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A NEW FRAMEWORK FOR SELF-REGULATION

Human Biomedical Research Act 2015[1]

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I. INTRODUCTION

On 18 August 2015, Parliament passed the *Human Biomedical Research Bill*, which establishes two separate, but related, frameworks for the regulation of human biomedical research and tissue banking.[2] The aim of these frameworks is "to protect research subjects and tissue donors, so that dealings are conducted in an ethical and responsible manner."[3] The Minister of State for Health, in moving the Bill however, was careful to emphasise that the Ministry of Health's ("MOH") intention is to use the *HBRA* as an instrument "to ensure the safety and welfare of research subjects whilst not stifling sound, ethical research."[4]

While the law is not yet in force,[5] it is apt to start assessing the main features of the *HBRA*, particularly its framework for regulating human biomedical research. Part II of this comment examines the scope of the Act as well as its relationship with existing laws. Part III outlines the envisaged framework of self-regulation for human biomedical research. Part IV examines specific provisions relating to the obtaining of research participants' consent and to restricted research. Part V briefly highlights some of the provisions concerning tissue banking. Part VI concludes.

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1 This article refers to the *Human Biomedical Research Act 2015* [*HBRA*] contained in the *Human Biomedical Research Bill* (Bill No 25/2015).

2 Most jurisdictions regulate these two areas in separate pieces of legislations, so it is noteworthy that both are covered by a single legislation in Singapore. A copy of the *HBRA* may be found online: Parliament of Singapore <https://www.parliament.gov.sg/sites/default/files/Human%20Biomedical%20Research%20Bill%2025-2015.pdf>.

3 Nadia Jansen Hassan, "Human Biomedical Research Bill passed to protect research subjects, tissue donors", Channel News Asia (22 August 2015) online: Channel News Asia <http://www.channelnewsasia.com/news/singapore/human-biomedical-research/2058862.html>.

4 *Parliamentary Debates Singapore: Official Report,* vol 93 (18 August 2015) (Dr Lam Pin Min) [Dr Lam Pin Min, Second Reading Human Biomedical Research Bill].

5 Section 1 of the Bill states that the Act shall "come[s] into operation on such date as the Minister may, by notification in the Gazette, appoint." *HBRA*, *supra* note 1.

II. Scope of the *HBRA*

A. *Defining "Human Biomedical Research"*

The *HBRA* governs all "human biomedical research" ("HBR") conducted in Singapore and has a potentially wide coverage. HBR is defined in two ways in the Act. First, a research constitutes HBR if it involves the use of specific categories of biological materials, as listed in the Act's Fourth Schedule. These are materials from one or more of the following technical categories:

(a) human gametes or human embryos;
(b) cytosplasmic hybrid embryos;
(c) the introduction of any human-animal combination embryo into an animal or human;
(d) the introduction of human stem cells or human neural cells into an animal at any stage of development; or
(e) any entity created as a result of any process referred to in point (c) or (d) above.[6]

Secondly, research constitutes HBR if it satisfies a prescribed two-pronged test outlined in section 3(2). The first prong ("purpose prong") states that the research be intended to study:

(a) the prevention, prognostication, diagnosis or alleviation of any disease, disorder or injury affecting the human body;
(b) the restoration, maintenance or promotion of the aesthetic appearance of human individuals through clinical procedures or techniques; or
(c) the performance or endurance of human individuals.[7]

The second prong ("means prong") specifies that the research must involve a physical, mental or physiological intervention, or "individually-identifiable human biological material", or "individually-identifiable health information."[8] Any research that satisfies *both* prongs is considered HBR under the Act.

While the categories in the Fourth Schedule are rather specific and well-defined, the two-pronged definition of HBR risks being overly broad. Specifically, various research projects from the social sciences would probably meet the *HBRA*'s two-pronged definition without, at the same time, being the kind of research that would ordinarily be considered 'human *biomedical* research'. One example would be experiments run by economists that compare the effectiveness of various incentive structures aimed at improving human performance.[9] Indeed, the potentially broad coverage of the two-pronged definition of HBR is recognised by the explicit exclusion in the Second Schedule of "research and studies on normal psychological responses and behaviour" that are "not intended to study psychiatric or psychological disorders", as well as research for measuring human intelligence that are "not

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6 See *HBRA*, *supra* note 1, Fourth Schedule.
7 *Ibid*, s 3(2).
8 *Ibid*.
9 See *eg*, Robert J Oxoby "The Effect of Incentive Structure on Heuristic Decision Making: The Proportion Heuristic" (June 2007) IZA Discussion Paper No 2857.

designed or intended to study mental or intellectual disability," provided that these studies "involve no more than minimal risk to the research subject."[10] Nonetheless, more could perhaps be done to exclude research projects that generally speaking involve interventions with no more than minimal risk. Indeed, from a regulatory perspective, making such research projects subject to the *HBRA*'s regulations by default might unnecessarily burden institutions that conduct low-risk human subject research in the social sciences and other disciplines.

Additionally, any research that is already regulated by other specialist legislation is also carved out from the scope of *HBRA*. This includes research in accordance with provisions of the *Infectious Diseases Act*,[11] the collection of health information under the *National Registry of Diseases Act*[12] and the *Statistics Act*,[13] as well as any research that falls under the *Health Products Act*[14] and the *Medicines Act*.[15]

Despite these exclusions the reach of the *HBRA* remains broad. Indeed, it might be worth drawing a comparison with the *MA*, which applies to a particular kind of applied human biomedical research, namely research in the form of clinical trials.[16] According to the *MA*, the purpose of clinical trials is to garner evidence of the safety and efficacy of novel medicinal products.[17] The *MA* incorporates this underlying objective into its definition of clinical trials: they are investigations conducted by a licenced clinician (*ie* a doctor or dentist) involving his or her patients "for the purpose of ascertaining whether, or to what extent the product has, or the products have, those or any other effects, whether beneficial or harmful."[18] The *MA* as well as subsidiary regulations *only* apply to research fitting this narrow description.

In contrast, the *HBRA*'s "human biomedical research" does not have to be conducted for any specific purpose, such as testing for safety and efficacy.[19] Nor does the *HBRA* only regulate research conducted by a licenced clinician. Instead, the *HBRA* applies to *any* research that meets the above two-pronged test, where research is defined as "any systematic investigation with the intention of developing or contributing to generalisable knowledge."[20]

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10 *HBRA, supra* note 1, Second Schedule, paras 1, 2.

11 Cap 137, 2003 Rev Ed Sing.

12 Cap 201B, 2008 Rev Ed Sing.

13 Cap 317, 2012 Rev Ed Sing.

14 Cap 122D, 2008 Rev Ed Sing.

15 Cap 176, 1985 Rev Ed Sing [*MA*].

16 The *MA* is here referenced in conjunction with the *Medicines (Clinical Trials) Regulations* (Cap 176, Reg 3, 2000 Rev Ed Sing) promulgated under the *MA*. For a concise overview of the regulations concerning clinical trials see *eg*, Mak Wei Munn, "The Legislative Framework Governing Clinical Trials in Singapore" (2006) 10 APBN 1210.

17 Only if clinical trials establish, in various phases of testing, the safety and efficacy of a novel medicinal product, would governments generally permit the product to be marketed for therapeutic purposes. This approach expresses the Precautionary Principle adopted by most regulatory bodies worldwide. See *eg*, Ed Soule "The Precautionary Principle and the Regulation of U.S. Food and Drug Safety" (2004) 29 J Med Philos 333. For a recent critical discussion on the principle's role see *eg*, Brigitte Bloechl-Daum *et al*, "The Risks of Risk Aversion in Drug Regulation" (2013) 12 Nature Reviews Drug Discovery 907.

18 *MA*, *supra* note 16, s 2.

19 Of course, the research must still have as its purpose the study of certain health conditions, *ie* it must still meet the purpose prong of the *HBRA*'s two-pronged test for "human biomedical research". But the point is that the net cast by the purpose prong is much broader than what is covered under the *MA*.

20 *HBRA*, *supra* note 1, s 2.

B. *The Definition of "Individually-Identifiable"*

An important element of the *HBRA*'s two-pronged test is the concept of "individually-identifiable" material or health information. Following the *HBRA*, material or information is considered "individually-identifiable" if the individual can be identified from the biological material or health information either *by itself* or *in conjunction with* "other information to which the person, research institution, tissue bank or other organisation has or is likely to have access"[21] to. Notably, the *HBRA*'s definition of "individually-identifiable" mirrors the interpretation of "personal" in the *Personal Data Protection Act 2012*.[22] The *PDPA* regards data as personal if the individual can be identified from that data alone or in conjunction with other information an organisation is likely to have access to. Under the *PDPA*, personal data thus includes unique direct identifiers (*eg*, a person's NRIC, passport number, or DNA profile) as well as sets of indicative identifying information (*eg*, name, age, address, telephone number, or occupation), which when considered jointly would identify the individual.[23] To the extent that health information includes data of this kind, it is likewise considered individually-identifiable.

A research project can avoid involving individually identifiable health information if the data is rendered *anonymous* before becoming part of the research.[24] Anonymisation can be achieved, *inter alia*, through 'data reduction', 'pseudonymisation', 'masking', or 'data suppression'.[25] Alternatively, the data set may be coded such that, while the set remains complete, *only* those who are in possession of the relevant code ('the key') are able to extract individually identifiable information from it. While such 'coding' may be the most attractive option (it avoids the irreversibly discarding of data), it needs to be ensured that the research institution cannot readily de-code the data. Thus, true anonymisation would require that the key to the code be *not* held by the research institution but rather entrusted to a third party.

C. *Framing of Research Questions*

A final observation about the scope of the *HBRA* is that whether certain research projects fall within the scope of the Act might very much depend on the framing of the underlying research question. This is due to the fact that the definition of 'human biomedical research' incorporates the *intended purpose* of research. Consider, for instance, a research project that seeks to study the independent living skills of individuals with Down syndrome. The project, it may be assumed, involves the

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21 *Ibid*.

22 No 26 of 2012 [*PDPA*].

23 For further clarification on the meaning of "personal data" in *PDPA*, *ibid*, see Personal Data Protection Commission Singapore, *Advisory Guidelines on the Personal Data Protection Act for Selected Topics* (11 September 2014) [Personal Data Protection Commission Singapore, *Advisory Guidelines*], Part 3, online: Personal Data Protection Commission <https://www.pdpc.gov.sg/docs/default-source/advisory-guidelines—selected-topics/advisory-guidelines-for-the-pdpa-on-selected-topics-%28 110914%29.pdf?sfvrsn=2>. Note that, while the Guidelines list DNA profile as a direct identifier, there is no separate indication on how to handle human tissue.

24 For more information on how to render data anonymous in accordance with *PDPA*, *ibid*, see Personal Data Protection Commission Singapore, *Advisory Guidelines*, *ibid*.

25 These techniques are further explained in Personal Data Protection Commission Singapore, *Advisory Guidelines, ibid*.

use of some individually-identifiable health information, and hence meets the means prong of the *HBRA*'s two-pronged test. Thus, whether the project falls within the scope of the *HBRA* would depend on whether it also meets the purpose prong. This would be the case if, for instance, the focus is on the alleviation of the physiological effects of living with Down syndrome. However, if, in contrast, the research puts its *focus* on the *social aspects* of living with Down syndrome, the research might no longer fall within the *HBRA*'s scope.[26] This is to illustrate that the very framing of the research question might decide whether or not a particular study falls within the scope of the Act, *even if* the data collected or the intervention conducted is identical under either framing.

III. Framework of Self-Regulation

Perhaps because of its broad scope, the *HBRA* does *not* envisage direct governmental oversight of biomedical research activities. Rather it sets up the framework for a system of self-regulation. During the Parliamentary debate on the second reading of the Bill, the Minister of State referred to this framework of self-regulation as the *HBRA*'s "accountability framework".[27]

There are three key players within this framework. First, there is the Research Institute ("RI"), which is, loosely speaking, the 'institutional home' of any human biomedical research. In fact, the *HBRA* stipulates that *no* human biomedical research may take place outside the supervision and control of an RI.[28] Secondly, there is the Institutional Review Board ("IRB"),[29] which is tasked with reviewing research proposals. And, thirdly, there are the individual researchers who are in charge of the research project. They must submit protocols that delineate the proposed human biomedical research and they must ensure that their execution of the research adheres to the submitted protocols. In addition, MOH's Director of Medical Services ("DMS") oversees the accountability framework on behalf of MOH.

The next few sections examine the role and functions of each individual player within this accountability framework in greater detail.

A. *Duties of the RI*

Section 2 of the *HBRA* defines the "research institution" as "a body of persons" which "(a) engages… one or more researchers to conduct human biomedical research in Singapore; and (b) exercises supervision and control over human biomedical research in Singapore by the researchers the institution has engaged."[30]

Moreover, section 22(1) specifies that any RI that supervises and controls human biomedical research must have "(a) a place of business in Singapore; and (b) at least 2 individuals ordinarily resident in Singapore who are responsible on behalf of the

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[26] I owe the description of an example along these lines to Owen Schaefer.

[27] Dr Lam Pin Min, Second Reading Human Biomedical Research Bill, *supra* note 4.

[28] *HBRA*, *supra* note 1, s 22(1).

[29] In the United Kingdom and Australia, the term "Research Ethics Committee" tends to be used *in lieu* of "Institutional Review Board", but there is no substantive difference between the two terms.

[30] *HBRA*, *supra* note 1, s 2.

research institution for the supervision and control of the biomedical research."[31] These provisions would prevent an overseas RI from conducting human biomedical research in Singapore without an established local presence.

The RI has two types of duties under the *HBRA*. First, an RI is under a *duty to monitor* research. In concrete terms, an RI must ensure that any human biomedical research under its supervision and control undergoes the appropriate review process. For this purpose, every RI must appoint *at least one* IRB. Moreover, the duty to monitor entails that the RI continuously monitors all research for compliance, and that "any areas of concern"[32] arising from the research are identified and, if necessary, "remedial measures"[33] are taken.

Secondly, an RI is under a *duty to notify* the DMS about various events.[34] The RI must submit to the DMS an initial declaration before the commencement of any human biomedical research, and subsequently it must notify the DMS of its appointment of an IRB,[35] of certain changes in the composition of the appointed IRB, of "any suspected offence or contravention under [the] Act",[36] and of the "occurrence of any serious adverse event"[37] defined as "any untoward medical occurrence as a result of… human biomedical research".[38]

Besides the duty to monitor and the duty to notify, section 63(2) stipulates that the Minister of Health may make further regulations with regards to the "duties of research institutions [and] appointing bodies of institutional review boards".[39] These would appear in the form of subsidiary legislation under the Act.

For the purpose of coordinating compliance within RIs, the *HBRA* requires RIs to put a single individual in charge of ensuring compliance *with* as well as proper discharge *of* the duties imposed by the Act. This designated individual is referred to as the RI's "principal person in charge."[40]

Finally, the *HBRA* recognises that some research is not supervised and controlled by a single RI *alone*. For such jointly conducted research, section 23(2)(g) requires collaborating RIs to appoint a "lead research institution for the purpose of coordinating the research."[41]

B. *Primacy of IRB Review*

The second group of actors that make up the self-regulation framework are the IRBs. The *HBRA* defines an IRB as "a board or committee appointed by a research institution. . . to conduct an ethics review of proposed human biomedical research."[42] In practice, such a review process requires the IRB to critically assess research

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31 *Ibid*, s 22(1). Note that "ordinarily resident in Singapore" includes not just citizens and Permanent Residents, but also holders of long-term passes, such as valid Employment Passes.

32 *Ibid*, s 23(2)(e).

33 *Ibid*.

34 *Ibid*, ss 23(1), (3).

35 Nothing in the *HBRA*, *ibid*, would prevent an RI from appointing more than *one* IRB.

36 *Ibid*, s 23(3).

37 *Ibid*.

38 *Ibid*, s 2.

39 *Ibid*, s 63(2).

40 *Ibid*, s 23(2)(b).

41 *Ibid*, s 23(2)(g).

42 *Ibid*, s 2.

protocols that researchers submit. The IRB would then decide whether to exempt, approve, conditionally approve, or disapprove of the research proposal outlined in the protocol.[43] If an IRB issues a negative decision, the submitting researcher may lodge an appeal to the RI. It is then up to the RI to decide whether to grant the appeal and have the research protocol undergo a second IRB review.[44] Importantly, while the *HBRA* imposes no duty on IRBs to actively monitor research conduct, it must "review. . . the progress of the proposed research on ethical grounds at such times as may be prescribed"[45] and it must assess whether a separate data and safety monitoring board should be tasked with actively monitoring the research.[46]

The *HBRA* makes important concessions for the review of collaborative research. As discussed above, section 23(2)(g) requires collaborating RIs to appoint a lead RI. Additionally, concerning IRB review, section 16(2) states that collaborating RIs *may* "appoint a common institutional review board which may be the institutional review board appointed by the lead research institution or such institutional review board as may be agreed among the institutions."[47] This provision streamlines the review process of collaborative research, without substantially weakening it.

The *HBRA* offers only a few specifications for the required composition of an IRB, but it is expected that MOH will issue supplementary legislation on this point in due time. Section 63(2) accords such power to MOH, stating that the Minister of Health may issue further regulations with respect to the "composition, duties, procedures, responsibilities and powers of institutional review boards."[48] Even though the full set of regulations is still forthcoming, the Minister of State, during the Parliamentary debates on the Bill, already revealed that "the IRB will be required to include at least one scientific member and one lay person"[49] and that "the IRB chairperson must be a registered medical practitioner as an added measure for accountability."[50]

In that same speech, the Minister clarified to what extent the *HBRA* and its subsidiary legislation will hold individual IRB members liable. According to the Minister, the *HBRA* "does not impose criminal sanctions on individual IRB members for the decisions they make in discharging their IRB functions."[51] The Minister also expects "research institutions to indemnify their IRB members against legal liability arising from the decisions of members who have discharged their duties in good faith."[52] These remarks should be a welcome assurance for IRB members who assume their duties on a voluntary basis.

One thing that the *HBRA* does not yet specify is how the *appointed* IRB must relate to the institutional structure of the *appointing* RI. In particular, the Act does not yet specify to what extent the administrative infrastructure of an IRB may (or may not)

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43 *Ibid*, ss 17(1)(k)(i)-(iii).
44 *Ibid*, ss 21(1), (2).
45 *Ibid*, s 17(1)(b).
46 *Ibid*, s 17(1)(h).
47 *Ibid*, s 16(2).
48 *Ibid*, s 63(2).
49 Dr Lam Pin Min, Second Reading Human Biomedical Research Bill, *supra* note 4. The added measure of accountability is owed to the fact that medical practitioners are accountable to their respective professional boards.
50 *Ibid*. The additional accountability is owed to the fact that medical practitioners are accountable to their respective professional boards.
51 *Ibid*.
52 *Ibid*.

be external to an RI. To explain this point, consider that some RIs, especially those that supervise only a small number of research projects, might prefer appointing an externally-run IRB. This would be more economical than supporting the administrative infrastructure of a rarely-used in-house IRB. Indeed, such outsourcing of IRB-related services would not be entirely novel in Singapore: a number of local IRBs have, for some time, been offering review services for biomedical research protocols submitted by individuals from outside their own institutions—these are, in the public sector, the National Healthcare Group's Domain Specific Review Board ("DSRB") and SingHealth's Centralised Institutional Research Board ("CIRB"), and, in the private sector, Parkway Hospitals' Parkway Independent Ethics Committee. It is important to clarify that these three IRBs operate on a *for-fee* basis, where the (flat) fee is understood to cover the administrative and secretarial costs that directly arise from processing and reviewing research protocols. This contrasts with the operations of *for-profit* (or *for-hire*) IRBs, as they exist, for instance, in the United States.[53] Under the for-profit model, IRB members are not merely compensated for volunteering their time and effort, but receive remuneration. Hence, under that model, RIs would pay for the *service* of protocol review.

While some commentators praise the successful track-record, increased efficiency, as well as the institutional independence of for-profit IRBs, the for-profit model remains controversial.[54] Many have voiced concerns about the inherent conflict of interest that occurs when entities or individuals conduct an (ethical) review of research under a for-profit motive.[55] MOH has already communicated in public consultation that it will not allow for-profit IRBs to conduct the protocol review that is required under the *HBRA*.[56] Section 63 of the *HBRA* empowers the Minister of Health to issue such regulations.

C. *Individual Researchers Under RI Supervision*

The *HBRA* imposes a number of duties directly on individual researchers, where a "researcher" is understood to be the "natural person who conducts human biomedical research under the supervision and control of a research institution."[57] Section 22 states that no researcher may conduct human biomedical research outside the supervision and control of an RI.[58] Furthermore, researchers must receive either the approval of an IRB before commencing any human biomedical research or they must have otherwise been notified that their research is exempted from review. They must also *discontinue* their research should an IRB revoke its approval. These provisions are clear.

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53 The term 'Institutional Review Board' might cause confusion here because it suggests that the review board must be tied, by definition, to an institution, *eg*, a research institution. However, this is misleading. US-based for-profit IRBs are commercial entities that may work closely with, but ultimately operate separately from, research institutions, on a 'stand-alone' basis.

54 See *eg*, Ezekiel J Emanuel *et al*, "Should Society Allow Research Ethics Boards to Be Run As For-Profit Enterprises?" (2006) 3 PLOS Medicine 941; Caroline McNeil, "Debate Over Institutional Review Boards Continues as Alternative Options Emerge" (2007) 99 J Natl Cancer Inst 502.

55 See *eg*, Ruth Macklin "How Independent are IRBs?" (2008) 30 IRB: Ethics & Human Research 15.

56 I am grateful to the anonymous referee for bringing to my attention the MOH's position on this matter.

57 *HBRA*, *supra* note 1, s 2.

58 *Ibid*, s 22.

Less clear is the provision listed in section 22(3)(a) which states that researchers must ensure that their "research does not deviate from the research proposal that has been reviewed and approved"[59] by an IRB. The intention is obviously to ensure that researchers conduct human biomedical research only *to the extent that* and only *under the description under whic*h the research underwent IRB review. However, researchers as well as RIs might be concerned about what *exactly* counts as deviation under the *HBRA*. This is particularly troubling because, in practice, research often does not unfold in the way anticipated when a protocol was submitted for review. For instance, a researcher might be led to deviate from a protocol where the initial protocol indicated that the researcher had sought to gather data for answering a particular biomedical question X; but, over the course of the research, data surfaces that sheds light on a different and more interesting biomedical question Y; and, accordingly, the researcher shifts focus and concentrates on answering Y. On a strict understanding of what counts as 'deviation', the *HBRA* would require the researcher to resubmit the modified protocol for IRB review. Not only would this increase the workload of IRBs, the additional administrative burden might also frustrate researchers. One solution might be for the *HBRA* to permit *minor* deviations from the submitted research protocol, while requiring protocol resubmission for *substantial* deviations.[60] Alternatively, it might be left to RIs to develop, in conjunction with their appointed IRB, their own policies on how to handle the issue of minor protocol deviations. This possibility is opened up by section 22(3)(a)(i), which reads that deviations from protocol are prohibited "*unless* the deviation… has been reviewed and approved, or *otherwise exempted from review*, by the institutional review board".[61] So, there appears to be room for the RI and its appointed IRB to set a *policy* according to which minor deviations from protocol are generally exempted from review. Of course, the RI might still require the researcher to internally report minor deviations (*eg*, to the principal person in charge) for the purpose of discharging its duty to monitor research.

D. *Monitoring the Role of the Director of Medical Services*

The *HBRA* does not envisage the DMS playing the role of actively reviewing and monitoring human biomedical research. Instead, the DMS assumes the position of an oversight entity that ensures compliance. As mentioned, the *HBRA* places RIs under a duty to notify the DMS about various events relating to their human biomedical research activities. This gives the DMS the informational basis to exercise his functions. Further, the *HBRA* furnishes the DMS and his authorised officers with

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59 *Ibid*, s 22(3)(a).

60 Of course, the challenge would then be to develop criteria for separating 'substantial deviations' from their 'non-substantial' counterparts. A deviation might be classified as 'substantial', if, *inter alia*, it results in changes to the level of risk that research subjects are exposed to.

61 *HBRA, supra* note 1, s 22(3)(a)(i) [emphasis added]. This passage gives rise to a curious complication because it is not clear how, by definition, a 'deviation' of protocol can be *approved*. To explain, if an IRB indeed approves a 'deviation' from protocol, this might be more properly regarded as approving a 'change' of protocol. But the researcher who follows the changed (or amended) protocol would then not deviate from protocol.

wide ranging enforcement powers, including powers of entry, inspection and search, and seizure without warrant.[62]

IV. Research Subject Protection and Risk Minimisation

In addition to establishing a general accountability framework for reviewing, conducting, and monitoring human biomedical research, the *HBRA* contains a number of provisions that set more specific parameters for permissible research. These provisions spell out, *inter alia*, areas of prohibited and restricted research, specifications for obtaining valid consent from research subjects, and safeguards for research involving vulnerable individuals.

A. *Prohibited and Restricted Research*

The *HBRA*'s Third Schedule lists human biomedical research that is categorically *prohibited*. This encompasses research that involves human-animal combination embryos, research that involves "the introduction of human stem cells (including induced pluripotent stem cells) or human neural cells into the brain of living great apes,"[63] and research "involving the breeding of animals which had any kind of pluripotent stem cells… introduced into them."[64] Arguably, the reason why the *HBRA* prohibits these lines of research is that they are considered ethically questionable and do not carry enough scientific promise to merit the potential violation of ethical standards.[65] Indeed, by incorporating these prohibitions, the *HBRA* responds to some of the concerns that the Singapore Bioethics Advisory Committee ("BAC") raised in its 2010 report on human-animal combinations in stem cell research.[66]

For research that falls into the category of *restricted* human biomedical research listed under the *HBRA*'s Fourth Schedule, a model of direct governmental oversight (to be spelled out in subsidiary legislation) supplements the *HBRA*'s accountability framework. To this effect, the *HBRA* states that no person or RI may conduct or supervise restricted human biomedical research "*except in accordance with such requirements* as the Minister may prescribe and such prescribed requirements are in addition to and not in lieu of the requirements in this Act."[67] At the Parliamentary reading of the Bill, the Minister further added that MOH intends to set up "a national advisory committee of experts [which] will deliberate upon the ethical and scientific

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62 *Ibid*, s 45. The DMS is, however, *not* furnished with powers to exempt entities or persons from the provisions of the *HBRA*. These powers are accorded only to the Minister and, at the Minister's discretion, may also be delegated to his Second Minister or his Minister of State. See *HBRA*, *ibid*, ss 57, 58.

63 *Ibid*, Third Schedule, para 3. A note on nomenclature: stem cells are "pluripotent" because they have the capacity to grow into virtually any kind of human tissue cell (*eg*, liver, kidney, skin, *etc* cells). The term "induced pluripotent stem cells" describes adult cells that were non-pluripotent but have been 'reprogrammed' to obtain pluripotent capacity.

64 *Ibid*, Third Schedule, para 4.

65 See *eg*, David DeGarcia, "Human-Animal Chimeras: Human Dignity, Moral Status, and Species Prejudice" (2007) 38 Metaphilosophy 309. For an opposing view, see *eg*, Mark Greene *et al*, "Moral Issues of Human-Non-Human Primate Neural Grafting" (2005) 209 Science 386.

66 See Bioethics Advisory Committee, *Human-Animal Combinations in Stem Cell Research—A Report* (September 2010), online: BAC <http://www.bioethics-singapore.org/images/uploadfile/54403%20PMHAC%20Report%20.pdf>.

67 *HBRA*, *supra* note 1, s 31(1) [emphasis added].

rationale of such [restricted] research, and recommend to the Minister whether or not to approve such protocols."[68]

Notably, offences by individuals against both sets of provisions, those relating to prohibited and to restricted research, attract a maximum penalty of a $100,000 fine, 10 years' imprisonment, or both.[69] For a body corporate, the maximum penalty doubles to $200,000.[70] This signals the seriousness with which the government views these matters.

B. *Incorporating the Importance of Consent*

The requirement to obtain appropriate consent from research participants prior to their involvement in human biomedical research is a key component of the *HBRA*. This is in line with the authoritative international documents on the ethical conduct of research involving human subjects, such as the *Nuremberg Code*,[71] the World Medical Association's ("WMA") *Declaration of Helsinki*,[72] and the Council for International Organisations of Medical Sciences' ("CIOMS") *International Ethical Guidelines for Biomedical Research Involving Human Subjects*.[73]

The *HBRA* spells out the specific ways in which this consent must be informed and voluntary. To this effect, section 12 provides an extensive list of information to be provided to the research subject before obtaining consent;[74] and section 26(1) spells out the prohibitions against coercing, deceiving, or intimidating a person to give consent to participate in such research.[75] Lacking is, however, any prohibition of "inducement". On this point, the *HBRA* deviates from the BAC's 2015 *Guidelines on Human Biomedical Research*, which specify that valid consent must be obtained with "no coercion, deception *or inducement*"[76] and, further, that any "reimbursement for expenses incurred in relation to the research, whether monetary or in kind, should not amount to an inducement".[77]

Finally, the *HBRA* does recognise that there are circumstances in which it is appropriate to *waive* the requirement to procure consent. Such a waiver may be granted by a reviewing IRB if the circumstances listed in the *HBRA*'s Fifth Schedule

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68 Dr Lam Pin Min, Second Reading Human Biomedical Research Bill, *supra* note 4.

69 Commenting on the general structure of the *HBRA*'s penalty scheme, the Minister of State pointed that it is "consistent with other Singapore laws, for example, the Human Cloning and Other Prohibited Practices Act and the Human Organ Transplant Act." See *ibid*.

70 *HBRA*, *supra* note 1, s 50 specifies the enhanced penalty for corporations convicted of an offence under this Act as "a fine not exceeding 2 times the maximum amount that the court could, but for this section, impose as a fine for that offence."

71 See *Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No 10* (Washington, DC: US Government Printing Office, 1946-1949) vol 2 at 182.

72 WMA, *Declaration of Helsinki—Ethical Principles for Medical Research Involving Human Subjects* adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, rev at the 64th WMA General Assembly, Fortaleza, Brazil, October 2013, online: WMA <http://www.wma.net/en/30publications/10policies/b3/>.

73 CIOMS, *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (2002) [CIOMS, *International Ethical Guidelines*], online: CIOMS <http://www.cioms.ch/publications/guidelines/guidelines_nov_2002_blurb.htm>.

74 *HBRA*, *supra* note 1, s 12.

75 *Ibid*, s 26(1).

76 BAC, *Ethics Guidelines for Human Biomedical Research* (June 2015) at 25, online: BAC <http://www.bioethics-singapore.org/images/uploadfile/fullReport.pdf> [emphasis added].

77 *Ibid*.

permit. The circumstances that must obtain for a waiver to be permissible include that the research imposes no more than minimal risk on the research subject and that the research would "reasonably be considered to contribute to the greater public good."[78] The requirement to obtain consent may also be waived for "emergency research", *ie* research that involves individuals in "a life-threatening situation".[79]

C. *Vulnerable Research Subjects*

The *HBRA* contains various safeguards for protecting vulnerable research subjects, specifically minors and mentally incapacitated individuals. A "minor" is defined in section 2 as a "person who is below 21 years of age and who has never been married".[80] This threshold appears to be rather high, especially when compared to European countries, which set the age of majority for clinical or biomedical research at 18 or lower.[81] However, one consideration in favour of setting a high threshold in the case of Singapore has to do with the fact that male Singapore citizens and second-generation permanent residents must serve two years as full-time National Servicemen ("NSFs"). A majority of NSFs are between the ages of 18 and 21. Thus, by setting the age of majority at 21, the *HBRA* ensures that NSFs, if they are recruited for (military) human biomedical research, enjoy the safeguards that are afforded to minors.[82]

As for "mentally incapacitated individuals", section 2 defines an adult as mentally incapacitated if the "adult… lacks capacity within the meaning of section 4 of the Mental Capacity Act (Cap 177A)."[83] The *HBRA* however does not provide a separate definition of "minors who lack mental capacity", even though such individuals are referenced in sections 8(1)(d), 10(1)(c) and (e), and 37(2)(b).

Any safeguards that the *HBRA* incorporates for the protection of such vulnerable individuals need to strike a delicate balance between protecting the rights and welfare of vulnerable individuals and yet leaving *sufficient* room for the practicable inclusion of these individuals in HBR. Indeed, the inclusion of vulnerable individuals in research is often necessary in order to improve the health of members of that very group. For instance, biomedical research on children allows researchers to study certain medical conditions that only affect children or that affect children in specific ways.[84] Likewise, it is often essential to involve mentally incapacitated individuals, *eg*, individuals with severe dementia or cognitive impairment, in biomedical research in order to improve our understanding and treatment of the very conditions that afflict them.

One noteworthy safeguard that the *HBRA* affords to vulnerable individuals comes in the form of strict provisions for obtaining consent. For research involving

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78 *HBRA*, *supra* note 1, Fifth Schedule, para 3(d).

79 *Ibid*, Fifth Schedule, para 4.

80 *Ibid*, s 2.

81 For a discussion of this point, see *eg*, Tracey E Chan "Minors and Biomedical Research in Singapore" (2008) 28 Legal Studies 396.

82 The definition of 'human biomedical research' would apply to combat-simulating human subject research because it includes research on human performance and endurance. *HBRA*, *supra* note 1, s 3(2)(c).

83 *Ibid*, s 2.

84 See *eg*, CIOMS, *International Ethical Guidelines*, *supra* note 74, commentary on Guideline 14.

minors, the *HBRA* stipulates that consent must be obtained from at least one parent or guardian.[85] In addition, "where the minor has sufficient understanding and intelligence to enable the minor to understand what is proposed in the biomedical research,"[86] consent must be obtained from *both* the minor and at least one parent or guardian.[87] For research involving adults who lack mental capacity, consent must be obtained from a donee or deputy or, where there is no donee or deputy, from a relative of the individual (*eg*, spouse, adult child, parent/guardian, sibling).[88]

V. Tissue Banks and Tissue Banking

Besides regulating human biomedical research, the *HBRA* also seeks "to regulate tissue banks and tissue banking activities".[89] A tissue bank is a kind of biorepository that collects and stores various types of (human) biological tissue. It allows researchers comparatively convenient access to large numbers of biological samples.

The *HBRA* defines both "tissue banking *activity*" and the institution of a "tissue bank". The activity of tissue banking is defined in section 2 as the "structured and an organised activity involving human tissue for the purposes of facilitating current or future research… including… (a) the collection, storage, procurement or importation of human tissue; (b) the supply, provision or export of human tissue."[90]

A tissue bank is defined as an "individual or a body of persons, whether corporate or unincorporate, or other organisation, that carries on or conducts any tissue banking activity."[91] However, "an individual, a body of persons or an organisation that conducts any tissue banking activity *solely* for the purpose of the person's or organisation's *own* human biomedical research approved or exempted from review by an institutional review board"[92] is *not* considered a tissue bank under the *HBRA*. In other words, if tissue is collected under the auspices of an RI for the execution of a particular research protocol that has gained IRB-approval (or exemption from IRB review), the activity of tissue banking takes place without there being established a tissue bank. In turn, if the tissue is also to be stored and/or used for future unspecified research, this would entail the establishment of a tissue bank.

A. *Provisions Regarding Tissue Banks*

The *HBRA* allows tissue banks to be operated under the supervision of an RI, but they may also be operated independently. In either setting, however, the *HBRA*

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85 An IRB may waive the requirement to obtain parental consent if the research involves no more than minimal risk and the research is of "a private and sensitive nature that it is not reasonable to require permission, (such as adolescents in studies concerning treatment of sexually transmitted diseases)", *HBRA*, *supra* note 1, s 13(2).

86 *Ibid*, s 8(1)(a).

87 Such an arrangement is often referred to as 'Dual Consent', even though the *HBRA* contains no explicit reference to that term. For a discussion of that concept (and term), see *eg*, Imelda Coyne, "Research with Children and Young People: The Issue of Parental (Proxy) Consent" (2010) 24 Children & Society 227.

88 *HBRA*, *supra* note 1, s 9(1).

89 *Ibid*, Long Title.

90 *Ibid*, s 2.

91 *Ibid*.

92 *Ibid* [emphases added].

requires that, when a tissue bank is established, the DMS be furnished with certain particulars, the details of which will be the subject of subsidiary legislation.[93] Once instituted, the *HBRA* requires the bank to "supervise, review and proactively monitor the conduct of the tissue banking activity".[94] It however does not require tissue banks to appoint an IRB (or a comparative review board). This means that applications or requests by researchers to access materials from a tissue bank do not have to undergo IRB review *on the side of the tissue bank*. Instead, section 35(2)(g) specifies that, before releasing any tissue materials, a bank must ensure that IRB-approval has been obtained from the IRB appointed *by the RI* under whose supervision and control the research is to take place.

B. *Provisions Regarding Tissue Banking*

Among the various provisions that regulate the activity of tissue banking the most important ones concern the *procurement* of tissue from individual donors as well as the *release* of such materials to researchers. The *HBRA*'s provisions for the procurement of human tissue stipulate that tissue may be taken from a person only with the appropriate consent of that person.[95] The consent to donate tissue must be voluntary in the same sense as discussed in the context of human biomedical research: consent must *not* be obtained by means of coercion or intimidation. Further, the consent to donate tissue must be 'informed' which requires that the potential donor be told, *inter alia*, about the storage of tissue for use in unspecified future research and about the handling of so-called incidental findings.[96] If the tissue is "to be exported… from Singapore to a place outside Singapore",[97] this must have likewise been disclosed to the donor at the time of obtaining consent.

Particularly stringent provisions apply to the removal of tissue from individuals who are mentally incapacitated and from minors who lack sufficient understanding and intelligence to give consent.[98] Tissue may be removed from these individuals *only if* the removal of the tissue was "primarily for a therapeutic or diagnostic purpose"[99] and an IRB has judged that:

(a) the removal of the tissue involves no more than minimal risk to that person; and
(b) there are reasonable grounds for believing that the proposed areas of research cannot be carried out without the use of the tissue from the class of persons to which that person belongs.[100]

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93 *Ibid*, s 35(3).
94 *Ibid*, s 35(2)(a).
95 *Ibid*, s 25.
96 The *HBRA* defines an 'incidental finding' as "a finding about a research subject that has potential health or reproductive importance to the research subject and is discovered in the course of conducting research but is unrelated to the purposes. . . of the study": *ibid*, s 2. To emphasise, the *HBRA* does *not* require the disclosure of incidental findings in the context of tissue banking but the Act *does* require that potential donors be informed, prior to taking consent, as to how incidental findings will be handled.
97 *Ibid*, s 12(2)(q).
98 *Ibid*, ss 37(2)(a)-(c).
99 *Ibid*, s 37(3).
100 *Ibid*.

Finally, the *HBRA* explicitly forbids commercial procurement of human tissue through its ban on commercial trading of human tissue, understood as the sale or supply of any human tissue.[101] Equally prohibited is any *advertisement* relating to buying or selling of any human tissue.[102] This firm stance against commercialisation of human tissue follows the recommendations made in the BAC's 2002 *Report on Human Tissue Research*[103] and is consistent with the *Human Organ Transplant Act*'s[104] prohibitions of trading in human organs and blood.

VI. Conclusion

The *HBRA* is a rich and comprehensive piece of legislation, and many of its provisions could not be discussed in the short space of this comment.[105] Indeed, the Act's scope needs to be broad in order to properly "ensure the safety and welfare of research subjects."[106] At the same time, the extensive scope of the *HBRA* has led some members of Singapore's research community to become worried about compliance once the Act is signed into law. In light of this, the Minister's assurance that the MOH will continue to work *with* stakeholders from the research community "to ensure a smooth and successful implementation"[107] of the Act is a welcome one. Concrete measures include "forums and dialogue sessions with the biomedical research community to address any implementation issues that they may have."[108] This inclusive approach will be crucial to ensure a successful implementation of the *HBRA*.

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[101] *Ibid*, s 32.

[102] *Ibid*, s 33.

[103] See BAC, *Human Tissue Research—A Report* (November 2002), online: BAC <http://www.bioethics-singapore.org/images/uploadfile/2002-11%20-%20Human%20Tissue%20Research.pdf>.

[104] Cap 131A, 2012 Rev Ed Sing.

[105] To mention just three additional aspects of the *HBRA* that this comment was unable to address: There is a general concern whether the inclusion of criminal sanctions is *appropriate* for a law that governs research activities. This might be a concern especially for those who think that criminalisation has an *expressive* function. See *eg*, Joel Feinberg, "The Expressive Function of Punishment" (1965) 49 The Monist 397; Cass R Sunstein, "On the Expressive Function of *Law"* (1996) 144 U Pa L Rev 2021. The *HBRA* uses an interpretation of the "minimal risk" standard that, while being invoked in various international guidelines, is not uncontested. The *HBRA* defines "minimal risk" in s 2 as the:

> . . . probability and magnitude of harm and discomfort anticipated. . . that are not greater, in and of themselves, than those ordinarily encountered —
>
> (a) in the daily life of normal and healthy persons; or
>
> (b) during the performance of routine physical or psychological examinations or tests.

This is an 'absolutists' interpretation of "minimal risk" in the sense that it appeals to the level of risk *ordinarily* encountered by *normal and healthy* persons. It does not take into account how different people might have different levels of 'baseline' risks that they are exposed to in their individual lives. See *eg*, Loretta M Kopelman, "Moral Problems in Assessing Research Risk" (2000) 22 IRB: Ethics & Human Research 3. Finally, there is an interesting question of how the *HBRA* compares with legislation in other jurisdictions as well as with international guidelines on the ethical conduct of human biomedical research. For an early comparative evaluation of the *HBRA*, see *eg*, Shermian Koh Jin Hui & Voo Teck Chuan "The Human Biomedical Research Act: Overview and International Comparisons" (2016) 20 Asia-Pacific Biotech News 14.

[106] Dr Lam Pin Min, Second Reading Human Biomedical Research Bill*, supra* note 4.

[107] *Ibid*.

[108] *Ibid*.