RESEARCH INVOLVING HUMAN SUBJECTS

GUIDELINES FOR IRBS

A REPORT BY
THE BIOETHICS ADVISORY COMMITTEE

SINGAPORE

November 2004

FOREWORD

This report, *Research Involving Human Subjects: Guidelines for IRBs*, embodies the third set of recommendations by the BAC, which has been submitted to and accepted by the Life Sciences Ministerial Committee. It follows two earlier reports, the report on *Ethical, Legal and Social Issues in Human Stem Cell Research, Reproductive and Therapeutic Cloning* (June 2002), and the report on *Human Tissue Research* (November 2002).

As biomedical science progresses, research involving human subjects will increasingly gain public interest and attention. Concerns regarding the safety and welfare of research participants and measures taken to protect these participants must be addressed adequately.

The recommendations in this report incorporate many of the existing regulatory standards and practice guidelines governing various aspects of biomedical research involving human subjects. It is hoped that these recommendations will help to maintain the standards of practice in human biomedical research in Singapore comparable with the best internationally.

This Report is the product of the Human Genetics Subcommittee (HGS) of the BAC after a thorough process of research and consultation, which began in April 2003. The BAC is much indebted to the parties, which participated in the consultation process and took time to consider and provide thoughtful feedback. We are pleased to append to this Report a complete record of the representations received. The BAC also sought the views of several local and international experts during its deliberations.

Finally, I would like to thank my fellow Committee members, especially the Chairman of the HGS, Associate Professor Terry Kaan, as well as the members of his Subcommittee, for their commitment and dedication to the project and for ensuring that these recommendations remain a considered, fair and sensitive response to the many difficult issues relating to the ethical conduct of research involving human subjects.

Professor Lim Pin
Chairman
Bioethics Advisory Committee
November 2004

THE BIOETHICS ADVISORY COMMITTEE

Chairman

Professor Lim Pin
University Professor
National University of Singapore

Members

Mr Jeffrey Chan Wah Teck
Principal Senior State Counsel (Civil), Attorney-General's Chambers

Mr Cheong Yip Seng
Editor-in-Chief, English/Malay Newspapers Division, Singapore Press Holdings

Associate Professor John Elliott
Department of Social Work & Psychology, National University of Singapore

Associate Professor Terry Kaan Sheung-Hung
Faculty of Law, National University of Singapore

Ms Lim Soo Hoon
Permanent Secretary, Ministry of Community Development, Youth and Sports

Professor Edison Liu
Executive Director, Genome Institute of Singapore

Mr Richard Magnus
Senior District Judge, Subordinate Courts of Singapore

Professor Ong Yong Yau
Emeritus Consultant, Singapore General Hospital

Professor Kandiah Satkunanantham
Director of Medical Services, Ministry of Health

Professor Tan Chorh Chuan
Provost, National University of Singapore

Mr Zainul Abidin Rasheed
Mayor, North East Community Development Council

About the Bioethics Advisory Committee

The Bioethics Advisory Committee (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 report and on any bioethical issues within the BAC's remit. All feedback should be addressed to:

Bioethics Advisory Committee
20 Biopolis Way
#08-01 Centros
Biopolis
Singapore 138668

Web: http://www.bioethics-singapore.org/
E-mail: *contactus@bioethics-singapore.org*

CONTENTS

PART C: ETHICS GOVERNANCE

ANNEXES

RESEARCH INVOLVING HUMAN SUBJECTS

GUIDELINES FOR IRBS

EXECUTIVE SUMMARY

Principle

1. There is general agreement internationally that human biomedical research involving risk of harm to human subjects should be subject to independent ethics review.

2. This principle is reflected in international documents such as the Nuremberg Code of 1949, the Declaration of Helsinki of 1964 and the International Conference on Harmonisation's "Guideline for Good Clinical Practice" (ICH GCP Guideline) of 1996.

Pharmaceutical Trials

3. In Singapore, pharmaceutical trials are currently governed under the Medicines Act and the Medicines (Clinical Trials) Regulations. All proposals for pharmaceutical trials are required to undergo an independent ethics review process and to comply with the "Singapore Guideline for Good Clinical Practice" (SGGCP), which is based on the ICH GCP Guideline.

4. This independent review is carried out first at the institutional level by the institution's ethics committee or institutional review board (IRB). If approved, the proposal is then submitted to the Health Sciences Authority (HSA), which is the licensing body for pharmaceutical trials. Clinical Trial Certificates will be issued for proposals approved by the HSA.

Human Biomedical Research other than Pharmaceutical Trials

5. Currently, there is no provision requiring human biomedical research other than pharmaceutical trials to be submitted for independent ethics review. This is so even if the proposed research programme entails a risk to the health, safety or welfare of the human subject.

6. Since 1998, the Ministry of Health (MOH) has required all government and restructured hospitals to establish ethics committees or IRBs. Hospitals are required to comply with the "Ethical Guidelines on Research Involving Human Subjects" (NMEC Guidelines) issued by the National Medical Ethics Committee (NMEC) in 1997.

7. The NMEC requires all research protocols that involve human experimentation, whether pharmaceutical trials, trials of new medical devices, new procedures or any other forms of clinical studies that require the participation of human subjects or the use of human tissues or organs, to be submitted to ethics committees or IRBs for review.

8. Considerable changes have taken place since the NMEC issued its guidelines. Most significantly, the volume of human biomedical research other than pharmaceutical trials has increased sharply and now far exceeds that of pharmaceutical trials. There is also a much greater diversity in the kinds of human biomedical research being carried out in Singapore.

Objectives

9. In these Guidelines, we build on the work of the NMEC. Our primary objectives are:

   (a) To review the current system of ethics governance of human biomedical research in Singapore, with particular focus on the processes and procedures;

   (b) To advance recommendations and operational guidelines on the constitution and role of ethics committees or IRBs in the ethics governance of human biomedical research; and

   (c) To provide guidance in Singapore for the promotion of ethically responsible human biomedical research conforming to the best international standards and practice.

10. These Guidelines aim to make clear the roles and responsibilities of IRBs, researchers and institutions in order to achieve objective and independent ethics review of research proposals involving human subjects.

11. In advancing these Guidelines, we also aim to foster a culture of good practice, transparency and accountability for IRBs and the adoption of sound standard operating procedures and other elements of good practice. In doing so, we also aim to encourage the best qualified persons to come forward to serve on the IRB of their institutions.

12. Finally, we hope that in establishing clear and transparent rules, standards and procedures, the reputation of Singapore as a global centre of excellence in biomedical research will be upheld and strengthened.

Does All Biomedical Research Involving Human Subjects Require Ethics Review?

13. In our view, not all biomedical research involving human subjects needs to undergo the full formal process of ethics review. Human biomedical research is of fundamental importance to the advancement of biomedical knowledge, and hence to the public good. A balance, therefore, has to be drawn between the imperatives of advancing and encouraging human biomedical research in the public interest and the need to protect the health, safety, dignity, welfare and privacy of human subjects.

14. It is generally and internationally accepted that some categories of human biomedical research may be either exempted from ethics review (Exempted Review) or may undergo a less formal fast-track ethics review process (Expedited Review) if there is no risk or minimum risk to the human subjects. The adoption of these two categories is consistent with the current practice in the biomedical research and medical communities of leading scientific jurisdictions around the world.

15. In Section III, we review and offer guidelines on the kinds of human biomedical research that ought to be subject to ethics review and on the categories of such research that could be considered for Exempted Review and Expedited Review.

16. We make a distinction between Direct Human Biomedical Research, which involves direct interference or interaction with the physical body of a human subject, and Indirect Human Biomedical Research, which does not involve such direct interference or interaction (for example, populational studies involving only the examination of medical information with no contact or interaction with human subjects). As risks of harm to the health, safety and

welfare are likely to be much less and much more remote in Indirect Human Biomedical Research, we suggest that research proposals of this class could be considered for Exempted Review or Expedited Review.

Applicable Principles

17. In Section IV, we expand on the principles laid down by the NMEC in the NMEC Guidelines and generally on the ethical principles to be applied by IRBs in the ethics review of research proposals.

18. The fundamental objective of having a system of ethics governance for research involving human subjects is the protection of the safety, health, dignity, welfare and privacy of these subjects.

Summary of Main Recommendations:

General

19. All Human Biomedical Research should be reviewed and approved by a properly constituted IRB before it is allowed to proceed. Some research, however, could qualify for Exempted Review or Expedited Review if it involves no risk or minimal risk to the safety, health, dignity and welfare of the research subjects and provided that the protection of the subjects' privacy is strictly observed.

20. It is recommended that all IRBs be formally accredited by the MOH.

21. These Guidelines apply to all Human Biomedical Research wherever such research may be carried out in Singapore, whether or not such research is carried out in an institution under the direct jurisdiction of the MOH pursuant to the Private Hospitals and Medical Clinics Act.

IRBs

22. IRBs are accountable to their appointing institutions and they are responsible for:

(a) The ethics review and approval of proposed Human Biomedical Research programmes;

(b) The continuing review and supervision of the research programmes approved by them;

(c) Reporting to their respective institutions any unusual or unexpected events arising from the research;

(d) Providing feedback to and maintaining dialogue about applicable standards with their constituent researchers; and

(e) Receiving feedback from research subjects.

23. In the ethics review process, IRBs must be aware of any actual, potential or apparent conflict of interest and take reasonable steps to avoid or minimise such conflicts.

24. The scientific review of research proposals does not lie with the IRB. It is for the researchers to satisfy the IRB that an objective review of scientific merit has been carried out and to make these findings (whether positive or negative) available to the IRB.

25. In multi-centre research, a "lead" IRB should be designated from among the IRBs of participating institutions. The lead IRB will play the main role in conducting a full ethics review, in coordinating the research programme and in keeping other participating IRBs informed of any decisions and amendments made during the whole research period. The local portion of a multinational research programme should be subject to review by the local IRB.

Researchers

26. Researchers must comply with all the conditions laid down by the IRB that approved their project.

27. Researchers are also responsible for ensuring that their research complies with all relevant laws and other regulatory obligations and requirements.

28. Researchers are required to inform and seek approval from their IRBs for any proposed variations from the terms of approval of the projects before such variations can be implemented.

29. Researchers should submit annual (or more frequent) progress reports as required by their IRBs, as well as project completion reports and reports of adverse events.

30. Researchers should inform and discuss with the research subjects' attending physicians if the research involves interfering with the subjects' medical management.

Institutions

31. Institutions have the overall responsibility of ensuring the proper conduct of Human Biomedical Research carried out by their employees on their premises.

32. Every institution involved in Human Biomedical Research as defined in these Guidelines should establish and maintain an effective IRB. The institution must accept legal responsibility for the decisions of its IRB. IRBs may be shared by more than one institution. They could also be domain specific, providing more focused and specialised ethics review.

33. Each institution must set up clear policies for the establishment and operation of its IRB. The institution will determine the composition and constitution of the IRB, the specific operating procedures for ethics review and categories of research for Exempted Review and Expedited Review.

34. Institutions are responsible for providing their IRB members with full indemnity.

35. Institutions, in particular those with sizeable research programmes, should have in place programmes for the training and education of their IRB members.

36. Institutions should, in consultation with their IRBs, ensure that clear formal procedures are laid down for the release of all kinds of patients' medical information.

37. Institutions should also ensure that there are adequate resources to enable their IRBs to discharge their duties and responsibilities in an effective and timely manner.

RESEARCH INVOLVING HUMAN SUBJECTS

GUIDELINES FOR IRBS

PART A: INTRODUCTION AND CURRENT FRAMEWORK

SECTION I: INTRODUCTION

1. Introduction

About these Guidelines

1.1. The Bioethics Advisory Committee (BAC) 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. These Guidelines are issued by the BAC and were prepared by the Human Genetics Subcommittee (HGS). The members of the HGS are detailed in Annexe A.

1.3. These Guidelines are the third of a series of recommendations submitted to the Government by the BAC. The first set of recommendations issued by the BAC dealt with human embryonic stem cell research and cloning. These recommendations were issued in a Report entitled "Ethical, Legal and Social Issues in Human Stem Cell Research, Reproductive and Therapeutic Cloning" ("Human Stem Cell Report") in June 2002. The second set of recommendations dealt with issues arising from human tissue banking and human tissue research and was issued in a Report entitled "Human Tissue Research" ("Human Tissue Research Report") in November 2002.

1.4. These Guidelines were shaped and informed by feedback and suggestions received by the BAC on a Consultation Paper entitled "Advancing the Framework of Ethics Governance for Human Research" released on 16 September 2003 to 37 bodies concerned with the ethics governance of human biomedical research. The Consultation Paper is set out in Annexe B, the 37 bodies are listed in Annexe C and the responses to the Consultation Paper are set out in Annexe D. Annexe E is a summary of the dialogue session with the hospital ethics committees or institutional review boards (IRBs), which was held on 7 November 2003.

1.5. Where common ground is covered in these Guidelines and the earlier Reports issued by the BAC, it should be understood that the more particular and specific recommendations made in the earlier two Reports in relation to human embryonic stem cell research, human cloning and human tissue research should prevail.

Objectives

1.6. Our objectives in advancing these Guidelines are:

(a) To review the current system of ethics governance of human biomedical research in Singapore, with particular focus on the processes and procedures;

(b) To advance recommendations and operational guidelines on the constitution and role of ethics committees or IRBs in the process of ethics governance of human biomedical research; and

(c) To provide guidance in Singapore for the promotion of ethically responsible human biomedical research conforming to the best international standards and practice.

SECTION II: THE CURRENT FRAMEWORK

2. The Current Framework

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 some of the principal achievements in the modern history of the human race. In the main, such advances in biomedical knowledge have been beneficial and are considered to be research conducted in good faith for the benefit of humankind.

2.2. Events during World War II, however, gave rise to concerns that research conducted on human subjects should be subject to agreed ethical norms. The Nuremberg Code[1] 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 research on human subjects.

2.3. These ethical norms were given full consideration and description in the World Medical Association's Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects,[2] 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

[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.

each experimental procedure involving human subjects should be clearly formulated in an experimental protocol" and that this protocol should be submitted to an independent ethics 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 and by other medical communities in the great majority of nations. In Singapore, the need for ethics committees or IRBs and the requirement for the ethics review of research proposals involving human subjects have long been an accepted and integral part of biomedical research in the institutional setting.

2.7. The principles of the Declaration of Helsinki today find expression in regulatory standards and practice guidelines governing various aspects of clinical research such as those contained in the Medicines (Clinical Trials) Regulations, promulgated pursuant to Section 74 of the Medicines Act (Cap. 176), the "Singapore Guideline for Good Clinical Practice" (SGGCP) and the "Ethical Guidelines on Research Involving Human Subjects" (NMEC Guidelines) issued in August 1997 by the National Medical Ethics Committee (NMEC). We discuss these regulatory standards and practice guidelines in detail below.

Pharmaceutical Trials in Singapore

2.8. In Singapore, pharmaceutical trials involving the testing of drugs on human subjects are regulated by the Health Sciences Authority (HSA). The HSA regulates the conduct of pharmaceutical trials under the Medicines Act and the Medicines (Clinical Trials) Regulations (2000, Revised Edition). Under the Medicines Act, these pharmaceutical or drug trials are known as "clinical trials".

2.9. The system of regulation requires that sponsors and researchers conducting pharmaceutical trials obtain both ethics and regulatory approval before initiating a study.

2.10. The current approval system is sequential. Approval from the HSA is sought only after the relevant hospital ethics committee has approved an application. Regulatory approval is provided in the form of a Clinical Trial Certificate issued by the HSA to the applicant.

2.11. The HSA, in deciding the regulatory approval for a pharmaceutical trial, consults an expert advisory committee known as the Medical Clinical Research Committee (MCRC). The MCRC 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" (Section 1.37 of the SGGCP). It currently comprises five members, all of whom are clinical specialists.

2.12. In this way, pharmaceutical trials are subject to ethics review at more than one level.

2.13. Additionally, pharmaceutical trials are also required to conform to the SGGCP issued by the MOH in 1998. The SGGCP is a set of guidelines adapted from the 1996 "Guideline for Good Clinical Practice" of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH GCP Guideline), which is the international gold standard for conduct of pharmaceutical trials. Accordingly, the SGGCP reflects best international practice in its approach to the governance of pharmaceutical trials. Since 1998, the SGGCP has been incorporated by reference in Regulation 21 of the Medicines (Clinical Trials) Regulations. Sponsors and researchers in pharmaceutical trials are required by law to comply with the SGGCP unless specifically exempted under the Medicines (Clinical Trials) Regulations.

2.14. The SGGCP sets out in detail a framework for the ethics governance of pharmaceutical trials. The SGGCP begins its statement of applicable principles by declaring that "[c]linical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki" (Section 2.1).

2.15. Section 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."

2.16. The SGGCP sets out detailed guidelines as to the roles and duties of researchers and sponsors in a pharmaceutical trial, and lays down requirements such as monitoring procedures, audits and other matters to be included in trial protocols.

2.17. Of note are the provisions in Part 3 of the SGGCP requiring all pharmaceutical trials to be reviewed and approved by the hospital ethics committees concerned and the MCRC of the HSA before a Clinical Trial

Certificate will be issued. The responsibilities, composition, functions and operations of the MCRC are set out in detail in Section 3.1 of the SGGCP, while those of the ethics committee are detailed in Section 3.2.

2.18. In keeping with the principles of the Declaration of Helsinki, the Medicines (Clinical Trials) Regulations require researchers to ensure that free and informed consent be obtained from the potential research subject and that researchers are under a duty to fully inform the subject by explaining, among other issues, the risks and objectives of the proposed pharmaceutical trial.

Human Biomedical Research other than Pharmaceutical Trials

The Ethics Governance of Human Biomedical Research other than Pharmaceutical Trials

2.19. While the ethics governance of pharmaceutical trials in Singapore is comprehensively and appropriately regulated by statutory rules and practice guidelines, the picture for the ethics governance of human biomedical research other than pharmaceutical trials is less clear.

2.20. Currently, there is no statutory scheme for the ethics governance of human biomedical research apart from pharmaceutical trials. In Section III, we define and explain "Human Biomedical Research".

2.21. Indirectly, however, the MOH has long exercised jurisdiction over, and given informal ethical guidance on, human biomedical research carried out in hospitals, clinics and clinical laboratories in its role as the statutory regulator under the Private Hospitals and Medical Clinics Act.

2.22. In January 1994, the MOH set up the NMEC, a national-level policy advisory body, to "assist the medical profession in addressing ethical issues in medical practice and to ensure a high standard of ethical practice in Singapore."[3]

2.23. 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."[4]

[3] "National Medical Ethics Committee: A Review of Activities, 1994-1997" published in 1998, page 1
[4] Ibid.

2.24. Several sets of ethics guidelines were issued by the NMEC and adopted by the MOH. In the sphere of ethics governance of human biomedical research, the most significant of these ethics guidelines is the NMEC Guidelines.

2.25. In a written directive dated 25 June 1998 (Directive), the MOH required all government and restructured hospitals to set up hospital ethics committees (if they had not already done so) for the ethics governance of research involving human subjects. Before 1998, the practice of reviewing research proposals involving human subjects by hospital and medical institution ethics committees in Singapore was not governed by any formal rules or directives.

2.26. We quote from the Directive:

"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 clinical trials or 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."

2.27. The NMEC Guidelines set out in detail suggested principles of the ethics governance of research involving human subjects, the constitution of ethics committees and the implementation of the framework for the ethics governance of biomedical research. These NMEC Guidelines represent the principal controlling document governing research involving human subjects in Singapore today, but despite this they remain non-directive in nature.

2.28. 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, ethics governance of biomedical research involving human subjects at that time.

2.29. We have reviewed the NMEC Guidelines and have no hesitation in using them as a basic framework for these BAC Guidelines. Although the NMEC Guidelines were formulated in the restricted context of research carried out by the medical profession, we are of the view that the principles they espouse are appropriate for all human biomedical research, whether such research is carried out by the medical profession or by others. We also take the view that the same principles should apply to all human biomedical research wherever such research may be carried out in Singapore, and whether or not such research is carried out in an institution under the direct jurisdiction of the MOH pursuant to the Private Hospitals and Medical Clinics Act.

The Future of Human Biomedical Research

2.30. Until recently, the vast majority of human biomedical research (whether pharmaceutical trials or research other than pharmaceutical trials) were carried out by researchers who were medical practitioners registered under the Medical Registration Act (Cap. 174), in government medical institutions directly controlled by the MOH 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 MOH.

2.31. In recent years, however, the development of the biomedical industry in Singapore has led to an increasing proportion of human biomedical research other than pharmaceutical trials. In 2002, for example, hospital ethics committees of the five main restructured hospitals reviewed nearly three times as many applications for such research as they did for pharmaceutical trials.

2.32. Human biomedical research increasingly tends to be institution-driven, rather than being researcher-driven (the traditional model assumed in the current regulatory regime). Institution-driven pharmaceutical trials received by the HSA now outnumber researcher-driven pharmaceutical trials.

2.33. Concomitantly, an increasing proportion of human biomedical research is now conducted outside the traditional paradigm assumed by the current regulatory environment: many research projects are now led by researchers who, although being qualified and competent for the research 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 MOH. Such entities include companies and other commercial entities in the biomedical industry, research institutes and statutory agencies with an interest in the biomedical industry.

2.34. The vast majority of these new players in the field of human biomedical research in Singapore are keenly aware of the need for proper ethics governance. Most researchers are anxious to conform to internationally accepted standards for ethics governance. In many cases, researchers are involved as collaborators in multinational or multi-centre (or both) biomedical research projects.

2.35. With the development of the biomedical sector in Singapore, new avenues of biomedical inquiry are rapidly emerging. The traditional categorisation of research for ethics governance, which separates research into pharmaceutical trials and non-pharmaceutical trials, is becoming irrelevant and obsolete. Some new kinds of research may blur the border between these two categories. New kinds of biomedical research include trials of medical devices, experimental therapeutic procedures (which may or may not involve drugs), new modes of non-drug treatment and new diagnostic methods. Other increasingly important research includes epidemiological or population studies (which may or may not require invasive interaction with human subjects), genetic screening, genetic research and research that involves no direct interaction with human subjects but only access to their medical, personal or genetic information.

PART B: HUMAN BIOMEDICAL RESEARCH

SECTION III: HUMAN BIOMEDICAL RESEARCH

3. Human Biomedical Research

Defining Human Biomedical Research

3.1. In this section, we consider what kinds of human biomedical research ought to be subject to the framework of ethics governance that we recommend in these Guidelines.

3.2. In keeping with our terms of reference, we consider only such human biomedical research that involves an interaction (whether direct or otherwise) with a human subject or human biological material, and therefore exclude any human biomedical research in relation to:

(a) Genetically modified organisms;
(b) Animals and their treatment; and
(c) Economic, sociological and other studies in the disciplines of the humanities and social sciences.

3.3. Human biomedical research is a term capable of a very broad definition. In our review of the approaches taken by national ethics bodies or agencies in other countries, we have found that there is considerable variation in what is to be included in the definition of human biomedical 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, while in other jurisdictions this requirement does not apply.

3.4. Currently, there is no international agreement on the exact scope of human biomedical research that should be subject to IRB review. But that is not to say that there is no agreement at all on what should be subject to IRB review. Clearly, there is universal and unanimous agreement in all reputable research communities that research involving direct physical interference or interaction with human subjects, and where such direct physical interference or interaction may result in death, injury or other physical or emotional harm to the research subject, must be subject to proper IRB review. These core values and principles are captured in international documents such as the Nuremberg Code, the Declaration of Helsinki and the ICH GCP Guideline.

3.5. At the edge of this core of certainty, however, international consensus is still in a state of development. Increasingly, human experimentation and human biomedical research have moved away from direct physical interference or interaction with human subjects themselves, towards research conducted largely on cell lines, tissues or other bodily samples given by human donors, and on medical information derived from patients and other human subjects.

3.6. Increasingly, it is the case that there is no direct physical contact at all between the researchers and the human subjects. In such circumstances, there is no possibility of physical injury or harm befalling the human research subjects. In these situations, the ethical, legal and social concerns centre not on the possibility of physical injury or harm but on the larger penumbra of *indirect* harms to the patient or donor such as the breach of the patient's or donor's expectation of confidentiality of his medical information, or his expectation that his tissue should not be used for research without his consent.

3.7. It is therefore appropriate that a fundamental distinction be made between:

(a) Direct Human Biomedical Research. This comprises any kind of human biomedical research that involves any direct interference or interaction with the physical body of a human subject, and that involves a concomitant risk of physical injury or harm, however remote or minor. A research programme which involves the administration of any drug (whether it is for the purpose of testing the effects or efficacy of the drug, or whether it is a means for establishing any other objective of the research programme), the trial or use of a medical device on a human subject, or any test of a human subject's physiological, emotional or mental responses (not being tests conducted for diagnostic purposes with a view to the therapeutic management of a patient) all qualify as Direct Human Biomedical Research; and

(b) Indirect Human Biomedical Research. This comprises any research (not qualifying as Direct Human Biomedical Research) 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.

3.8. For the purposes of these Guidelines, we define Human Biomedical Research as Direct Human Biomedical Research and Indirect Human Biomedical Research taken together.

Ethics Review of Direct Human Biomedical Research

3.9. Every research programme involving Direct Human Biomedical Research should be reviewed and approved by a properly constituted ethics committee or IRB.

Ethics Review of Indirect Human Biomedical Research

3.10. There is currently no international consensus on what kind of Indirect Human Biomedical Research needs to be formally reviewed by an IRB. Laws, social attitudes and concerns, and ethical formulations vary from jurisdiction to jurisdiction.

3.11. Subject to the recommendations set out in our earlier Reports (the Human Stem Cell Report and the Human Tissue Research Report), we recommend that every research institute have clear policies for the ethics review (full, exempted or expedited review) of all categories of research involving Indirect Human Biomedical Research, as set out below.

Exempted Review and Expedited Review of Human Biomedical Research

3.12. Not every proposed programme of Human Biomedical Research requires a full review. In some cases, such a requirement would introduce unnecessary bureaucracy and might also discourage valuable research. For many kinds of Human Biomedical Research (particularly Indirect Human Biomedical Research) that involve minimal or remote risks to the safety, health, welfare or other interests of the patient or human subject, there is widespread agreement that a full review is unnecessary. In such cases, research institutions may have specific categories of Human Biomedical Research that may be exempted from IRB review (Exempted Review) or permitted expedited review (Expedited Review). We further discuss these categories of review below.

Exempted Review

3.13. Exempted Review should in general only be permitted for categories that are widely accepted by the community as being eligible for Exempted Review.

3.14. There can be no hard and fast rule dictating which categories of Human Biomedical Research ought to be allowed exemption from review, and which categories ought to undergo full review. Each institution should determine for itself, after due deliberation and consultation with its IRB, the categories of Human Biomedical Research that could be exempted from ethics review. The most important consideration is that there should be no likelihood of harm to the research subject.

3.15. In general, we suggest that categories for Exempted Review should be drawn from categories of Indirect Human Biomedical Research. By way of illustration, the following categories of Indirect Human Biomedical Research could be considered for Exempted Review, taking into account current practice:

(a) Writing up or reporting of individual patients' clinical results by the patients' doctors, provided that the patients' consent for procedures and interventions in clinical management have been obtained and the patients' privacy protected, for example, the review of a clinical programme that includes demographic, clinical and outcome parameters, which are useful in the audit of the programme; or the review of a procedure or treatment (a surgical technique or drug treatment outcome) by a physician or surgeon, where the choice of the drug or technique is based on the clinical judgment of the physician or surgeon and on best practices and not on any randomisation procedure. Researchers who are not the attending physicians in the programme but wish to have access to such information should send their proposals to the IRB in the usual way;

(b) Research using appropriately designed data escrow or other arrangements in which personal or other identity information is securely withheld from researchers by a third party provider of information, there being no possibility of researchers by themselves being able to trace or reconstruct significant information on the identity of subject donor;

(c) Research using established commercially available cell lines or commercially available anonymous DNAs, RNAs and fixed tissues; and

(d) The development of diagnostic tests using existing samples for test validation purposes provided that the necessary consent for the taking and use of the samples has been obtained.

Expedited Review

3.16. Some categories of research programmes may be permitted a less formal process of review than that of a standard full review. For example, the Chairperson or other IRB delegate(s) (the reviewer) may be empowered to conduct Expedited Review.

3.17. The same principles and general considerations set out above in relation to the categories of Human Biomedical Research that qualifies for Exempted Review also apply to IRBs' determination of categories permitted Expedited Review. Research qualifying for Expedited Review should present no more than minimal risks to research subjects.

3.18. By way of illustration, the following categories of Human Biomedical Research could be considered for Expedited Review, taking into account current practice:

(a) Minor changes to previously approved research;

(b) Annual reviews of previously approved research in which there has been little or no change in the on-going research;

(c) The analysis of patients' information without interacting with the patients. Researchers may be allowed access to medical records only if the IRB is satisfied that there is potential scientific / medical benefit of the research and that the researchers will take appropriate measures to protect the privacy of the individuals;

(d) The local portion (at the level of specific institutions) of a multi-centre or multinational research programme that has already received a full review and approval by the lead IRB (as elaborated in paragraphs 5.49 to 5.56 of this Report); and

(e) Research involving human tissues from tissue banks. IRBs must be satisfied that the tissues are obtained from a reliable source in which consent has been obtained for the tissues to be used for research and that the donor's privacy is protected.

Stem Cell Lines

3.19. We make clear that all research involving the use of human embryonic stem cell lines or the creation of such human stem cell lines requires full ethics review.

Cadaveric, Foetal and Legacy Tissues

3.20. We reiterate that nothing in these Guidelines is intended to displace the recommendations we advance in our Human Tissue Research Report. We take the view that human biomedical research to be conducted on legacy tissue as defined in our Human Tissue Research Report should always be subject to full review. In the case of other tissues donated with the free and informed consent of living donors, or of cadaveric or foetal tissue donated under the Medical (Therapy, Education and Research) Act, review should be considered, but Expedited Review may be allowed as appropriate, provided always that the use of the tissue concerned is within the terms of the gift of the tissue.

Therapy versus Research

3.21. In Section 2.2.1 of the NMEC Guidelines, it is stated 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".*

3.22. In its Guidelines, the NMEC also considered the relationship and distinction between research and therapy. It 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 /

investigator. The patient is always entitled to the best clinical management, and research considerations must never override this." (Section 2.2.2)

3.23. We agree with these NMEC statements and adopt them.

3.24. We therefore exclude therapeutic activities undertaken with the sole intention of benefiting the patient from our definition of Human Biomedical Research. In this respect, we note that medical therapy is already subject to regulation by the MOH under the Medical Registration Act (Cap. 174) and the Private Hospitals and Medical Clinics Act (Cap. 248).

Legal Considerations

3.25. In advancing these recommendations, we make clear that we do so only from the perspective of ethics governance. In working out institutional policies for Exempted Review, Expedited Review and Full Review of Human Biomedical Research, it is essential that institutions take into account not only ethical considerations, but also the requirements of the law, as well as social attitudes. Mere compliance with these Guidelines or any other ethical or professional standards or guidelines does not guarantee compliance with the law, as the law may prescribe a different and higher standard in specific situations. The converse may also apply. At minimum, institutions should ensure that their decisions and actions are consistent with the law and do not infringe on the rights and protection afforded to human subjects and patients by the law.

3.26. Institutions should take into account not only ethical considerations, but also the requirements of the law and social attitudes.

Savings

3.27. We make clear that nothing in these Guidelines 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 these Guidelines are intended to supplement those advanced in our first two Reports.

Exceptional Situations

3.28. 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, it should be permissible for IRBs in consultation with the proper authorities such as the MOH, 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.

3.29. We also exclude from ethics review procedures and requirements all clinical audit and quality assurance activities, which require the institution to review patients' information and are conducted for the sole purpose of improving the quality of patient care within that institution.

3.30. We therefore recommend that all Human Biomedical Research as defined in this section, save for the exceptions expressly provided above, be subject to review and approval by and to the continued supervision of an IRB in accordance with the principles discussed in Section IV.

PART C: ETHICS GOVERNANCE

SECTION IV: PRINCIPLES OF ETHICS GOVERNANCE

4. Principles of Ethics Governance

The Purpose of Ethics Governance

4.1. Article 5 of the Helsinki Declaration states: "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." Article 8 of the Declaration states: "Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights."

4.2. Continuing human biomedical 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, Human Biomedical Research has 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 leads to new scientific insights, which when coupled with continuing human biomedical research leads to a virtuous circle that supports and advances biomedical knowledge to the benefit of both individuals and society at large. 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 ethics governance in relation to biomedical research is to ensure the protection and assurance of the safety, health, dignity, welfare and privacy of human research subjects and to safeguard against research practices and objectives that are not ethically acceptable to society at that point in time.

4.5. But as with most kinds of diagnostic, prophylactic or therapeutic interventions, most forms of human biomedical 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 involve an assessment and balancing of the potential harms and benefits. In general, human biomedical 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 privacy of the human subject and the ethical standards of society at that point in time.

4.7. To this end, a system of ethics governance must ensure that there is a proper assessment and weighing of the potential harms against the potential benefits of all human biomedical research, in accordance with the ethical values of the community. A proper system of ethics governance serves to strengthen public confidence in human biomedical research by ensuring that all forms of human biomedical research conform to the accepted body of ethical values of the community.

4.8. These fundamental ethical values 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's "Universal Declaration on the Human Genome and Human Rights" (1997) and the WHO's "Proposed International Guidelines on Ethical Issues in Medical Genetics and Genetic Services" (1998).

4.9. In Singapore, these same principles are found or reflected in regulations such as the Medicines (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.

4.10. 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."

4.11. 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.

4.12. In the interests of consistency and fairness of the judgments of IRBs, a code of applicable principles for ethics governance should eventually be formulated for the common guidance of IRBs, research institutions, researchers, the human research subjects and all other parties involved in human research.

4.13. 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 IRBs 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.

4.14. We take the view that it is part of the function of a responsive and dynamic system of ethics 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.

4.15. We emphasise that it is not the intention of this document to prescribe the specific ethical principles to be applied by IRBs and researchers in the process of ethics governance. We believe that these are professional

judgments that are appropriately and properly left to members of IRBs, researchers and other parties involved in the process of ethics governance.

4.16. We note, however, that certain broad ethical principles are universally accepted and applied in all the leading research jurisdictions. We find it appropriate and desirable for IRBs, researchers and other parties involved in the process of ethics governance to consider taking these ethical principles into account.

4.17. Such principles, in addition to or in elaboration of those identified by the NMEC, include:

(a) 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.

(b) Respect for free and informed consent. This principle is discussed at length in our Human Stem Cell Report, our Human Tissue Research Report and the NMEC Report (Section 2.5). In addition, the Medicines (Clinical Trials) Regulations and the SGGCP recommend strict requirements regarding consent.

(c) 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.

(d) Respect for vulnerable persons. This is discussed in Sections 2.5.5 and 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 physical conditions or other circumstances, such as being in a dependent relationship.

(e) 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 researchers and IRBs.

SECTION V: INSTITUTIONAL REVIEW BOARDS

5. Institutional Review Boards

The Role of Institutional Review Boards

5.1. Ethics review bodies having the first responsibility for ethics review in the ethics 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 most commonly used.

5.2. We prefer instead the term "Institutional Review Board" (IRB). 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 level 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" best reflects this role.

5.3. We differentiate here between IRBs that review, approve and supervise biomedical research involving humans, and hospital ethics committees that address issues arising out of clinical practice (clinical practice ethics committees). For the avoidance of doubt, we make clear that our recommendations in these Guidelines cover only IRBs that review, approve and supervise Human Biomedical Research, and are not intended to apply to clinical practice ethics committees.

5.4. We further clarify that the term "institution" is not limited to hospitals or medical clinics, but also includes any organisation or entity that carries out Human Biomedical Research as defined in these Guidelines. This includes commercial entities and government agencies.

5.5. We recognise that valuable Human Biomedical Research is also carried out by biomedical researchers who have no formal affiliation with IRB-guided institutions. Such biomedical researchers include medical practitioners in private practice (such as specialist consultants and general practitioners), and biomedical researchers who are employed by or who are affiliated with institutions that do not have and do not propose to constitute an IRB because of the low volume of Human Biomedical Research carried out by their employees or affiliates. In the case of registered medical practitioners and specialists in private practice, we suggest that they seek ethics approval for the conduct of their proposed research from the IRBs of

appropriate hospitals or other medical institutions. This approach could also be applied to biomedical researchers who are not registered medical practitioners. In any event, the requirements for appropriate ethics review as defined in these guidelines should apply regardless of the institutional affiliation of researchers.

5.6. There is universal agreement in all developed countries that IRBs are central to a proper framework of ethics governance of human research and that the primary objective of an IRB is to protect and assure the safety, health, dignity, welfare and well-being of human research subjects, in keeping with the principles outlined above.

5.7. Increasingly, collaborative research programmes are carried out across international borders (in multinational 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 multinational or multi-centre collaboration research programmes.

5.8. From this viewpoint, the harmonisation of our national ethics governance framework with that in leading research jurisdictions is of national strategic importance.

5.9. The ultimate responsibility for the ethics compliance of human biomedical research rests with the researchers who carry out the research, and with the institution that sanctions the research or in which research is carried out.

5.10. The IRB is the vehicle through which such institutions act to implement a proper system of ethics governance of research carried out in such institutions.

5.11. We accordingly recommend that every institution that conducts Human Biomedical Research, or allows such research to be carried out on its premises, or on its patients, or involving access to or use of human tissue collections in its custody, or involving access to or use of medical records or other personal information in its custody, should establish and maintain an effective IRB.

Shared and Domain Institutional Review Boards

5.12. 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 for research proposals to be considered by the IRBs of larger institutions.

5.13. Alternatively, it is permissible for several such institutions to jointly appoint a shared IRB.

5.14. Even in cases of institutions that 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 that 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, special competence and knowledge in their field of specialisation.

5.15. We note that some hospitals and institutions in Singapore have set up domain specific IRBs with the intention of providing more focused and specialised ethics review. For example, sister or subsidiary institutions under the direction and control of a parent institution may choose to organise IRBs along domain lines, which can be shared by all the related institutions within the group. Such an arrangement is acceptable to us, as it is entirely in keeping with the ethical principles we have set out. Under this arrangement, the parent institution for all the hospitals and other institutions within the group will be responsible for constituting the necessary IRBs for all its constituent institutions and arranging for the accreditation of the IRBs.

5.16. We have no objections to other groups of research institutions adopting such a similar approach, provided that the terms of the arrangement between the institutions are clearly spelt out.

5.17. We therefore recommend that related institutions under the direction and control of a parent institution should be permitted to share an IRB or IRBs constituted by the parent institution.

The Responsibilities of Institutional Review Boards

5.18. 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.

5.19. Accordingly, we emphasise that the institution is responsible for the acts and decisions of the IRB(s) that it appoints.

5.20. Ethics Review Gateway. The fundamental responsibility of an IRB is to act as an ethics review gateway for all Human Biomedical Research carried out under the auspices of its appointing institution, with the primary objectives of the protection and assurance of the safety, health, dignity, welfare and well-being of human research subjects. An IRB has a duty to ensure that all Human Biomedical Research carried out under the auspices of its appointing institution are ethically acceptable, and to comply with the principles outlined in Section IV.

5.21. Review of Scientific Merits. A review of the scientific merits of any proposed programme of Human Biomedical Research is an integral part of a proper assessment of the ethical acceptability of the programme. A research programme with little or no scientific merit is ethically unacceptable.

5.22. In its assessment of the ethical acceptability of any proposed research programme, an IRB will need to be satisfied that an objective review of the scientific merits of the proposed programme of research has been carried out, and that there is sufficient evidence of scientific merit before the IRB makes a decision on the ethical acceptability of the proposed research programme.

5.23. The IRB is not responsible for carrying out the scientific review of research proposals. It is for the researchers to satisfy the IRB that an objective review of scientific merit has been carried out, and that the findings (whether positive or negative) of any review of scientific merit are made available and are fully disclosed to the IRB.

5.24. The review of scientific merits may be carried out by such committees, bodies or agencies as the IRB may in its judgment recognise as appropriate. Thus such reviews may be carried out by a scientific review committee constituted by the appointing institution or by the funding agency.

5.25. We note that it is an accepted practice for the initial scientific review to be carried out by or for the agency that funds the research. When the grant funding agency is satisfied with the scientific merits of the proposed programme of research, it then gives in-principle approval on the condition (among others) that ethics approval is granted by the appropriate IRB. In such cases, IRBs may rely on the review of scientific merits carried out by or for the grant funding agency, on the proviso that IRBs must make their own determination as to the sufficiency and adequacy of the review of scientific merits that has been carried out. In these cases, IRBs should be empowered to require a more extensive or rigorous review of the scientific merits if deemed necessary.

5.26. In addition, appointing institutions may give IRBs authority for:

(a) Continuing Review and Supervision. The institution has an overall duty to ensure that approved research programmes are conducted in accordance with the terms of the approval. We elaborate on this responsibility in Section VII. IRBs may assist the appointing institution in the discharge of this duty, but such delegation will have to be made clear in the terms of constitution of the IRB. Such delegation should only be made if the IRB is given sufficient resources to carry out such a responsibility. In this responsibility, IRBs will require Principal Investigators (PIs) to submit annual (or more frequent) progress reports and final reports within three months of completion of projects. PIs will also have to inform and seek approval from IRBs for any proposed deviations from the terms of approval of the projects before they can be implemented except when they are necessary to eliminate immediate hazards to participants, or when the changes involve only logistical or administrative aspects of research, in which case IRBs should be informed within seven days. 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 or continuation of the research programme.

(b) Reporting and Feedback. IRBs will require PIs to inform them of unusual or unexpected events within 15 days of occurrence and report such events to the appointing institutions. Another major aspect of the role of IRBs is to provide feedback to and maintain dialogue about application standards with their constituent researchers. In the discharge of their role, IRBs can and should also act as the key institutional agency that receives and reports to their appointing institutions on concerns and feedback expressed by research subjects.

5.27. 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.

5.28. We therefore recommend that IRBs should have responsibility for the ethics review and approval of proposed Human Biomedical Research programmes on behalf of their appointing institutions. This should take into account the scientific merits of the proposed research.

5.29. Additionally, as institutional resources may permit, and on the mutual agreement of IRBs and their appointing institutions, IRBs may also be given authority by their appointing institutions for:

(a) The continuing review and supervision (including evaluation of feedback from research subjects) of Human Biomedical Research programmes approved by them;

(b) The receiving of feedback from research subjects and the providing of feedback to researchers; and

(c) The reporting of unusual or unexpected events arising from the Human Biomedical Research programmes carried out under the auspices of its appointing institution to the management of that institution.

The Constitution of Institutional Review Boards

5.30. IRBs should be established at the highest administrative level 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.

5.31. The IRB should be appointed by and report to at least an authority at the level of the Chief Executive Officer (as recommended by the NMEC Guidelines in the case of hospitals falling under the jurisdiction of the MOH pursuant to the Private Hospitals and Medical Clinics Act) or senior management.

5.32. 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 institutions work with their standing IRBs to appoint special subcommittees co-opting experts or reviewers to assist the standing IRBs 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.

Composition

5.33. We are of the opinion that the SGGCP (in particular Section 3.2.3) and the NMEC Guidelines (in particular Section 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.

5.34. In addition, we propose to highlight certain general requirements for the composition of an IRB:

(a) Impartiality and objectivity are fundamental principles to be observed in the appointment of members to IRBs. An IRB should be carefully composed in order that there can be no room for any public perception that it is not independent of those who are required to submit to its review;

(b) Where a majority of the IRB members are drawn from within the appointing institutions, these persons should be the institutions' most senior, most respected and scientifically competent officers, researchers or consultants, who possess the appropriate experience and training;

(c) An IRB should include non-medical and/or non-scientific persons (lay representation) who are not members of or otherwise associated with the appointing institution of the IRB. Their inclusion is to reinforce the impartiality and objectivity of the work of the IRB;

(d) To further reinforce the independence of the IRB and to ensure that the decisions of the board are carried out in accordance with scientific thinking accepted within the community, external representation may include specialists of favorable reputation from other institutions; and

(e) Lay representation may include respected lay members of the community and 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.

5.35. 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 IRB, there will be at least one specialist or expert (and preferably more) on the IRB who may give a specialist viewpoint as needed.

Institutional Conflicts of Interest

5.36. In the relationship between an institution and its IRB, the fundamental underlying principles are the independence of the IRB in the exercise of its powers and duties, and its ethical integrity.

5.37. The research programmes that 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 any potential or apparent conflict of interest involved and take reasonable steps to avoid and minimise the conflict.

5.38. It is for this reason, among others, that we have recommended that IRBs report directly to the highest level of management of their institutions.

5.39. 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.

5.40. To facilitate greater understanding and in keeping with the ethical principle of informed consent, potential research subjects in Human Biomedical Research may need to be informed of any financial arrangements offered by corporate sponsors to researchers or their institutions (or both).

5.41. 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 an actual, potential or apparent conflict of interest. This special report should be made directly to the board of directors of the institution.

Multinational and Multi-Centre Research Projects

5.42. As we have previously pointed out, biomedical research projects increasingly involve collaborators in more than one country. Indeed, one of the hallmarks of current leading edge research is 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

5.43. 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 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.

5.44. This conclusion is based on Singapore law and Singapore ethical standards and rules, which are not necessarily the same as those of other countries. This approach is supported in other jurisdictions. Without this approach a moral hazard would exist in the temptation of researchers to pick as their ethical jurisdiction of choice the jurisdiction with the perceived most liberal regime.

5.45. Nonetheless, we envisage that expedited review may be permissible in certain circumstances. For example, where human 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.

5.46. 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 lead IRB (defined in paragraph 5.50), 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.

5.47. The local IRB may then elect to grant expedited approval of such applications after reviewing the documentation, and the reasons for the decision of the lead IRB. 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.

5.48. In summary, we recommend that the local portion of a proposed multinational research programme should be subject to review by the IRB of the local partner institution or institutions.

Lead IRBs for Multinational and Multi-Centre Research Projects

5.49. Currently, the situation is that ethics review is required by the IRBs of every institution that will be involved in the proposed research programme. There is no mechanism or requirement that any one of the ethics committees involved should act as a principal or coordinating ethics committee.

5.50. We recommend that a "lead" IRB be designated from among the IRBs of the participating institutions. The lead IRB will be responsible for the primary ethics review of the research proposal and for keeping other participating IRBs informed of any decisions or amendments, including those made during the whole period of the research.

5.51. The choice of the lead IRB should be dictated by considerations such as the principal institution of affiliation of the PI, 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.

5.52. The primary ethics assessment should be made by the lead IRB, which is also responsible for ensuring that a proper scientific assessment has been carried out. Copies of its decision should be sent to the IRBs of the other institutions or organisations involved, which may then choose to conduct expedited review while reserving their rights to give further consideration to ethical and administrative aspects of the research that are specific to their own institutions or organisations.

5.53. 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).

5.54. At the time the research proposal is submitted, researchers should inform their respective IRBs as to which IRB is the designated lead IRB responsible for the primary ethics review.

5.55. Researchers are also expected to disclose to the lead IRB any previous decisions made by their IRBs regarding the research.

5.56. IRBs should:

(a) Coordinate their review of multi-centre research proposals and communicate any concerns that they may have with other IRBs reviewing the project; and

(b) Determine how the conduct of multi-centre research will be supervised and the respective roles each of the institutions or organisations and their IRBs will have.

5.57. In summary, for multi-centre research, a "lead" IRB should be designated from among the IRBs of participating institutions. The lead IRB will play the main role in conducting a full ethics review, in coordinating the research programme and in keeping other participating IRBs informed of any decisions and amendments made during the whole research period.

Specific Operating Procedures for Institutional Review Boards

5.58. 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.

5.59. If for any reason a member of an IRB or the IRB itself should be of the view that there exist circumstances or considerations that might impair, adversely affect or make impossible the impartial, objective and independent discharge of duties, the member or IRB concerned should decline to review or process the research proposal or proposals in question and immediately report such concerns to the highest level of management of the institution.

5.60. 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.

5.61. A situation of real, potential or apparent conflict of interest amounts to circumstances that adversely affects the impartiality, objectivity and independence of the IRB or of its members as described above.

5.62. 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 IRB on the particular research under review.

5.63. The IRB member should make full disclosure of such an actual, potential or apparent conflict of interest to the IRB.

5.64. 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 IRB and the researchers.

5.65. All discussions of the IRB should be appropriately minuted and all opinions recorded. The decisions of the IRB should be provided in written form and, where appropriate, a fair and frank account of the reasons for those decisions should be provided.

5.66. 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 ethics review.

5.67. IRBs may also require the submission of a lay summary of the research proposal, where this may aid the lay members of the IRB in the conduct of ethics review. This summary should set out concisely the salient features of the research proposal. In certain cases, it may also be useful to have a lay summary of the scientific review.

5.68. Research proposals should not consist of the same or substantially the same documents submitted for the purpose of a proposal for funding. IRBs should bear in mind that research proposals submitted for ethics review are directed at a completely different end to that of proposals submitted for funding purposes.

5.69. The requirements of impartiality, fair review and documentation of decisions should apply equally to IRBs engaged in the continuing review or supervision of a research programme.

5.70. 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 pharmaceutical trials should be applied to all other kinds of human biomedical research with appropriate modifications.

5.71. Both researchers and IRBs should take especial care to ensure that potential research 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.

5.72. Both researchers and IRBs should ensure that research participants are aware that they have the right to withdraw from the research programme at any time.

5.73. We recommend that IRBs and institutions formalise arrangements that 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, research participants can have access to independent officers in order to give feedback on the research, or to express their concerns.

5.74. For related reasons, we further recommend that researchers consider appointing a member of their research team to serve as a one-stop participant contact. This contact person should be a registered medical practitioner or a senior member of the research team. It will be the responsibility of this person to handle initial contact in all cases in which a research programme involves any level of clinical intervention or interaction with the participants, and in cases where the interaction with participants is delegated to support and field workers or assistants (for example, the collation of medical histories or physical examination). We also recommend that IRBs make the appointment of a contact person a condition of approval.

5.75. A copy of every document signed by research subjects or given to them to read, including the consent documentation, should be retained by the research subjects.

5.76. 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 Human Biomedical Research.

5.77. Meetings. IRBs should have regular, 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 or those that present significant risk to participants should be debated and discussed in face-to-face meetings.

5.78. Exempted Review and Expedited Review. We have already discussed the basis for allowing Exempted Review and Expedited Review. When an institution (in consultation with its IRB) has decided on the categories of

Human Biomedical Research that could qualify for Exempted Review or Expedited Review, it should draw up a set of standard operating procedures to provide for these categories.

5.79. Instead of requiring consideration by the entire IRB, the standard operating procedures may allow the Chairperson or his delegate(s) to make decisions on applications that qualify for Expedited Review.

SECTION VI: RESEARCHERS

6. Researchers

The General Responsibilities of Researchers

6.1. Researchers share with institutions and IRBs a primary and central role in the ethics governance of Human Biomedical Research. More than any other party or parties in the ethics review and governance process, researchers have the fullest access to the facts on which ethical judgments are to be made.

6.2. Researchers 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 the subjects.

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 Human Biomedical Research rests with the researchers. IRBs bear the responsibility for the overall ethics review and approval of Human Biomedical Research programmes.

6.5. This responsibility of the researcher is a non-delegable and personal responsibility. It is a responsibility that cannot be transferred or delegated to an IRB or to 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 for ensuring that their research complies with all relevant laws and legal or regulatory obligations and requirements. Ethics 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 IRBs 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 IRBs proposals that they are objectively and professionally satisfied are entirely ethical in all aspects and are prepared to defend them as such.

6.9. By submitting a research proposal to an IRB, researchers indicate to all involved parties that the proposed research is, in the researchers' objective and professional judgement, ethical in all aspects.

6.10. Researchers should not submit to IRBs the same or substantially the same documents for ethics review that they submitted to prospective funding agencies, unless these documents focus on or evaluate the potential impact of the research on the safety, health, dignity, welfare and privacy of the subject in addition to solely describing the scientific merits of the research. However, we nonetheless prefer researchers submit a separate document for ethics review. Researchers should be aware that research proposals submitted for ethics review and research proposals submitted for funding purposes are directed at completely different ends and should be drafted accordingly.

6.11. In no circumstances should researchers use IRBs and the ethics review process as a means of gaining ethics 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 if researchers believe, in good faith, that the proposed research is ethical, then such proposed research may be submitted for ethics review *provided* that the researchers fully disclose all such differing opinions and potential ethical difficulties or controversies known to them; that the researchers fully disclose the ethical reservations or doubts they hold; and that researchers fully disclose all other material facts and issues that might 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 ethics review a research proposal that the researchers themselves feel that they need ethical guidance.

6.14. 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 conflict arises, researchers have a duty to make a declaration of the conflict, to give full disclosure of the facts giving rise to such conflict and to 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. Researchers should not 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. 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 ethics 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 have no independent control over the conduct of the research. Examples of such research support personnel would be administrative clerks and nurses assisting in clinical duties.

Principal Investigators

6.18. Where a research project involves more than one researcher, the term "investigator" refers to any one of the researchers generally, while the term "Principal Investigator" specifically refers to the researcher who has been designated to undertake the role of Principal Investigator (PI) of that research project.

6.19. If a single researcher is carrying out a research project, then he or she shall be the PI. If multiple researchers are carrying out a research project, then the researchers must among themselves designate a PI. The PI is the researcher who shall be regarded as the lead researcher of the research project.

6.20. A research application by a group of collaborating researchers should be submitted in the name of a single PI and his or her collaborating researchers.

6.21. It is permissible for a research project to have more than one PI, especially for large projects, projects with different parts or different (but related)

objectives and projects in which the research is to be carried out at many locations (multi-centre research). Where more than one PI is involved, then each and every one of the PIs shall be held jointly and severally responsible as PIs.

6.22. PIs have special additional responsibilities over and above that of ordinary researchers.

The MOH has recently proposed a definition of "Principal Investigator" and of a PI's roles and responsibilities:

"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."

6.23. We commend and adopt this definition and summary of the role and responsibilities of a PI, and extend it to all Human Biomedical Research as defined in these Guidelines.

6.24. We however also point out that in multi-centre, multinational trials of new drugs, there is often an international committee that designs and analyses the results of protocols. Thus, in the case of such pharmaceutical trials, the term "Principal Investigator" would apply to the appropriate and relevant person on that international committee, whether appointed to act as such or otherwise.

6.25. In large, multi-part, multi-centre or complex research programmes, it is especially critical that the exact roles and responsibilities of each of the researchers in a team should be made clear and reduced to writing. This makes clear to every researcher what each other's responsibilities are, and helps identify overlooked areas requiring supervision or direction by a member of a team. Such statements outlining the roles and responsibilities of each of the researchers in a team should be included in the submission to the IRB.

6.26. The PI 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 that apply at least for the lifetime of the research project, which is defined as the time the research project is submitted to the IRB for ethics review until the time the research project is deemed to have concluded or been terminated.

6.28. When an IRB approves a research application, its judgment is 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 may 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, for example, resign or take a less active role, while other researchers may be recruited. There are other situations in which deviation may occur. A proposed course of action may be found to pose greater risks for the proposed subject population than originally assessed, or that the research has resulted in greater harm (whether of degree or of incidence) than originally contemplated. Or it may be discovered in the course of the research 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 his continuing responsibilities, the PI 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 the initial research application was considered and approved. The PI shall in his request or report detail the changes, giving his 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 (Section 3.2.5). The NMEC 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 researcher who signs the application that the research programme will be carried out strictly in accordance with the submitted protocol.

6.32. Researchers are obliged to suspend their research immediately, pending their report to the IRB, if deviations or changes to the original project submitted are substantial. Researchers are under the same obligation if deviations and changes have resulted or will likely result in greater harm or greater likelihood of harm (whether of degree or incidence) to the subjects involved.

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 research 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 stopped and the research programme varied to such extent, without the need for immediate reporting. Reporting of such changes by the PI to the relevant IRB should however take place within a 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 research or for meeting its objectives, do not fall within this category and should be immediately reported.

6.34. PIs have an obligation to submit regular reports to IRBs regarding the status of their research programmes. These reports are intended to aid the IRBs in its role of continuing review and supervision.

Researchers and Attending Physicians

6.35. Human subjects for research projects are often recruited from patients who are already receiving treatment from physicians.

6.36. 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:

"When 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."

6.37. In our view, however, this does not apply to situations where physicians wish to write up or publish summaries or analyses of the results of their therapeutic interventions or treatment of their 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.

6.38. In some circumstances, it may be difficult or impractical for researcher-physicians to comply with the letter of Article 23 of the Declaration of Helsinki. Such a situation might arise, for example, where the patient and prospective research subject is receiving specialist treatment at a centre or institution at which a majority of the attending physicians are also actively involved in institution-level research programmes. Or it may be that there is only one relevant specialist at the given institution, and that specialist is at the same time the treating physician as well as the proposed researcher. We recommend that in such cases, the IRB may give directions for the consent to be taken by the researcher so long as safeguards are documented in the protocol.

6.39. In the conduct of research programmes involving any kind of clinical or social interaction with human subjects who are receiving treatment for medical conditions, researchers should be aware of the possibility, however remote, that such interaction may have the inadvertent effect of interfering with the therapeutic care of the subject-patient.

6.40. Subject to our specific recommendations in paragraph 6.44, we therefore recommend that where researchers are aware that the potential research subjects are currently receiving treatment or otherwise being attended to by physicians for a medical condition or disease relevant to the proposed programme of research, efforts should be made by the researchers to inform and discuss with the attending physicians. If the research subject customarily attends a hospital or clinic and is attended to by different physicians on each visit, efforts should be made to inform the institution

concerned and to discuss with the consultant or a senior person having charge of the department or clinic.

6.41. We make clear that this obligation on the part of researchers, in those circumstances that it exists, extends only to informing and discussing with the attending physicians and to giving information about the proposed research programme, its objectives and protocols. This obligation does not require researchers to obtain the consent of the attending physicians.

6.42. The existence of attending physicians (or the likelihood of the existence of such attending physicians) should be disclosed to the IRB by the PI at the time that the research application is being made.

6.43. The IRB may then consider whether informing and discussing with the attending physicians should be made a formal requirement of ethics approval. Such a requirement should be made upon considerations that include, but are not limited to, the following:

(a) In the case of research that involves *any* level of clinical interaction with patients being treated or managed for medical conditions relevant to the proposed programme of research, researchers should be required to contact and inform the attending physicians. The IRB should decide on the facts of each case whether or not there is a sufficient connection between the proposed programme of research and the clinical treatment and management of the subject-patients, bearing in mind the interests of ensuring the safety, health, dignity, welfare and privacy of the subject-patients. Where the IRB is satisfied that there is no reasonable connection between the research programme and the treatment and management of the subject-patient, the researchers may dispense with informing and discussing with the attending physicians of their subjects;

(b) In the case of research that involves access to patients' medical records but with minimal levels of clinical interaction (e.g. the taking of blood or urine samples) or only social interaction (e.g. interviewing the subject-patient for a history), the IRB may in its discretion make formal contact and discussion a condition of ethics approval if it takes the view that the proposed interaction is relevant to the continued medical treatment and management of the subject-patient. Otherwise, researchers may in such cases dispense with contacting the attending physicians; and

(c) In the case of research that involves access to and a study of patients' medical records without any kind of contact between researchers and the patients, researchers need not inform or discuss with the

attending physicians (on the assumption, of course, that they have complied with all other applicable requirements).

6.44. 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 subjects without first seeking and obtaining the approval of both the attending physicians *and* the IRB.

SECTION VII: INSTITUTIONS

7. Institutions

The Responsibilities of Appointing Institutions

7.1. Institutions have the overall responsibility of ensuring the proper conduct of Human Biomedical Research and the protection of human subjects in all Human Biomedical Research carried out on their premises or facilities, or by their employees, or on their patients, or involving access to or use of human tissue collections in their custody, or involving access to or use of medical records or other personal information in their custody.

7.2. Every institution involved in Human Biomedical Research as defined in these Guidelines should establish and maintain an effective IRB. The IRB is accountable to the appointing institution, which must accept legal responsibility for the decisions of its IRB.

7.3. Institutions should lay policies for the composition of IRBs and the formal appointment of IRB members in accordance with the general principles and guidance presented in these Guidelines and, in particular, those set out under "Specific Operating Procedures for Institutional Review Boards" in Section V.

7.4. It is the responsibility of institutions to provide adequate resources and administrative support so as to enable IRBs to discharge their duties and responsibilities in an effective and timely manner.

7.5. Workload. Institutions should ensure that IRBs are not given a workload that compromises the quality of their work and IRBs should likewise ensure that their workload does not compromise the quality of their review. If this is likely, the institution is obliged to establish additional IRBs, to enlarge the membership of the IRB or to make formal arrangements for other IRBs to provide an opinion.

7.6. Institutions are obliged to ensure that IRBs receive adequate administrative support that is commensurate with the central role of the IRB in the ethics governance process. In this respect, the institution may take steps to lighten the workload of IRBs by delegating review in specific areas to a subcommittee, or by delegating some of its administrative or supervisory tasks to a separate well-staffed administrative body.

7.7. Such full-time administrative support should be sufficient to allow the IRB to:

(a) Ensure continuity and consistency in the work of the IRBs;

(b) Discharge any continuing review and supervisory obligations, outcome assessment and reporting duties;

(c) Ensure that the IRB's decisions are made with regard to previously established precedents and decisions that they and their predecessors have made; and

(d) Ensure that proposals are reviewed and dealt with in a timely manner within the target time frames set by the institution.

7.8. The core members of the IRB should be able to devote sufficient and protected time commensurate with the workload of the IRB.

7.9. Institutions are also responsible for providing their IRB members with a full indemnity as set out in paragraphs 7.17 to 7.22 and this should be reflected in their letters of appointment.

7.10. Institutions providing care should retain responsibility for the quality of all aspects of care afforded to human subjects whether or not some aspects of care are part of a research study.

7.11. Medical Records and Patient Information. We recognise that the issues arising from access to the use of and the custody of medical records and other patient information are 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.

7.12. In the context of institutions such as hospitals with centralised patient records and databases, we recommend that appointing institutions take steps to determine who within the administrative structure should be the proper administrative custodians responsible for patients' medical information in the institution, and to advise their IRBs accordingly.

7.13. In situations where any of the researchers are also the administrative custodian of patients' medical information within the institution, procedures should be established to address actual, potential or apparent conflicts of interest.

7.14. Institutions should ensure that clear formal procedures are laid down for the release of all kinds of patients' medical information, and should formulate these procedures in consultation with their IRBs.

7.15. It is desirable that the IRB be given authority by its appointing institution for the ethical clearance of access to patients' medical information for research within the institution, so that no patients' medical information may be released for research purposes without clearance by the IRB except for cases of Exempted Reviews referred to in paragraph 3.15.

7.16. Training and Education for IRB members. We recognise that training for IRB members can only be beneficial in the scheme of ethics governance of human research. We therefore recommend that institutions that conduct Human Biomedical Research and which are required in the context of these Guidelines to have IRBs, should also have in place programmes for the training and education of IRB members. Hospitals that have sizeable research programmes should in particular have such programmes. Such training and educational programmes should, where possible, also be provided to research staff.

The Protection of Institutional Review Boards

7.17. Notwithstanding the important role played by IRBs in research institutions, IRBs sometimes experience difficulties in attracting members of their 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 that has an unexpectedly adverse impact on human subjects. Few such candidates have any legal training and their reluctance on this ground is understandable.

7.18. On this point, we note that the NMEC Guidelines recommend that IRBs should look to the authority appointing them to give IRB members formal indemnity "against the cost of any legal representation and any compensation ultimately awarded to human subjects" (Section 3.34). The NMEC Guidelines further recommend that such an indemnity be given in IRB members' letters of appointment.

7.19. IRB members 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.

7.20. We take the view that IRB members should be fully protected in the discharge of their duties, provided that they do so in good faith, against any liability arising from their actions. Appointing institutions should give IRB members a full indemnity and arrange for the necessary insurance.

7.21. Legal protection for IRB members 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.

7.22. Because IRBs act as their appointing institutions' officers and agents, institutions 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 that may arise in the course of the work of the IRB (for example, in relation to the approval of multi-centre or multinational research).

SECTION VIII: ACCREDITATION

8. Accreditation

The Accreditation of Institutional Review Boards

8.1. The current regulatory regime governing the review and approval of pharmaceutical trials (which we described in Section II) provides for a system in which applications for pharmaceutical trials are first screened by IRBs at the local institutional level before being forwarded to a national regulatory agency (the HSA) for approval. This system has served us well and is well understood by all parties involved in the process. It should continue to apply in the case of pharmaceutical trials.

8.2. In the case of Human Biomedical Research other than pharmaceutical trials there is currently no national agency or regulatory body fulfilling a function equivalent to that of the HSA. The exception is the MOH, but it only has jurisdiction over hospitals, private clinics and other institutions falling within its purview under the Private Hospitals and Medical Clinics Act.

8.3. The MOH provides guidance from time to time for IRBs falling within its jurisdiction. For example, the MOH 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.

8.4. The role of the NMEC, however, is to advise the MOH on ethical issues arising in the practice of medicine. The NMEC does not advise IRBs directly and does not function as a higher level appeal or advisory body to IRBs.

8.5. Apart from complying with the directives issued by the MOH (including the NMEC Guidelines), IRBs in institutions under its jurisdiction are free to adopt such procedures, formulate their own standard operating procedures and determine their constitution, operating principles and other administrative practices.

8.6. We recommend that all IRBs be formally accredited by the MOH, which should be empowered to audit, to investigate complaints (including complaints from research subjects) and to appoint external auditors and investigators at the cost of the institution being audited as part of the accreditation check or as a matter of routine audit for compliance.

ANNEXES

Annexe A: The Human Genetics Subcommittee

Annexe B: Consultation Paper entitled "Advancing the Framework of Ethics Governance for Human Research"

Annexe C: Distribution List

Annexe D: Responses to the Consultation Paper

Annexe E: Summary of the Dialogue Session

Annexe F: Select References

Annexe G: List of Abbreviations

HUMAN GENETICS SUBCOMMITTEE

Chairman

Associate Professor Terry Kaan Sheung-Hung
Faculty of Law
National University of Singapore

Members

Mr Jeffrey Chan Wah Teck
Principal Senior State Counsel (Civil)
Attorney-General's Chambers

Associate Professor Samuel Chong
Department of Paediatrics
National University of Singapore

Professor Yap Hui Kim
Senior Consultant, National University Hospital
Professor in Paediatrics, National University of Singapore

Associate Professor Chia Kee Seng (from September 2004)
Department of Community, Occupational and Family Medicine
Faculty of Medicine
National University of Singapore

Dr Denise Goh Li Meng (from September 2004)
Consultant
The Children's Medical Institute
National University Hospital

Dr Lee Soo Chin (from September 2004)
Consultant
Department of Haematology-Oncology
National University Hospital

ADVANCING THE FRAMEWORK OF ETHICS GOVERNANCE FOR HUMAN RESEARCH

A CONSULTATION PAPER

THE BIOETHICS ADVISORY COMMITTEE

SINGAPORE

16 September 2003

THE BIOETHICS ADVISORY COMMITTEE

Chairman

Professor Lim Pin
University Professor
National University of Singapore

Members

Mr Jeffrey Chan Wah Teck
Principal Senior State Counsel, Civil Division, Attorney-General's Chambers

Mr Cheong Yip Seng
Editor-in-Chief, English/Malay Newspapers Division, Singapore Press Holdings

Associate Professor John Elliott
Department of Social Work & Psychology, National University of Singapore

Associate Professor Terry Kaan Sheung Hung
Faculty of Law, National University of Singapore

Ms Lim Soo Hoon
Permanent Secretary, Ministry of Community Development and Sports

Professor Edison Liu
Executive Director, Genome Institute of Singapore

Mr Richard Magnus
Senior District Judge, Subordinate Courts of Singapore

Professor Ong Yong Yau
Chairman, National Medical Ethics Committee

Professor Tan Chorh Chuan
Director of Medical Services, Ministry of Health

Mr Zainul Abidin Rasheed
Mayor, North East Community Development Council

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:

Bioethics Advisory Committee
10 Science Park Road
#01-01/03 The Alpha
Singapore Science Park 2
Singapore 117684

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 Code[1] 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 Subjects[2], 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 form 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 proper 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.

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) then 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

The Human Genetics Subcommittee

Chairman

Associate Professor Terry KAAN Sheung Hung
Faculty of Law, National University of Singapore

Members

Mr Jeffrey CHAN Wah Teck
Principal Senior State Counsel, Civil Division, Attorney-General's Chambers

Professor YAP Hui Kim
Faculty of Medicine, National University of Singapore

Associate Professor Samuel CHONG Siong-Chuan
Faculty of Medicine, National University of Singapore

Dr ONG Toon Hui *(until 31 August 2003)*
Director, Social Support Division, Ministry of Community Development & Sports

CONSULTATION PAPER ON "ADVANCING THE FRAMEWORK OF ETHICS GOVERNANCE FOR HUMAN RESEARCH"
(16 SEPTEMBER 2003)
DISTRIBUTION LIST

	Name	**Designation**	**Organisation**
1	Dr Ng Swee Cheng	Chairman Research & Ethics Committee	Alexandra Hospital
2	Dr Gunaretnam Rajagopal	Acting Executive Director	Bioinformatics Institute
3	Prof Miranda Yap	Director	Bioprocessing Technology Centre
4	Dr Khoo Teng Kew	Chairman Medical Ethics Committee	Changi General Hospital
5	A/Prof Lionel Lee	Director	Defence Medical & Environmental Research Institute DSO National Laboratories
6	Prof Hew Choy Leong	Head	Department of Biological Sciences National University of Singapore
7	Dr Ronnie Tan	General Manager	East Shore Hospital
8	Prof John Wong	Dean	Faculty of Medicine National University of Singapore
9	Prof Edison Liu	Executive Director	Genome Institute of Singapore
10	Dr Khoo Chong Yew	Chairman Parkway Independent Ethics Committee	Gleneagles Hospital
11	Mr Art Oullette	Chief Executive Officer	HMI Balestier Hospital
12	Prof. Jackie Yi-Ru Ying	Executive Director	Institute of Bioengineering and Nanotechnology
13	A/Prof Chong Siow Ann	Chairman Research and Ethics Committee	Institute of Mental Health/ Woodbridge Hospital
14	Prof Hong Wan-Jin	Deputy Director	Institute of Molecular & Cell Biology National University of Singapore
15	Dr Alex Chang	Chief Executive Officer	John-Hopkins-NUH International Medical Centre
16	Dr Chay Oh Moh	Chairman Research Committee	KK Women's and Children's Hospital
17	Mr Thomas E. Lee	Chief Executive Officer	Mount Alvernia Hospital

	Name	**Designation**	**Organisation**
18	Mrs Nellie Tang	General Manager	Mount Elizabeth Hospital
19	Prof Soo Khee Chee	Director	National Cancer Centre
20	Dr Kwa Chong Teck	Executive Director	National Dental Centre
21	A/Prof Koh Tian Hai	Medical Director	National Heart Centre
22	Mr Tan Tee How	Group Chief Executive Officer	National Healthcare Group
23	Dr Yee Woon Chee	Deputy Director Research	National Neuroscience Institute
24	Prof Goh Chee Leok	Chairman Research Ethics Committee	National Skin Centre
25	Prof Lee Kok Onn	Chairman Institutional Review Board	National University Hospital
26	Prof Yap Hui Kim	Director	NUMI Directorate National University of Singapore
27	Prof John Wong	Director	Office of Life Sciences National University of Singapore
28	Dr James J Murugasu	Chairman Ethics Committee	Raffles Hospital
29	Prof James P. Tam	Dean	School of Biological Sciences Nanyang Technological University
30	A/Prof Donald Tan	Director	Singapore Eye Research Institute
31	Dr Aw Swee Eng	Chairman Ethics Committee	Singapore General Hospital
32	Dr Ang Chong Lye	Director	Singapore National Eye Centre
33	Ms Theresa Chow Pui Fun	Deputy Director	Singapore Tissue Network
34	Prof Low Yin Peng	Chairman Ethics Committee	Tan Tock Seng Hospital
35	Mr Allan Yeo	Chief Group Executive	Thomson Medical Centre
36	Prof Tan Ser Kiat	Group Chief Executive Officer	Singapore Health Services
37	Dr Predeebha Kannan	Secretariat	National Medical Ethics Committee

RESPONSES TO THE CONSULTATION PAPER "ADVANCING THE FRAMEWORK OF ETHICS GOVERNANCE FOR HUMAN RESEARCH"

The Consultation Paper "Advancing the Framework of Ethics Governance for Human Research" was sent to 37 parties, and 19 responses were received.

Written Responses:

1. Alexandra Hospital (Private Communication)
2. Defence Medical & Environmental Research Institute
3. Faculty of Medicine, National University of Singapore
4. National Cancer Centre
5. National Dental Centre
6. National Healthcare Group
7. National Heart Centre
8. National University Hospital
9. Parkway Group Healthcare
10. Raffles Hospital
11. Singapore General Hospital
12. Singapore Tissue Network

Email Responses:

1. Bioprocessing Technology Centre
2. Genome Institute of Singapore
3. Institute of Mental Health/ Woodbridge Hospital
4. Institute of Molecular and Cell Biology
5. KK Women's and Children's Hospital
6. National Medical Ethics Committee
7. National Skin Centre

Defence Med & Env Research Institute
DSO(Kent Ridge) Building
27, Medical Drive
Singapore 117510
Tel: (65) 64857001 Fax: 64857033
Website: http://www.dso.org.sg

6 October 2003

A/Prof Terry Kaan,
Chairman,
Human Genetics Subcomittee,
Bioethics Advisory Committee,
10, Science Park Road,
#01-01/03 The Alpha
Singapore Science Park 2
Singapore, 117684

Dear Terry,

Feedback on BAC Consultation paper Entitled "ADVANCING THE FRAMEWORK OF ETHICS GOVERNANCE FOR HUMAN FOR HUMAN RESEARCH."
(Ref: BAC letter dated 15 Sep 2003)

I refer to your letter above. Pardon me for the one week delay in reply but your letter was received when I was on overseas duties. Since returning my Institute had been incorporated into the DSO National Laboratories, we merged with a sister centre to form the new DMERI@DSO and moved to a new building at the Kent Ridge Medical Campus.

You may like to know

- That MINDEF has adopted the National Medical Ethics Committee (NMEC) Guidelines in formulating policies and procedures governing Research involving Human Subjects since 2000. On consultation and advice from the NMEC chaired by Dr Chew Chin Hin and from MOH, the Armed Forces Council (AFC) approved the implementation of these guidelines on the 25 Oct 1999. The Armed Forces Council is the highest decision making body for the Singapore Armed Forces and MINDEF and is chaired by the Minister of Defence.

- DMRI, which is MINDEF's human science research institution implemented the decision and set up its IRB called the DMRI Research Ethics Committee in Jan 2000.

- Regarding Para 3.8 of your draft, the same AFC had set the overall direction by which, under defence and security considerations, abbreviation, waiver or temporary suspension of the ethics procedures and requirements is made.

Because we had largely implemented the NMEC guidelines and having read the BAC draft, I can support the 8 recommendations and have no further comments to add.

HOWEVER I would like to point out that I am giving my feedback entirely as the Director of the Institute as the letter intended. These views do not represent the official feedback from the Ministry of Defence. Should the BAC desire to solicit the official view of the ministry, you are advised to right to the "Permanent Secretary, MINDEF."

I hope the above feedback is useful to you.

Yours Truly,

BG(ret) A/Prof Lionel Lee
Director, DMERI@DSO

Copy to

CEO, DSO

Faculty of Medicine
Dean's Office

NUS National University of Singapore

Professor John Wong
Dean
Faculty of Medicine

20 October 2003

Associate Professor Terry Kaan
Chairman, Human Genetics Subcommittee
Bioethics Advisory Committee
10 Science Park Road
#01-01/03 The Alpha
Singapore Science Park 2
Singapore 117684

Dear Terry

REQUEST FOR FEEDBACK ON BAC CONSULTATION PAPER ENTITLED "ADVANCING THE FRAMEWORK OF ETHICS GOVERNANCE FOR HUMAN RESEARCH"

Thank you for asking for the Faculty of Medicine's input on this paper.

We are unanimous that this is an excellent step forward and most timely.

There were 3 comments which I would like to share with you, namely:

(i) The commitment required for IRBs to be effective. Staff feel that hospitals need to be told that staff involved in IRB work should have this regarded as part of their job description, that is a part or all of a full-time equivalent (FTE) of a Senior Clinician.

(ii) Some staff raised the issue regarding monitoring of the hospital IRBs to determine their effectiveness and ability to monitor and enforce research standards.

(iii) Staff were uncomfortable about utilizing a commercial IRB because of potential conflicts of interest or because of inability to have these reflect institutional policy and standards.

Thank you.

With kindest regards,

Yours sincerely

John

Professor John Wong
Dean
Faculty of Medicine

JW/rf

Block MD11, 10 Medical Drive, Singapore 117597 Tel: (65) 6874 3297 Fax: (65) 6778 5743
Website: www.med.nus.edu.sg

National Cancer Centre SINGAPORE

KON OI LIAN
MBBS, FRCPC, Diplomate ABIM,MD.
Head
Division of Medical Sciences

Tel : (65) 6436-8307
Fax : (65) 6372-0161
Email : dmskoi@nccs.com.sg

22 September 2003

Associate Professor Terry Kaan
Chairman
Human Genetics Subcommittee
Bioethics Advisory Committee
10 Science Park Road
#01-01/03 The Alpha
Singapore Science Park 2
Singapore 117684

Dear Professor Kaan,

Response to BAC Consultation Paper: 'Advancing the framework of ethics governance for human research'

Thank you for inviting the views of Professor Soo Khee Chee and others of the National Cancer Centre on this excellent consultation paper which clearly demonstrates deep understanding of the increased complexity of current biomedical research and advances thoughtful recommendations for an enlarged national framework to serve the interests of both the research fraternity and society at large.

I appreciate the opportunity to offer my personal views below. These are mine alone and do not necessarily reflect those of my colleagues or the National Cancer Centre. For ease of reference, I shall present my responses by page and section of the BAC Consultation Paper.

Section 2.13 (page 9)

Greater importance needs to be attached to the level of understanding that human research subjects attain during informed consent procedures. We need to move beyond acquiring the external façade of seeking and obtaining informed consent. Substantially more attention ought to be paid to assessing the comprehension of research subjects and to developing and implementing culturally appropriate informed consent processes.

Section 2.23 (page 11)

Directives to streamline ethics reviews (especially of pharmaceutical trials) must never lead, directly or indirectly, to any compromise of standards.

Recommendation 1 (page 16) and Section 3.6 (page 18)

The term 'human subjects' should be understood to encompass research involving use of any human biological material (tissues, blood and derivative products,

cells and body fluids), clinical, research and disease databases, data from imaging studies in addition to face-to-face encounters with patient subjects.

Section 4.19 (pages 23 - 24), Section 5.27.1 (page 31), Sections 5.30 & 5.32 (page 32)

It is my view that major obstacles to high ethical integrity are powerful and pervasive self interests of career advancement (for individual investigators) and financial incentives (for host institutions and industry). IRBs can become vulnerable to peer, institutional and administrative pressures to be non-probing and to grant the imprimatur of ethics approval with least delay. Unless IRB members feel assured that truly independent actions and decisions will not attract personal disadvantage (particularly for those who are themselves in the employ of the institution), the possibility that some ethics decisions may be self-serving is difficult to dispel. The BAC is undoubtedly cognizant of high capitation fees that pharmaceutical companies offer for enrolment of human subjects and the invidious use of clinical trials as a marketing tool.

Human subjects who are approached for voluntary enrolment in clinical studies should be informed of financial arrangements offered by corporate sponsors (typically of drug trials) to the trial investigators and their institutions, together with an explanation of how such fees are justified.

Section 5.15.3 (page 28)

The rationale for evaluating actual versus anticipated outcome or results is unclear *vis-à-vis* bioethics.

Section 5.16.1 (page 28) and Section 5.18 (page 29)

While it is axiomatic that 'bad science is bad ethics', it is nonetheless my view that IRBs should not be encouraged to undertake in-depth expert scientific assessments of research proposals. In fact, they should be actively discouraged from doing so. There are at least two reasons why scientific review by IRBs is undesirable and could easily undermine the quality of research ethics. First, IRBs are optimally comprised of a significant proportion of non-scientific and non-medical lay members. Second, medical and scientific members of IRBs may not easily dissociate their professional interest in research from the accompanying ethical issues. The unintended failure of an IRB member to distinguish between his role as ethics overseer from his professional interest in promoting research (i.e. 'good science may not be good ethics') is unhelpful in achieving consistently high standards of bioethics. This may be compounded within relatively small specialty groups whose members often find themselves sitting in judgement over each other's research proposals.

Section 5.20 (page 30)

I applaud and commend the Consultation Paper for recommending that IRBs receiving much higher standing and support than they currently receive. It needs to be equally recognised that appointment to IRBs must be preceded by training to serve competently as IRB members i.e. it is insufficient merely to appoint well-intentioned individuals in good standing with the community. National standards of IRB performance could be helpful in developing greater uniformity of scrutiny, failing which investigators may resort to 'ethics shopping' if some IRBs are known to have a record of greater laxity than others.

The performance standards of IRBs ought to be monitored e.g. time taken to render decisions, number of face-to-face meetings, active and inactive IRB members,

National Cancer Centre
11 Hospital Drive • Singapore 169610 • Tel: (65) 436 8000 • Fax: (65) 225 6283 • Web site: www.nccs.com.sg

frequency of dissenting opinions (if any), frequency of queries directed to investigators and proportion of approved versus unapproved applications.

Notwithstanding the considerable difficulty in recruiting conscientious members to serve on IRBs, each member's term of office should be limited to 2 – 3 years. Prolonged IRB membership without prospect of termination usually leads to decreasing participation and loss of rigour.

The Consultation Paper correctly recommends that additional IRBs be established if the workload justifies. It will be helpful to provide some guideline on what level of work should trigger an additional IRB e.g. number of applications per year, hours expended per year.

Section 5.27.3 (page 31)

External and lay representation on IRBs should be mandatory rather than optional.

Sections 5.49 – 5.50 (page 36) and Section 6.10 (page 41)

A lay summary of research proposals could be useful and required for submission to IRBs. However, it would be unwise and possibly risky not to provide IRBs also with the scientific research proposal (i.e. the proposal submitted for funding). Approved and funded projects will implement the experimental or study design detailed in the scientific proposal - details that may be absent in a separate description of the same project submitted for ethics review. Such omissions will not be apparent to the IRB if it does not also receive the scientific proposal. A possible consequence of this is ethics approval on the basis of incomplete information.

In order not to impose burdensome requirements on investigators, the lay summary could be brief and concise setting out salient features e.g. study objectives and rationale, experimental design, definition of study population/materials, data analytical methods, ethical considerations relevant to the proposed study and measures implemented by investigators to address ethical issues.

Sections 6.37 & 6.39 (pages 46 - 47)

Careful consideration should be given to allowing researchers (whether medically trained or not) access to medical records. In theory, non-medically trained research personnel could be entrusted to maintain confidentiality. In practice, there may not be sufficient general awareness among research personnel of the responsibilities that attend privileged access to personal information. The requirement for researchers to provide a signed undertaking to respect confidentiality of medical information on every occasion that clinical records are accessed may help to address this concern.

Harmonising ethics and scientific reviews

A significant proportion of the present workload of IRBs relates to the requirement of both the National Medical Research Council (NMRC) and Biomedical Research Council (BMRC) that research proposals must have prior ethics approval before scientific review to determine funding. In recent years, NMRC and BMRC have announced deadlines for submission of proposals that give institutions such as the National Cancer Centre only about one month to complete internal reviews (assuming investigators have pre-written their proposals much in advance) and to obtain ethics approval. These timelines are quite unrealistic if we aspire to high quality research and ethics. On the ethics front, it has resulted in extremely hurried reviews that, in my view, do not pass muster if we are sincere about upholding high standards of bioethics.

National Cancer Centre
11 Hospital Drive • Singapore 169610 • Tel: (65) 436 8000 • Fax: (65) 225 6283 • Web site: www.nccs.com.sg

Two alternatives are clearly preferable. The better option is to reduce unnecessary work now imposed on IRBs by seeking ethics reviews only of proposals that have successfully secured funding. This should substantially reduce the work of already overextended IRBs because the scientific review culls many proposals. An obvious disadvantage is the perceived additional delay incurred if scientific and ethics reviews proceed in sequence. The second option therefore might be to consider simultaneous reviews. Since scientific reviews typically take several months to complete, this same period could be used for more thorough and meaningful ethics review without incurring any additional disadvantage to investigators. If the present system of rushed IRB reviews is not rectified, one fears that ethics reviews will be merely an instrument for conferring a shallow patina of respectability to human research.

I should like to reiterate my personal appreciation to the BAC for its thoroughgoing approach and the opportunity to provide feedback.

Yours sincerely,

OL Kon

Copy: Director, National Cancer Centre

National Dental Centre (NDC) – Summarised Response

Paragraph 2.1
Amended as:
"In the main, such advances in biomedical knowledge have been beneficial, and research *"has been" (added)* conducted in good faith for the benefit of humankind."

Footnote 2
Amended as:
"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 *"more recently amended" (amended)* at the 52nd World Medical Association General Assembly in Edinburgh, Scotland, in October 2000."

Paragraph 2.13
Amended as:
"... researchers are under a duty to give full explanation and information of (among others) the objectives *"and risks" (added)* of the proposed drug trial."

Paragraph 3.6
The definition statement is too long. Could be improved. How about:
"Clinical research refers to any research study, trial or activity involving human subjects, human tissue or use of medical / genetic information of identifiable or anonymous individuals. These are undertaken with a view to generate data about the medical, genetic or biological processes in human physiology or diseased states; to determine the safety, efficacy, effect or function of any drug device; and diagnostic, surgical or therapeutic (whether invasive , observational or otherwise) procedure in human subjects.It 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 of the family members of any of the human subjects or donors thereof."

Paragraph 4.5
Amended as:
"...most forms of biomedical human research *"may" (added)* unavoidably involve some degree of risk of harm (however minimal or remote) to the human subject."

Paragraph 4.6
Amended as:
"Ethical assessment and judgment therefore necessarily involves an assessment and *"weighing" (added)* of the potential harms and benefits."

Paragraph 4.13
Amended as:
"It is desirable that a "common" (added) code of applicable principles for ethical governance be eventually formulated for the *"common" (deleted)* guidance alike of ethics committees, institutional review boards, research institutions, researchers, *"the*

human subjects of research" (deleted) and all other parties involved in human research..."

Recommendation 3
The word "institution" here is not limited to a medical/dental institution? May include a research laboratory?

Section on "Shared, "Domain" and Other Special Institutional Review Boards"
In this section, the proposal of a 'shared IRB' may not be practical. It may be possible to share an IRB secretariat but not an IRB. Even then there may be logistics problems. Does the specialist IRB or domain IRB refer to a scientific review panel/board? These two terms may add to confusion.

Paragraph 5.15.1
Amended as:
"... before the proposed research *"can" (amended)* be carried out. In the majority of developed countries, this is made a statutory or otherwise legal requirement."

Paragraph 5.40
"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."
This is not necessary as it adds to paper work and increases time taken for the processing of the applications. The researcher would have decided which IRB would be the lead IRB to apply to.

Paragraph 5.43 (first bullet point)
This statement suggests that the research is simultaneously assessed by variable IRBs. Better to standardize SOPs inclusive of standard criteria for reviewing protocols, etc. The lead IRB approves and this approval can then be submitted to other respective IRBs which can then 'cross-recognise' the approval, expediate the application process with or without minor modifications. If the application is submitted to various IRBs at same time, the researchers may get conflicting feedback from the IRBs. For such projects, the scientific merit should be done by the CTCC or its equivalent for non-drug trials?

Paragraph 5.57
Amended as:
"Both researchers and IRBs should take especial care to ensure that the proposed human subjects *"and / or their legal guardians" (added)* will be able to understand *"the objectives of the research project" (added)* and assess the risks of participation, and that the consent-taking procedure and the documentation are properly designed to achieve this end."

Paragraph 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"

This is beyond the scope of IRBs. It should be a policy matter undertaken by MOH/ the institution following legal advice

Paragraph 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."
Problems may also arise with present day computerized records as any one with a password to access the computer may access patient records easily.

Paragraph 6.9
Query whether the requirement that the research proposal must, in the professional judgment of the researcher be ethical in all aspects, is legally binding.

Paragraph 6.11
Who will judge whether researchers are using 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?

Paragraph 6.37
Efforts by researchers to contact and inform the attending physicians, or the institution, consultant or senior person in charge of the department or clinic attending to the research subject of the proposed research programme should be in the form of a **formal** note to the physician to inform them, rather than an informal procedure.

Paragraph 6.39.1
Requirement for researchers to formally contact and inform attending physicians in cases of research involving any level of clinical interaction with patients can become quite touchy as it may result in patient dissatisfaction with previous physicians / surgeons. There may also be some patients who can pose a potential medical legal problem whom the primary provider may not be keen to include in the studies. Professional ethics issues are also involved.
Also, is there a need to obtain permission from the attending physicians?

Paragraph 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" (deleted)* inform the attending physicians, and the IRB *"in its discretion" (deleted)* may make such formal contact and information a condition of ethics approval

General Comment:
It may be pertinent to explore the time frame of storage of project protocols, reviews, materials , etc by IRBs following the completion of the research study, from a medico-legal point of view. Similarly for medical records?

Note: Minor suggestions as to grammatical errors, formatting and spelling have not been included in this summary.

Adding years of healthy life

6 Commonwealth Lane
Level 6 GMTI Building
Singapore 149547
Tel: 6471 8900 Fax: 6471 2129
www.nhg.com.sg

7th October 2003

Assoc Prof Terry Kaan
Chairman
Human Genetics Subcommittee
Bioethics Advisory Committee
10 Science Park Road
#01-01/03 The Alpha
Singapore Science Park 2
Singapore 117684

Dear A/Prof Kaan

FEEDBACK ON BAC CONSULTATION PAPER ENTITLED "ADVANCING THE FRAMEWORK OF ETHICS GOVERNANCE FOR HUMAN RESEARCH"

I would first like to commend on the high quality of work done by the BAC Human Genetics Subcommittee. The Consultation Paper issued is indeed comprehensive and "timely" in our cluster's effort to address the potential ethical and legal issues arising from research within the cluster.

In May 2003, an Ad-hoc Committee on Ethics & IRB Review was set up under the advice of CEO NHG to study the report and recommendations made by the MOH Committee of Inquiry arising from the investigation on the NNI's study. The Committee has developed a framework for the implementation of MOH panel recommendations, and recommended critical measures that will strengthen the ethical framework of research in the cluster.

The Committee was also tasked in reviewing the consultation paper, with particular focus on the processes and procedures to be adopted in the ethical governance process and recommendations on the constitution and role of institutional review boards.

In view of the short time frame, the Committee has outlined a few points arising from the consultation paper. These points were viewed as critical and having immediate relevant effects in the cluster's effort to establish a more robust and effective ethics review processes and boards. The Committee will further review the issues outlined in the consultation paper in more details. The views are attached in Annex A.

National Healthcare Group

Adding years of healthy life

6 Commonwealth Lane
Level 6 GMTI Building
Singapore 149547
Tel: 6471 8900 Fax: 6471 2129
www.nhg.com.sg

On behalf of NHG, I would like to thank your Committee for inviting the cluster to offer our views and comments that 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.

Thank you

Yours sincerely

DR WONG JIEUN SHYARD
DEPUTY DIRECTOR
CLINICAL PROGRAM
PROFESSIONAL POLICY & PLANNING

Annex A

FEEDBACK ON BAC CONSULTATION PAPER ENTITLED "ADVANCING THE FRAMEWORK OF ETHICS GOVERNANCE FOR HUMAN RESEARCH"

(A) Recommendation 3 (page 26)
The current requirement that every hospital have an institutional review board should be statutorily formalized, 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.

Comments:
With reference to the above recommendation, the Committee felt that this is not fully in accordance with the new ethics review processes and structure that the cluster will adopt, arising from the recommendation put forth by NHG Clinical Research Advisory Committee, chaired by Prof Edison Liu, Executive Director of GIS.

NHG is currently in the process of reconstituting and reorganizing the Institutional Review Board (IRB) into Domain-Specific Review Board (DSRB). DSRB, being non institutional-based, will not satisfy the requirement as stated in the above recommendation that every hospital should have an effective IRB. In the new DSRB system, respective hospitals will not have an IRB. DSRB will be centralized and managed by the cluster HQ. Each DSRB (there are altogether 4) will review and approve protocols for all the institutions within the cluster.

Although item 5.12 describes the possibility of having domain specific IRB, it would probably be better to reformulate recommendation 3 and to include domain specific IRB, which is non institutional-based upfront.

(B) Recommendation 4 (Para 2 and 3, page 29)
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.

Comments
With reference to the above recommendation, the Committee felt that a highly trained and efficient administrative support staff would be required to assist the IRB in its recommended role of "continuing review, supervision and audit", particularly since the IRB is only part-time, and the number of protocols to track will multiply over time. The caution really is, would the IRB be able to deliver what is expected. It would be of considerable help if it were mandated that the PI report regularly on the research project.

(C) Item 5.69 Medical Records and Patient Information (page 38)
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.

Comments
With reference to the above recommendation, the Committee felt that this issue should be explored as soon as possible as the question of whether patient consent is required is being debated in many quarters with differing opinions.

(D) Item 5.73 (page 39)
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.

Comments
The NHG Ad-Hoc Ethics Review Committee had recommended that the custodian of medical records in any institution should be the CMB, Medical Director, or CEO of NHG Polyclinics. In the event that the aforementioned is the PI of a research proposal, the Chairman of the IRB would be the custodian. Thus, the IRB would give the ethical clearance for release of patient medical information, but the final approval would come from the institution's custodian of medical records.

National Heart Centre
SINGAPORE

Mistri Wing
17 Third Hospital Avenue
Singapore 168752
Tel : 6436 7800
Fax : 6227 3562

2nd October 2003

A/Prof Terry Kaan
Chairman
Human Genetics Subcommittee
Bioethics Advisory Committee
10 Science Park Road
#01-01/03 The Alpha
Singapore Science Park 2
Singapore 117684

Dear A/Prof Kaan

REQUEST FOR FEEDBACK ON BAC CONSULTATION PAPER ENTITLED "ADVANCING THE FRAMEWORK OF ETHICS GOVERANCE FOR HUMAN RESEARCH"

Thank you for your letter of 15 September 2003.

Please find enclosed comments from my main research staff.

Yours sincerely

A/Prof Koh Tian Hai
Medical Director
National Heart Centre

A:bac-021003

MAK Koon Hou

30/09/2003 01:50 PM Dept : Department of Cardiology; National Heart Centre; 17 Third Hospital Avenue; Singapore 168752 Tel : 65-6-436-7545

To: KOH Tian Hai/CARDIO/NHC@NHC
cc: Sally KOK/DIROFF/NHC@NHC, Margaret LIM SH/CARDIO/NHC@NHC

Subject: Bioethics Medical Committee reply

The following are my comments:

1. Training and funding of IRB personnel, especially with regards to monitoring.

2. Multicentre trial should consider having a central IRB comprising of members from each institutional IRB.

3. Patient records for retrospective reviews should be waived. There should be a statement in the hospital attendance for patients to allow their information to be used, in confidentiality, for the purpose of research.

4. Extension of IRB to family and private practitioners

Request for feedback on BAC consultation paper entitled " advancing the framework of Ethics Governance for Human Research"

With Regards to part A:

There is currently a very gray area of what constitutes a drug and non-drug trial.

e.g. for Cardiology, present trials focus on a stents that are drug coated: Is this thus a interventional trial or a drug trial? The consequent EC review of the trial will be different depending on what view the EC takes. The EC should therefore have very clear guidelines on what constitutes a drug and non-drug trial.

There should be open channels of communication between the PI of the protocol and the EC. If need be, direct interviews of the PI by the EC should be conducted to enlightened both the EC and the PI of what are the needs on both sides. In this era of a very competitive spirit of research, this may cut time, because of the quick clarification of issues, for the approval of protocols by EC.

Increasingly, more animal work is being performed. Guidelines for the ethical care of animals should also be addressed in a clear manner. I understand that all issues are addressed with regards to human research only. Will there be separate reviews for animal research?

With Regards IRBs:

It may be pertinent to ensure that IRBs are formally trained and the members of the IRBs made known. This may allow more transparency to the review process. The IRBs bare a heavy burden and if there are many members rotating on the same IRB, a specific quorum should be specified and made public. This may help to enhance the moral authority of the EC.

To further enhance standards, I fully agree with the setting up an overall supervisory authority as stated in Recommendation 7. This will allow the full accreditation of all IRBs. This national supervisory authority may also aid in the same role with animal experimentation issues.

Sincerely,

Philip Wong
National Heart Centre

30 September 2003

Assoc Prof Terry Kaan
Chairman
Human Genetics Subcommittee
Bioethics Advisory Committee
Singapore

Dear A/Prof Kaan,

REQUEST FOR FEEDBACK ON BAC CONSULTATION PAPER ENTITLED "ADVANCING THE FRAMEWORK OF ETHICS GOVERNANCE FOR HUMAN RESEARCH"

Thank you for your letter dated 15 Sep 2003.

The NUH IRB members would like to meet and discuss this consultation but due to the short timeframe, we have not been able to do so.

My initial views, without in-depth consultation and discussion, are as follows :

1) Definition of the Principal Investigator (section 6.23). This should be modified to take into account pharmaceutical company initiated multi-centered, multi-national clinical trials on new drugs. There is often an international committee that designs (and analyses results of) the protocols. The notional PI in Singapore will NOT be involved in many aspects, but will officially be the PI as far as the legal situation goes if your recommendations are implemented. This will seriously deter any local involvement in important multinational clinical trials.

   Within Singapore, that definition proposed is acceptable.

2) Another concern is that there is nothing that addresses Conflict of interest issues. This is quite important in scientific research in a small country like Singapore. Perhaps there should be some mention of this area.

3) Finally, section 5.15.2 mentions that the IRB is supposed to "supervise and audit on a continuing basis" the research programmes. And 5.15.3 mentions that the IRB is supposed to "monitor outcomes" of research and "evaluate" them, provide "feedback and maintain dialogue" with researchers. These 2 points imply that the IRB is also an enforcement agency, with staff to do that sort of work. These tasks will require a totally different mind set from the reviewers who evaluate the ethical and scientific aspects of a study, and are not trained to evaluate how well the implementation is being carried out. The auditing tasks will also require much more resources, than exists at present in Singapore (or in other countries) for IRBs. While I recognise that this is an important area, perhaps a separate audit committee should be responsible

for audit and these other similar tasks, rather than the IRB which approved the protocol.

I have circulated the copies to all the members of the NUH IRB and are awaiting their comments. I shall inform you again, once I have consolidated all their comments.

Thank you.

Yours sincerely

Professor Lee Kok Onn
Chairman, Institutional Review Board
National University Hospital
C/o Medical Affairs Department

cc. Professor Lee Hin Peng
Chairman, IRB
National University of Singapore

Further Comments from National University Hospital IRB

1. Expectation of IRBs to perform the role of "continuing review, supervision and audit" will add considerably to the current workload of IRB members.

2. Adequate resources, such as administrative support, time and training for IRB members would be needed in order to meet the expectations of IRBs.

3. Will IRBs be held responsible for giving approval to a research which later goes wrong?

PARKWAY GROUP HEALTHCARE PTE LTD

29 September 2003

Assoc. Prof Terry Kaan
Chairman
Human Genetics Subcommittee
Bioethics Advisory Committee
10 Science Park Road
#01-01/03 The Alpha
Singapore Science Park 2
Singapore 117684

Dear A/Prof Kaan,

FEEDBACK ON BAC CONSULTATION PAPER ENTITLED "ADVANCING THE FRAMEWORK OF ETHICS GOVERNANCE FOR HUMAN RESEARCH"

Thank you for inviting us to give our views on the above consultation paper.

Our comments relate to the following articles:

1.7 You may wish to add:

- To keep abreast of ethical governance of clinical research in other countries, many of which carry out multicentre studies with centres in Singapore.
  (Rationale: There are some who feel that creating more statutory requirements will discourage research work in Singapore. On the contrary, it will attract multicentre studies and researchers who expect high ethical standards).

2.23 Please note that some changes are imminent, such as the dissolution of the MCRC and the CTCC.

POSTAL ADDRESS
Gleneagles Hospital
6A Napier Road
Singapore 258 500
Tel: 473 7222
Fax: 475 1832

REGISTERED ADDRESS
80 Marine Parade Road
#22-01/09
Parkway Parade
Singapore 449 269
Tel: 345 8822
Fax: 344 0386

Recommendations 1 & 2:
One way of implementing these is to expand the purview of the Medicines (Clinical Trials) Regulations 1998 and the SGGCP to include all research studies. Some IRB's are reviewing animal research studies as well.

Recommendation 3:
This may not be necessary, as approval for Clinical Trials is not given unless the trial has been reviewed and approved by an IRB/HEC. It is also not necessary for smaller hospitals which do little research work to form an IRB. They can always ask the IRB of a larger hospital to vet their research work.

5.17 You may wish to add:
If a research study is scientifically flawed, it is unethical to carry it out.

6.5 You may wish to add:
"Researchers and their supervisors are not absolved of responsibility for their work by the existence of the IRB/HEC. The IRB can only give guidance and approval for the application of a Clinical Trial Certificate. Physicians are not relieved from criminal, civil and ethical responsibilities.

The IRB recognizes that the only real protection for the subject lies in the scrupulousness, conscience and personal integrity of the investigator.

7.6 There is a move now for hospitals to adopt the same/similar SOP.

7.10 & 7.11

Accreditation and licensing of Clinical Research Centres and Auditing of IRBs for compliance are now the responsibility of the Health Sciences Authority.

You may wish to touch on the Ethical Training for IRB members and also for Investigators. This is important for successful implementation of your recommendations.

In keeping with Accreditation and Audit of IRB's, there is a need to carry out Ethical Training of IRB members and Investigators. A couple of training programmes are available. One is the FERCAP (Forum for Ethical Review Committees in Asia and the Western Pacific). FERCAP receives support from many institutions such as WHO, CIOMS, UNAIDS, UNESCO and the European Forum for Good Clinical Practice. Another programme is run by the American accreditation body, AAHRPP® (Association for the Accreditation of Human Research Protection Program, Inc®, http://www.aahrpp.org/). Training can be on-line (such as the NIH-OHRP Human Subject Assurance Training) to certify knowledge of "human participation protection".

Recommendation 8:
Most (if not all) Hospitals have Indemnity and Insurance for their IRB members.

In the Private Hospitals and Medical Clinics (Amendment) Act 1999, it is stated that:
"A. Members of the Quality Assurance Committees are protected against legal action when they have acted in good faith.

D. Medical experts appointed by MOH to assist in the administration of the Act, e.g. members of advisory committees, are protected from any personal or professional liability in the exercise of their responsibility and judgement, when it is done in good faith."

Ultimately, it is the sponsor of the Clinical Trial who should provide insurance and indemnity (legal and financial coverage) for the investigator/institution against any claims arising from the trial, except for claims that arise from malpractice and negligence.

Yours Sincerely,

Dr Khoo Chong Yew
Chairman, Parkway Independent Ethics Committee

POSTAL ADDRESS
Gleneagles Hospital
6A Napier Road
Singapore 258 500
Tel: 473 7222
Fax: 475 1832

REGISTERED ADDRESS
80 Marine Parade Road
#22-01/09
Parkway Parade
Singapore 449 269
Tel: 345 8822
Fax: 344 0356

30th Sept 2003

Assoc Prof Terry Kaan
Chairman
Human Genetics Subcommittee
Bioethics Advisory Committee

Dear Terry,

RE: REQUEST FOR FEEDBACK ON BAC CONSULTATION PAPER ENTITLED "ADVANCEING THE FRAMEWORK OF ETHICS GOVERNANCE FOR HUMAN RESEARCH"

Thank you for sending me the above paper. First of all let me congratulate you and your Committee for a work well done. It is very comprehensive and complete; the result I am sure of much thought and hard work.

My only comments are a few of not that much import, which I have already discussed with you.

1) In section (v) under "Institutional Conflicts of Interest" para 5.30 "The highest level of governance in an Institution"; is a bit vague for the ordinary reader. You have explained this to me, but I was wondering if it could be modified somehow; especially since the IRB should not report to the Medical Board of the Institution. In fact if I am not wrong, some IRBs do report to the Chairman of the Medical Board.

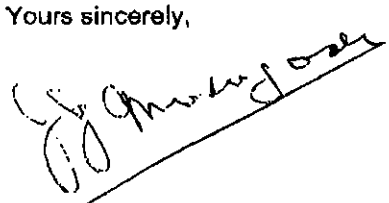
2) The word "Recuse", as you have told me is used in the Legal fracternity but a lay man (doctor) will look it up in the dictionary to find no such verb in the "Queen's English".

3) Under Section (v) "Medical Records & Patient Information" para 5.70 line 5. It may be useful to add the following or such.
"Establish a system through which the custodian only releases the patient medical information (eg the case notes) for the patient follow-up. If they are required for any other purposes such as research, the custodian shall inform the attending physician before releasing ----------.

4) Under Section (vi) "Researchers and Attending Physicians" para 6.37 line 3. "Being attended to by Physicians", ---- it is incumbent on the Researcher to contact and inform the attending Physicians of the proposed research programme.
Para 6.37 line 7 "By different Physicians on their visits," ------ efforts should be made to contact and inform the institution concerned.
(In other words cut out "reasonable" and "on an informal basis")

5) Para 6.39.3
Cut off completely or modify as follows:- In the case of Research which involves access to and study of the patients' medical records without any kind of contact at all between the Researchers and the subject patients, the Researchers should also formally contact and inform the attending Physicians

Yours sincerely,



Dr J J Murugasu BBM
Chairman
Ethics Committee
Raffles Hospital
585 North Bridge Road
Singapore 188770

Singapore General Hospital
A Tradition of Caring & Excellence

DEPARTMENT OF NUCLEAR MEDICINE AND PET, BLOCK 2 BASEMENT 1, SINGAPORE GENERAL HOSPITAL
TELEPHONE: 6321 4200 FAX: 6224 0938

DR AW SWEE ENG
FAMS, MBBS,
PhD (Chem Path)(Lond),
FRCPath (Lond),
Senior Consultant
Director of Endocrine Laboratories

8 October 2003

Assoc. Professor Terry Kaan
Chairman
Human Genetics Subcommittee
Bioethics Advisory Committee

Dear Terry

REQUEST FOR FEEDBACK ON BAC CONSULTATION PAPER ENTITLED "ADVANCING THE FRAMEWORK OF ETHICS GOVERNANCE FOR HUMAN RESEARCH".

Thank you for your invitation to submit our views on the Consultation Paper. The Paper is a comprehensive and well-thought out document for which you and your subcommittee deserve every congratulation. SGH IRB has sent its response through SingHealth.

There are two additional comments I would like to make.

1 As the Health Sciences Authority (HSA) is the accreditating authority of the country's IRBs, it should be the HSA which provides the monitors for the institutional IRBs. This does not preclude the individual institution having its own monitors to assist the day-to-day running of the trials. But random checks from an external authority is a great help towards objectivity of the process.

2 Institutions are beginning to realise that research is a communal activity and not the preserve of a few individuals. As such, resources, financial and manpower, must be allocated to ensure the success of the enterprise. An important aspect is the provision for the monitoring of all research. There is a shortage of qualified monitors. This vacuum should be filled at the level of the HSA, to begin with, so that the few now available may be shared. Training scholarships for appropriate candidates, I understand, are already available.

With warm regards,

Swee Eng

Dr Aw Swee Eng
Chairman, SGH IRB

Further Comments from Singapore General Hospital IRB

"It is commendable for the Bioethics Advisory Committee to clarify decisively the broad range of activities that nowadays constitute clinical research and to make the necessary provisions for their ethical governance.

It is also gratifying to note that the paper specifically lays on the researchers the responsibility of making "the first judgement as to whether in their professional judgement, the proposed research is ethical". This will expedite the recognition of the importance of the ethics of research and lead to the growth of ethical education in our young research community.

It is to be hoped that the recommendation... "that institutions have an obligation to ensure that IRBs receive adequate administrative support that is commensurate with their central role in the ethics governance process" will receive a clear, unambiguous response from those in a position to do so.

[Paragraph 5.18] would be cumbersome to realise in practice and could be deleted. It would also be helpful for the IRB always to receive, whenever applicable and available, a summary of the scientific review by the grant-funding agency"

From:
Theresa Chow
Deputy Director, Singapore Tissue Network

Date: October 8, 2003

Dear BAC members,

I would like to thank the BAC for the excellent work in the drafting of the consultation paper which covers all the pertinent grounds in the ethical governance of biomedical research involving human subjects. The recommendations for establishing a unified national framework for the ethical governance and a national statutory agency for the supervision, regulation, accreditation and auditing of the ethics review boards are most outstanding. The effort to place patient's rights as first place is clear, and the recommendations for how to strike a balance for research benefits and protection of patient's rights is elegantly covered. I have only a few comments to make.

Some comments:

"Applicable Principles" (sections 4.4 to 4.17) cover the important rationales behind the underlying principles for ethical governance, that of respect for the individual, respect for free and informed consent, respect for privacy and confidentiality, respect for vulnerable persons and the avoidance of conflicts of interest, or the appearance of conflicts of interest.

In addition to the basic principles, the following sections are of particular interests to me:

Section 4.8: *We recognise, however, that there can be neither absolute certainty or 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.*

Section 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.*

Section 4.13: *It is desirable that a code of applicable principles for ethical governance be eventually formulated for the* ***common guidance*** *alike of ethics 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 ethics review boards.*

Section 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.***

Comments:
A national statutory board would be instrumental in defining standards and ensuring that such standards will be adhered to through auditing. In particular, this would provide the proper channel for continuous improvement in policy settings taking into account the changing needs and attitudes of the local community. Guidelines from the national statutory board would alleviate the research communities and ethics committees from uncertainties generated from independent interpretations of recommendations of the BAC, which, without the establishment of a statutory agency, is left up to the individual ethics committee to interpret and implement, creating possible inconsistencies.

- Section 3.6: the BAC's proposed definition of "biomedical research" which should be regulated:

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 the 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.

Comments:
This carefully thought out definition has safely bracketed all the categories of research that should be under the purviews of a properly constituted ethics review board including research involving the use of human tissue samples, whether identifiable or anonymized.

The ability to have 'expedited review' for appropriately designed data escrow or other arrangements in which personal and other identity information is securely withheld from the researchers by a third party provider of the information under the above definition undoubtedly will help to expedite research process, particularly in legacy tissues and historical paraffin blocks.

I would like to add that what is worth consideration is the granting of a waiver of consent for research that involves no further direct contact with the patients (examples as in section 5.66), , or if the waiver will not harm the rights and welfare of the subjects, and that if the research cannot be practically completed without the waiver of consent.

Section 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 ethical 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.

Comments:
The 'proper authorities' is a vague term and needs clearer definition.

- Ethics Review Boards
  Shared "Domain" and Other Special Ethics Review Boards (sections 5.10 to 5.13)

Comments:
These sections address the need to share ethics review boards when an institution is of a 'small size' or having a 'small number of research proposals' making it impractical to establish and maintain a standing ethics review board of its own.

Alternatively, in section 5.11 , it is stated that it is permissible for several such institutions to jointly appoint a shared ethics review board and in section 5.13 , the mention of a possibility of accreditation given to a commercial ethics review board by the national supervisory agency are all measures which will be essential to support research of a small institution without incurring extra expenses in maintaining a full board for reviewing. Small institutions and private companies conducting research would find this welcoming and necessary.

Section 5.12 -: the mention of a specialist ethics review board or a domain ethics review board having the capacity to assess research in the particular specialist area allows quality review as this would allow special expertise being tapped for the review, and having a core group dealing with a specific research field will allow a continuation of ideas and maximize the lessons learnt as the field evolves with new technologies. This in turn will help to formulate new requirements for review that is in pace with the most current trends and practices.

Responsibilities of Ethics Review Boards

Section 5.15.3 Outcome Assessment, Reporting and Feedback

In this responsibility, ethics review boards (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 ethics review boards in providing feedback and maintaining a dialogue on applicable standards with its constituent researchers. In the discharge of role, ethics review boards 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.

Comments:
Clarification is sought from the BAC to define the term 'the relevant authorities'.

Section : Review of Scientific Merits

Ethics review boards are also required to carry out peer or expert assessments of the scientific merits and soundness of proposed research programmes. Thus a proposed research programme may, although it otherwise satisfies all ethical considerations, be properly rejected by an ethics review board on the basis that the scientific objectives of the research programme do not meet the standards set by the institution or the ethics review board. This is a distinct and separate responsibility of ethics review boards. Importantly, 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

Comments:
What will the policies be when differences arise in opinions for scientific merits in the evaluations of the institution, grant funding agency and/or the ethics committee?

The Constitution of Ethics Review Boards

Section 5.22 : *Ethics review boards 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 ethics review boards to appoint special ad hoc committees in consultation with their standing ethics review boards to consider special research proposals. We prefer, in such cases, that the institution works with their standing ethics review board to appoint special subcommittees co-opting experts or reviewers to assist the standing ethics review board in the particular project concerned. For example, an ethics review board may receive a research proposal involving an area of research with which no member of the ethics review board is familiar. In such a case, the institution may work with the ethics review board to identify and co-opt ad hoc experts or reviewers to assist the ethics review board in its assessment and review of the proposal. The co-opted ad hoc experts or reviewers sit as a subcommittee of the ethics review board.*

Comments:
Does the subcommittee has the voting rights or only serves as a review panel?

Composition

Sections 5.26 to 5.27 defines the composition of the ethics review board.

Comments:
To support the concept of an ethics review board being a key full-time management office and not merely as honorary *ad hoc* committee, there is a foreseeable amount of involvement in time and expense. How would the cost of setting up this office be provided for? Would there be a charge levied for the approval? If so, should there be differences in charge structure depending on whether it is an in-house application or from an outside source?

Section 5.27.5 : *Ethics review boards should also have lay, non-scientific or non-medical representation. Where practical, and where the size and volume of the workload of the ethics review board permits, lay representation may include respected lay members of the community, experts in philosophy, ethics, psychology, sociology or the law.*

Comments:
Should the board include a pharmacist and a statistician?

Specific Operating Principles

Section 5.70 : *In the context of institutions such as hospitals with centralised patient records databases, we recommend that ethics review boards 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.*

Comments:
This is only possible if approval from the attending physicians is not a necessary condition to be satisfied after informing, provided that the approval for the study and the use of medical information related to the study has been approved by the ethics committee. Otherwise it will slow down the process and would render the process impractical. A clear definition of 'who' are the 'administrative custodians' together with clear procedures for the release of medical information by the designated classes of custodians would be essential, especially in situations where physicians enrolls their own patients for research.

Responsibilities of Researchers

Continuing Responsibilities, Deviation and Variation

Section 6.28 *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 are recruited. Or it may be discovered that a proposed course of action poses greater risks than originally assessed for the proposed subject population, or that the trial has resulted in greater harm (whether of degree or of incidence) then 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.*

As part of their continuing responsibilities stated in paragraph 6.29 above, 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 no yet been made, or otherwise report any changes where such changes have already been made, to the ethics review board 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.

Comments:
The statement "or otherwise report any changes where such changes have already been made" alludes to the fact that un-approved changes are allowed. Can the BAC elaborate under what unusual circumstances (besides that stated in section 6.33) that changes are allowed without first informing the ethics review committee to obtain approval before implementing the changes?

Section 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 ethics review board. 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 ethics review board should however take place as soon as may be practicable. But 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.*

Comments:
Can the BAC consider the option of expedited review for minor changes made for the greater effectiveness of the trial provided that the change does not increase risks to the patient's health or welfare?
Researchers and attending physicians

Section 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".*

Comments:
Can one further define the "researcher / physician"? Currently, a lot of research projects involve collaboration between an attending physician and a researcher at an institute. The administration of informed consent is often conducted under that setting. Is a physician who is named as a co-investigator in a project, who enrolls patients from his patient pool, supplies medical information with informed consent, but does not handle the samples for research a researcher / physician?

If he/she is defined as such, then the engagement of another informed physician could be a potential issue, as almost all physicians are busy, and it would take a lot of convincing to engage another physician.

Does the consenting need to be done by another independent physician or can it be done by a consenting nurse as physicians have a very busy schedule?

If a nurse is administering the consent, can the nurse be someone working for the researcher/physician? According to section 6.17, where it is stated that: "*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."* **Does this exclusion apply to the nurse working for a researcher/physician who sees patients in a physician/patient setting?**

For the statement : *"[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.* **Would a standard statement in the consent form to the effect that the patients are free to decide whether to participate, and that their decision will NOT be affecting their medical treatment in anyways sufficient to address this possible conflict of interest?**

Section 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.*

Section 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 ethics review board may in its discretion make such formal contact and information a condition of ethics approval.*

Section 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 ethics review board 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).*

Section 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, as the ethics review board may direct.*

Section 5.70 *"In the context of institutions such as hospitals with centralised patient records databases, we recommend that ethics review boards 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."*

Comments:

Given the complexity of how medical information should be handled, it is best that there be clear policies and standard operating procedures to be set out for

the access of medical information. We hope that there would be guidance as to when to 'inform' versus 'inform and obtain approval' with regards to release of medical information and under what circumstances these modes of action should apply. It would be helpful to list the different scenarios of who would be asking for access to medical information and issuing guidelines for the proper procedures to follow.

Section 8: The protection of ethics review boards

Comments:
An excellent recommendation. This is what is needed most for the establishment of vital ethics committees that can attract a consistent pool of members, ethics assurance auditors, ethics investigators or members of committees of inquiry.

EMAIL RESPONSES TO THE CONSULTATION PAPER "ADVANCING THE FRAMEWORK OF ETHICS GOVERNANCE FOR HUMAN RESEARCH"

Professor Miranda Yap, Director, Bioprocessing Technology Centre

"I endorse what is being proposed in the Ethics Governance Consultation Paper for human research ... The recommendations such as setting up Institutional Review Boards, developing a national and unified framework for processes and procedures, highlighting roles and responsibilities of researchers doing clinical research in Singapore covered by the paper appear to be comprehensive and implementable."

Professor Edison Liu, Executive Director, Genome Institute of Singapore

"[With reference to paragraph 5.16.1 – Review of scientific merits.] The BAC subcommittee should consider the following possibility – that the IRB may accept the recommendations of, or delegate the primary scientific review to an officially constituted scientific review board. Such a board, progressively common in active research institutions, provide the scientific coordination and review in progressively complex experimentation. The ethics review board, then will expedite its scientific review and concentrate on the procedural, ethical and social implications of the research.

[With reference to paragraphs 6.38, 6.39 and 6.19.1] This is ambiguous and confusing...This may lead to a completely impracticable situation when there are many attending physicians that rotate (as in medical schools), or that, more commonly now than ever, there are several key doctors for the patient... In addition, is it required that the researcher have written acknowledgement from the attending physician, or the attending physician refuses to acknowledge the research. Can the attending physician bar the patient from participating even if the patient wishes to join a study?... I believe that this section is not enforceable unless as a recommendation of proper etiquette or as guidelines of behaviour and not as requirements."

A/Prof Chong Siow Ann, Director of Research and Member of Clinical Research and Ethics Committee, Institute of Mental Health

"In most institutions, the medical board is considered the senior management, and it may not be desirable to give the impression as that the IRB could report to a single person like the CEO.

I'm not particularly clear about the examples in which an exemption can be made from review or an expedited review may be permitted, does it include case reports? An example given is the analysis of patient information without any interaction with the patients themselves – this could be interpreted to include retrospective case reviews in which patients' medical records are accessed, but...the Committee has stated the complexity of this issue and has yet come to any conclusion.

It is recommended that a well-informed physician who is not involved [in the proposed research] should take the consent. I'm not certain of how this could be achieved practically – would [this] be left to the judgement of the physician/researcher? In which case, if the physician has indeed deemed that no such factors were present at the times of obtaining the consent, but subsequently an allegation is made that the consent was taken under some duress, how could this then be resolved? On the other hand, the recommendation that consent should be taken by other physician not involved in the study might not be very practical given the amount of clinical work that most physicians have to do.

I agree with all 8 recommendations."

Dr Ang Ah Ling, Chairman, Clinical Research and Ethics Committee, Institute of Mental Health

"I agree with the views expressed by the [Human Genetic Subcommittee] (HGS) and their recommendations. However I would expect that in the eventual implementation of these recommendations, there may have to be changes made as long as the underlying guiding principles are adhered to. For example, the [National Healthcare Group (NHG)] Clinical Research Advisory Committee has recommended the restructuring of IRBs into Domain-Specific Review Boards (DSRBs) and this is likely to be adopted by the NHG cluster. Hence the HGS's recommendations for IRBs will have to be adapted for application to the DSRBs."

Mrs Tay-Png Hong Lan, Deputy Director (Administration), Institute of Molecular and Cell Biology

She suggested that "research trial" be used in place of the term "clinical trial" and that human research should include research using "human tissue material". She also proposed to specify for the length of time for ethics review. She further recommended that the IRB include biomedical scientists or invite them to form an ad hoc panel or subcommittee. The term of the IRB members and their roles and expertise should be stated clearly.

Dr Chay Oh Moh, Chairman, IRB, KK Women's and Children's Hospital

"In general, I don't see [any] major conflict with our [standard operating procedures].

The idea of a national framework for ethical governance and to streamline clinical research involving human subjects is good for transparency and is beneficial to study subjects. Accreditation of IRB is what we are also working towards. Having protected time for IRB members will be ideal.

However, the definition of research on human subjects was taken to also include review of medical records. This will have impact on many small projects such as retrospective studies, audit of clinical practice. This will increase the job scope of IRB by a large proportion as most institutions will have many such studies ongoing often

times. They may not be so time-consuming but nevertheless will add [on to] our already busy schedule.

Recommendation 8 is important for IRB to discharge effectively their duties and I strongly support this."

National Medical Ethics Committee

Name	Feedback
Ms Ang Beng Choo	Very comprehensive paper. Paras 6.37 and 6.38 cast some uncertainty on the existence of attending physicians. It is the responsibility of the researcher to confirm this information with the proposed research subjects. The researcher should emphasise to the proposed research subjects that it is in their interest to declare if they are receiving treatment or under the care of a physician.
Dr Lee Kheng Hock	Comprehensive and well argued paper. To convey his compliments to Prof Terry Kaan and committee for their fine effort.
A/Prof Lee Kok Onn	Initial views (due to time constraints) without in-depth consultation and discussion with other NUH IRB members are as follows: 1. Definition of the Principal Investigator (section 6.23). This should be modified to take into account pharmaceutical company initiated multi-centered, multi-national clinical trials on new drugs. There is often an international committee that designs (and analyses results of) the protocols. The national PI in Singapore will NOT be involved in many aspects, but will officially be the PI as far as the legal situation goes if your recommendations are implemented. This will seriously deter any local involvement in important multinational clinical trials. 2. Within Singapore, that definition proposed is acceptable. 3. Another concern is that there is nothing that addresses Conflict of interest issues. This is quite important in scientific research in a small country like Singapore. Perhaps there should be some mention of this area.

Name	Feedback
	4. Section 5.15.2 mentions that the IRB is supposed to 'supervise and audit on a continuing basis' the research programmes. And 5.15.3 mentions that the IRB is supposed to 'monitor outcomes' of research and 'evaluate' them, provide 'feedback and maintain dialogue' with researchers. These 2 points imply that the IRB is also an enforcement agency, with staff to do that sort of work. These tasks will require a totally different mind set from the reviewers who evaluate the ethical and scientific aspects of a study and are not trained to evaluate how well the implementation is being carried out. The auditing tasks will also require much more resources, than exists at present in Singapore (or in other countries) for IRBs. While I recognise that this is an important area, perhaps a separate audit committee should be responsible for audit and these other similar tasks, rather than the IRB which approved the protocol
Dr Lim Sok Bee	I have discussed with Prof K O Lee and I am in support of his views
Prof Ong Yong Yau	The paper is all encompassing and well thought out. May have some practical problems for implementation e.g. full time ethics Committee.
Dr A Vathsala	1. I agree fully with the current document to include all research proposals including retrospective analyses of outcomes of accepted therapeutic maneouvers to EC for approval. Nevertheless, I write to point out that the vast number of studies and publications from Singapore actually fall into this category. Thus at the practical level, incorporating such a schema in Singapore immediately may nevertheless create the following problems: a. Overwhelm existing IRBs/ECs thereby preventing efficient processing b. Stifle applications especially by junior investigators c. Limit serendipitous discoveries that may yet have clinical importance and potentially benefit patients Given that the current document actually proposes expedited approval of such forms of research by the Chairperson of the EC, it may be worthwhile considering a different and simplified SOP for all retrospective analyses where there is no interaction

Name	Feedback
	between the investigators and patients (including investigations or therapeutic interventions). In fact, for the most part such analyses may require access to medical records of patients and consent from the Departmental Head /Attending Physician. A simplified SOP without recourse to an IRB/EC should be considered so as to avoid unnecessary delays in processing these research proposals. 2. I particularly support the need for establishment of national standards for ECs and IRBs. In particular, I write to offer 2 suggestions that may further enhance the ethical review of research proposals. a. Firstly, there may be a need for ECs to have access to an expert panel for various conditions. This may be necessary especially if the expertise within a particular institution or organization on that aspect of health care is limited. The CTCC may be particularly vulnerable to such a dilemma. While I note that the Current document proposes that the IRB/EC has the option to discuss issues of Concern with the researcher himself, the IRB/EC should have the option to call in for expert opinions either from Singapore or outside, especially from those experts in the field who are not involved in the research proposal. Ministry and the national supervisory body should have a panel of experts that they can easily access for such situations. b. Furthermore, a national level EC/IRB may be necessary at times to directly address either appeals from individual researchers or to assist ECs in resolving very difficult ethical research issues. 3. The greatest difficulty I see in the proposal is the lack of enough Clinicians/Scientists in Singapore with the caliber and experience needed to carry out the mandate of this document. As such, it may be necessary for many hospitals to share IRBs/ECs so as to capitalize on this limited expertise.

Professor Goh Chee Leok, Chairman, Research Ethics Committee, National Skin Centre

"This paper is very comprehensive. I have no comment except in item 6.10 where I think it is not necessary for the PI to submit different protocol from their funding application so long as there [is] adequate information and [is] presented in [the] format required by the IRB. PI may be encouraged to provide [an] addendum to provide more details in the study methodology if so needed."

DIALOGUE SESSION ON THE CONSULTATION PAPER "ADVANCING THE FRAMEWORK OF ETHICS GOVERNANCE FOR HUMAN RESEARCH"

20 Chairpersons and Representatives of the hospital ethics committees or institutional review boards (IRBs) of 17 organisations met with seven members of the Bioethics Advisory Committee (BAC) on 7 November 2003. This Annexe provides a summary of the comments and concerns raised at the dialogue session between the parties.

Organisation Represented:

1. Alexandra Hospital
2. Changi General Hospital
3. Health Promotion Board
4. Institute of Mental Health/Woodbridge Hospital
5. Institute of Molecular and Cell Biology
6. KK Women's and Children's Hospital
7. National Cancer Centre
8. National Dental Centre
9. National Healthcare Group
10. National Heart Centre
11. National Medical Ethics Committee
12. National Neuroscience Institute
13. National University Hospital
14. National University of Singapore
15. Parkway Group Healthcare Pte Ltd
16. Singapore Tissue Network
17. Tan Tock Seng Hospital

Summary of Comments and Concerns Raised at the Dialogue Session

Intention of the Consultation Paper

IRB: Rules set for the industry quickly become obsolete given the speed of progression in biomedical sciences.

BAC: The preliminary Recommendations advanced in the Consultation Paper (Paper) are not meant to be cast in iron but will be reviewed as and when the need arises. This is to be expected not only with the advancement of science, but also as values and laws of the society evolve over time. The intention behind the Paper is to establish a framework for the Government to consider when to implement appropriate policies on the ethics governance of human research. One of the main motivations of the Recommendations is to harmonise the ethical standards for all research institutions and their IRBs. Such standards, as prescribed in the Paper, are universally accepted and hence would provide greater public assurance.

Role of Principal Investigators

IRB: In large multinational studies, a local principal investigator (PI) should have a greater role in the design, conduct, monitoring and analyses of the studies.

BAC: This concern is noted and will be highlighted to the Ministry of Health (MOH).

Requirements in Obtaining Informed Consent

IRB: One of the provisions in the Paper is for a witness to be present at the consent-taking process (paragraph 5.57). Will the witness be required to observe the entire process or just the endorsement of the consent form?

BAC: The purpose of that provision is to have an independent person ensure that the human subject understands what he/she is consenting to. This requirement does not entail any departure from normal medical procedures. As the Paper is meant to provide only a framework for ethics governance, the actual procedure for the procurement of consent will not be prescribed here.

Role of a Supervisory Body for IRBs

IRB: Will there be a central body to keep check on the standards of ethics governance of each institution? If so, some form of penalty needs to be prescribed for non-compliance so that the standards can be effectively maintained. Revocation of the accreditation of an IRB can be such a penalty.

BAC: The BAC recommends that a central supervisory authority be established to either license each institution or grant an umbrella licence to a group of institutions. This authority will be empowered to accredit and audit licensed institutions. A majority of the large hospitals will be licensed by their areas of competence. Licence can also be granted based on specific conditions. Such a

supervisory authority will therefore impose two kinds of checks – licensing and accreditation.

Role and Responsibilities of IRBs

Continuing Review, Supervision and Audit

IRB: Can the BAC clarify what it means by "continuing review" (paragraph 5.15.2)?

BAC: The BAC has received several responses on this issue. By "continuing review", the BAC intends to empower IRBs to carry out audits. This empowerment will change the mindset of some PIs who consider the IRB approval of research proposals as a one-off threshold clearance. IRBs should review on-going research even after it has given its initial approval for the research proposal. The Paper will be amended to clarify this issue.

IRB: Can a separate body be assigned to conduct audit in order to alleviate the workload of IRBs?

BAC: An IRB need not perform the audit itself but it has to have the means to monitor any deviations from the proposed research protocol. For example, the IRB can mandate an annual report and a completion report, or it can appoint independent auditors to carry out audits.

However, it may be better for IRBs to carry out audits themselves, as appointing independent auditors may result in IRBs having to check on two parties. A research may have wide social impact and IRBs should ensure that the research is done in accordance with the approved protocol, with particular focus on the safety and privacy of human subjects. Other concerns, such as scientific validity of the research, are secondary.

IRB: This is not feasible. Some IRBs are currently overloaded with protocols for review (200-400 per year). It is not only difficult for IRBs to find time for the added audit responsibilities, but is also difficult for IRBs to find people with the time and capability to perform independent audits on their behalf. In addition, certain IRBs have difficulty coping with a large number of annual reports.

BAC: Institutions should provide their IRBs with adequate resources to enable them to discharge their responsibilities.

In addition, institutions should be the ones to select the independent auditors. The main requirement of audit is to assess ethical merits, not scientific merits.

IRB: Although not officially or legally empowered, one impression is that IRBs have the power to investigate ethics violations even after the protocol has been approved. Do the recommendations require more of IRB than what is already being done?

BAC: IRBs will need to report to a national supervisory body.

IRB: The Singapore Guideline for Good Clinical Practice (SGGCP) has clearly delineated the roles of monitors, sponsors and auditors. The Paper should follow the SGGCP's framework so that the IRB's responsibility is clearly and primarily confined to a review of documents.

BAC: One of the purposes of this Paper is to extend the rules in the SGCCP on clinical drug trials to non-drug trials. An IRB is not the enforcer of these rules and these provisions should not lead to unnecessary bureaucracy that stifles research.

IRB: There are situations where IRB members find it difficult to confront researchers who are very senior in rank. In fact, many researchers in certain countries who have flouted ethics rules were highly regarded PIs.

There is a huge gap between the recommended standards and what IRBs can achieve. While the responsibilities spelt out are probably appropriate, IRBs currently do not have the capacity to take on all of them.

BAC: In the UK, IRBs are not the ones who conduct investigation at the research level. It is important for IRBs to have the power to require that an audit be performed. Such controls will reassure the public that adequate protection is in place.

IRB: The responsibilities of IRBs in reviewing, supervising and auditing, as well as the means of discharging these responsibilities, need to be more clearly defined. Often, the problem lies not with the lack of regulations (because these are present), but with the lack of people to implement them. Monitoring and auditing of research protocols should be conducted at two levels: at the institution-level, at which independent inspectors are authorised to examine any records at random and report their findings to the IRB; and at the level of the accreditation body, which can mandate that research institutions submit reports.

However, the two-tier approach will be cumbersome. Instead, IRBs should be allowed to decide which projects will require continuing review. It is likely that the IRBs will be asked by their institutions to recommend suitable candidates for the role of auditors, but IRBs may not be able to do so. Therefore recommendations from the BAC or the national supervisory body will be desirable.

BAC: It is the PIs' responsibility to report changes in the protocol to their IRBs and should not require the IRBs to press them to do so. The BAC will make clear recommendations for necessary resources to be made available by institutions and for reports to be made available to the IRBs. The BAC will attempt to do this without introducing excessive bureaucracy to the system. Reports are required for internal audits of most institutions. Hence the requirement for reports to be submitted to the IRBs should be no more than a small responsibility. The kind of audit which the BAC has in mind should be simple

and manageable at a certain level by non-medical staff. More important, institutions should ensure that IRBs have sufficient time to perform their functions. IRBs should grow beyond honorary bodies to become full administrative bodies. There is also a need for institutions to provide legal protection for IRB members.

Responsibility for Scientific Review

IRB: IRBs are often required to assess scientific merits besides ethical merits. Most institutions do not have enough resources to support both an ethics review board and a scientific review board.

BAC: The BAC understands that a proper ethics review should take into account scientific merits, but the BAC's focus is on the social impact of the research. The BAC recognises that small institutions may not be able to set up a separate scientific review body. Hence it allows institutions the freedom to decide if they want their IRBs to be responsible for both ethics and scientific review.

Requirement for IRB Members to Meet Face to Face

IRB: Other forms of meeting such as by teleconference or video-conference should be acceptable forms of meetings besides a face-to-face meeting. Such forms of meetings were used by institutions during the SARS crisis.

BAC: These other forms of meetings are acceptable. The intention of requiring face-to-face meetings is to ensure proper communication and decision-making. Decisions should not be made by way of e-mail correspondence. The BAC is concerned that an IRB member may not be fully aware of another member's evaluation of, and comments on, a research proposal under review.

IRB: There are international requirements, such as in the US, for IRB members to meet face to face. Singapore should conform to such international practices.

BAC: Certain research proposals may be subject to expedited review and thus a decision need not be made at a face-to-face meeting.

Special IRBs

IRB: In some countries, IRBs are removed from the auspices of institutions and yet some other institutions, such as the UK National Health Services, share IRBs. The motive is to secure the independence of IRBs from their appointing institutions and thereby avoid conflict of interest.

However, it is the institution's responsibility to ensure that its appointment of IRB members will not result in any conflict of interest. If an IRB is separated from an institution, it will not be able to familiarise itself with the operations of that institution. Hence, the two-tier approach is a good one.

However, there are commercial IRBs in the US that are independent of an institution. These IRBs have been mentioned in the Paper. They can be an option for us. The members of commercial IRBs are recruited from a large range of institutions. They do not serve on the IRB full-time and are paid about US$200 per protocol reviewed.

BAC: A reason for the acceptance of commercial IRBs in the US is that they provide a liability shield for research institutions, as these IRBs are adequately insured. The concept of commercial IRBs is culturally new to Singapore and may not be applicable within the local context.

In a small nation like Singapore, IRBs operating outside an institution will not solve issues of conflict of interest. Nonetheless, the BAC welcomes the idea of shared IRBs or domain-specific IRBs, which have been described in the Paper.

IRB: Domain-specificity is advantageous as there will be a need for IRB members with the suitable expertise for evaluating specialty research protocols. Another potential problem to note with respect to the small size of the local medical community is the 'rubber-stamping' of one another's research protocol, because most of members of the community recognise one another's field of work.

Conclusion

BAC: The BAC will consider all suggestions that have been made and will try to address as many of the issues that have been raised. Some of the provisions in the Paper may have been misinterpreted as excessive. These provisions will be clarified by the BAC in its recommendations to the Government. It is emphasised that the provisions and recommendations issued by the BAC are only intended as general guidelines. The BAC thanks all participants for their time and valuable input.

SELECT REFERENCES

International

1. Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects (2000)
   World Medical Association

2. ICH Topic E6 - Guideline For Good Clinical Practice (1996)
   International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

3. International Ethical Guidelines for Biomedical Research Involving Human Subjects (2002)
   Council for International Organizations of Medical Sciences

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

5. Operational Guidelines for Ethics Committees that Review Biomedical Research (2000)
   World Health Organization

6. Proposed International Guidelines on Ethical Issues in Medical Genetics and Genetic Services (1998)
   World Health Organization

7. Universal Declaration on the Human Genome and Human Rights (1997)
   United Nations Educational, Scientific and Cultural Organization

Singapore

1. Ethical, Legal and Social Issues in Human Stem Cell Research, Reproductive and Therapeutic Cloning (June 2002)
   Bioethics Advisory Committee

2. Human Tissue Research (November 2002)
   Bioethics Advisory Committee

3. National Medical Ethics Committee: A Review of Activities, 1994-1997 (1998)
   National Medical Ethics Committee, Ministry of Health

4. Singapore Guideline for Good Clinical Practice (1998)
   Ministry of Health

Other Countries

1. National Statement on Ethical Conduct in Research Involving Humans (1999)
   National Health and Medical Research Council, Australia

2. Human Research Ethics Handbook (2001)
   National Health and Medical Research Council, Australia

3. Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (1998, with 2000, 2002, 2003 updates)
   Medical Research Council, Natural Sciences and Engineering Research Council, and Social Sciences and Humanities Research Council, Canada

4. Governance arrangements for NHS Research Ethics Committees (July 2001)
   Department of Health, United Kingdom

5. Research Governance Framework for Health and Social Care, 2nd edition draft (April 2003)
   Department of Health, United Kingdom

6. Code of Federal Regulations Title 45 Public Welfare – Part 46: Protection of Human Subjects (2001)
   Office for Protection from Research Risks, National Institutes of Health, Department of Health and Human Services, U.S.A.

7. Ethical and Policy Issues in Research Involving Human Participants (August 2001)
   National Bioethics Advisory Commission, U.S.A.

8. The Belmont Report (1979)
   National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, U.S.A.

LIST OF ABBREVIATIONS

BAC	Bioethics Advisory Committee (Singapore)
CEO	Chief Executive Officer
DNA	Deoxyribonucleic acid
EC	Ethics committee
GCP	Good Clinical Practice
HGS	Human Genetics Subcommittee
HSA	Health Sciences Authority (Singapore)
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
MCRC	Medical Clinical Research Committee
MOH	Ministry of Health (Singapore)
NHG	National Healthcare Group (Singapore)
NMEC	National Medical Ethics Committee (Singapore)
NUH	National University Hospital
PI	Principal Investigator
RNA	Ribonucleic acid
SGGCP	Singapore Guideline for Good Clinical Practice
SOP	Standard Operating Procedure
UNESCO	United Nations Education, Scientific and Cultural Organization
WHO	World Health Organization