THE CHALLENGE OF REGULATING HUMAN BIOMEDICAL RESEARCH

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1. Introduction

Biomedical research involving human participants has had a checkered history. It has given humankind important new knowledge about our physiology and ailments, and important prophylactics and treatments. But it has also imposed significant harms on human participants.1 At the core of the tension that the conduct of human biomedical research (‘HBR’) raises for society is the conflict of commitments a researcher has between his quest for knowledge - the demands of scientific rigour and adherence to the requirements of research protocol - and the interests of his human participants.2 Post-World War II, and the Nazi atrocities that continue to serve as a beacon of how badly research can go wrong, HBR has had its continuing share of scandals and abuses.3 These have prompted the scientific community and societies around the global to search for means to manage these tensions. Protecting human participants will necessarily involve trade-offs in the progress of research,4 and the common challenge facing societies that fund and support research is how best to regulate the conduct of research to achieve a fair balance between the two often competing goals.

This paper will review the developing regulatory framework for HBR in Singapore. It will first chart the origins of the current ‘ethics committee’ (termed institutional review boards (‘IRBs’) in Singapore) based governance framework and examine the Ministry of Health’s (‘MOH’) guiding regulatory philosophy and its envisaged contours. Secondly, it will examine several critical challenges facing IRBs as the core regulatory tool to ensure

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the ethical conduct of HBR – to protect the rights and interests of human participants without unnecessarily hindering the progress of research. These are: the need for IRB independence, a co-operative model for IRB deliberations and keeping IRB workloads manageable in order to promote efficacy and efficiency. Finally, the paper will examine the MOH’s regulatory role within the current framework in respect of standard-setting, monitoring and enforcement, and make observations and suggestions on how these functions might be discharged.

2. The developing regulatory framework

a. Pre-2000

(1) Medicines (Clinical Trial) Regulations

Prior to the new millennium, the only statutory regulation concerning human biomedical research involved clinical trials under the Medicines Act (‘MA’). The conduct of a clinical trial must comply with the requirements of the Medicines (Clinical Trials) Regulations (‘CTR’) and the Singapore Guideline for Good Clinical Practice (SGGCP). A clinical trial is defined in s. 2 of the MA as:

...an investigation or series of investigations consisting of the administration of one or more medicinal products of a particular description by, or under the direction of —

(a) a doctor or dentist to one or more of his patients; or
(b) two or more doctors or dentists, each product being administered by or under the direction of one or other of those doctors or dentists to one or more of his patients,

where (in any such case) there is evidence that medicinal products of that description have effects which may be beneficial to the patient or patients in question and the administration of the product or products is for the purpose of ascertaining whether, or

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5 Cap. 176, 1985 Rev. Ed.
7 Singapore: MOH, 1999
to what extent the product has, or the products have, those or any other effects, whether beneficial or harmful;

Not all research involving the administration of a medicinal product would fall within the ambit of this definition. For instance, observational or non-interventional studies where the medicinal product is prescribed in accordance with its marketing authorization, as well as physiological or pathological studies involving the use of a medicinal product, are not covered.\(^8\) However, it would appear that the definition would cover equivalence studies without the specific goal of registration of the relevant medicinal product.\(^9\) A comprehensive review is put in place by the CTR, which includes both local review by a hospital ethics committee based in the hospital where the clinical trial (CT) is to conducted and the national Medical Clinical Research Committee, before a CT certificate is issued by the Health Sciences Authority as the relevant regulator.\(^10\)

(2) \textit{NMEC’s Ethical Guidelines on Research Involving Human Subjects}

Apart from this, there is no general statutory framework for human biomedical research. However, professionally, research ethics received specific attention by the National Medical Ethics Committee’s \textit{Ethical Guidelines on Research Involving Human Subjects}, issued in 1997.\(^11\) The guidelines were issued with the objective of providing

\ldots a broad framework of ethical principles which local ethics committees should take into consideration in their deliberations and to suggest procedures which these committees should follow in the decision making process. The ultimate goal is the encourage awareness among research workers of ethical values which are acceptable to the community, bearing in mind that ethical principles may change with time and changes in public perception.\(^12\)

\(^10\) \textit{Ibid.} at B-65, paras. 2.18-2.21
\(^12\) \textit{Ibid.} at para. 1.3
The guidelines therefore devote first attention to the general ethical principles governing human subject research (which largely map to those espoused by the influential US Belmont Report issued in 1979), and in particular the specific issues of risk assessment, consent (for competent and vulnerably groups of participants) and confidentiality. Of particular relevance are the recommendations concerning the implementation of ethical governance of research via the use of the device of the Research Ethics Committee (REC). The REC is the research institution’s instrument of ethics governance, on the basis of the principle that the individual researcher should not be the “sole judges of ethical acceptability of their proposed studies.” This REC therefore have “primary responsibility for decision-making” on research ethics. Although institutional in character and authority, the REC’s membership has broad based representation from the community, relevant experts and other relevant professionals. The guidelines also outlined operational measures and the specific issues that the REC is to look into, in particular, scientific validity, risks to participants, selection of subjects, procedure for informed consent, protection of confidentiality and safeguards during the course of the research protocol. Finally, RECs also have continuing review responsibilities, although these are largely contingent on reports, updates and specific information provided by the investigator as the research protocol progresses. In addition, REC are to remain accessible to individual participants who may have concerns or complaints during or after enrolment, in order to provide advice or take appropriate action.

The NMEC Guidelines were formally adopted by the MOH in 1998 and all government and restructured hospitals were directed to comply. However, they did not otherwise have legal or normative effect save through the enforcement of professional responsibilities of individual medical or other allied professional researchers, and the

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13 Ibid. at para. 3.1
14 Ibid. at para 3.2.1 [emphasis added]  
15 Ibid. at para. 3.2.2  
16 Ibid. at para. 3.2.5  
17 Ibid. at para. 3.2.6  
18 See BAC Guidelines, supra note 9 at para. 2.26
regulatory authority of the MOH. Only the requirements of the CTR in its specific domain had legal sanctions to back them up.19

b. Post-2000

(1) BAC’s Third Report on Guidelines for IRBs

With the growth of the biomedical sciences industry and research funding in the last decade, given extensive national backing, two important developments occurred. The first was a timely review of research ethics governance by the Bioethics Advisory Committee in 2004.20 The BAC Guidelines addressed a number of important issues concerning the ‘ethics committee’ model of research governance, which was internationally ubiquitous in conception, but not in nomenclature or operational details.

First of all, it discussed and provided a more careful definition of the subject matter of regulation – what is research that is of concern?21 Second, the report also recognised the need for differentiation in terms of ethics review given the increase in the volume of research and concomitant need for review, and the varying risks, from remote to significant, that research falling within the definition above would pose.22

Third, and principally, the report makes more elaborate recommendations for IRBs (preferring this term over REC to emphasise the nature of the authority and responsibility for ethics governance). The BAC reaffirmed the function of an IRB as the “Ethics Review Gateway” within institutions that support and conduct research, endorsing most of the earlier recommendations made by the NMEC in its 1997 guidelines.23 Amongst other sub-topics, the report focused on:

(a) an elaboration of the scope of functional responsibilities of an IRB

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19 BAC Consultation Paper, ibid. at B-70, para. 2.46
20 Supra note 9
21 Ibid. at paras. 3.1-3.8
22 Ibid. at paras. 3.9-3.18.
23 Ibid. at para. 5.20
(b) its constitution and composition
(c) institutional conflicts of interest on the part of the IRB
(d) the management of review of multinational and multi-centre research projects; and
(e) Specific operational issues facing IRBs

Finally, the BAC report also makes more detailed recommendations for other important actors in biomedical research: namely, the researchers themselves, research institutions (in particular their fundamental responsibility to adequately fund, support and protect IRBs) and recommendations concerning accreditation to be implemented by the MOH.

(2)  MOH’s Governance Framework for HBR

More recently, in June and December 2007, the MOH itself issued its own documents concerning the basic governance of biomedical research and operational guidelines for IRBs. Arguably the more significant of the two, the former aims to consolidate the prior statutory and ethical recommendations into an “over-arching governance framework” for HBR. The language of the framework stipulations is couched in general terms, without any restriction in jurisdiction based on the Ministry’s existing statutory powers.

Crucially, the overall regulatory philosophy of the MOH is captured in the following two paragraphs:

3 MOH intends to adopt a light-touch, risk-based approach such that research is not unnecessarily stifled, while still ensuring safety and well-being of research subjects. Regulatory requirements will be set for various types of

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24 This is a perennial issue in the modern research landscape where multi-jurisdictional and centre trials are a common feature of clinical trials and other HBR. An analysis of the efficacy of the recommendations in this respect is beyond the scope of this paper.
research activities according to the level of ethical concerns, sensitivities and risks to patient safety and well-being, as what is appropriate for one type of research activity may be excessive or inadequate for another.

4 MOH’s role is to demarcate acceptable limits within which all human biomedical research should be conducted. The out-of-bound markers set clear prohibitions while allowing flexibility within boundaries. Within these boundaries, our preference is for self regulation. However, where necessary, MOH will not hesitate to exercise its enforcement powers to ensure that the safety and well-being of research subjects is protected. Benchmarks for ethical standards expected of various parties involved in research will also be set through guidelines or codes of practice.27

In addition, the governance document goes on to summarise the key responsibilities of three major HBR players: institutions, researchers and IRBs based largely on the earlier work of the NMEC and BAC. Interestingly, there is no mention of the duties or responsibilities of funders of research, although arguably they play as crucial a role in the overall research environment in their decisions to fund and support HBR within or without Singapore. In comparison, for e.g., the U.K Department of Health’s Research Governance Framework for Health and Social Care (2nd Ed., 2005) provides that funders of research have the “critical role in assuring the quality of the study... establishing that the research proposal is worthwhile, of high scientific quality, and represents good value for money [through independent expert review].”28

Prima facie, the regulatory philosophy is responsive in nature, in the sense that primary responsibility for decision-making and monitoring is delegated to the institutions conducting research, with authority to set their own more detailed standards, implement and enforce them – principally through the IRB and other institutional

27 MOH Governance Framework, supra note 25 at 1 [emphasis added].
processes. The MOH, obviously undertaking the overall regulatory role, stipulates for itself (at least) two explicit regulatory functions: standard setting and enforcement.

On the first of these regulatory functions, it appears that these cover two distinct but related areas: regulatory boundaries and substantive ethical standards. The former is described in more concrete terms as “out of bound markers”, presumably related to either no go areas, such as the proscriptions laid out in the Human Cloning and Other Prohibited Practices Act, or to areas outside the jurisdictional or policy concerns of the MOH, e.g. social and behavioural science research outside the definition of HBR. The second appears to be in some conflict with the stated goal of encouraging self-regulation within the out-of-bounds markers. Perhaps some balance is inevitably necessary, as efficiencies can be obtained by standardising ethical guidelines in some common areas of research, rather than leave it to individual institutions to reinvent the wheel from scratch. More will be said on the topic of regulatory standard setting below.

Enforcement is left decidedly vague. Apart from the governance framework statement, the statutory framework remains patchy vis-à-vis research actors outside the health care and health professions’ regulatory environment, and the specific penal sanctions under relevant statutes such as the HCOPPA and National Disease Registries Act which draw no distinction on the basis of health care setting or professional status. Within those existing spheres, the MOH has a slim but potent arsenal of enforcement powers to clamp down on errant institutions and individuals, but not without. The regulatory reach of the MOH was originally intended to be expanded by the Regulation of Biomedical Research Bill 2003 to cover all institutions or individuals conducting HBR, but since the initial public consultation on the draft circa 2003, the bill has yet to see the light of day.

(3) **MOH Operational Guidelines for IRBs**

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29 See infra part 6.
30 Cap. 131B, 2005 Rev. Ed. [HCOPPA]
31 MOH Guidelines, supra note 26 at para. 4.4
32 Cap. 201B, 2008 Rev. Ed.
Accompanying the governance framework statement is the separate, MOH issued, *Operational Guidelines for Institutional Review Boards*. Again, the instrument seeks to build upon earlier local work on research ethics governance, and many of the recommendations overlap those made in the BAC Guidelines, and therefore the NMEC’s 1997 Guidelines. Several important differences in approach, or issues more specifically elaborated upon, should be noted:

(a) The definition of human biomedical research and the categorisation of ethics review classification:

The MOH’s operational guidelines adopt a definition of HBR that is subtly but significantly different from that in the BAC report. The definition is an all encompassive one that stretches beyond direct interventions with the human body to include research that involves:

- intervention on, interaction with, or observation of, humans;

- use or manipulation of any human biological derivative (e.g. human cells, tissues and body fluids), including those which were previously acquired and stored;

- review, analysis and publication of previously compiled identifiable data;

for the purpose of studying, diagnosing, treating and/or preventing, any ailment, injury or adverse condition of the human mind or body.

In contrast, the BAC report adopted a bifurcated, and rather convoluted, definition distinguishing between biomedical research involving direct interventions with the concomitant risk of some physical injury or harm however remote or minor (“Direct HBR”), and any other biomedical research that involves human subjects, human tissue or medical or genetic information with a wider concomitant range of risks to the safety,

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33 *Supra* note 26
34 *Supra* note 26 at para 2.2
35 *Supra* note 9 at para. 3.7(a)
An edited version of this paper will appear a forthcoming special issue of the Singapore Academy of Law Journal (2010)

health, welfare, dignity or privacy of the human subject, donor or their family members (“Indirect HBR”). The reference to risks to safety and health under Indirect HBR unfortunately lead to some overlap with the first arm of the definition. This could possibly lead to difficulties in categorizing research for the purposes of assigning an appropriate level of ethics review.

While the MOH guidelines adopt a more streamlined and readily comprehensible set of definitions, these have had to be supplemented by an additional concept of ‘minimal risk’ for the purposes of channeling for ethics review. Thus while the BAC did not commit to an exhaustive definition or classification of research warranting expedited review or exemption, the MOH’s approach is purely risk-based. Protocols imposing only “minimal or remote risk” are eligible for expedited review, while those with “no likelihood of harm” are exempted from review. Any other type of biomedical research imposing more than minimal risk must therefore undergo full ethics review by an appropriately constituted IRB. The efficacy of such sorting purely along quantitative risk lines depends substantially on the clarity of the definition of “minimal risk”. In this respect, the MOH Guidelines adopt the U.S. Code of Federal Regulations, §46.102 definition, namely:

 Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

(b) Concrete requirements for IRB Composition, DSMP and continuing review:

The MOH Guidelines concretise the composition requirements for IRBs, inter alia, stipulating a quorum of at least 5 members, their appointments, and voting

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36 Ibid. at para. 3.7(b)
37 Ibid. at paras. 3.13-3.18
38 Supra note 26 at para. 7.4
39 Ibid. at para. 7.7
40 Ibid. at para. 7.3; Protection of Human Subjects 46 C.F.R. §46.102
requirements at meetings. In additional, specific requirements for Data Safety and Monitoring plans are spelt out for the purposes of IRB review and institutional implementation beyond the confines of IRB review.

(c) Quality Assurance for Ethics Review Systems:

Significantly, the MOH guidelines also spell out the need for institutions to undertake a “monitoring and improvement programme” in respect of the “working processes involved in ethics review of research projects” in order to “improve overall standards of ethics review and human subject protection.” It is envisaged that such monitoring may be performed by one or more bodies within or without the institution in question, which may include the IRB in question. Given these parameters, this quality assurance initiative is envisaged to be part and parcel of the ethics governance systems within a particular institution, rather than an aspect of enforced self-regulation where an entity external to the institution (whether the regulator or an accreditation body) monitors it for the purposes of ensuring adherence to the agreed parameters of self-regulation. Accordingly, there remains some uncertainty of the specific nature of regulatory oversight on the part of the MOH and what shape such oversight should take, given that the BAC’s modified recommendations on MOH audit and investigations have not been elaborated upon beyond general endorsement.

3. The Independence of IRBs in Ethics Governance

Notwithstanding the universal endorsement of the need for independent ethics review, and ubiquity of the use of institutional committees to conduct ethical review, the IRB

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41 Ibid. at para. 7.12
42 Ibid. at para. 7.10.9
43 Ibid. at para. 11.1
44 Ibid. at para. 11.2
45 BAC Guidelines, supra note 9 at paras. 8.1-8.6
46 See MOH Directive 1A/2006 dated 18 January 2006, which accepted the recommendations of the BAC for the purposes of evaluating professional ethical conduct by the Singapore Medical Council under the Medical Registration Act, Cap 174, 2004 Rev. Ed.
47 See e.g. World Medical Association, Declaration of Helsinki, Ethical Principles for Medical Research Involving Human Subjects (October 2008), Part B, para. 15; online: <
model of research ethics governance has not gone without criticism. Foremost of concern in the minds of commentators is the true independence of a committee drawn principally from the ranks of employees of, and accountable primarily to, the institution that itself undertakes biomedical research.

Coming from the perspective that IRBs may have become too eager to lean in favour of ethics approval, Edgar & Rothman argue that many of the assumptions prevailing at the time the concept of the IRB was first promulgated lent themselves in support of the viability of a local institutional committee providing effective and independent review of the ethics of research.49 For instance, the fact that research funding was principally public and abundant. That the typical biomedical research institution was the university teaching hospital, where one could point to “a shared commitment to the ideals of good science” that could outweigh the financial and other interests of the institution.50 Finally, human participants were generally suspicious of research and could be relied on, once adequately informed of research risks, to refuse protocols that posed undue risk to themselves.51

Each of these three assumptions has since been eroded significantly, thus exposing the vulnerability of the IRB in offering an independent and reliable external review of research ethics. First, research funding has grown more competitive and is increasingly being funded by industry, not just the state. As both private and public research institutions compete for such funding, one wonders whether the interests of the institution, even at its highest levels of management, are appropriately balanced between the need to attract research funds, and protecting research participant interests

by supporting the independence of the local IRB in its evaluations.52 Related to this, one can no longer assume that universities and other research institutions are immune from financial considerations as they are pushed to diversify their funding sources and rely less on public funding for research. On the other hand, more privately owned research institutions may have too great an incentive to see research proceed because of commercial interests, for us to assume adequate institutional integrity in carrying out local research oversight.53

Finally, participants, in particular patients, can no longer be assumed to be able to protect their interests when the line between research and therapy is blurred. “The IRB assumption that a well-crafted consent form was a meaningful protection has weakened: subjects may well be simply too eager to obtain what they see as the most advanced and potentially therapeutic intervention.”54 This places greater responsibility on the IRB to carefully weigh the risks and benefits of a research protocol even where competent adults are targeted for research enrolment.

Responding to these criticisms, developed countries around the world have sought to increase community representation on ethics committees in order to right this imbalance. For example, in Denmark and New Zealand, lay membership should be at least half the total membership of their IRB equivalents, while Australia has received recommendations that not less than half the committee should be non-medical members from outside the institution.55

Locally, the recommendations of the NMEC and BAC have consistently recognised the need for broad ranged representation of the community, specialists and other professionals external to the institution, without going into the numerical specifics of membership.56 The MOH guidelines state that the IRB should be “carefully composed such that there can be no room for any public perception that it is not independent of its

52 Ibid. at 499
53 Ibid. at 500
54 Ibid. at 499
55 McNeill, supra note 48 at 251.
56 NMEC Guidelines, supra note 11 at para. 3.2.2; BAC Guidelines, supra note 9 at para. 5.34
There is understandably a basic need for collective expertise to review the types of research that come before the board, with the Chair (who must be a registered medical practitioner) and Deputy chair to be respected clinicians drawn from the institution, other institutional members having requisite experience and training, while external specialist representation is “encouraged”. Strangely, no mention is made about the specific requirements for lay representation under “composition”, but under the meeting requirements, the quorum for an IRB meeting must include one lay member and one medical practitioner external to the institution. There is additionally provision for the appointment of independent consultants which may encompass “representative of communities, patients, special interest groups or major local religions.” However, as their title suggests, such consultants are not allowed to vote, and are thus not envisaged as members of the IRB with a personal responsibility to protect the interests of research participants.

Reading the requirements for independence in composition, and the two-thirds majority decision making rule for full IRB review approval, a fair interpretation would suggest that any meeting exceeding the minimum quorum of 5 members must have external representation that exceeds one third of the total membership at the meeting. Although this would strengthen the independence of each IRB meeting, it is however not made explicit in the guidelines. Notwithstanding these arrangements, it may fairly be said that most meetings are likely to be dominated by clinicians or researchers who are likely to have a pro-research stance. Experience from other jurisdictions also shows that institutional members (who must live with disappointed colleagues whose protocols they have rejected) in the majority dominate the discussion over non-professional lay members and even external specialists. Other commentators ask why it is that institutional members with the same biases towards research are to be relied on to

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57 Supra note 26 at para. 6.3
58 Ibid. at para. 6.5
59 Ibid. at para. 6.6
60 Ibid. at para. 7.12(e)
61 Ibid. at para. 6.8
62 Edgar & Rothman, supra note 49 at 492.
provide impartial review? This There are also no formal controls over exactly how these external members (specialists, professional or lay) are to be selected, appointed or dismissed, save that these must be clearly formulated in advance and depend on the local circumstances.

As a matter of independence from institutional interests, the main response in Singapore seems to be that (1) IRBs are to “report directly to the highest level of management of their institutions”, (2) there should only be transparent communications between the IRB and its management board, and (3) finally that research participants may have to be informed of any financial interests that the institution or its researchers have in the conduct of the project. With respect, for the reasons mentioned above, these may not be adequate safeguards in a situation where the principal goals of the relevant institution are attracting and/or conducting biomedical research on a competitive or commercial basis. In addition, the MOH guidelines rely on the “public and professional duty” of IRB members to act with total impartiality, objectivity and independence; it is even contemplated that where the interests adversely affect the IRB, it should decline to review the research. This presupposes that there is readily available some other willing IRB or committee to review the application, otherwise the consequences may be too drastic for the institution and IRB itself to accept such a fundamental conflict in fact exists. Unfortunately, given the uncertainties inherent in ethics review, it may not be such a straightforward exercise in ascertaining whether institution-based IRB members were faithfully discharging their public duties over their institutional and local interests. Reliance on professional duties can also only be effective against those who hold them, and to the extent that it can be effectively shown that they have not acted impartially. Ethical duties notwithstanding, there is something to be said for ensuring structural independence of the IRB.

63 McNeill, supra note 48 at 245.
64 MOH Guidelines, supra note 26 at paras. 6.1-6.2
65 BAC Guidelines, supra note 9 at para. 5.38.
66 MOH guidelines, supra note 26 at para. 5.7-5.8.
It may be likely that the contextual focus of the guidelines was the publicly subvented hospital, where most HBR currently takes place within the health care system. Its primary goals in delivering and promoting health care, and accompanying reputational concerns, may offer an adequate alignment of interests in its oversight of research ethics review in general, and its IRB in particular. Even so, outside such quasi-public institutions, one wonders if reliance on the self interests of the research institution is a wise assumption to make.

This suggests a need to strengthen the independence of IRBs on the starting premise that there remain important advantages to delegating primary supervision to a local, institution-based committee. Edgar & Rothman speak of strengthening the IRB through a quasi-professionalization of the external members, linked in conversant groups that examine common issues facing IRBs. In this respect, a page can be taken out of the book on ethics governance in living organ transplantation in Singapore. Transplant Ethics Committee (TEC) review was recently strengthened in Singapore on the back of further liberalisation to the reimbursement provisions for living organ donations. In particular, to improve the rigour of TEC review, the MOH established a dual panel of independent clinician and lay members to sit on every TEC meeting. The obvious advantage of this is that it creates a special pool of external members who have been vetted and trained by the MOH, impressed with a public duty to protect the interests of the donor, and have independent reporting and feedback channels to the MOH as regulator. Such arrangements arguably contribute to a better sense of independence and impartiality on the part of TECs in reviewing living transplant applications.

There are obviously some difficulties in adapting these measures in respect of TECs to IRBs. Two immediate challenges may be stated: the volume of research applications is likely to be significantly greater, and the available pool of clinical and research experts,

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67 See BAC Guidelines, supra note 9 at para. 2.30
68 See I. Ayres & J. Braithwaite, Responsive Regulation (OUP, 1992), c.4 at 104-106.
69 Supra note 49 at 504.
71 Ibid., reg 5(5)
and knowledgeable professionals and lay persons is already limited in a small jurisdiction like Singapore. Nevertheless, these are challenges that any institution is going to face anyway in constituting their own IRBs. The difference is that the involvement of the MOH as regulator in vetting or certifying a pool of external members would go some way in injecting a greater dose of impartiality in the process, as has been the case in respect of TECs. Furthermore, there are indirect advantages to having a centrally managed and trained pool of experts and lay persons – they can provide feedback on and indirect oversight over the day to day workings of the system, in particular the dynamics of local ethical deliberation, of a different qualitative measure beyond what any ex post external audit, based unavoidably on documentation, can achieve. This could also be enhanced by a statutory reporting duty to notify the regulator of any concerns that arise over the integrity or reliability of the local process.

4. Promoting a co-operative approach to IRB ethics review

Interestingly, criticism to the converse of the perceived unduly pro-research stance of IRBs has also been made – that IRBs may be/are too risk averse, and unnecessarily bureaucratise or impede the progress of beneficial research by taking an “adversarial” stance towards research ethics review, particularly in the U.S.72 Concern was also expressed early on, before any adversarial stance had clearly set in the Australian ethics committee review system, by the Australian Health Ethics Committee73 of the undesirable costs that an adversarial approach would impose.74 No system of policing is fool-proof and cannot by itself promote ethical conduct on the part of researchers. In fact, unduly bureaucratic or draconian approaches would likely put them off and


74 Chalmers & Pettit, supra note 4 at 80. Similar concern has also be raised in the U.K.: A. George et al., “Research governance at the crossroads” (2002) 8(2) Nature Medicine 99
promote indifference or distrust and active rebellion.\textsuperscript{75} Rather, a co-operative model based on the starting assumption of trust that “most researchers, once made aware of ethical concerns, are disposed to take them seriously,”\textsuperscript{76} is preferred as this would promote a research culture in which ethics is taken seriously rather than resisted on the perception that it represents bureaucracy.

The risks of an adversarial approach and culture in research ethics governance are heightened by certain structural features of a local IRB system. False positives (i.e. approved research that should not have been for ethical concerns) are potentially likely to generate greater costs, through public scandal accentuated by hind-sight bias, significant reputational costs, litigation and disciplinary proceedings.\textsuperscript{77} These promote institutional risk aversion on the basis of a fear of increased litigation costs and loss of research funding especially if this is largely publicly sourced.\textsuperscript{78}

On the other hand, false negatives (research that failed to obtain approval but should have) have more diffuse and indirect costs on individual researchers, who would as repeat players probably rather not agitate their concerns over IRB performance, and potential research beneficiaries downstream, who cannot by definition be aware of their loss and are thus invisible.\textsuperscript{79} This mismatch in the costs of error potentially encourages a more adversarial, risk averse approach by IRBs in reviewing research that is likely to produce imbalanced outcomes in favour of preventing false positives at the expense of impeding otherwise beneficial but ethically challenging research.

There is some implicit evidence within the existing governance framework in Singapore that a co-operative model is preferred to an adversarial one. First and foremost, this is seen in the recommendations concerning the composition of IRBs. The NMEC

\textsuperscript{75} Chalmers & Pettit, \textit{ibid.}; see also, Ayres & Braithwaite, \textit{supra} note 68, c.2 at 20-27.
\textsuperscript{76} Chalmers & Pettit, \textit{ibid.}
\textsuperscript{77} D. Hyman, “Institutional Review Boards: Is this the least worst we can do?” (2007) 101 Northwestern University Law Review 749 at 754. Chalmers & Pettit, \textit{ibid.} at 79, describe this as the “controversy mechanism”.
\textsuperscript{78} Halpern, \textit{supra} note 72 at 94-95
\textsuperscript{79} Hyman, \textit{supra} note 77.
recommended that in choosing community representatives, a balanced perspective is required:

... these members need to be people of goodwill, with a high regard for the human individual, for truthfulness, and for the continued advancement of medical science. Those who are totally opposed to human research should be left to attack the system from the outside. On the other hand, individuals who are likely to give automatic approval are also not suitable to be members.80

Secondly, based on the MOH operational guidelines discussed above, the majority of IRB membership is likely to be constituted by both internal and external specialist researchers and clinicians, at least in the health care setting. Such a composition profile of persons would more appropriately appreciate the necessary balance between research progress and the protection of research participants, and therefore better internalise in their decision making the costs not just of false positives, but also false negatives on the progress of biomedical research. Admittedly this will be a fine and challenging balance to be achieved.

Thirdly, the decision making process could also play an important role in redressing the structural imbalance. The BAC and MOH guidelines both emphasise the need to provide reasons for an IRB’s decision in appropriate situations, and encourage interaction between researchers and IRB members. Thus, IRBs are required to “provide a fair hearing to those involved” and “decisions should be provided in written form and, where appropriate, a fair and frank account of the reasons for those decisions should be provided.”81 Indeed, as a matter of common law natural justice, IRBs might be actually be required to give researchers who are adversely affected by their decisions the right to be heard.82 Furthermore, although a majoritarian decision making rule is stipulated,

80 NMEC Guidelines, supra note 11 at para. 3.2.2(a)
81 BAC Guidelines, supra note 9 at paras. 5.64-5.65
IRBs are encouraged to reach a decision by consensus, and where not possible, minority views are to be addressed and documented. On the whole, these requirements if taken in the right spirit would serve to encourage IRBs to engage in serious consideration and debate concerning each proposal brought before it, thus mitigating somewhat the underweighting of the costs of a false negative, as compared to a situation where IRBs are not required to consult or hear from researchers, nor give reasons for their decision.

Nevertheless, the experience in the U.S. also indicates that the disposition of IRBs towards their regulatory function is greatly influenced by the regulatory environment in which they operate. In the wake of an aggressive, high profile enforcement strategy by the Office for Protection from Research Risks (predecessor to the Office for Human Research Protections (‘OHRP’)), IRBs began to adopt a very strict reading of the requirements of the Common Rule and insisted on rigid conformity to procedural requirements. This was apparently exacerbated by institutional risk adversity in reaction to increasing litigation brought by human research participants against both research institutions and their IRBs, and the financial and reputational costs (particularly disruption or loss of federal funding) that were incurred in the wake of both these phenomenon. These factors might be mitigated locally by a more measured, responsive enforcement philosophy on the part of the MOH (which needs to be more clearly articulated) and the less litigious culture in Singapore. Furthermore, it might be worthwhile to also consider some form of statutory immunity (beyond institutional indemnity) for individual IRB members as is the case with Transplant Ethics Committee members under the Human Organ Transplant Act. In that respect, section 15B(4) provides that:

83 MOH Guidelines, supra note 26 at paras. 7.12(g), (h)
84 Chalmers & Pettit, supra note 4 at Box 2, Recommendation 3. Cf. the position in the U.S. under the Common Rule, where it is noted that researchers are generally left out of the ethical deliberations: see S. Burris, “Regulatory innovation in the governance of human subjects research: A cautionary tale and some modest proposals” (2008) 2 Regulation & Governance 65 at 67.
85 Halpern, supra note 72 at 93-95.
86 Ibid.
87 See part 6.c. below.
88 Cap. 131A, 2005 Rev. Ed. Sing. [emphasis added]
... Anything done by the transplant ethics committee of a hospital, a member of the transplant ethics committee, or any person acting under the direction of the transplant ethics committee or the Director, in good faith for the purposes of the exercise of the functions of the transplant ethics committee or in accordance with this Act, shall not subject the member or person personally to any action, liability, claim or demand.

How realistically these current measures will work in promoting a fair balance between competing interests also depends on the workload that is placed on IRBs, a significant portion of whose members will likely be serving as volunteers in fulfillment presumably of some sense of public duty, or employees for whom IRB service is likely to be secondary to their primary institutional responsibilities. How will the governance framework seek to manage workloads in an area that is likely to see more, and not less, research funding and hence proposals for ethics review?

5. Managing IRB workload through risk-based assessment

A critical feature of the risk-based governance framework is the adoption of variable levels of ethics review in order to streamline processes commensurate with the risks posed by HBR. This is one important strategy in managing the workload of IRBs, in order to allow them to focus their efforts on applications that pose more serious levels of risk and/or greater ethical difficulty.89 Under the more definitive approach adopted by the MOH operational guidelines,90 research review may be conducted on a full, expedited or exempted basis. The definitive yardstick adopted is the concept of “minimal risk”.91

89 The importance of manageable IRB workloads was an important lesson learnt from the inquiry into the ethical lapses discovered in a National Neuroscience Institute’s research project: See MOH, Report of the Committee of Inquiry into the Conduct of the Study titled: A Study on Haplotype Structure and SNP Frequencies in Candidate Genes in Neurological Disease and Response (March 2003) at paras. 6.1-6.9; online <http://www.moh.gov.sg/mohcorp/pressreleases.aspx?id=1152> [MOH NNI Report].

90 Cf. BAC Guidelines, supra note 9 at paras. 3.12-3.18: the BAC recommended ethical review sorting along the same lines, but without committing itself to the specifics of the different levels of review.

91 See supra note 40 and accompanying text.
Minimal risk based on the underlying “risks of daily life” or “routine examinations” standards are essentially lifted from the US Common Rule and serve a sorting function. Any research project that imposes greater than minimal risk requires a full IRB review by a duly constituted board. Anything less (or imposing “remote risk”) may undergo expedited review by the IRB chairperson or two members of the board alone.92 However, sorting is supplemented by the concept of “no likelihood of harm”, in which case such projects are exempted from ethics review.93 The BAC also utilised the concept of minimal risk without defining it, preferring to use examples to illustrate the point.94

There are two important concerns with the use of the concept of minimal risk as a sorting device. The first is the long standing uncertainty with the definition adopted: There is research pointing out the difficulties with what is apparently a relative concept of risk, dependent on the risks normally experienced in the daily lives of research participants.95 If so, the level of minimal risk may vary significantly depending on the subject population or group, and could infringe the ethical principle of justice, which is concerned with the fair allocation of research risks.96 This might be improved by specifying that the definition refers to the daily lives of healthy individuals, instead of the research participants.97 However, as a quantitative concept of risk, the definition is unworkable – a British study has concluded that the risks encountered in daily life encompass such a wide, varying range of less or more significant levels of risk (e.g. at work, in sport or during travel), that it would be meaningless to attempt to extract a common range of risks from which to ground the use of minimal risk as a sorting device.98

A more workable concept is that suggested by Freedman et al, who point out that the risks of daily life is intended as qualitative or categorical standard, rather than a

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92 MOH Guidelines, supra note 26 at paras. 7.4-7.5
93 Ibid. at para. 7.7-7.8
94 Supra note 90
95 See e.g. Burris, supra note 84 at 70; Woodward, “Challenges to Human Subject Protections in US Medical Research (1999) 282(20) JAMA 1947 at 1949-1950
96 NBAC Report, supra note 73, Vol. 1, c.4 at 83
98 R. Nicholson ed., Medical Research with Children: Ethics, Law & Practice (Oxford: OUP, 1986), c. 5 at 84-87
quantitative one. While it may be difficult to quantify such risks, they are well known to us all and if we are uncertain about the commonality of a risk of harm, it is necessarily excluded.\textsuperscript{99} Therefore, the daily risks standard approximates a level of risk which most reasonable people feel is safe enough to ignore or discount in making choices.\textsuperscript{100} It is therefore argued that a qualitative gloss to the approach proposed by the U.S. NBAC some time ago is preferable in interpreting ‘minimal risk’. According to the NBAC, the risks of daily life should refer to:

... to common risks—for example, driving to work, crossing the street, getting a blood test, or answering questions over the telephone. Research, then, involves no more than minimal risk when it is judged that the level of risk is no greater than that encountered in the daily lives of those in the general population. The general population standard is less restrictive than the healthy individual standard; however, the general population standard more accurately captures the risks that are familiar to most persons.\textsuperscript{101}

Two important factors introduced in this interpretation of the concept are the general population and familiarity of risk. The first addresses the concerns of justice, such that only risks typical to members of the general population fall with the acceptable range. The second, familiarity, should, it is argued, introduce a qualitative aspect to minimal risk assessment. The inquiry should be whether members of the general population would be familiar with the risks posed by the research participation on the basis of their encountering similar risks in their daily lives, and making choices which ignore or discount such risks in unmitigated form (without requiring or taking some measures to manage or reduce such risks). This qualitative, rather than quantitative approach, ties in better with the requirement for informed consent, on the basis that competent research participants are appropriately placed to evaluate and decide for themselves whether to ignore or discount such risks in serving the cause of biomedical research. In a similar

\textsuperscript{99} B. Freedman \textit{et al}, “\textit{In Loco Parentis}: Minimal Risk as an Ethical Threshold for Research upon Children” (1993) 23(2) Hastings Center Report 13 at 16

\textsuperscript{100} Ibid. at 17

\textsuperscript{101} Supra note 96 [emphasis added].
vein, the reference in the second clause of the definition to routine medical tests and procedures should also be guided by the concept of familiarity with risk and discounting such risk in unmitigated form in making decisions concerning such interventions in the health care context.102

Operationally, however, it may be better to supplement this modified definition with a standard list of well-established categories of minimal risk procedures, in order to improve consistency across the board, and provide a basis for assessing new instances of minimal risk procedures or protocols. For example, the U.S. Department of Health and Human Services issues a list of minimal risk research activities that are eligible for expedited review (including e.g. collection of blood samples by finger stick or venipuncture, collection of biological specimens by non-invasive means, collection of data through non-invasive procedures, which exclude anaesthesia, sedation, x-ray or microwave devices, etc.).103

The second concern, which follows from these observations, is that there is a distinct function for minimal risk when used in the context of research involving children and other individuals who are incompetent to make such decisions for themselves. Here minimal risk serves as a protective threshold in order to safeguard the welfare interests of individuals whose developing or deteriorating autonomous capacity prevents them from offering informed consent.104 Accordingly, a more stringent risk threshold standard is considered necessary to protect them. I have discussed the difficulties of such a concept in relation to minors elsewhere; suffice it to say here that a more carefully considered conception needs to be worked out both internationally and locally.105 The conception of minimal risk as a protective device is functionally different from that used in streaming research review where independent review is meant to work

102 Nicholson, supra note 98, in fact ultimately recommends such an approach focused on risks arising from medical sources and then using quantitative methods to evaluate other types of medical risks: at 87-90, 117-119.
104 See T. Chan, “Minors and Biomedical Research in Singapore” (2008) 28 Legal Studies 396 at 409
in conjunction with informed consent to minimise harm to research participants. For present purposes, minimal risk research involving incapacitated individuals requires both careful expert scrutiny of the risks posed to incapacitated participants and careful ethical deliberation over the acceptability of such research enrolment.\footnote{See Chan, supra note 104 at 426-428} It follows that in such a situation, expedited review is generally not appropriate even though it superficially may attract the same label of “minimal risk” research. Instead, a full IRB review should be necessary. The MOH guidelines should thus be clarified to place such research as outside the typical sorting process based on minimal risk for ethics review.

6. The role of the regulator in a self regulation paradigm

Finally, we return to the proper role of the regulator, at present the MOH, in HBR governance. The MOH’s stated preference is for self regulation within the boundaries set for HBR. This strategy reflects current thinking on appropriate \emph{responsive} regulatory strategies:

When self-regulation works well, it is the least burdensome approach from the point of view of both taxpayers and the regulated industry. When the state negotiates the substantive regulatory goal with the industry, leaving the industry discretion and responsibility of how to achieve this goal, then there is the best chance of an optimal strategy that trades off maximum goal attainment at least cost to productive efficiency. But given that the industry will be tempted to \emph{exploit the privilege of self-regulation by socially sub-optimal compliance with regulatory goals}, the state must also communicate the willingness to escalate its regulatory strategy up another pyramid of interventionism.\footnote{Ayres & Braithwaite, supra note 68, c. 2 at 38 [emphasis added].}

Given a changing HBR environment where the incidence and influence of private and commercially-oriented research funding and interests are increasing, and the status of the individual researchers extending beyond the traditional health care professions,\footnote{See BAC Guidelines, supra note 9 at paras. 2.30-2.35}
relying on self regulation alone in respect of corporate interests is likely naïve. Some form of enforced self-regulation is necessary; indeed, the IRB model of ethics governance in the U.S. has been conceptually compared to Ayres & Braithwaite’s concept of enforced self-regulation. This model envisions:

...that the government would compel each company to write a set of rules tailored to the unique set of contingencies facing that firm. A regulatory agency would either approve these rules or send them back for revision if they were insufficiently stringent... Rather than having governmental inspectors enforce the rules, most enforcement duties and costs would be internalized by the company, which would be required to establish its own independent inspectoral group... The primary function of governmental inspectors would be to ensure the independence of this internal compliance group and to audit its efficiency and toughness.

All aspects of regulatory functional delegation are observed in the MOH’s governance framework, albeit to differing extents: standard setting, monitoring and enforcement. There is perhaps also a hint that there will be the potential for regulatory enforcement escalation as a motivation for voluntary institutional self compliance, although the form of this is not explicitly articulated. Several issues concerning the MOH’s regulatory role arise in respect of each of these functional aspects of regulation.

a. Standard setting

The numerous sources of ethical and operational guidelines for IRB ethics governance are an indication of the strong public interest in setting clear minimum standards. In addition, as there is some consensus on the basic ethical requirements for the conduct of research, it makes sense to harmonise these requirements across the board to spare research institutions the expense of reinventing the wheel. A persistent issue however will be the need to decide on the balance between public and delegated private standard

109 Ayres & Braithwaite, supra note 68, c.4 at 106.
110 Burris, supra note 84 at 67.
111 Ayres & Braithwaite, supra note 109.
112 Ibid. at 103.
setting. The formulation of procedural minutiae on IRB models of decision making and processes are rightly left to institutions to formulate. These are highly contextual, and should be moulded to fit the nature of research conducted, the particular compositions of each IRB and other local circumstances.

Conversely, standards that are crucial in protecting the core interests of relatively weaker or disenfranchised research participants should be the subject of publicly determined standards of legal force, or at the least, stringent default standards, for which institutions would have to strictly justify any modifications thereof. In this respect, there seems to be a clear international consensus on the basic requirements for ethical research:

A clear-cut consensus has emerged in all of these official policies about the basic conditions of the licitness of research on human subjects. Procedurally, such research needs to be approved in advance by a committee that is independent of the researchers. Substantively, informed voluntary consent of the subject must be obtained, the research must minimise risks and involve a favourable risk-benefit ratio, there should be an equitable non-exploitative selection of subjects, and the privacy of the subjects and, the confidentiality of the data must be protected. These substantive standards are rooted in fundamental moral commitments to respect for persons, to beneficence, and to justice.

In addition, there may be matters in respect of which the interests of research institutions may not be fully aligned with that of the public interest in promulgating appropriate standards. Burris has suggested that in HBR, standards or rules concerning, e.g. informed consent, conflicts of interest, adverse reporting and data confidentiality should be the subject of a public-centred formulation processes. Relying on institutions to formulate specific standards concerning issues like conflicts of interest may be unwise, where there is no assurance of consistency of formulation or application. Institutions may also be concerned about their competitiveness in attracting individual

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113 See Ayres & Braithwaite, supra note 68 at 108
114 B.A. Brody, The Ethics of Biomedical Research: An International Perspective (New York: Oxford University Press, 1998) at 36; see also McDonald, supra note 82 at 30-31
115 Burris, supra note 84 at 75-76
clinical/research talent. Consequently, there may be a potential race to the bottom if institutions were given too free a hand in formulating conflict of interest type standards. The current MOH governance framework and operational guidelines, however, speak only in broad general terms without going into specific requirements to counteract potential conflicts of interest and commitment amongst research actors. Furthermore, the MOH Guidelines also entrust IRBs to review study-related and non-project related financial incentives, which, as a local institutional committees, they may not be best placed to formulate in the absence of clearer national rules or guidelines on the matter. In this respect, the only legal rules on conflicts of interest only apply to the conduct of clinical trials under the CTR, where investigators may not hold a direct or indirect financial interest in the trial.

Another area which appears to require clearer publicly set legal standards is on the basic requirements of informed consent, and its exceptions. Informed consent serves important ethical principles such as autonomy and beneficence, and is the basic legal device to protect bodily integrity. However, there remains lacking consistent or clear requirements for informed consent in respect of HBR participation. Detailed informed consent requirements are only to be found in the CTR, which cover minors and incapacitated adults. Outside this limited realm, the default standards offered by the common law are sufficiently vague to create much uncertainty as to basic requirements especially with respect to the standard of risk disclosure required for research participation and the nature of surrogate consent (and accompanying substantive protections) required for minors and incapacitated adults.

116 See e.g., MOH Governance Framework, supra note 25 at paras. 7, 10 and 19; MOH Guidelines, supra note 26 at para. 7.10.7.
117 CTR, supra note 6, reg. 20. The NMEC has only issued guidelines on financial interests in medical practice, although some of these recommendations might be adapted for to address trust and integrity concerns in the conduct of research: NMEC, An Ethical Approach to Financial Issues in Medical Practice (January 2000), online: <http://www.moh.gov.sg/mohcorp/uploadedFiles/Publications/Guidelines/nmec_finanwholebook.pdf>
118 Supra note 6, regs. 11-14
120 For the uncertainties concerning consent for minors in research participation, see Chan, supra note 104 at 417-419.
There are other areas where clear *ex ante* rules are simply not possible given the dynamic nature of research and the variety of circumstances. While delegating the application of such broad ethical standards to IRBs makes sense as a second order decision-making strategy, there is cause for devising a mechanism to capture these local decision-making insights and translate them into clearer intermediate standards, in order to improve the consistency of ethical deliberations across the board in all IRBs. One general idea for doing so is the concept of “virtuous learning loops” at an inter-institutional level, where deliberative feedback is sought from within the local IRB network and channeled into an appropriate forum where these issues can be examined systematically, whether concerning research ethics in general or in particular areas of ethical difficulty.

Provision for this is made intra-institutionally under the MOH governance framework, where institutions are required to put in place a “monitoring and improvement programme”, which may be administered either internally or externally, to systematically review and evaluate working practices in ethics governance. The focus of this programme is on the monitoring and evaluation of feedback and complaints from research subjects and others, internal compliance monitoring and benchmarking of processes. There would arguably be a better critical mass of information and experiences if this learning loop were extended across institutions and included national deliberative bodies such as the BAC and the NMEC. A national learning network would ideally envisage a national forum for the consolidation of such deliberative feedback from IRBs, discussion of general issues of risk, mitigating strategies and the promulgation of learning from this in the form of clearer or better standards and guidelines, at the initiative of the MOH as regulator. For example, in the U.K., the

121 Although the recent *Mental Capacity Act*, Cap. 177A Rev. Ed., empowers donees of a lasting power of attorney (s.13(7)) and court deputies (s.22(1)(d)) to enroll an incapacitated person in a clinical trial, there is no general power to give surrogate consent in respect of research generally (s.7(3)(c)). *Cf.* the U.K. *Mental Capacity Act*, 2005, c.9, ss. 30-34, which make general provisions research participation for incapacitated individuals.


123 See McDonald, *supra* note 82 at 301-303

124 MOH Guidelines, *supra* note 26 at para. 11.1

125 *Ibid.* at para. 11.2

126 *Cf.* McDonald, *supra* note 82 at 307-308
Department of Health promotes the development of learning networks to support better individual and organizational exchange of good practices, such as the NHS R&D Forum.\textsuperscript{127}

b. Monitoring

Quite apart from the local monitoring of research conducted by IRBs or Data and Safety Monitoring Boards (DSMBs), the model of enforced self-regulation envisages that the primary function of the regulator must be to ensure the independence of the IRB and to "audit its efficiency and effectiveness".\textsuperscript{128} External audit might itself encourage greater conscientiousness of IRB and improve its performance.\textsuperscript{129} Something has already been said about how it is envisaged the independence of IRBs can be ensured and how this can be further improved. Interestingly, very little is said in the MOH governance framework about the nature of external audit to be implemented. Presumably, the BAC recommendation that:

\begin{quote}
... all IRBs should be formally accredited by the MOH, which should be empowered to audit, to investigate complaints... and to appoint external auditors and investigators at the cost of the institution being audited as part of the accreditation check or as a matter of routine audit for compliance.
\end{quote}

will set the direction for MOH exercising its jurisdiction over hospitals under the \textit{Private Hospitals and Medical Clinics Act}.\textsuperscript{130} Apart from this health care based regulatory framework, additional legislative basis is needed to extend audit and enforcement powers in respect of other institutions that conduct HBR outside the \textit{PHMCA} framework.


\textsuperscript{128} Ayres \& Braithwaite, supra note 68, c.4 at 106, 129, 132.

\textsuperscript{129} Edgar \& Rothman, supra note 49 at 505.

\textsuperscript{130} Cap. 248, 1999 Rev. Ed. [PHMCA]
What form should external audit take? Bearing in mind the tendency of documentary based audits to over-bureaucratize ethics governance, the most basic audit by the MOH as regulator could ensure that (a) internal guidelines and rules are consistent with MOH and other publically approved guidelines, (b) through a sample review, IRB deliberations, especially in higher risk studies, roughly correspond with established guidelines, and (c) (inevitably) a documentation based review to ensure that monitoring and other oversight functions have been implemented by the institutions and, where appropriate, their IRBs. The MOH might be limited in its expertise to review (b), in which case it is suggested that in tandem with the suggested national panels of experts and community representatives outlined above, MOH could rely on specially appointed experts (both local and international) to conduct the sample review. Perhaps further downstream, sufficient local expertise will be developed to warrant the setting up a national level board like the Australian Health Ethics Committee to advise on and review deliberations of IRBs under audit in order to ensure substantial compliance with ethical guidelines.

Private accreditation, where external oversight is also delegated to the private sector, is another alternative, but it is unlikely that economies of scale would support the development of indigenous accreditation programs in Singapore. In fact, preliminary observations in the U.S. on private accreditation programmes note that IRB accreditation is burdensome due to the fees of the accrediting organisation and the additional institutional workload involved. The entire process has taken some U.S. institutions several years to complete. Anecdotal evidence also indicated that institutions there prefer more targeted annual audits rather than accreditation as they “provide better information... that is more useful for improving IRB services.”

Furthermore, take up for private accreditation in the U.S. has been less ready than that

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131 See Burris & Welch, supra note 72
132 Chalmers, supra note 73 at A-17: The AHEC, a multi-disciplinary committee, was established under the National Health and Medical Research Council Act 1992 (Cth) to, inter alia, monitor and advise on the workings of institutional ethics committees.
133 For a description of the nature of accreditation programmes, see NBAC Report, supra note 74, c.3 at 49-50.
134 Halpern, supra note 72 at 96
135 Ibid. See also, NBAC Report, supra note 74 at 50
for hospital accreditation – the case for accreditation perhaps seems far less compelling in respect of ‘competing’ for research participants, who may not fully appreciate or consider accreditation status in their decisions to enrol.\textsuperscript{136} In any case, unless accreditation is made compulsory (which may not be cost ineffective for many institutions with multiple functions and other accreditation imperatives), there will be institutions that are left out of the loop. Accordingly, it is suggested that while private accreditation remains a possibility, it is likely that this would only be feasible through recourse to foreign accreditation bodies such as the U.S. Accreditation of Human Research Protection Programs (AAHRPP). The direct and indirect costs of such an exercise are likely to persuade only the most research intensive institutions to consider accreditation, in which case some other audit programme would still have to be developed locally by the MOH as regulator.

Finally, complaints are the usual means by which violations in HBR legal or ethical standards are detected.\textsuperscript{137} The MOH\textsuperscript{138} and BAC\textsuperscript{139} guidelines emphasize the importance of IRBs in developing and maintaining open channels of communication with research participants. This is likely to be more effective than asking them to cross institutional lines to lodge complaints with another, less familiar institutions. However, equally important are complaints or concerns raised by staff and colleagues who might have a better appreciation of the substantive and procedural requirements. What needs to be further considered is some form of whistle-blower protection for such internal informants who might otherwise be dissuaded from raising concerns for fear of reprisals. For example, protection has been afforded in respect of information provided by health care workers under the auspices of the \textit{Mental Capacity Act} in respect of elder abuse.\textsuperscript{140} Apart from this, the IRB or its administrative staff would be best placed to evaluate such complaints and deal with them accordingly, and the complaints

\begin{footnotesize}
\textsuperscript{136} \textit{Ibid.} at 97
\textsuperscript{137} Burris, \textit{supra} note 84 at 78; See also MOH NNI Report, \textit{supra} note 89 at paras. 5.44-5.49
\textsuperscript{138} MOH Governance Framework, \textit{supra} note 25 at para. 6(vii); MOH Guidelines, \textit{supra} note 26 at para. 11.2.1: These recommendations focus on the protection of the identity of research participants.
\textsuperscript{139} BAC 3\textsuperscript{rd} Report, \textit{supra} note … at para 5.73
\textsuperscript{140} See \textit{MCA}, \textit{supra} note 121, s. 43
\end{footnotesize}
mechanism could be a suitable item on the audit review agenda by the MOH or its appointees.

c. **Enforcement**

Subject to the regulatory jurisdictional limits discussed above, the existing guidelines do not specify the forms of enforcement or sanctions that may be deployed to incentivize compliance by institutions and individuals conducting HBR. This is an important part of making enforced self-regulation effective. In respect of the optimal enforcement game strategy, Ayres & Braithwaite argue that:

> Regulatory agencies have maximum capacity to lever cooperation when they can escalate deterrence in a way that is responsive to the degree of uncooperativeness of the firm, and to the moral and political acceptability of the response. In respect of the optimal enforcement game strategy, Ayres & Braithwaite argue that:

> ... compliance is most likely when regulators (1) have access to an armoury of deterrent and incapacitative weapons [an “enforcement pyramid”], and (2) when they avoid both the mistake of selecting a sledgehammer to swat a fly and selecting a flyswatter to stop a charging bull. Compliance is predicted by both the existence of an awesome armoury and by the avoidance of the clumsy deployment of it.

Burris & Welsh’s analysis of the U.S. OHRP enforcement actions sketches an outline of what an optimal enforcement pyramid might look like in the context of research regulation. They reviewed OHRP’s findings from site inspections and complaints investigations over a two-and-a-half year period and noted the deployment of various approaches and sanctions in a responsive regulatory strategy to promote compliance by research institutions and their IRBs. Starting out with informal guidance and persuasion on the assumption that institutions are minded to comply, the OHRP were

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141 Ayres & Braithwaite, *supra* note 68 at 103
142 *Ibid.* at 36
143 *Ibid.* at 52
144 Burris & Welsh, *supra* note 72
145 *Ibid.* at 647
prepared to escalate enforcement to opening a formal investigation where it detected an institution that is only prepared to comply to the extent that it is justified by the cost. If it detected further resistance or indifference, then it further escalated enforcement to the level of a formal investigation, a general audit or a site visit. In the most serious of situations, the OHRP had the power to shut down some or all research conducted at the institution, but this was rarely exercised.\textsuperscript{146}

Wielding this arsenal of enforcement measures, the OHRP as regulator first appeals to virtuous motivations of the relevant actors, unless it detects that a more rational, calculating mindset is present. In which case, it is able to respond with a more serious, but appropriately tuned intervention or sanction. In addition, the regulated entities would also take into consideration the possibility for future escalation if the responses are not considered genuine or adequate to address the regulator’s concerns. While there are some limitations to such a regulatory enforcement strategy, it offers substantial promise in promoting greater compliance by appealing to the varied motivations of research actors (individuals or institutions), rather than via a rigid sanction-oriented enforcement strategy.\textsuperscript{147}

Moving to the local context, we do not at present see a clear articulation of a regulatory enforcement strategy. The enforcement powers are at present sanctions of two forms. First, the maximally devastating suspension or revocation of a hospital’s operating licence under s. 9 of the \textit{PHMCA}. It is difficult to imagine when this sanction might be deployed to deprive the hospital of its licence to offer its primary services in health care in respect of even a serious breach in respect of its conduct of research. In respect of non-compliance with directives issued by the Director of Medical Services (‘DMS’), which presumably could include all its directives or guidelines in respect of HBR, the \textit{PHMCA Regulations} offer the blunt option of a criminal sanction of a fine or imprisonment in respect of individual actors.\textsuperscript{148} Beyond this, there are no specifically

\textsuperscript{146} \textit{Ibid.} at 671-672. \textit{Cf.} less positive comments on OPRR’s enforcement strategy in the late 1990s: Halpern, \textit{supra} note 72 at 88, 93-94

\textsuperscript{147} \textit{Ibid.} See also Burris, \textit{supra} note 84 at 67.

\textsuperscript{148} \textit{PHMCA Regulations}, Cap. 248 R.1, reg. 60
tailored responses in respect of institutional lapses, although much of the interventions and enforcement actions of the OHRP could arguably be adopted here indirectly as part of directions issued by the DMS in respect of reported or discovered instances of non-compliance.\footnote{Ibid., reg. 4(1).}

However, there are some more specific sanctions that could be considered in respect of both individual researchers and institutions. First, a more fine-tuned sanction would be to confer on the MOH the power to suspend research activities at an institution for determined period of time, pending which investigations and rectificatory measures to address lapses could be put in place. Secondly, the MOH could also usefully deploy a power to restrict or ban individuals or institutions from apply or receiving research funds for a determined period of time. Finally, each of these sanctions could be ordered in an appropriate enforcement pyramid calibrated to suit the lapse or breach in question. In addition, such an enforcement pyramid needs to be explicitly articulated to the research community, who can respond accordingly in their decision making over compliance strategies, both before and after any particular breach of HBR legal or ethical requirements.

7. Conclusion

In summary, much welcome direction has been given on the framework for governance of HBR in Singapore, backed up by ethical and operational guidelines for IRBs, which are the principal ethics gateways within the regulatory system. However, an overarching statutory backing for this framework is still lacking, with the implication that various key requirements concerning the ethics of research remain non-binding and unenforceable against institutions and individual researchers who are outside the MOH’s existing regulatory jurisdiction under the \textit{PHMCA} and the \textit{Medical Registration Act}.\footnote{Supra note 46} In respect of IRBs, further measures may be necessary to reinforce their structural independence through the development of national panels of properly trained experts and lay persons who act as community representatives. A co-operative model of ethical deliberation and decision-making should also be encouraged, with the initiative lying at all levels of the system, although the MOH as regulator is probably best placed
to set the overall tone through its audit and enforcement measures. Following this, strategies to manage the workload of IRBs in order to facilitate focus on their core function of ethical deliberation would require clearer risk-based definitions of research to sort research applications into appropriate levels of review. Finally, several observations and recommendations were made on the regulatory functions of the MOH in standard setting, monitoring and enforcement, in order to encourage an optimally responsive regulatory system that properly balances the interests of research participants and the progress of HBR in Singapore.