where ethical review of research protocols is reasonably strongly enforced and publication may depend on evidence of adequate ethical oversight. The desire for public and international legitimacy thus provides a counter imperative to enact and enforce regulation,

LMICs attempting to develop and implement a regulatory framework must also deal with the fact that the regulatory and scientific practices espoused by wealthier countries present "universal standards, often created 'elsewhere', that are not conducive to local policies of economic, health and scientific development" (Sleeboom-Faulkner et al., 2016: 241). In such situations, these states adopt a strategic 'national homekeeping' approach which seeks to balance expectations of appropriate conduct set by scientific authorities in developed countries and availability of local resources and needs by developing policies, like the 2009 Ministry of Health Guidelines that set a particular form, extent and authority for regulation (Sleeboom-Faulkner et al., 2016).

Sleeboom-Faulkner et. al. (2016) characterise Malaysia as a small LMIC, by comparison with India and China, with relatively limited capacity to invest in regulatory

Commented [TR9]: In English the usual expression is housekeeping rather than homekeeping. Please check.

Commented [FC10]: We merely borrow this term, which was used by Margaret Sleeboom-Faulkner and colleagues in their paper 'Comparing national home-keeping and the regulation of translational stem cell applications: an international perspective'. We indicate the term has a specific meaning, derived from that paper, by use of the inverted comas around 'national-homekeeping'

infrastructure for science. This is in keeping with the accounts of minimal direction from regulators, limited or absent monitoring and enforcement of regulations, and unclear or out-dated provisions reported by respondents in this study. As a national investment strategy this approach maybe based on a recognition of limited resources and a need to accelerate innovation by keeping regulatory barriers to entry low. However, as the accounts reported above demonstrate this approach also produces its own tensions for practitioners in the field.

Having oversight bodies that are relatively 'hands off' may facilitate research, for example by not enforcing strict checks on informed consent or by avoiding formal statutory regulation of hESC work, but the same light touch approach can also mean that there is uncertainty about what is actually permitted and what is not, leading to variable practices on the ground. For the respondents quoted in the section on '*awareness and adequacy of existing regulations*' above, the reported lack of clarity of existing regulations was more often perceived as an obstacle than a benefit (e.g. Respondents 5 and 12).

To understand why regulation might be perceived as desirable, there is a useful parallel in Faulkner's (2009) work on regulation and innovation. Faulkner (2009) argued that having a regulatory framework can actually facilitate innovation by providing guidelines for what will be needed to get marketing approval for a product. Without this guidance companies may be reluctant to invest in an area for fear that their investment will be wasted on research trajectories that will ultimately not be marketable. Although Faulkner (2009) was writing about the commercial sector, there are parallels for academic scientists as well. It is worth remembering that for academics collaboration and competition often co-exist in uneasy tension (Atkinson, Batchelor and Parsons 1998).

Limited or poorly enforced regulation may offer an opportunity to get ahead of rival scientists at home and abroad, but having a clear and well understood regulatory framework also has advantages including facilitating international collaboration, and ensuring research is publishable in leading journals that demand evidence of regulatory and ethical oversight. Communication between regulators and regulatees can also help to ensure regulations are updated to take account of promising new areas of scientific investigation such as iPSCs technology, nuclear transfer, or genome editing.

In addition, limited or laxly enforced regulation may also allow practices that some scientists consider underhand or unethical to flourish. In other words, not all forms of competition may be considered fair. This is especially evident when it comes to private sector stem cell companies in Malaysia who remain largely unregulated compared to their public sector counterparts. For some, such as Respondent 18 (cited above), concern about the absence of regulation of the private sector was expressed as disapproval for practices considered unscientific and potentially harmful to human recipients. Others, such as Respondent's 1 and 10 expressed concern that a scandal, involving harm to a recipient of an unproven stem cell therapy, could damage the credibility and the future of Malaysian hSCR as a whole both locally and internationally.

In addition, several of the hSCR companies reported by Sleeboom-Faulkner et al (2016) to be operating in Malaysia are owned or operated by overseas concerns based, for example in India. There may therefore be an additional concern in Respondent 10's comment that a facilitative regulatory environment is "good if you want to get in and get started" but "bad if you got something good and someone else spoils the market for you", that negligent practice by foreign-owned hSCR companies operating in Malaysia

could have negative repercussions for Malaysian clinicians and companies wanting to deploy a locally developed stem cell treatment.

The challenge for Malaysian policymakers then is to devise polices that promote national competitiveness in the global market for stem cell science but to do so in ways that accommodate both scientific completion and collaboration within the field and which manage the concerns of both the public and private sector researchers. Respondent 10's comment is also interesting because it suggests a temporal dimension to the development of a regulatory framework. A 'national homekeeping' strategy that is relatively facilitative can be beneficial in the early stages of building a stem cell research base and a nurturing a regenerative medicine industry, but over time the drawbacks of minimal regulation may begin to outweigh the benefits. The findings reported in this study suggest that for Malaysian scientists this tipping point may be approaching.

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Conclusion

This paper has explored the current regulatory framework for hSCR in Malaysia by examining the existing regulation and investigating how stakeholders perceived the framework. It has highlighted the challenges faced by Malaysia as the country seeks to join the other 'rising powers' and the 'traditional players' in the realm of translational hSCR. Given the existing regulatory patchwork in the governance of hSCR at the global level, Malaysia faces challenges in shaping its regulatory strategies that are suitable for its own local context and would be able to stimulate scientific and medical progress. The strategy also needs to be able to protect public safety and maintain the reputation of this technology.

The complexities surrounding this area are compounded by Malaysia's limited resources making the state at the disadvantage compared to other 'rising powers' such as India and Singapore. Today, its under-enforced regulation may serve, as its strategy given its low barrier currently would attract scientists and companies to enter into this area. However, in the light of the current regulatory climate, some local actors have raised strong concerns that if the state continues with its lax regulation, in the long run, this could open the gate to negligent practices. This approach might also affect translational collaboration with and investment by reputable players.

The accounts of the stakeholders are important as they could facilitate policymakers to consider the complexities of this area and the possible ways to face the regulatory challenges. The communicative approach, a strategy adopted by the FDA and HFEA could be considered to make the current regulation functions and to address the 'disconnect' between regulators and regulatees. However, an 'appropriate' regulation requires more than a communicative approach. Given the current international standards are espoused by the developed nations such as the UK, Canada, and Australia, the traditional players in this area, Malaysia could benefit from an improved regulatory framework rather than continue with its current 'national homekeeping' strategy.

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Given the 'regulatory patchwork' pattern of the current global practice, Malaysia could adopt some of the regulatory elements of other countries that are more experienced in regulating SCR, but will also need to carefully examine the provisions and not adopt them without critical scrutiny. The connection with the UK's legal framework resulting from their shared colonial history suggests one possible option, but one that requires further examination in light of Malaysian historical and social context and capabilities in terms of the resources and infrastructure available.

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