

ADVANCING THE
FRAMEWORK OF
ETHICS GOVERNANCE
FOR HUMAN RESEARCH

A CONSULTATION PAPER

THE BIOETHICS ADVISORY COMMITTEE
SINGAPORE

16 September 2003

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About the Bioethics Advisory Committee

The Bioethics Advisory Committee ("the BAC") was appointed by the Singapore Cabinet in December 2000. The BAC was directed to "examine the legal, ethical and social issues arising from research on human biology and behaviour and its applications" and to "develop and recommend policies ... on legal, ethical and social issues, with the aim to protect the rights and welfare of individuals, while allowing the Life Sciences to develop and realise their full potential for the benefit of mankind".

The BAC reports to the Ministerial Committee for Life Sciences. For further information about the BAC and its work, please visit <http://www.bioethics-singapore.org>

Contacting the Bioethics Advisory Committee

The BAC welcomes views, comments, suggestions and other feedback on the issues raised in this and other consultation papers, or on any bioethical issue within its remit. All feedback should be addressed to:

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ADVANCING THE FRAMEWORK OF ETHICS GOVERNANCE FOR HUMAN RESEARCH

A CONSULTATION PAPER

PART A: INTRODUCTION AND BACKGROUND

SECTION I: INTRODUCTION

1. About this Paper and the Consultation Process

- 1.1. The Bioethics Advisory Committee was appointed by the Cabinet to examine the potential ethical, legal and social issues arising from research in the biomedical sciences in Singapore, and to recommend policies to the Life Sciences Ministerial Committee.
- 1.2. This Consultation Paper on the Governance of Human Research is issued by the Bioethics Advisory Committee, Singapore (BAC) as part of its efforts to obtain medical and scientific feedback on the issues outlined in

this Paper. The Paper was prepared by the Human Genetics Subcommittee (HGS) of the BAC. The members of the HGS are detailed in Annexe A to this Paper.

- 1.3. The feedback and suggestions received by the BAC will help inform and shape the recommendations which the BAC will be making to the Government in the form of a proposed Report on the Ethical Governance of Human Research.
- 1.4. This proposed Report (“the Ethics Governance Report”) will be the third of a series of Reports submitted to the Government by the BAC. The first Report entitled “Ethical, Legal and Social Issues in Human Stem Cell Research, Reproductive and Therapeutic Cloning” (“the Human Stem Cell Report”) was issued in June 2002, and the second, entitled “Human Tissue Research” (“the Human Tissue Research Report”) was released in November 2002.
- 1.5. The recommendations advanced by the BAC in these first two Reports have since been accepted by the Government.
- 1.6. The recommendations to be advanced in the Ethics Governance Report are intended to supplement and amplify those advanced in the first two BAC Reports. Where common ground is covered in the Ethical Governance Report and the earlier Reports, it should be understood that the more particular and specific recommendations which we made in the earlier two Reports in relation to human embryonic stem cell research, on human cloning, and on human tissue research should control.

Objectives

- 1.7. Our objectives in this Consultation Paper and in the proposed Report are:
 - To review the current system of ethical governance of clinical research in Singapore, with particular focus on the processes and procedures of ethical governance of clinical research;
 - To advance recommendations on the constitution and role of ethics committees or institutional review boards in the process of ethical governance of clinical research;
 - To make recommendations for the future development of the national framework for the ethical governance of clinical research in Singapore; and
 - To advance recommendations for an unified framework of common processes and procedures to be applied in the ethical governance of clinical research in Singapore.

SECTION II: THE CURRENT FRAMEWORK

2. The Background

- 2.1. In Singapore and other technologically-advanced societies, advances in biomedical technology and knowledge have been the main foundation for the vast improvement in health, life expectancy and the quality of life of the general population. These advances represent one of the principal achievements in the modern history of the human race. In the main, such advances in biomedical knowledge have been beneficial, and research conducted in good faith for the benefit of humankind.
- 2.2. The events of World War II however, gave rise to concerns that biomedical research conducted on human subjects should be subject to agreed ethical norms. The Nuremberg Code¹ was born out of these concerns, and represents the first universally-accepted code spelling out the minimum content of the ethical norms governing the conduct of biomedical research on human subjects.
- 2.3. These ethical norms were fleshed out and received fuller treatment and consideration in the World Medical Association's Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects², which since its adoption by the 18th World Medical Association General Assembly at Helsinki, Finland, has become universally accepted as the core body of ethical norms governing human research.
- 2.4. The principal theme of the Helsinki Declaration is that the life, health, privacy and dignity of the human subject in biomedical research are the first considerations before all others. To this end, the Helsinki Declaration advocates safeguards such as the principle of freely given informed consent of the human subject, and the need for rigorous scientific assessment of the risks to the human subject in relation to the benefit sought to be gained from the research.
- 2.5. One of the basic principles enunciated in the Declaration of Helsinki is spelt out in Article 13. This provides that the "design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol", and that this protocol should be

¹ Derived from Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No. 10, Vol. 2 at pages 181-182 (Washington D.C.:U.S. Government Printing Office, 1949).

² Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects adopted by the 18th World Medical Association General Assembly in Helsinki, Finland, in June 1964 and most recently amended by the 52nd World Medical Association General Assembly in Edinburgh, Scotland, in October 2000.

submitted to an independent ethical review committee for “consideration, comment, guidance, and where appropriate, approval”.

- 2.6. The basic principles of the Declaration of Helsinki have been long accepted by the medical community in Singapore, as with other medical communities in the great majority of nations. The need for ethics committees or institutional review boards and the requirement for the ethical review of research proposals involving human subjects have long been an accepted and integral part of medical research in the institutional setting in Singapore. The principles of the Declaration of Helsinki today find expression in regulatory standards and practice guidelines governing various aspects of biomedical research such as those contained in the Medicines (Clinical Trials) Regulations, promulgated pursuant to s.74 of the Medicines Act (Cap. 176), the Singapore Guideline for Good Clinical Practice, and the Ethical Guidelines on Research Involving Human Subjects of the National Medical Ethics Committee (NMEC). We discuss these regulatory standards and practice guidelines in detail below.

The Ethical Governance of Clinical Trials in Singapore

Clinical Trials

- 2.7. In this section, we summarise the current regulatory regime for the ethical governance of drug trials in Singapore.
- 2.8. Since 1978, the Medicines (Clinical Trials) Regulations (RG3 2000 Rev Ed) has statutorily regulated the conduct of clinical trials. These Regulations (“the Clinical Trials Regulations”) were made under the Medicines Act (Cap 176). The Clinical Trials Regulations set out the procedures and conditions which have to be satisfied before a licence for a clinical trial is issued by the competent authorities, which is currently the Health Sciences Authority (HSA).

The Meaning of “Clinical Trials”

- 2.9. It is important to note, however, that the term “clinical trial” in the context of the Clinical Trials Regulations and its parent Act (the Medicines Act, Cap. 176) has a special meaning. As defined in the Clinical Trials Regulations and its parent Act, the term “clinical trial” is restricted essentially to pharmaceutical drug trials, in which the effect, safety and efficacy of new drugs (or new applications of existing drugs) are intended to be tested.

- 2.10. As such, the Clinical Trials Regulations and its parent Act have no application to other research or trials involving human subjects or human biological materials.
- 2.11. The term “clinical trial” for example, does not cover observational trials or interventional trials (we further discuss these and other terms below) involving human subjects, even if such trials involve the administration of drugs (or control placebos), so long as the objectives of the research do not relate to the effect, safety and efficacy of the drugs concerned.
- 2.12. For this reason, and to avoid confusion, we avoid the use of the term “clinical trial”. We instead use the term “drug trials” in this Consultation Paper when referring to “clinical trials” in the legal sense of that term, as used in the Clinical Trials Regulations and the Medicines Act.
- 2.13. In keeping with the principles enunciated in the Declaration of Helsinki, an important component of the requirements of the Clinical Trials Regulations is that the researchers must ensure that the free consent of the proposed research subject must be obtained, and that researchers are under a duty to give full explanation and information of (among others) the risks and objectives of the proposed drug trial.

The Singapore Guideline for Good Clinical Practice

- 2.14. In 1998, the Ministry of Health released the Singapore Guideline for Good Clinical Practice (SGGCP), which is a set of guidelines adapted from the Good Clinical Practice Guidelines of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Accordingly, the SGGCP reflects best international practice in its approach to the governance of drug trials. Since 1998, the SGGCP has been incorporated by reference in the Clinical Trials Regulations, and sponsors and researchers in drug trials are required by law to comply with the SGGCP unless specifically exempted under the Clinical Trials Regulations.
- 2.15. The SGGCP sets out in detail a framework for the ethical governance of drug trials. The SGGCP begins its statement of applicable principles by declaring that drug trials “should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki”.
- 2.16. Article 1.12 of the SGGCP treats the terms “clinical trial” and “clinical study” as being synonymous, and defines them as being any “investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an

investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy”.

- 2.17. The SGGCP sets out detailed guidelines as to the roles and duties of researchers and sponsors in a pharmaceutical drug trial, and lays down the requirements such as monitoring procedures, audits and the matters to be included in trial protocols.
- 2.18. Of relevance to this Consultation Paper are the provisions in Part 3 of the SGGCP requiring all drug trials to be reviewed and approved by the Medical Clinical Research Committee (MCRC) of the Health Sciences Authority (“HSA”) and hospital’s “ethics committees” before an application may be made for a clinical trial certificate from the HSA. The responsibilities, composition, functions and operations of the MCRC are set out in detail in Article 3.1 of the SGGCP, while the responsibilities, composition, functions and operations of ethics committee are detailed in Article 3.2.

The Current Approval Process for a Proposed Pharmaceutical Drug Trial

- 2.19. It may be useful to summarise the current approval process for a proposed pharmaceutical drug trial under the current regulatory regime. Researchers seeking a clinical trial certificate under the Medicines Act are required to submit their trial protocol and application first to their hospital ethics committee or IRB for review and approval. If the proposed pharmaceutical drug trial is a multi-centre trial (where the trial is carried out at more than one institution or centre), the application is submitted to the Clinical Trials Coordinating Committee (CTCC) instead for review and approval. The CTCC was established in 1999 by the Ministry of Health to coordinate the ethical governance of multi-centre drug trials in Singapore.
- 2.20. If the protocol and application are approved by the hospital ethics committees (and the CTCC, if the application is for a multi-centre trial), they are then submitted to the Centre for Pharmaceutical Administration (CPA) of the HSA for review and approval.
- 2.21. The CPA is aided in its task by the MCRC. The MCRC is an advisory committee appointed by the Ministry of Health to review applications for drug trials in Singapore. It is an “independent body constituted of medical members, whose responsibility is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial ... and documenting informed consent of the trial subjects” (Article 1.37 of the SGGCP). The MCRC currently comprises five members, all of whom are clinical specialists.

- 2.22. The current formal regulatory regime for drug trials as constituted under the Medicines Act, the Clinical Trials Regulations and the SGGCP has worked very well, and the standards of ethical governance in Singapore for drug trials conform to the highest internationally agreed standards of ethical governance for drug trials.
- 2.23. We understand that the rules are being examined with a view to procedural changes in the interests of streamlining processes, emphasising a risk-based approach and perhaps also for the inclusion of the trial of medical devices to be included within the ambit of the current regulatory regime. We agree with these moves, and they do not detract from or alter the core principles for ethical governance currently in place for drug trials.

Non-Drug Trials

The NMEC Guidelines on Research Involving Human Subjects

- 2.24. While the ethical governance of drug trials in Singapore is comprehensively and appropriately regulated by statutory rules and practice guidelines, the picture for the ethical governance of clinical research other than for drug trials is less clear.
- 2.25. Currently, there is no statutory scheme for the ethical governance of clinical research apart from drug trials. We expand on the definition of “clinical research” in Section III below.
- 2.26. Indirectly, however, the Ministry of Health has long exercised jurisdiction over, and given informal ethical guidance on, clinical research carried out in hospitals, clinics and clinical laboratories in its role as a statutory regulator under the Private Hospitals and Medical Clinics Act.
- 2.27. In January 1994, the Ministry of Health set up a national-level policy advisory body, the National Medical Ethics Committee (NMEC) to “assist the medical profession in addressing ethical issues in medical practice and to ensure a high standard of ethical practice in Singapore”.
- 2.28. One of the objectives of establishing the NMEC was to “identify and study ethical issues relating to medical practice and research in Singapore and to provide an ethical framework for medical practitioners to carry out their duties and responsibilities”.
- 2.29. Several sets of Ethical Guidelines were issued by the NMEC and adopted by the Ministry of Health. In the sphere of ethical governance of clinical

research, the most significant of these Ethical Guidelines is the Ethical Guidelines on Research Involving Human Subjects issued by the NMEC in August 1997 (“the NMEC Guidelines”).

- 2.30. The NMEC Guidelines were accepted and adopted by the Ministry of Health, and copies of these Guidelines were circulated to all hospital ethics committees for their adoption and implementation.
- 2.31. In 1998, the previously informal practice of hospitals and medical institutions in Singapore of having ethics committees (sometimes on an *ad hoc* basis) to review research proposals involving human subjects was formalised by a written direction dated 25 June 1998 from the Ministry of Health to all government and restructured hospitals to set up hospital ethics committees (if they had not already done so) for the ethical governance of research involving human subjects.
- 2.32. We quote from the written direction:

“The National Medical Ethics Committee has recommended that:

- (i) *hospital ethics committees vet for ethical considerations, all research protocols that involve*
- *human experimentation be they drug trials, trials of new medical devices, new procedures and any other forms of clinical studies that require the participation of human subjects or the use of human tissues and organs*
- ...
- (ii) *a senior nursing representative be included as a member of hospital ethics committee.*

The Ministry has accepted these recommendations”.

- 2.33. The NMEC Guidelines set out in detail suggested principles of the ethical governance of research involving human subjects, the constitution of ethics committees and the implementation of the framework for the ethical governance of biomedical research. These Guidelines represent the principal controlling document governing research involving human subjects in Singapore today, but despite this they remains non-directive in nature,
- 2.34. In developing the Guidelines, the NMEC drew extensively from similar guidelines published in other technologically-advanced countries, notably those issued by the Canadian Medical Research Council, and the Royal College of Physicians, London. The NMEC Guidelines are therefore consistent with internationally-accepted approaches to, and norms of,

ethical governance of biomedical research involving human subjects at that time.

- 2.35. We have reviewed the NMEC Guidelines. We have no hesitation in using the NMEC Guidelines as the starting point of the larger enquiry in this Consultation Paper. Although it was formulated in the restricted context of the governance of biomedical research on human subjects by the medical professions (as appropriate and in keeping with the NMEC's terms of reference), the principles expressed in it and the framework which it recommended for the ethical governance of clinical research are entirely sound and are universally accepted within the medical professions.
- 2.36. We therefore are of the view that the principles and the framework for ethical governance of biomedical research on human subjects set out in the NMEC Guidelines are an appropriate foundation for our proposals for a scheme of ethical governance of all clinical research on human subjects in Singapore, whether or not such research is carried out by members of the medical professions, and whether or not such research is carried out in an institution under the direct jurisdiction of the Ministry of Health pursuant to the Private Hospitals and Medical Clinics Act.

Limitations of the Current Regulatory Regime

- 2.37. The evolution of regimes for the ethical governance of clinical research and drug trials must be seen in the context of the history of clinical research and drug trials in Singapore. At the time when the Clinical Trials Regulations were first enacted, drug trials were the most common kind of clinical research trial. As such, it was entirely appropriate to enact the Clinical Trials Regulations as subsidiary legislation under the Medicines Act, which deals principally with medicines.
- 2.38. Likewise, until recently, the vast majority of clinical research (whether drug trials or non-drug trials) were carried out by researchers who were medical practitioners registered under the Medical Registration Act (Cap. 174), or in Government medical institutions directly controlled by the Ministry of Health, or in hospitals and medical clinics licensed under the Private Hospitals and Medical Clinics Act. In all of these cases, the competent supervisory authority was the Ministry of Health.
- 2.39. In recent years, however, the development of the biomedical industry in Singapore has led to an increasing proportion of non-drug trials. For example, in 2002, hospital ethics committees of the five main restructured hospitals in Singapore reviewed nearly three times as many applications for non-drug trials as they did for drug trials.

- 2.40. Clinical research tends increasingly to be institutionally-driven, rather than being researcher-driven (the traditional model assumed in the current regulatory regime). Company-driven drug trials received by the HSA now outnumber researcher-driven drug trials.
- 2.41. Concomitantly, an increasing proportion of clinical research trials are now also being carried out outside the traditional paradigm assumed by the current regulatory environment: many trials are now led by researchers, who although being qualified and competent for the trials proposed by them, are not medical practitioners registered under the Medical Registration Act, or by researchers who work in or for entities not subject to the regulatory jurisdiction of the Ministry of Health. Such entities include companies and other commercial entities in the biomedical industry, research institutes and statutory agencies with an interest in the biomedical industry.
- 2.42. The vast majority of these new players in the field of clinical research in Singapore are keenly aware of the need for proper ethical governance. Most researchers are anxious to conform to internationally-accepted standards for ethical governance. In many cases, researchers are involved as collaborators in multi-jurisdictional or multi-centred (or both) clinical research projects.
- 2.43. With the development of the biomedical industry in Singapore, new avenues of biomedical inquiry are rapidly emerging, and the traditional categorisation of research trials into drug trials and non-drug trials for the purposes of ethical governance is rapidly becoming irrelevant and obsolete. Some new kinds of research may blur the border between drug and non-drug trials. For example, the first use of a new drug already approved elsewhere on the local population: in this situation, is the trial one for the drug, or a trial to observe and determine the responses of the local population to the drug? New kinds of research trials include trials of medical devices, experimental therapy procedures (which may or may not involve drugs), new modes of non-drug treatment and new diagnostic methods. Other increasingly important research include epidemiological or population studies (which may or may not require invasive interaction with human subjects), genetic screening, genetic research and research which involve no direct interaction with human subjects but only access to their personal medical or genetic information.

2.44. In summary:

- The most comprehensive formal framework for the ethical governance of clinical research trials at the moment is limited largely to drug trials, or “clinical trials” as defined in the Medicines Act. The principal documents setting out this framework of ethical governance are the Medicines Act, the Clinical Trials Regulations, and the SGGCP. In this framework, the HSA is the principal regulatory agency.
- For clinical research other than drug trials, the Ministry of Health exercises indirect control over hospitals and medical clinics under the Private Hospitals and Medical Clinics Act. The Ministry of Health has directed that hospitals establish ethics committees to review and approve applications for both drug and non-drug trials.
- For clinical research other than drug trials, the main document spelling out a framework for ethical governance is the NMEC Guidelines.
- There is some uncertainty as to whether the jurisdiction of the Ministry of Health under the Private Hospitals and Medical Clinics Act extends to clinical research entities or institutions which are not hospitals or clinics liable to be licensed under the Act.
- Non-drug trials have in recent years surpassed drug trials in number, and new kinds of clinical research projects not contemplated when the current controlling documents were drafted have since emerged. New types of clinical research have evolved, blurring and making irrelevant the traditional distinction between drug trials and non-drug trials.

2.45. The current framework for ethical governance of clinical research has evolved incrementally and cautiously. In our view, this evolutionary approach was an entirely appropriate response to specific needs and technological advances as they developed over the years.

2.46. At a time when the bulk of medical research was centred about drug trials carried out by the medical professions, it was entirely appropriate to provide for a scheme of ethical governance within the framework of the Medicines Act. But the present and future of clinical research on human subjects embraces a diversity of research inquiry which can no longer be accommodated within the current framework. Accordingly, we think that it is now the appropriate time to undertake a global review of the current rules and framework for the ethical governance of clinical research, and a new, unified framework be created for the ethical governance of all research involving human subjects whether involving drug or non-drug trials.

- 2.47. The principles and ethical governance framework expressed in the Clinical Trials Regulations, the SGGCP and the NMEC Guidelines have served us well in their restricted contexts, and are universally accepted. We take the view that these remain sound guides, and should wherever possible be applied and extended as appropriate to all other forms of clinical research involving human subjects. To this end, the current provisions relating to drug trials should be substantively retained insofar as drug trials are concerned, subject to the procedural changes currently being proposed by the HSA.
- 2.48. In the sections that follow, we will consider the elements of the proposed new unified framework for ethical governance of clinical research involving human subjects.

Recommendation 1:

A new national framework for the ethical governance of all clinical research involving human subjects should be established.

PART B: CLINICAL RESEARCH

SECTION III: CLINICAL RESEARCH

3. Defining Clinical Research

- 3.1. In this section, we attempt a definition of what kinds of clinical research ought to be subject to the framework of ethical governance that we recommend in this Consultation Paper.
- 3.2. Clinical research is a term capable of a very broad definition. In our review of the approaches taken by national ethical bodies or agencies in other countries, we have found that there is considerable variation in what is to be included in the definition of clinical research coming within the purview of institutional ethics review bodies. For example, in some jurisdictions, ethics committees are required to review proposals for sociological research or humanities-based research if they involve human subjects.
- 3.3. But in keeping with our terms of reference, we consider only such clinical research that involves an interaction (whether direct or otherwise) with a human subject or human biological material, and therefore exclude for our present purposes any clinical research issues in relation to:
- Genetically-modified organisms;
 - Animals and their treatment; and
 - Economic, sociological and other studies in the disciplines of the humanities
- unless such research directly impacts upon (or otherwise has the potential impact on) the safety, health, welfare or dignity of individual human subjects directly involved in the research.

- 3.4. In the NMEC Guidelines, the NMEC wrote that “Human research can be broadly defined as studies which generate data about human subjects which go beyond what is needed for the individual’s well-being. The primary purpose of research activity is the generation of new information or the testing of a hypothesis. The fact that some benefit may result from the activity does not alter its status as “research”. Defined in this manner, human research includes not only studies which involve human subjects directly, but also epidemiological surveys and reviews of patient records, for purposes not related to the patient’s immediate health care needs” (at paragraph 2.2.1). We agree with this statement and adopt it.

- 3.5. The NMEC also went on to consider the relationship and distinction between research and therapy. They held that when “an activity is undertaken with the sole intention of benefiting the patient, the activity may be considered to be part of “therapy”. The progressive modification of methods of diagnosis and treatment in the light of experience is a normal feature of medical practice and should not be considered as research. There could be potential conflicts between research (intended to generate new information) and therapy (intended to benefit the individual patient directly). Their resolution rests on the integrity of the physician / researcher. The patient is always entitled to the best clinical management, and research considerations must never override this”. We agree with these statements of the NMEC, and likewise adopt them. In keeping with the spirit of this definition, we therefore exclude therapeutic activities undertaken with the sole intention of benefiting the patient from our definition of clinical research.
- 3.6. Subject to the preceding qualifications, we propose to define clinical research in the following terms:

Any research study, trial or activity involving human subjects, human tissue, or medical, personal or genetic information relating to both identifiable and anonymous individuals, undertaken with a view to generating data about medical, genetic or biological processes, diseases or conditions in human subjects, or of human physiology or about the safety, efficacy, effect or function of any device, drug, diagnostic, surgical or therapeutic procedure (whether invasive, observational or otherwise) in human subjects whether as one of the objectives or the sole objective, of the research study, trial or activity

and

which research study, trial or activity has the potential to affect the safety, health, welfare, dignity or privacy of the human subjects involved in the study, or of the donors of human tissue or information used in the research, or of the family members of any of the human subjects or donors thereof, or to which such medical, personal or genetic information relates.

Savings

- 3.7. We make clear that nothing in this Consultation Paper is intended to supplant the recommendations that we have made in the Human Stem Cell Report and the Human Tissue Research Report, and that the recommendations contained in this Consultation Paper are intended to supplement those advanced in our first two Reports.

Exceptional Situations

- 3.8. We note that there may be some exceptional circumstances in which it may be ethically acceptable to abbreviate or temporarily suspend the usual ethics review procedures and requirements, provided that all the applicable legislative and regulatory requirements are satisfied. We have in mind situations of national security or emergency health situations, in which urgent research may have to be carried out to avert harm to national security or for the urgent protection or treatment of whole populations at risk. In such cases, we think that it is permissible for institutional review boards in consultation with the proper authorities to formulate and lay down written guidelines for the exemption or expedited review of defined classes or types of such emergency or urgent research in the national interest.
- 3.9. We therefore recommend that all clinical research as defined in this section be statutorily subject to review and approval by and to the continued supervision of an institutional review board in accordance with the principles discussed below.

Recommendation 2:

- **The current statutory requirement for review and approval by an institutional review board in drug trials should be extended to all kinds of clinical research involving human subjects, as defined in this section.**
- **All clinical research proposed to be carried out in Singapore must be submitted to and approved by a properly constituted institutional review board.**
- **No programme of clinical research may be commenced or carried out without the approval of such an institutional review board, or other than on terms as set out by such an institutional review board.**

PART C: ETHICAL GOVERNANCE

SECTION IV: PRINCIPLES OF ETHICAL GOVERNANCE

4. Principles of Ethical Governance

The Purpose of Ethical Governance

- 4.1. Article 5 of the Helsinki Declaration states that in “medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society”. At Article 8, the Declaration states that “[m]edical research is subject to ethical standards that promote respect for all human beings and protect their health and rights”.
- 4.2. Continuing biomedical human research is fundamental to improving our understanding of biological processes, and ultimately to the improvement of the health and welfare of humankind. Whereas diagnostic, prophylactic and therapeutic research have as their objective the immediate needs of individual patients, biomedical human research have wider and longer-term objectives in the discovery of new knowledge that may lead to an improvement in the methods of diagnosis, prophylaxis and therapy of individuals, and to the health and welfare of society in general.
- 4.3. The experience of physicians in the management of patients often lead to new scientific insights, which when coupled with continuing biomedical human research leads to a virtuous circle that supports and advances biomedical knowledge to the benefit of both individuals and society at large. As Article 4 of the Helsinki Declaration states: “Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects”.

Applicable Principles

- 4.4. The fundamental objective of having a system of ethical governance is ultimately the protection and assurance of the safety, health, dignity, welfare and well-being of human research subjects.
- 4.5. But as with most kinds of diagnostic, prophylactic or therapeutic interventions, most forms of biomedical human research unavoidably involve some degree of risk of harm (however minimal or remote) to the human subject.

- 4.6. Ethical assessment and judgment therefore necessarily involves an assessment and balancing of the potential harms and benefits. In general, clinical research should be directed towards the minimisation of risks and the maximisation of benefits, always bearing in mind the overriding considerations of the safety, health, dignity, welfare and well-being of the human subject.
- 4.7. To this end, a system of ethical governance must ensure that there is a proper assessment and weighing of the potential harms against the potential benefits of all biomedical human research, in accordance with the ethical values of the community. A proper system of ethical governance serves to strengthen public confidence in biomedical human research by ensuring that all forms of biomedical human research conform to the accepted body of ethical values of the community.
- 4.8. We recognise, however, that there can be neither absolute certainty nor finality as to the precise content of the body of ethical values to be applied in such an assessment. This is so in Singapore, as it is everywhere else in the world. The body of ethics in any given society is neither fixed nor clearly defined for all time, but evolves in response to advances in knowledge, technology, changes in social mores, and community dialogue and debate.
- 4.9. These fundamental principles are expressed and repeated in international documents such as the Declaration of Helsinki, the Nuremberg Code, the Belmont Report (Ethical Principles and Guidelines for the Protection of Human Subjects of Research, 1976), the UNESCO Universal Declaration on the Human Genome and Human Rights 1997, and the WHO's Proposed Guidelines on Ethical Issues in Medical Genetics and Genetic Services 1997 (as updated 2001).
- 4.10. In Singapore, these same principles are found or reflected in regulations such as the Clinical Trials Regulations, and in documents such as the SGGCP and the NMEC Guidelines. We have already addressed some of these principles at length in the Human Stem Cell Report and the Human Tissue Research Report.
- 4.11. These core principles are expressed, restated and elaborated upon in many ways. For example, the NMEC expresses some of these fundamental principles as follows:

“2.3.1 The fundamental principle of research involving human subjects is respect for life. From this principle, others follow: that of beneficence, justice, and autonomy. Beneficence concerns the benefits and risks of participating in research. Justice relates to

the fair distribution of risks in research in relation to the anticipated benefits for research subjects. Autonomy refers to the right of individuals to decide for themselves what is good for them.

2.3.2 *With respect to beneficence, the benefits and risks of research must always be carefully assessed. Research on human subjects should only be undertaken if the potential benefits arising from the expected new knowledge are of sufficient importance to outweigh any risk or harm inherent in the research, bearing in mind that risks and benefits may not be measurable on the same scale.*

2.3.3 *...Justice must be exercised in the allocation of the anticipated risks and the anticipated benefits...*

2.3.4 *A corollary of autonomy is that any research procedure must have, as far as possible, the free and informed consent of the experimental subject. Similarly, respect for the individual implies that safeguards should be provided to protect the experimental subject from physical and emotional harm including provisions for confidentiality.”*

- 4.12. Despite some uncertainty at the edges, a core of universally accepted principles and ethical values lie at the heart of most societies in their application to the protection of human research subjects.
- 4.13. It is desirable that a code of applicable principles for ethical governance be eventually formulated for the common guidance alike of ethics committees, institutional review boards, research institutions, researchers, the human subjects of research and all other parties involved in human research, in the interests of consistency and fairness of the judgments of institutional review boards.
- 4.14. We do not attempt, and it is beyond the scope of this document, to attempt to list all these fundamental principles. In our view, the applicable principles of the proposed code are best settled in an incremental and evolutionary manner through dialogue and discussion between institutional review boards and the other parties in the research governance process. This process of dialogue and discussion should be informed by and have reference to the experiences of the parties involved.
- 4.15. We think that this process of dialogue and discussion is best sponsored or promoted through a national agency. We elaborate on this in our discussion on the national organisation of ethical governance in Part D

below. Likewise, the draft of such a code, and the revisions thereto, should be sponsored and led by such a national agency.

- 4.16. We take the view that it is part of the function of a responsive and dynamic system of ethical governance that the applicable body of ethics be reviewed and assessed from time to time to keep it relevant to and reflective of community values and the needs of research.
- 4.17. We emphasize that it is not the intention of this document to prescribe the specific ethical principles to be applied by institutional review boards and researchers in the process of ethical governance. We believe that these are professional judgments which are appropriately and properly left to members of institutional review boards, researchers and other parties involved in the process of ethical governance.
- 4.18. We note, however, that there are broad ethical principles which are universally accepted and applied in all the leading research jurisdictions, and we take the view that it would be appropriate and desirable if institutional review boards, researchers and other parties involved in the process of ethical governance consider taking these ethical principles into account.
- 4.19. Such principles, in addition to or in elaboration of those identified by the NMEC, might include:
- Respect for the human body, welfare and safety, and for religious and cultural perspectives and traditions of human subjects. We elaborated on this principle in our Human Tissue Research Report. In the context of a diverse society such as Singapore, researchers have an especial obligation to be sensitive to religious and cultural perspectives and traditions of their human subjects.
 - Respect for free and informed consent. Again, this principle is discussed at length in our Human Stem Cell Report, and our Human Tissue Research Report. A detailed discussion of the requirements of consent is also set out at section 2.5 of the NMEC Report, and we note also the strict requirements with regards to consent laid down by the Clinical Trials Regulations and the SGGCP.
 - Respect for privacy and confidentiality. This is treated in detail in section 2.6 of the NMEC Guidelines, and again in our Human Tissue Research Report.
 - Respect for vulnerable persons. This is discussed in paragraphs 2.5.5 to 2.5.6 of the NMEC Guidelines. In essence, the ethics governance

process must pay especial attention to the protection of persons who may not be competent to give consent themselves, or whose ability to give free and full consent may be compromised by reason of their physical condition or other circumstances, such as being in a dependent relationship.

- Avoidance of conflicts of interest, or the appearance of conflicts of interest. We further elaborate on this principle below in our discussion of the roles and responsibilities of investigators and institutional review boards.

SECTION V: INSTITUTIONAL REVIEW BOARDS

5. Institutional Review Boards

The Role of Institutional Review Boards

Nomenclature

- 5.1. Ethical review bodies having the first responsibility for ethical review in the ethical review and governance process are variously known as “ethics committees”, “research ethics committees” or “institutional review boards”. In the context of Singapore, the term “ethics committees” is presently most commonly used.
- 5.2. We prefer instead the term “institutional review boards”. Our main reason for doing so is our desire to see institutional review boards established as full-time permanent supervisory bodies organised at and integral to the function of the highest administrative levels in all institutions in which research is carried out. For instance, we think that institutional review boards in hospitals should be organised at the same level as medical boards, and that the institutional review board should report directly to the highest level of management of the hospital. We believe that the term “institutional review board” (“IRB”) best reflects this role.
- 5.3. We differentiate here between IRBs which review, approve and monitor clinical research involving humans, and hospital ethics committees that address medical practice issues. For the avoidance of doubt, the recommendations in this paper cover only IRBs which review, approve and monitor clinical research involving human beings.
- 5.4. There is universal agreement in all developed countries that IRBs are central to a proper framework of ethical governance of human research, and that the primary objective of an IRB is the protection and assurance of the safety, health, dignity, welfare and well-being of human research subjects, in keeping with the principles outlined above.
- 5.5. Increasingly, collaborative research programmes are carried out across international borders (in multi-national research programmes) or by researchers in several institutions (in multi-centre research programmes), or even a combination of both. It is usually a condition of such research programmes that the proposed or prospective researchers secure the approval of a properly constituted IRB in their own country or institution. Without a properly constituted IRB or access to such an IRB, an institution engaging in human research cannot hope to participate in such multi-national or multi-centre collaboration research programmes.

- 5.6. From this viewpoint, the harmonisation of our national ethical governance framework with that in leading research jurisdictions is of national strategic importance.
- 5.7. The ultimate responsibility for the ethical compliance of clinical research rests with the researchers who propose and carry out the research, and with the institution which sanctions the research or in which research is carried out.
- 5.8. The IRB is the vehicle through which such institutions act to implement a proper system of ethical governance of research carried out in such institutions.
- 5.9. Every institution that conducts research, or allows research to be carried out on its premises, or on its patients, or on or involving access to or use of human tissue collections in its custody, or on or involving access to or use of medical records or other personal information in its custody, should have an effective and properly constituted IRB.

Recommendation 3:

The current requirement that every hospital have an institutional review board should be statutorily formalised, and extended to all institutions that carry out clinical research. Every institution that conducts research, or allows research to be carried out on its premises, or on its patients, or on or involving access to or use of human tissue collections in its custody, or on or involving access to or use of medical records or other personal information in its custody should have an effective institutional review board.

Shared, “Domain” and Other Special Institutional Review Boards

- 5.10. Where by reason of the small size of the institution or the small number of research proposals it is impractical to establish and maintain a standing IRB of its own, such institutions should make clear arrangements with other institutions which maintain IRBs, to be supervised and audited by the IRBs of these other institutions.
- 5.11. Alternatively, it is permissible for several such institutions to jointly appoint a shared IRB.
- 5.12. Even in cases of institutions who already have their own IRBs, these institutions may prefer or wish to refer some kinds of research applications

(for example, a proposal for research in a specialist area) to a specialist IRB or a domain IRB which has the technical capacity to assess research in that specialised area. Again, several institutions could jointly appoint and share in the expertise of such an IRB in situations where such expertise is limited. Such a specialist IRB has the advantage of delivering consistent decisions, and special competent and knowledge in their field of specialisation. It is also acceptable that a cluster of hospitals cooperate in developing a panel of IRBs to cover all reasonable disciplines.

- 5.13. To our knowledge, there are currently no commercial IRBs in Singapore, in the sense of a board that offers ethics review on a commercial basis. In principle, we have no objection to such boards, provided that sufficient safeguards are taken against the obvious objections such as a lack of true independence, but will leave this issue to the national supervisory agency which we recommend in Section 7 below. In any event, we think that careful investigation and consideration by the national supervisory agency should be carried out before a commercial IRB is given accreditation as described in Section 7 below.

The Responsibilities of Institutional Review Boards

- 5.14. In its acts and decisions, and in the exercise and discharge of its duties and responsibilities, an IRB acts on the behalf of the institution that appoints it and exercises on its behalf the authority and powers of that institution in matters within the terms of reference of the IRB.
- 5.15. IRBs are required to carry out three distinct functions and responsibilities:
- 5.15.1. Ethical Review Gateway. In this responsibility, IRBs assume the role of an ethical review gateway through which all proposals for biomedical human research must be submitted and assessed for ethical acceptability and compliance, and for potential harms and benefits in accordance with the principles outlined in Section IV above. In this model of ethical governance, all proposed clinical research involving human subjects must be submitted for review and approval before the proposed research may be carried out. In the majority of developed countries, this is made a statutory or otherwise legal requirement. We recommend this model for adoption in Singapore.
- 5.15.2. Continuing Review, Supervision and Audit. In this responsibility, IRBs assume jurisdiction and authority for the continuing supervision and audit of approved research programmes upon their commencement. The IRB is also empowered to carry out audits of

research programmes, or to require such audits to be done, in order to ensure continued compliance with the terms of approval throughout the lifetime of the research programme. IRBs may also direct or otherwise require amendments or modifications to research proposals at any time, and to make such amendments or modifications a condition of approval for the conduct of the research programme.

5.15.3. Outcome Assessment, Reporting and Feedback. In this responsibility, IRBs (especially those in large institutions with a large number of research programmes) undertake the monitoring and collation of adverse event reports, the outcomes of the research programmes, an evaluation of the actual versus the anticipated outcome or results, and the reporting of outcomes and trends to the relevant authorities and to the institutions that they are appointed by and to whom they are responsible. Another major aspect of this role is the role of IRBs in providing feedback and maintaining a dialogue on applicable standards with its constituent researchers. In the discharge of their role, IRBs can and should also act as the key institutional agency which receives, acts upon and reports to the relevant authorities on concerns and feedback expressed by the human subjects of the research programmes.

5.16. Additionally, IRBs may (but not necessarily or invariably, according to the terms of their constitution and appointment) also undertake responsibility for:

5.16.1. Review of Scientific Merits. In this responsibility, IRBs carry out peer or expert assessments of the scientific merits and soundness of proposed research programmes. In view of the present system requiring the grant funding agency to conduct scientific review of the research, we clarify that the extent of the IRBs responsibility for scientific review may be delineated by the particular institution to which it belongs. By way of illustration, where the institution possesses the necessary expertise needed or where the research project is not subject to grant funding, the IRB may conduct scientific review; where the institution does not possess the necessary expertise, a summary of the scientific review conducted by the grant funding agency should be submitted to the IRB as one of the documents required for approval by the IRB. In all cases, we think it is important that clear standard operating procedures in this area are established by the particular institution. The fact that a particular proposed programme of research is judged to be of sufficient scientific merit does not necessarily mean that it satisfies ethical considerations, although in many cases, these two

considerations are linked, especially in the assessment of harms versus benefits.

- 5.17. It is the responsibility of all institutions to ensure that a proper review of the scientific merits of all clinical research proposals is carried out.
- 5.18. Institutions also have the responsibility for establishing clear standard operating procedures for the review of the scientific merits of all clinical research proposals, and whether this is to be done by a separate agency or committee (whether internal or external), or whether it is to be done by the IRB. If the review of scientific merits is also to be conducted by the IRB, this must be made clear to, and accepted by, the IRB.
- 5.19. The implementation of a framework for the work of IRBs has been laid down and discussed extensively by the NMEC in section 3 of the NMEC Guidelines. We agree generally with the principles of implementation laid down by the NMEC, and further elaborate on these principles in our discussion of the constitution of IRBs below.

Recommendation 4:

Institutional Review Boards should have responsibility for:

- **The ethical review and approval of proposed clinical research programmes. This should take into account the scientific merits of proposed clinical research programmes.;**
- **The continuing review, supervision and audit (including monitoring feedback from research subjects) of clinical research programmes approved by them. Reporting of the outcomes of the review and audit to proper authorities and to their appointing institutions and to principal investigators of the research programmes;**
- **Reporting on the clinical research programmes and in particular the results of the programme approved by them to the proper authorities and to their appointing institutions, feedback to the constituent researchers of the institutional review board, and monitoring feedback from research subjects.**
- **Additionally, and provided that this responsibility and jurisdiction is clearly set out by the terms of its constitution and appointment by the appointing institution, institutional review boards may also have responsibility for the review of the scientific merits of proposed clinical research programmes.**

The Constitution of Institutional Review Boards

- 5.20. IRBs should be established and appointed by and at the highest administrative levels of the institutions. They should be appropriately resourced relative to the research activity of the institution and, where this is substantial, should be regarded as one of the key full-time management offices within the organisation of institutions, and not merely as honorary or *ad hoc* committees.
- 5.21. The IRB should be appointed and report to at least an authority at the level of the Chief Executive Officer (as required by the NMEC guidelines in the case of hospitals falling under the jurisdiction of the Ministry of Health pursuant to the Private Hospitals and Medical Clinics Act) or senior management.
- 5.22. IRBs should not be appointed as *ad hoc* committees to consider research proposals as and when they arise, although it is acceptable for institutions with standing IRBs to appoint special *ad hoc* committees in consultation with their standing IRBs to consider special research proposals. We prefer, in such cases, that the institution works with their standing IRB to appoint special subcommittees co-opting experts or reviewers to assist the standing IRB in the particular project concerned. For example, an IRB may receive a research proposal involving an area of research with which no member of the IRB is familiar. In such a case, the institution may work with the IRB to identify and co-opt *ad hoc* experts or reviewers to assist the IRB in its assessment and review of the proposal. The co-opted *ad hoc* experts or reviewers sit as a subcommittee of the IRB.
- 5.23. Institutions have an obligation to ensure that IRBs receive adequate administrative support that is commensurate with their central role in the ethical governance process.
- 5.24. IRBs should have sufficient full-time administrative support so as to ensure continuity and consistency in the work of the IRBs, to discharge its continuing review, supervision and audit obligations, its outcome assessment and reporting duties, and to ensure that their decisions are made with regard to previously-established precedents and decisions made by themselves and their predecessors.
- 5.25. Institutions should also ensure that IRBs have sufficient administrative support so as to ensure that proposals are reviewed and dealt with in a timely manner within the target time-frames set by the institution.

Composition

- 5.26. We are of the opinion that the SGGCP, in particular paragraph 3.2.3, and the NMEC Guidelines, in particular paragraph 3.2.2, lay out appropriate and comprehensive guidelines regarding the composition of an ethics committee. We endorse these requirements, and propose that they be similarly used to form the framework for the composition of an IRB.
- 5.27. In addition, we propose to highlight certain general requirements for the composition of an IRB:
- 5.27.1 Given the importance of the IRB, it is important that the core members of IRB should be appointed from among the institutions' most senior, most respected and scientifically competent officers, researchers or consultants, who possess the appropriate experience and training.
- 5.27.2 The core members of the IRB should be able to devote sufficient time commensurate to the workload of the IRB.
- 5.27.3 Representation on an IRB should not be restricted to members of the institution, but should include external and lay representation.
- 5.27.4 External representation may be in the form of specialists of reputation from other institutions: the objective here is to lend impartiality and objectivity to the work of the IRB, and to ensure that the decisions of the board are carried out in accordance with scientific thinking accepted within the community.
- 5.27.5 IRBs should also have lay, non-scientific or non-medical representation. Where practical, and where the size and volume of the workload of the IRB permits, lay representation may include respected lay members of the community, experts in philosophy, ethics, psychology, sociology or the law. The IRB may consult representative religious leaders on an *ad hoc* basis where it feels that such a need exists.
- 5.27.6 As far as possible, the core membership of an IRB should be representative of the particular fields of research carried out in the institution, such that for every research proposal received by the board, there will be at least one specialist or expert (and preferably more) on the IRB that is competent to assess that proposal.

Institutional Conflicts of Interest

- 5.28. In the relationship between an institution and the IRB, the fundamental underlying principles are the independence of the IRB in the exercise of its powers and duties, and its ethical integrity.
- 5.29. The research programmes which IRBs are asked to review are often of considerable financial or other benefit (potential or otherwise) to the appointing institutions. In the review of these research programmes, both IRBs and institutions alike must be aware of the potential conflict of interest involved and take reasonable steps to minimise conflict.
- 5.30. It is for this reason, among others, that we have recommended that IRBs report directly to the highest levels of governance in an institution. In the case of hospitals and other similar medical institutions, the IRB should not report to the medical board of that institution.
- 5.31. At minimum, all communications in relation to the review of the research programme in question should be fully documented in writing. Informal communication between the institution and its officers and the individual members of the IRB in connection with such research programmes should be strongly discouraged.
- 5.32. As part of its duty to make periodic reports, we recommend that IRBs include a special report on all reviews of research programmes in which there is or is potentially such a conflict of interest. This special report should be made directly to the board of directors of the institution.

Multinational and Multi-Centre Research Projects

- 5.33. As we have previously pointed out, research projects or trials increasingly involve collaborators in more one country. Indeed, one of the hallmarks of current leading-edge research are the multinational and multi-centre collaborative nature of the research effort, which often involves a very large number of researchers based in many institutions in different countries.

Multinational Research Projects

- 5.34. Guidance has been sought from us as to whether ethics review should be required for the portion of multinational research projects carried out in Singapore. We take the view that ethics review should indeed be required for any portion of a research project or trial carried out in Singapore, or involving human tissue, or medical, personal or genetic information

collected in Singapore or derived from donors in Singapore, or which involves the export or transmission abroad of any human tissue, or medical, personal or genetic information collected in Singapore or derived from donors in Singapore.

- 5.35. This is on the basis that Singapore law and Singapore ethical standards and rules are not necessarily the same as that in other countries. This approach is supported in other jurisdictions. Otherwise there would be a moral hazard in the temptation of researchers picking the jurisdiction perceived to have the most liberal regime as their ethical jurisdiction of choice.
- 5.36. Nonetheless, we envisage that expedited review may be permissible in certain circumstances. For example, where patient tissues from an IRB approved study conducted in another country comes to Singapore for analysis, and the Singaporean institution does not have direct contact with the patient but merely performs tests on patient samples.
- 5.37. To avoid unnecessary bureaucracy, local research collaborators should be encouraged to provide their local IRBs with full documentation of ethics review applications made to the IRB of the lead jurisdiction, together with copies of all relevant queries and rulings of that IRB. If applications have been submitted or are proposed to be submitted to other IRBs in other jurisdictions, information on these applications, and on their outcome, should be provided to the local IRB as well.
- 5.38. The local IRB may then elect to give expedited approval of such applications after reviewing the documentation, and the reasons for the decision of the leading ethical review board. In general, local IRBs should consider a full ethics review if a substantial portion of the research project is to be carried out in Singapore. Similarly, local IRBs should be concerned to ask for evidence of approval by IRBs in the jurisdiction in which the major part of the research project will be carried out.

Recommendation 5:

The local portion of a proposed multinational research programme should be subject to review by the institutional review board(s) of the local partner institution or institutions.

Multi-Centre Research Projects

- 5.39. Currently, the situation is that ethics review is required by the ethics committees of every institution which will be involved in the proposed research programme. Except for drug trials, there is no mechanism or requirement that any one of the ethics committees involved should act as a principal or coordinating ethics committee (in drug trials, this function is currently carried out by the CTCC).
- 5.40. We recommend that a “lead” IRB be designated from among the IRBs of the participating institutions. The researchers may be asked to propose a lead IRB. On reviewing the proposal, the proposed lead IRB may then decide to accept nomination as the lead IRB, and if not, to give reasons why other IRBs may be more appropriate. If the proposal is accepted by the proposed lead IRB, the first application for review should be made to that lead IRB. The choice of the lead IRB should be dictated by considerations such as the principal institution of affiliation of the principal investigator, the location where the greater part of the research is carried out, the expertise of the constituted IRB, or the location where the largest number of subjects is located.
- 5.41. The primary ethical and scientific assessment should be made by the lead IRB, and copies of its decision should be sent to the other institutions or organizations involved. Each of the IRBs of the other institutions may still give further consideration to ethical and administrative aspects of the research which are specific to their own institutions or organisations.
- 5.42. Researchers should distinguish between core elements of their research (those components of their research that cannot be altered without invalidating the pooling of data from the participating institutions) and non-core elements (those that can be altered to comply with local IRB requirements without invalidating the research proposal).
- 5.43. Researchers should:
- Inform each IRB of all other IRBs at which the research is being proposed and considered at the time of submission of the research proposal.
 - disclose to each IRB any previous decisions regarding the research made by other IRBs; and
 - inform each IRB of whether the proposal has been put to any IRB in the past, or will be in the future, or is presently before another or other IRB or boards.

5.44. IRBs should:

- Coordinate their review of multi-centred proposals and communicate any concerns that they may have with other IRBs reviewing the project.
- Determine how the conduct of multi-centre research will be monitored and the respective roles each of the institutions or organizations and their IRBs will have.

Recommendation 6:

Researchers and institutional review boards should coordinate among themselves the review of multi-centre research programmes. Such coordination should extend to the appointment of a lead institutional review board, and keeping all parties informed of the outcome of all ethics review decisions.

Specific Operating Principles

- 5.45. Impartiality and independence. Although IRBs are appointed and supported by institutions, IRBs owe a public and professional duty to act with total impartiality, objectivity and independence in the discharge of their duties.
- 5.46. If for any reason any member of an IRB, or the board itself should be of the view that there exist circumstances or considerations which make impossible, or impair or adversely affect the impartial, objective and independent discharge of his or their duties, the member or board concerned should decline to review or process the research proposal or proposals in question and immediately report their concerns to the highest level of management of the institution.
- 5.47. Fair review and documentation of decisions. IRBs should provide a fair hearing to those involved. Where there exist any doubts or difficulties with particular aspects of proposals, IRBs should clarify these in writing with the researchers, or in a minuted face-to-face meeting between the board and the researchers.
- 5.48. All discussions of the board should be appropriately minuted, and all opinions recorded. The decisions of IRBs should be provided in written

form, and where appropriate, a fair and frank account of the reasons for those decisions should be provided.

- 5.49. Ethics review by an IRB should be based upon fully detailed research proposals, or where applicable, the most up-to-date progress reports. The proposals or progress reports on which ethics review is based should be drawn up specifically for the purposes of submission for ethical review.
- 5.50. Research proposals should not consist of the same or substantially the same documents submitted by the researchers for the purpose of a proposal for funding. IRBs should bear in mind that research proposals submitted for ethical review are directed at a completely different end to that of proposals submitted for funding purposes.
- 5.51. The requirements of impartiality, fair review, and documentation of decisions should apply equally to IRBs engaged in the continuing review, supervision or audit of a research program.
- 5.52. Conflicts of interest. IRBs and members of IRBs should take especial care to avoid conflicts of interest, whether actual conflict, potential conflict, or only the appearance of conflict as such.
- 5.53. A situation of real, potential or apparent conflict of interest amounts to circumstances which adversely affect the impartiality, objectivity and independence of the IRB or of its members as described above.
- 5.54. In the event that a member of the IRB has a personal interest in the research under review, that member should recuse himself or herself from any consideration of the case by the IRB, and he or she should refrain from offering his or her opinion to the board on the particular research under review.
- 5.55. The IRB member should make full disclosure of such an actual, potential or apparent conflict of interest to the board.
- 5.56. Free and Informed Consent. We recommend that the current statutory and legal requirements relating to the obtaining of free and informed consent of subjects in drug trials be in principle extended to all other kinds of clinical research with appropriate modifications.
- 5.57. Both researchers and IRBs should take especial care to ensure that the proposed human subjects will be able to understand and assess the risks of participation, and that the consent-taking procedure and the documentation are properly designed to achieve this end.

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- 5.58. Both researchers and IRBs should ensure that the participants of research projects are aware that they have the right to withdraw from the research programme at any time.
- 5.59. We recommend that IRBs and institutions formalise arrangements which allow participants a one-stop direct access to the full-time secretariat of the IRB or to a senior officer of the institution charged with quality service standards and control. In this way, participants in research trials can have access to independent officers in order to give feedback on the trial, or to express their concerns.
- 5.60. In the same vein, we further recommend that researchers consider (and IRBs should consider making it a condition of approval) appointing one of their number (who should be a registered medical practitioner or a senior member of the research team) as a one-stop participant contact in all cases where the research programme involves any level of clinical intervention or interaction with the participants, and in cases where the interaction (for example, the collation of medical histories, or physical examination) with participants is delegated to support and field workers or assistants.
- 5.61. A copy of every document signed by research subjects or given to them to read, including the consent documentation, should be given to and retained by the research subjects.
- 5.62. The requirements for free and informed consent as discussed in our Human Stem Cell Report and our Human Tissue Research Report apply to the use of human biological materials in clinical research.
- 5.63. Workload. Institutions should ensure that IRBs are not given a workload that compromises the quality of its work, and IRB should likewise ensure that its workload does not compromise the quality of its review. Where this is likely, it is the obligation of the institution to establish additional IRBs, or to enlarge the membership of the IRB, or make formal arrangements for other IRBs to provide an opinion.
- 5.64. Meetings. IRBs should have regular and frequent formal face-to-face meetings with a defined quorum. The work of the board should not be conducted routinely via circulation of documents. Applications that raise novel, unusual or difficult issues (from the ethical or scientific merit perspectives) or those which present significant risk to participants should be debated and discussed in face-to-face meetings.
- 5.65. Exempted and Expedited Review. IRBs may draw up and provide for exempted or expedited review of research proposals, in a properly-

deliberated and written set of Standard Operating Procedures for the work of the board.

- 5.66. Such expedited or exempted review should be allowed only for classes of research programmes which involve minimal or no risk to the safety, health, welfare and well-being of the participants and which are widely accepted in the research community as being eligible for exempted or expedited review.
- 5.67. The Standard Operating Procedures may allow decisions on applications qualifying for expedited or exempted review to be decided by the chairperson of the IRB or his delegate(s) instead of having to be considered by the whole board.
- 5.68. Examples of cases in which an exemption from review or an expedited review may be permitted are the analysis and publication of the clinical results of a regime of therapy given by a registered medical practitioner to his or her patients in which the regime of therapy is given purely for therapeutic objectives, or the analysis of patient information without any interaction with the patients themselves.
- 5.69. Medical Records and Patient Information. The BAC recognises that the issues arising from access to the use of and the custody of medical records and other patient information is becoming increasingly complex. In this area, the ethical issues are inextricably interwoven with legal considerations, and the impact of the existing law is currently unclear in many situations. We hope to explore these issues in a separate subsequent report.
- 5.70. In the context of institutions such as hospitals with centralised patient records databases, we recommend that IRBs should take steps to determine who should be the proper administrative custodians responsible for patient medical information in the institution, and to establish a system through which the custodians would inform the attending physicians before releasing patients' medical information for the purposes of medical research.
- 5.71. In situations where any of the researchers are also the administrative custodian of patient medical information within the institution, procedures should be established to address potential or apparent conflicts of interest.
- 5.72. Institutions should ensure that clear formal procedures are laid down for the release of all kinds of patient and medical information, and should formulate these procedures in consultation with their ethics committees.

- 5.73. It is desirable that the IRB should have the ultimate authority and responsibility for the ethical clearance of access to patient medical information within the institution, so that no patient medical information may be released for research purposes without clearance by the IRB. Such authority should by necessity also extend over the administrative custodians of patient medical information.

SECTION VI: RESEARCHERS**6. The Responsibilities of Researchers***The general responsibilities of researchers*

- 6.1. Researchers share with institutions and IRBs a primary and central role in the ethical governance of clinical research. More than any other party or parties in the ethical review and governance process, they are in the position of having the fullest access to the facts on which ethical judgments are to be made.
- 6.2. They are responsible for making the threshold decisions in conceiving, designing and putting together a proposed research project. In these decisions, they have the most freedom to shape the proposed research project in a way that gives fullest consideration and respect to ethical considerations, always cognizant of the fact that it is the human subjects whom they study who make their research possible, and are therefore under an obligation to respect and to protect.
- 6.3. IRBs therefore have to depend on researchers to make full material disclosure and give as full an account of the relevant facts as to enable them to make objective, impartial and fully informed ethical judgments.
- 6.4. Accordingly, the primary and ultimate responsibility for the ethical compliance of all aspects of the clinical research in question which involves human subjects rests with the researchers. IRBs bear the responsibility for the overall ethical review and approval of clinical research programmes, as explained in Recommendation 4.
- 6.5. This responsibility of the researcher is a non-delegable and personal responsibility. It is a responsibility which is not and cannot be transferred or delegated to an IRB or any party in the ethics review and governance process merely through the approval of a research proposal by an IRB.
- 6.6. By the same token, researchers remain entirely responsible to ensure that their research complies with all relevant laws as well as legal or regulatory obligations and requirements. Ethical approval given by an IRB is not to be taken as an assurance or representation by the IRB of such compliance, or as an assumption of legal liabilities arising out of the proposed research by the IRB. In short, it is unethical for researchers to treat ethical review boards and the review process merely as “legal insurers”, or as “legal insurance”.

- 6.7. Researchers are primarily and ultimately responsible for making the first judgment as to whether in their own professional judgment, the proposed research is ethical.
- 6.8. Researchers should only submit to ethical review boards proposals for research which they are objectively and professionally satisfied are entirely ethical in all aspects, and are prepared to defend them as such.
- 6.9. Submission of a research proposal to an IRB by researchers amounts to a representation by the researchers to the IRB and to all parties involved in the ethical review and governance process that, in the objective professional judgment of the researchers, the proposed research is ethical in all aspects.
- 6.10. Researchers should not submit the same or substantially the same documents submitted to IRBs for ethical review as that submitted by them to prospective funding agencies for funding. Researchers should bear in mind that research proposals submitted for ethical review are directed at a completely different end to that of proposals submitted for funding purposes, and should draft them accordingly.
- 6.11. Accordingly, in no circumstances should researchers use IRBs and the ethical review process as a means of gaining ethical approval for research projects that the researchers themselves entertain doubts or uncertainties about from the ethical point of view.
- 6.12. We recognise that there may be circumstances in which researchers may in good faith hold the view that the proposed research is ethical, but are nonetheless aware of differing opinions held in good faith by competent peers or an established body of public opinion, or that the proposed research may pose novel risks or other factors whose ethical implications may not be readily quantifiable or ascertained by them.
- 6.13. In such cases, we take the view that so long as the researchers in good faith are of the belief that the proposed research is ethical, then such proposed research may be submitted for ethics review *provided* that the researchers make full disclosure of all such differing opinions known to them, and any potential ethical difficulties or controversies known to them or ethical reservations or doubts held by them, and make disclosure of all other material facts and issues that would help the IRB carry out an impartial and objective review. In such a process, where the researchers in good faith effectively assist the IRB in its attempt to explore all potential ethical issues, and to carry out an impartial and objective review of a novel situation, there is no objection to researchers submitting in good faith for

ethical review a research proposal that the researchers themselves feel that they need ethical guidance.

- 6.14. As for IRBs and members of IRBs, it is important that researchers take special care to avoid any form of conflicts of interest, whether actual, potential, or merely an appearance of conflict as such. Where such actual, potential or apparent conflicts arise, researchers have a duty to make a declaration of the conflict, give full disclosure of the facts giving rise to such conflict, and detail the steps proposed or taken to minimise or avoid the actual or potential conflict of interest, or the appearance of such a conflict of interest.
- 6.15. In no case should any researcher be involved in, or give the appearance of being involved in, the ethics review and approval process of any research project in which he or she is involved in. For instance, a researcher who is a member of an IRB should recuse himself or herself from the review of any research project in which he or she is personally involved, and make a declaration of such an interest to the IRB.
- 6.16. In submitting a proposal for ethical review, *every* researcher involved in the research project should be named as a party and applicant in the proposal.
- 6.17. For the purposes of this Section, we exclude from the definition of researcher persons acting only in an administrative or support capacity, and who are under the direct supervision and control of a researcher. Examples of such research support personnel would be administrative clerks and nurses assisting in clinical duties.

Principal Investigators

- 6.18. It has been the practice in the past to informally refer to all researchers involved in a research project as “Principal Investigators” or “PIs”. We think, however, that this practice causes confusion, especially if a large number of researchers are involved in a research project.
- 6.19. Where a research project involves more than one researcher, we prefer to use the term “investigator” to refer to any one of the researchers generally, and the term “Principal Investigator” to specifically refer to the investigator who has been elected (and who has accepted) the role of Principal Investigator of that research project.
- 6.20. Where a research project is to be carried out by a single researcher, that researcher is the Principal Investigator. Where a research project is to be carried out by more than one researcher, then the researchers must elect

one of themselves to be designated as the Principal Investigator. The Principal Investigator is the researcher who shall be regarded as the lead researcher of the research project.

- 6.21. A research application by a group of researchers working in collaboration with each other should therefore ordinarily be submitted by the researchers in the name of a single Principal Investigator and his or her collaborating Investigators.
- 6.22. It is permissible for a research project to have more than one Principal Investigator. This is especially in a large project, or one with different parts or different (but related) objectives, or one in which the research is to be carried out at many places or trial locations (multi-centre trials). Where more than one Principal Investigator is contemplated, then each and every one of the Principal Investigators shall be held jointly and severally responsible as Principal Investigators.
- 6.23. Principal Investigators have special additional responsibilities over and above that of ordinary researchers.

A definition of the term “Principal Investigator”, and of the role and responsibilities of a Principal Investigator has recently been proposed:

“The Principal Investigator (PI) is the individual responsible and accountable for the design, conduct, monitoring, analyses and reporting of the protocol. The PI assumes full responsibility for the evaluation, analyses and integrity of the research data. The PI must assure that the protocol is followed and the data collected promptly and accurately. The PI assumes specific responsibilities to include: writing the protocol document, assuring that necessary approvals are obtained, monitoring the protocol during its execution, ensure that the protocol is conducted in accordance to the ethical guidelines, and to ensure that all participating investigators on the research teams, involved in implementing the protocol are adequately informed about the protocol and their responsibilities.”

- 6.24. We commend and adopt this definition and summary of the role and responsibilities of a Principal Investigator, and extend it to all clinical research as defined in this Consultation Paper.
- 6.25. In large multi-part or multi-centre or complex research programmes, it is especially critical that the exact roles and responsibilities of each of the researchers in the team should be made clear, and reduced to writing. This makes clear to every researcher what each other’s responsibilities are, and helps in the identification of overlooked areas requiring supervision or direction by a member of the team. Such statements outlining the roles

and responsibilities of each of the researchers in a team should be included in the submission to the ethics committee.

- 6.26. The Principal Investigator(s) shall be responsible for settling, coordinating and formalising the distribution of roles and responsibilities among the researchers in a research programme.

Continuing Responsibilities, Deviation and Variation

- 6.27. The ethical responsibilities of researchers outlined in this section are continuing responsibilities which apply at least for the lifetime of the research project, that is, from the time the research project is submitted by the researchers to the IRB for ethics review, until such time as the research project is deemed to have concluded or been terminated.
- 6.28. When an IRB grants its approval on a research application, it can only make its judgment as to whether approval should be granted to the research application based on the facts and proposals disclosed to it by the researchers in their application. Most significantly, the ethical judgment has to be made *before* the research project begins. Once the project is approved, and the research is underway, researchers often find that variations or departures from the original proposal may be dictated by such considerations as budget, access to subjects, unexpected clinical results and other factors. A research project may also expand in scope, in its objectives, or in the researchers involved – some researchers may resign, or decide to take a less active role, while other researchers may be recruited. Or it may be discovered that a proposed course of action poses greater risks for the proposed subject population than originally assessed, or that the trial has resulted in greater harm (whether of degree or of incidence) than originally contemplated. Or it may be discovered in the course of the trial that some part of the original protocol as proposed in the ethics review application has not been strictly adhered to, although such departure may have been made in good faith by mistake or by necessity, out of consideration for the welfare of the subjects.
- 6.29. As part of their continuing responsibilities, the Principal Investigator(s) in particular is under a strict obligation to *immediately* and in writing seek approval for any changes where such changes have not yet been made, or otherwise report any changes where such changes have already been made, to the IRB by which initial research application was considered and approved. The Principal Investigator(s) shall in their request or report detail the changes, giving their objective assessment of any impact and consequences (both from the clinical and ethical points of view) of the changes.

- 6.30. This continuing obligation of researchers is clearly referred to in the NMEC Guidelines (at paragraph 3.2.5). The Guidelines state that investigators are “bound to act in exact accordance with the details” of the protocol submitted for ethics review, and that investigators are “obliged to report to the [IRB] any adverse events and apparent risks beyond those predicted in the original submission. The investigator should also immediately inform the [IRB] of any new information that might alter the ethical basis of the research programme. The [IRB] should also be notified if the study is terminated prematurely”. We agree entirely with the NMEC in these statements, and adopt them.
- 6.31. The submission of a protocol operates as a representation and agreement by each and every researcher who signs the application that the research programme will be carried out strictly in accordance with the submitted protocol.
- 6.32. Where deviations or changes are substantial, or in every case where the deviations and changes from the original proposal submitted to the IRB has resulted or is likely to result in greater harm or a greater likelihood of harm (whether of degree or incidence) to the subjects involved, the researchers are under a duty to suspend the research immediately, pending their report to the IRB.
- 6.33. Minor changes intended *solely* for the greater safety, health, welfare and well-being of the human subjects taken after consultation with all researchers involved in the trial need not be immediately reported to the IRB. For example, if it appears to a researcher that a particular research subject is not altogether comfortable with one of the planned procedures, that procedure may be dropped and the research programme varied to such extent, without the need for immediate reporting. Reporting of such changes by the Principal Investigator to the relevant IRB should however take place within a set time frame that shall be decided by the IRB. We note, for example, that certain IRBs in institutions in the United States require such changes to be reported in annual updates. However, other changes, minor or otherwise, made for the greater effectiveness of the trial or of its objectives do not fall within this category and should be immediately reported.

Researchers and Attending Physicians

- 6.34. Human subjects for research projects are often recruited from patients who are already receiving treatment from physicians.
- 6.35. Where a proposed researcher is the attending physician, the researcher / physician should be aware of a potential conflict of interest, and of the fact

that their patients may feel obliged to give consent. We repeat and endorse Article 23 of the Declaration of Helsinki, which states that “[w]hen obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship”.

- 6.36. In our view, however, this does not apply to situations where clinicians wish to write up or publish summaries or analyses of the results of their therapeutic interventions or treatment of patients, provided that such interventions and treatment were carried out in the first place purely for therapeutic or diagnostic purposes and in the interests of the patients, and without regard to any consideration for research objectives, or for the subsequent publication of the results.
- 6.37. We further take the view that where researchers are aware that the proposed research subjects are currently receiving treatment or otherwise being attended to by physicians, reasonable efforts should be made on an informal basis by the researchers to contact and inform the attending physicians of the proposed research programme. If the research subjects customarily attend at a hospital or clinic, and are attended to by different physicians on their visits, reasonable efforts should be made on an informal basis to contact and inform the institution concerned, and the consultant or senior person having charge of the department or clinic concerned.
- 6.38. The existence of attending physicians (or the likelihood of the existence of such attending physicians) should be disclosed to the IRB by the Principal Investigator(s), at the time that the research application is being made.
- 6.39. The IRB may then consider whether contacting the attending physicians should be made a formal requirement of ethics approval, upon considerations which should include, but not be limited to, the following:
 - 6.39.1. In the case of research which involves *any* level of clinical interaction with patients, researchers should be formally required to contact and inform the attending physicians, in the interests of ensuring the safety, health, welfare and well-being of the subject patients.
 - 6.39.2. In the case of research which involves access to patient medical records, but with minimal levels of interaction for the purposes of obtaining more information (for instance, interviewing the subject

patient for a history), researchers should still be encouraged to contact and inform the attending physicians, and the IRB may in its discretion make such formal contact and information a condition of ethics approval.

6.39.3. In the case of research which involves access to and a study of patient medical records without any kind of contact at all between the researchers and the subject patients, the IRB need not require researchers to formally contact or inform the attending physicians (on the assumption, of course, that they have complied with all other applicable requirements).

6.39.4. We take the view that efforts to contact and inform the attending physician(s), or the consultant or senior person in charge of the department or clinic concerned, should be made before commencement of the research project. Where this is not possible, such contact must be made as immediately after commencement of the research project as may be practicable, or as the IRB may direct.

6.40. In no circumstances should any researcher alter or modify in any way (whether in formulation, dosage or timing) any drug or other clinical regimen prescribed by the attending physicians of the subject patients, without first seeking and obtaining the approval of both the attending physicians *and* the IRB.

PART D: THE NATIONAL ORGANISATION, ENFORCEMENT AND PROTECTION OF ETHICAL GOVERNANCE

SECTION VII: THE NATIONAL ORGANIZATION OF ETHICAL GOVERNANCE

7. The National Organization Of Ethical Governance

- 7.1. The current regulatory regime governing the review and approval of drug trials (which we described in Section II above) provide for a system in which applications for drug trials are first screened by IRBs at the local institutional level before being forwarded to a national regulatory agency (the CPA of the HSA) for approval. This system has served us well. It is well-understood by all parties involved in the process. We recommend that this system continue to apply in the case of drug trials.
- 7.2. In the case of clinical research other than drug trials there is currently no national agency or regulatory body fulfilling a function equivalent to that of the HSA. The exception is the Ministry of Health, but the Ministry only has jurisdiction over hospitals, private clinics and other institutions falling within its purview under the Private Hospitals and Medical Clinics Act.
- 7.3. The Ministry of Health provides guidance from time to time to IRBs falling within its jurisdiction. For example, it has directed all IRBs to adopt and apply the NMEC Guidelines. From time to time, other directions are issued. Some of these are on the advice of the NMEC.
- 7.4. The role of the NMEC, however, is to advise the Ministry of Health on ethical issues arising in the practice of medicine. It does not advise IRB directly, and does not function as a higher-level appeal or advisory body to IRBs.
- 7.5. Apart from complying with the directives issued by the Ministry of Health (including the NMEC Guidelines), IRBs in institutions under the jurisdiction of the Ministry are free to adopt such procedures, formulate their own Standard Operating Procedures, and determine their constitution, operating principles and other administrative practices.
- 7.6. As a result, there is considerable diversity in the constitution, procedures and practice among IRBs. On the informal feedback that we have received on this point, there is considerable support in favour of there being an

agreed standard model or set of guidelines for all IRBs to follow and apply.

- 7.7. We support this view, as we think that a national standard model or set of guidelines for standard operating procedures for all IRBs is desirable in the interests of promoting consistency and fairness in the decisions, especially in the case of multi-centre research programmes. We think, too, that having a national standard model or set of guidelines will also serve as a quality of service benchmark for all IRBs to judge themselves.
- 7.8. Such a national standard model or set of guidelines can consist of a set of documents issued by a national body or agency. These documents can be modelled on documents such as the SGGCP. The NMEC Guidelines itself is already such a document, but for the fact that it was intended only for the direction of hospitals and institutions falling under the jurisdiction of the Ministry of Health.
- 7.9. Likewise, we think that it would be desirable for all clinical research in Singapore to come under the formal statutory jurisdiction of a national government agency or ministry, as drug trials currently do. We suggest that this government agency could be the Ministry of Health, or the HSA, or the statutory agency proposed for the oversight of human stem cell search, cloning research and human tissue research as announced by the Government.
- 7.10. In addition to coordinating and promoting national standards for IRBs, such a national supervisory agency could also function as the accrediting agency for IRBs. No IRB should be permitted to operate without obtaining such accreditation.
- 7.11. The national supervisory agency should be empowered to conduct audit and investigations into complaints (including complaints from research subjects), and should have the power 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.
- 7.12. The national supervisory agency should be empowered to appoint committees of inquiry to investigate complaints arising from research programmes (including complaints from research subjects) and should have powers to compel the testimony of witnesses and the production of documents (in this, the statutory powers of the Singapore Medical Council in disciplinary proceedings may be used as an example).
- 7.13. The national supervisory agency should also be empowered to work towards developing a code of ethics and principles for the governance of

clinical research. This should be carried out by incremental and evolutionary development, through a process of dialogue and discussion between institutional review boards and the other parties in the research governance process, and having reference to the experiences of the parties involved.

Recommendation 7:

A national supervisory authority should be appointed for the statutory supervision, regulation, accreditation and audit of all IRBs in Singapore.

SECTION VIII: PROTECTION

8. The Protection Of Institutional Review Boards

- 8.1. Notwithstanding the important role played by IRBs in research institutions, IRBs sometimes experience difficulties in attracting members of its choice in that some of the most qualified potential candidates for membership decline the invitation to serve. These candidates may do so out of a fear of legal liability in the event of a contested decision, or a decision which has an unexpectedly adverse impact on human subjects. Few such candidates have any legal training, and their reluctance on this ground is understandable.
- 8.2. On this point, we note that the NMEC Guidelines suggests that IRBs should look to the authority appointing them to give them formal indemnity against the cost of any legal representation, and any compensation ultimately awarded to human subjects. The NMEC Guidelines further recommend that such an indemnity should be given in the letter of appointments of the members.
- 8.3. Members of IRBs discharge an important office in the public interest in the protection of human subjects. Often they do so for minimal or token remuneration, or none at all. Their only motivation being a call to duty, and their only reward being the satisfaction of a job well done.
- 8.4. We take the view that members of IRBs should be fully protected by the law in their discharge of their duties, provided that they do so in good faith, against any liability arising from their actions. Such protection should extend to immunity from liability in tort arising from any claim by human subjects, and to a defence of qualified privilege to any claim in defamation.
- 8.5. Appointing institutions should nonetheless be required to give members of IRBs a full indemnity. Such institutions should remain liable to human subjects from any claim in tort, and should be required to take out appropriate insurance coverage against the variety of claims which may arise in the course of the work of the IRB. For example, in relation to the approval of multi-centre or multinational trials.
- 8.6. We note that such protection would also promote frankness and transparency by the IRB in the discharge of their duties: members would be able to state their opinion frankly without fear of being sued for defamation, and would be able to give researchers a full and frank account of their reasons for rejecting an application. We believe that such full and frank account of reasons for rejection is an important key to helping

researchers understand their ethical obligations, and in helping them to redesign programmes for ethical compliance. Likewise, protection for members would also encourage earlier reporting of negative outcomes or suspicious trends to the authorities for investigation.

- 8.7. Legal protection for members of IRBs acting in good faith would also encourage the best and most competent individuals (both within and outside the medical profession) to contribute their skill and expertise to the IRBs, and help ensure that members are selected from the best available experts in their fields.
- 8.8. Statutory protection may be especially important in encouraging participation by lay non-medical persons to become members of IRBs.
- 8.9. The same protection should also be extended to ethics assurance auditors, ethics investigators or members of committees of inquiry appointed by the national supervisory agency.

Recommendation 8:

Members of institutional review boards should be fully protected by the law in the discharge of their duties, provided that they do so in good faith, against any liability arising out of their actions. Such protection should extend to immunity from liability in tort arising from any claim by human subjects, and to a defence of qualified privilege to any claim in defamation. The same protection should also be extended to ethics assurance auditors, ethics investigators or members of committees of inquiry appointed by the national supervisory agency.

Appointing institutions should nonetheless be required to give members of institutional review boards, ethics assurance auditors, and ethics investigators a full indemnity.

Annexe A

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