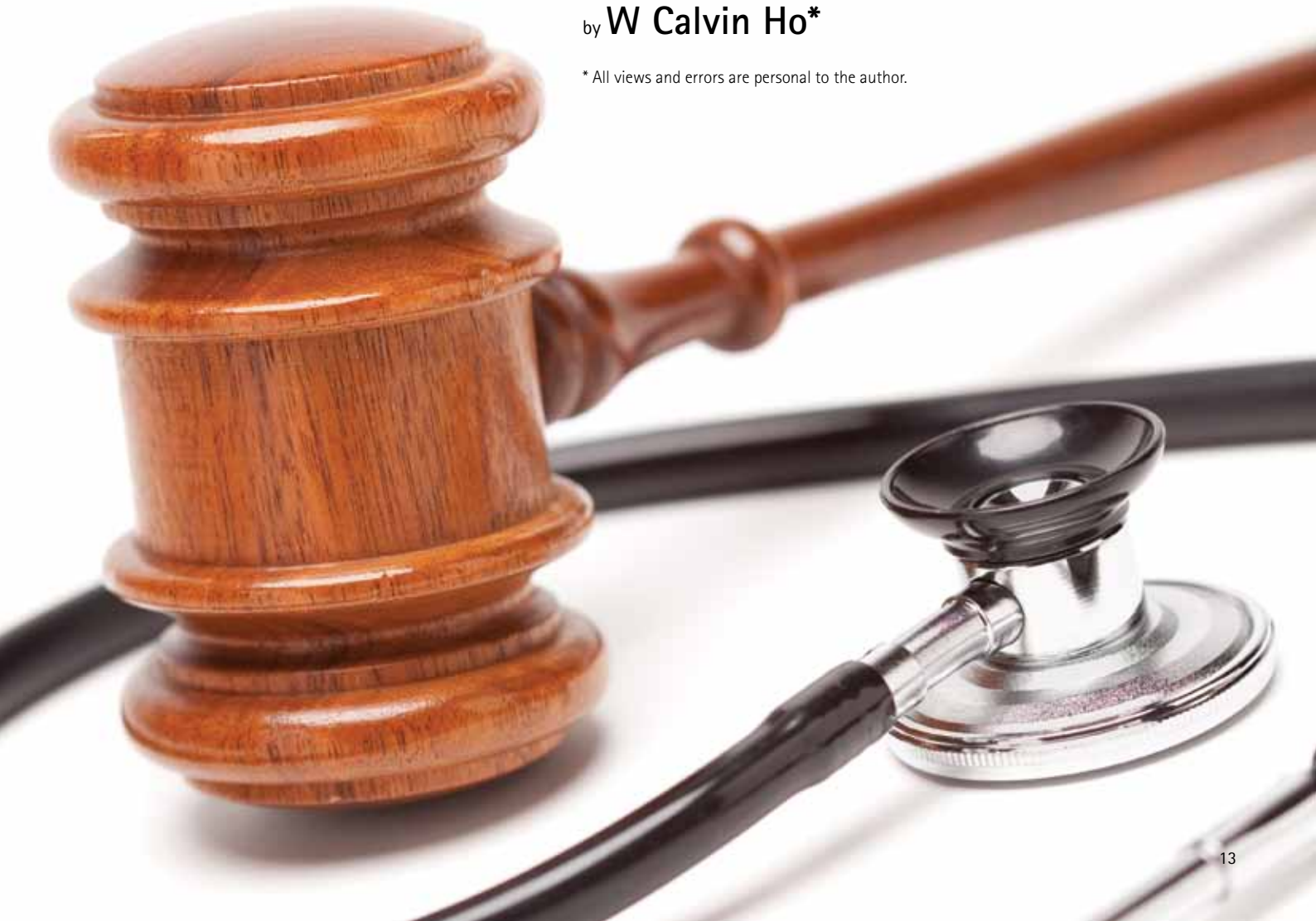
Governance Framework for Biomedical Research in Singapore:
A Risk-Based Account

by W Calvin Ho*

* All views and errors are personal to the author.



This paper attempts to present a general overview of the governance framework for biomedical research in Singapore. The framework conceptualised here is directed at risks management as a principal concern. At least three different kinds of risk arising from biomedical research have attracted regulatory attention. These are risks of physical or psychological harm to research participants, risks to social values (such as public trust in the ethical conduct of research) and risks to the objectivity and scientific integrity of research (Waring and Lemmens 2005: 157). As in leading scientific jurisdictions such as Britain and the United States, Singapore has put in place an elaborate framework comprising normative requirements and processes vis-à-vis the first two kinds of risk. For the third kind of risk, there has been an international movement to harmonise and systematise professional and normative expectations in recent years. This paper provides a broad analytical description of the overall framework. It also considers the impact that transnational measures on scientific integrity are likely to have on the framework. Finally, the paper concludes with a brief assessment of its likely developmental trajectory.

A Formalised System of Ethics Review

Prior to the year 2000, the governance framework for biomedical research in Singapore comprised statutory and regulatory requirements directed at specific practices and research areas (such as donation of body parts for research and clinical trials). There was no formal system of ethics review until a set of ethical guidelines was published by the National Medical Ethics Committee (NMEC 1997). These guidelines were adopted by the Ministry of Health (MOH) a year later by way of a written directive, with the effect that all government and restructured hospitals are required to set up ethics committees to review research proposals involving human subjects (BAC 2004: 13). Even then, ethics review was not widely perceived as necessary (Ho and Lim 2010: 3). With the adoption and implementation of the Biomedical Sciences Initiative from 2000, the guidelines of the NMEC were elaborated on and expanded by the Bioethics Advisory Committee (BAC) into a more comprehensive system of ethics review centred around institutional review boards (IRBs). The BAC defines IRBs as "full-time permanent supervisory bodies organised at and integral to the function of the highest administrative level in all institutions in which research is carried out" (BAC 2004: 28). The fundamental responsibility of an IRB is to act as an ethics review gateway to minimise the likelihood of harm to research subjects on the one hand, and to ensure that research proceeds on sound ethical basis, on the other hand. Hence, both the NMEC and the BAC gave considerable emphasis to the requirement of informed consent and appropriate safeguards for vulnerable subjects, such as children and people with reduced mental capacities in decision-making. However, IRBs are not concerned with risks to scientific objectivity and integrity as they do not review research proposals for scientific merits (BAC 2004: 31).

The importance of the BAC's 2004 guidelines lies not only in the articulation of the basic operational requirements of IRBs (such as composition and operational procedures), but also in the BAC's recognition of the need for IRBs to be provided with adequate resources and administrative support, as well as for their members who have acted in good faith to be fully indemnified from liability (BAC 2004: 51, 54). The substantive effect of the BAC's guidelines has been to entrench ethics review through IRBs within the governance framework. They also created a normative expectation for any biomedical research in Singapore that involves a human subject, personal information or human tissue to commence only after ethical clearance by an IRB has been secured. In spite of this seemingly broad normative reach, it is important to recognise that the BAC was established as a high-level advisory body to the government, and is not a regulatory body. Hence, the BAC's guidelines (or indeed, any of its recommendations) do not have any regulatory force or effect in and of themselves unless otherwise empowered by a regulator or through voluntary adoption by an organisation. In 2006, a Directive was issued by the MOH to require all registered medical practitioners to comply with the recommendations of the BAC, including its 2004 guidelines. The Agency for Science Technology and Research (A*STAR), the principal biomedical research funding arm of the government, has adopted the BAC's recommendations and guidelines on a voluntary basis, as have leading local academic institutions (primarily the National University of Singapore and the Nanyang Technological University). Hence, although the BAC's guidelines are not binding *per se*, they do have regulatory effect on biomedical research that (a) involve registered medical practitioners, government and restructured hospitals, and key local academic institutions, or (b) receive funding from A*STAR.

Specific Risks Regimes

Apart from a general requirement of ethics review as a means of baseline risks management in biomedical research, the governance framework includes more targeted ethical and/or statutory regimes for certain typified research risks. These include:

(1) Research involving human gametes, embryos and pluripotent cells;

(2) Research involving human-animal combinations and the use of laboratory animals;

(3) Human genetic research;

(4) Research involving human tissue and personal information;

(5) Biosafety; and

(6) Clinical trials.

The BAC has issued ethical recommendations and guidelines on the first four research categories. Its report on stem cell research and cloning (BAC 2002a) contributed to the enactment of the *Human Cloning and Other Prohibited Practices Act* (Singapore Statutes 2005), which prohibits human reproductive cloning but allows therapeutic cloning on a conditional basis. Its report on egg donation (2008) and human-animal combinations (2010) build on the ethical framework for stem cell research (BAC 2002a), and complements (in the case of egg donation) the regulatory regime on research involving human gametes and embryos (Singapore Regulations 2006), as well as (in the case of human-animal combinations) the ethical guidelines of the National Advisory Committee for Laboratory

Animal Research (2004). The BAC's guidelines and recommendations for genetic testing and genetic research were developed in consultation with the NMEC (BAC 2005: 14-15), which has earlier on published a set of guidelines on gene technology (NMEC 2001). Of relevance to biobanking are the BAC's recommendations on the use of human tissue and personal information in biomedical research, published in two separate reports (BAC 2002b and 2007). Its report on personal information contributed to clarification of the legal basis of disease registries (Singapore Statutes 2008).

In recent years, a statutory regime on biosafety was established and the existing regime on clinical trials was strengthened. In 2006, the *Biological Agents and Toxins Act* was enacted to regulate the possession, use and transportation of biological agents and toxins. Also in that year, the adverse outcome in the TGN1412 clinical trial in the UK provided the occasion for the NMEC to review its 1997 guidelines and to provide a set of recommendations on Phase I clinical trials. Observing an increase in the number of Phase I trials conducted in Singapore, the NMEC emphasised the importance of precautionary measures to prevent injuries from unexpected adverse events, the availability and adequacy of medical response should such events arise, and vigilance against undue inducement from the provision of excessive remuneration or benefits in recruiting research subjects (NMEC 2007). Clinical trials on medical products are regulated by the Health Products Regulation Group of the Health Sciences Authority under a licensing scheme. Clinical Trial Certificates issued under this scheme imposes a requirement for sponsors, principal investigators or any holder of the certificate to observe provisions set out in the *Singapore Guideline for Good Clinical Practice* (SGGCP) (Singapore Regulations 2000: Section 21). The SGGCP is in turn adapted from the *Guideline for Good Clinical Practice* of the International Conference on Harmonisation, which sets out the baseline standards for the conduct of clinical trials.

Comparative Governance Structures

The basic structure of the governance framework in Singapore, comprising a general requirement of IRB oversight and review of research protocols, complemented by more targeted regulatory regimes for specific risks,

is similar to that in the United States (US). The Common Rule (45 CFR 46) requires US federal agencies and research institutions receiving funding from the Federal Government to establish an IRB to review research proposals following a set of prescribed requirements. Research institutions that do not receive funding from the US government will nevertheless have to observe requirements similar to those under the Common Rule if they should require approval from the US Food and Drug Administration. Risk assessment is intrinsic to the Common Rule requirements in at least three respects. First, an IRB must determine if appropriate measures have been adopted in the research protocols to minimise risk (45 CFR 46.111(a)). Second, the extent of IRB review is dependent on whether the risks entailed are expected to exceed "minimal risk" (45 CFR 46.102(i) and 45 CFR 46.110). Third, any risks entailed must be reasonable in relation to the non-monetary benefits. In Britain, a nationalised health system has enabled a more centralised approach to ethics review. The National Research Ethics Service has the responsibility of ensuring that research ethics committees (similar to IRBs in Singapore) safeguard the rights, safety, dignity and well-being of research participants in the National Health Service. Like IRBs in the US and Singapore, research ethics committees (RECs) review research protocols and provide an opinion on their ethical acceptability. Although centralised, RECs are sub-divided into two groups: those that review clinical trials of investigational medicinal products ('recognised' RECs) and those that do not ('authorised' RECs). This division could be explained on the basis of the different degrees of risk entailed; the level of uncertainty being greater in clinical trials. Even for research with presumably lower risks, authorised RECs will need to determine the extent of oversight and acceptability of the research design as a matter of risk-benefit assessment (UK DOH 2001: paragraph 7.27 and 9.13). In Singapore, the requirement of risk assessment is evident in the guidelines of the NMEC (1997: paragraph 2.4) and the BAC (2004: 18), although the risk to benefit calibrations will undoubtedly vary among the three jurisdictions given that notions of 'risk' and 'benefit' are intermediated by social and cultural values and conditions.

Scientific Integrity and Professionalism

Neither IRBs in Singapore (as we have seen) and in the US nor RECs in Britain are directly concerned with scientific merit of a research protocol and scientific integrity. These are often seen to be more directly the concerns of research funders. Generally regarded as falling within the ambit of "peer review", the US was among the first jurisdictions to establish a national framework for research integrity. Whereas the Office of Human Research Protections is concerned with administering the Common Rule, the Office of Research Integrity and the Office of the Inspector General oversee the national framework for research integrity governance. In Britain, research institutions and their funders retain responsibility for research integrity. Although there is no national framework as such, the UK Research Integrity Office (an independent advisory body) collaborates with other organisations such as Research Councils UK and the Department of Health to harmonise and coordinate guidance in this area.

As in Britain, there is currently no national framework on scientific integrity governance in Singapore. The MOH has recently issued a code of ethical practice (2009) that highlights the need for professionalism in biomedical research, as well as proper treatment of fellow researchers, but this is not intended to be a national statement on the subject. Unlike the US and Britain, there is no specific organisation in Singapore that oversees or provides advice on scientific integrity and related issues. Given broadly divergent goals, practices and institutional setups on scientific integrity, there have been transnational efforts to achieve some level of harmonisation. Most recently, researchers, funders, representatives of research institutions and research publishers issued the *Singapore Statement on Research Integrity* (Kleinert 2010) at the 2nd World Conference on Research Integrity. The Statement sets out the principles and responsibilities directed at encouraging the development of greater integrity in research through unified policies, guidelines and codes of conduct. It remains to be seen how risks to scientific objectivity and integrity will be perceived and managed as a matter of public policy.

Prospective Developments

The governance structure for biomedical research in Singapore has developed in tandem with the ways in which risks from biomedical research are understood and responded to, both by policy makers and key stakeholders in Singapore, and in leading scientific jurisdictions. The "tools" by which these risks are responded to varies from ethical review to outright legal prohibition. Hence, whereas cost-benefit analysis may be deemed appropriate in the assessment of some research risks, certain types of research are prohibited as a precautionary measure (such as reproductive cloning).

In Singapore, a system of ethics review centred around IRBs has been institutionalised to mitigate risks of harm to research participants and to social values. This system is currently diffused and does not apply uniformly to all research entities in Singapore. It is likely that some degree of consolidation and re-calibration of regulatory reach will follow in the near future, in order to rationalise and systematise the ethics review process with more targeted regulatory regimes on categorised risks (such as clinical trials). It is less clear how risks to scientific objectivity and integrity will be responded to. Apart from Britain and the US, other leading scientific jurisdictions in Western Europe have responded to this category of risks as a distinct concern. What remains clear is that scientific objectivity and integrity are growing concerns as, for instance, conflicts of interest could grow with more commercial ventures becoming involved in the research of non-commercial institutions.

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About the Author

W Calvin Ho read law at Cornell University (New York), National University of Singapore, and University of Cambridge (England). In addition, he read sociology and economics at the London School of Economics and Political Science, and at the School of Oriental and African Studies, University of London. He practiced law in London and Singapore, and is currently Senior Research Associate with the Bioethics Advisory Committee. He will assume the position of Assistant Professor at the Centre for Biomedical Ethics, Yong Loo Lin School of Medicine, National University of Singapore, from July 2011.

Calvin has published articles and book chapters on biomedical law and ethics, intellectual property law, conflict of laws and scientific integrity. He has served as the deputy editor of the Singapore Law Review, associate editor of the Cornell International Law Journal, and assistant guest editor of the Singapore Academy of Law Journal. In 2010, he was co-editor (with Associate Professor John M Elliott and Dr Sylvia SN Lim) of the monograph "Bioethics in Singapore: The Ethical Microcosm", which was published by World Scientific. This book analyses the ways in which an ethical framework for biomedical research has been established in Singapore over the past decade. Ethical discussions in the book include stem cell research and cloning, genetics, research with human participants, as well as likely future developments. He is currently editing a book (with Associate Professor Terry Kaan) on genetic privacy (to be published by World Scientific), and is involved in a study on compulsory licensing for public health under the Agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS).