

ETHICS GUIDELINES FOR HUMAN BIOMEDICAL RESEARCH

BIOETHICS ADVISORY COMMITTEE
SINGAPORE

June 2015

FOREWORD

The *Ethics Guidelines for Human Biomedical Research* is a timely publication to mark the 15th anniversary of the Bioethics Advisory Committee (BAC). The landscape of the biomedical sciences in Singapore has changed tremendously since the inception of the BAC. When BAC first started in 2000, Singapore did not have a robust system of ethics review for human biomedical research in place. The BAC's recommendations over the years have contributed to the establishment of a framework of research ethics governance in Singapore. Today, all human biomedical research in public healthcare, tertiary and research institutions are reviewed, and there are ethics governance frameworks in place to ensure that research participants are properly protected.

The BAC strives to make recommendations that are aligned with international best practices, but also sensitive to and applicable in our local context. As some of the recommendations that BAC had made were issued more than a decade ago, it is important that these positions are revisited, to ensure their relevance given scientific, regulatory and legal developments. This will facilitate in ensuring that human biomedical research in Singapore continues to be conducted in accordance with ethical standards that are recognised internationally. Ethical pronouncements on what is considered sensitive or unacceptable may change with time as a result of research and technological advances, or in accordance with social or cultural developments. Regular reviews are therefore important to remain in touch with the public's sentiments and concerns, to ensure that there is adequate regulation for the protection of research participants, and not unduly impede potentially beneficial research. The BAC plays a crucial role in maintaining public trust so that biomedical sciences may flourish in Singapore.

Judge (ret.) Richard Magnus and his committee members have done a commendable job in producing such a comprehensive ethical guidance document for all who are involved in human biomedical research in Singapore. They have thoroughly reviewed the BAC's past recommendations, re-engaged the research community and public on pertinent issues arising from areas such as stem cell research and genetic research, and compiled the relevant recommendations into a single, concise volume. I am confident that the standards and recommendations advocated in the *Guidelines* will enhance the responsible and ethical conduct of human biomedical research in Singapore.

Professor Lim Pin
Emeritus Advisor
Bioethics Advisory Committee
June 2015

PREFACE

As the BAC celebrates its 15th anniversary this year, we have reviewed the recommendations that the committee has made in the seven reports issued since its inception in 2000. The BAC was set up with the aim of protecting the rights and welfare of individuals, while allowing the development of biomedical sciences for the benefit of mankind, and this continues to be the impetus guiding the BAC in its work.

In accordance with our mandate, the BAC has examined a wide range of topics, including human stem cell research, reproductive and therapeutic cloning, human tissue research, human genetics research, personal information, egg donation, and human-animal combinations – with an overarching focus on the area of human biomedical research. Given the extensive subject matter that the BAC has covered over more than a decade, we decided to consolidate our past recommendations into a single volume. We hope that the *Ethics Guidelines for Human Biomedical Research* will be an accessible resource for researchers and members of ethics committees, or any interested individual who is seeking guidance on the best practices for the ethical conduct of human biomedical research in Singapore.

During the course of preparing the *Guidelines*, we also took the opportunity to reflect on the BAC's past recommendations, review our positions where appropriate after taking into account new scientific, regulatory and legal developments. This was done to ensure that we are up-to-date with both local practices and international best standards. We sought to reconcile any apparent discrepancies, and to clarify any uncertainties that have emerged since publication of our original reports. This resulting document therefore contains the most current views of the BAC, advocating the standards expected of researchers and research institutions in Singapore, and setting out a framework for the ethics review of human biomedical research. Furthermore, in the course of our review, we have also deliberated on recent emerging issues, such as incidental findings and whole genome sequencing, and have incorporated new ethical guidance on these issues into the *Guidelines*.

The *Guidelines* was an ambitious project, and is the result of countless hours of deliberation and conversations. I would like to express my heartfelt gratitude to my dedicated committee members, and our distinguished panel of international experts, for their tireless commitment to the development of these *Guidelines*. I would also like to thank members of the research community and the general public, who participated in our public consultation sessions and provided us with valuable comments on the 2012 draft. Their thoughtful feedback spurred further debate, and helped us to refine our consideration of pertinent issues. While our views may not always be compatible, we are nevertheless grateful for all the inputs we have received.

Judge (ret.) Richard Magnus
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About the Bioethics Advisory Committee

The Bioethics Advisory Committee (BAC) was established by the Singapore Cabinet in December 2000 to examine the ethical, legal and social issues arising from biomedical research, and to develop and recommend policies to the Government on these issues. It aims to protect the rights and welfare of individuals, while allowing the biomedical sciences to develop and realise their full potential for the benefit of humankind.

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CONTENTS

EXECUTIVE SUMMARY		1
PART I	INTRODUCTION	9
	What is Human Biomedical Research?	10
	The Legislative and Regulatory Framework of Human Biomedical Research in Singapore	12
PART II	ETHICS GOVERNANCE OF HUMAN BIOMEDICAL RESEARCH	15
	General Ethical Principles That Have Guided The BAC	15
	Ethics Review of Human Biomedical Research in Singapore – The IRB System	19
	Guidelines on Ethics Governance of Human Biomedical Research	21
PART III	CONSENT	25
	Voluntary and Informed Consent	25
	Specific and General Consent	26
	Consent Involving Vulnerable Persons	27
	Waiver of Consent	31
	Clinically Significant Incidental Findings	32
	Guidelines on Consent	33
PART IV	PERSONAL INFORMATION IN RESEARCH	36
	Protection of Personal Information	36
	Use of Medical Records for Research	38
	Epidemiological and Public Health Research	38

	Guidelines on the Use of Personal Information in Research	39
PART V	BIOBANKING AND RESEARCH INVOLVING HUMAN BIOLOGICAL MATERIALS	41
	Guidelines on Biobanking and Research Involving Human Biological Materials	42
PART VI	HUMAN GENETIC RESEARCH	49
	Guidelines on Human Genetic Research	52
PART VII	HUMAN STEM CELL RESEARCH	53
	Legislation	54
	Ethical and Social Issues	55
	Guidelines on Human Stem Cell Research	57
GLOSSARY		61
BIBLIOGRAPHY		63
ANNEX A	CONSULTATION PAPER: ETHICS GUIDELINES FOR HUMAN BIOMEDICAL RESEARCH	
ANNEX B	CONSULTATION PAPER DISTRIBUTION LIST	
ANNEX C	WRITTEN RESPONSES RECEIVED DURING THE PUBLIC CONSULTATION	

ETHICS GUIDELINES FOR HUMAN BIOMEDICAL RESEARCH

EXECUTIVE SUMMARY

I. Introduction

1. The *Ethical Guidelines for Human Biomedical Research* are intended to serve as an ethical resource for researchers and members of ethics committees or institutional review boards (IRBs). It is based on a review of the previous seven reports and recommendations of the Bioethics Advisory Committee (BAC), issued between 2002 and 2010.
2. The *Guidelines* should be taken as definitive at the date of publication. It seeks, in part, to reconcile apparent discrepancies and clarify uncertainties emerging since the original reports were published. Some new material has also been included in the *Guidelines*.

II. Ethics Governance of Human Biomedical Research

3. An IRB should review all human biomedical research and the composition of the IRB should combine appropriate expertise with some lay representation to reinforce the objectivity and impartiality of the process. The composition of IRBs and specific functional and operational details are provided for in the MOH Operational Guidelines for Institutional Review Boards.
4. The level of detail required in a research protocol submitted for IRB review should vary in proportion to the identifiable risk or sensitivity of the research. IRBs may conduct either full or expedited reviews, or grant exemptions from ethics review. An expedited review is permissible for research that involves no more than minimal risk to research participants while exemptions from review must involve no likelihood of harm to research participants. The Chairperson or other IRB delegate(s) may be empowered to conduct expedited reviews or grant exemptions.
5. Minimal risk refers to an anticipated level of harm and discomfort that is no greater than that ordinarily encountered in daily life, or during the performance of routine educational, physical, or psychological tasks.
6. In multi-centre research, a lead IRB could be designated that plays the main role in conducting a full ethics review. Multi-national research should be subject to review by the IRB of the local partner institution(s).
7. Institutions have the overall responsibility of ensuring the proper conduct of human biomedical research carried out in their premises or facilities; or by their employees or

on their patients; or involving access to or use of human biological materials, medical records or other personal information in their custody. They are also responsible for ensuring research integrity.

8. Every institution that conducts human biomedical research, or allows such research to be carried out in its premises, should establish and maintain an appropriately constituted and effective IRB, or ensure that its research staff have access to an IRB at another institution. Should a research proposal be rejected by an IRB, an appeal mechanism should be available in which a second committee must be able to exercise independent judgement.
9. The responsibilities of the researchers include ensuring that their research is conducted with integrity and complies with all relevant laws and other regulatory obligations and requirements; submitting annual (or more frequent) progress reports as required by the IRBs; reports of adverse events arising from the research should be submitted to the IRBs within 15 days of their occurrence, while serious adverse events should be reported immediately; not altering or modifying in any way any drug or other clinical regimen without the IRB's and attending physician's approval; and ensuring that participants are informed of clinically significant findings that are discovered in the process of research, if they have indicated their desire to know these.

III. Consent

10. Consent for participation in research must be voluntary. There should be no coercion, deception or undue influence. Participants may be reimbursed for legitimate expenses. Any other payment, whether monetary or in kind, should not amount to an inducement, and should be approved by an IRB. Consent to participation in research should be documented in writing.
11. Keeping research participants in ignorance of a research hypothesis, or of which intervention group they have been assigned to, does not amount to deception. However, the need to keep participants ignorant of a research hypothesis should be disclosed and justified to the satisfaction of an IRB. It is also best ethical practice to highlight to the participant the fact that, for methodological reasons, not all information concerning the research hypothesis and protocol will be revealed.
12. Prospective research participants or their legally authorised representatives should be provided with sufficient information in an understandable form and appropriate manner, to enable them to make an informed decision.
13. Consent could be specific to a particular research project, or general for the storage and future use of biological materials or personal information in research. In any general consent, donors should be allowed to impose some limits to the use of their biological materials or personal information. IRBs should have the discretion to decide, when considering a research proposal, whether specific consent is required or general consent is sufficient, if previously given.

14. For research involving vulnerable persons not lacking mental capacity (for example, prisoners, uniformed personnel, and employees), consent should be taken by independent third parties, whenever possible. When it is not possible for consent to be taken by an independent third party, the IRB may give directions for the consent to be taken by the researcher so long as there are provisions to manage the conflict of interest and sufficient safeguards to protect the welfare and interests of the participants.
15. For research involving patients, consent for participating in research should be clearly separated from consent for treatment. When a researcher is also the attending physician, the consent for research should ideally be taken by an independent third person. If it is not possible, IRBs may give directions for the consent to be taken by the researcher-physician so long as there are provisions to manage the conflict of interest and sufficient safeguards to protect the welfare and interests of the patient.
16. For research involving minors with decision-making capacity, consent from both the minor and a parent should be obtained; such a minor's refusal of consent should be respected. Apart from this, it is still important to engage the minor in ways that respect his or her current level of understanding. Parents or guardians of minors lacking decision-making capacity are authorised to consent to their participation in research that involves no more than minimal risk and is not contrary to their best interests. For research that does not involve more than minimal risk, such as surveys seeking information relating only to the minor, IRBs should be able to waive parental consent for minors who have decision-making capacity, where there is otherwise no prohibition by law and parental consent is not a reasonable requirement for the protection of the minor's interests.
17. IRBs may consider a waiver of the consent requirement for research done in the public interest, typically in epidemiological or public health research carried out with medical records or with data from national registries.
18. For research involving recruitment of highly compromised patients who are unable to give consent and for whom no proxy is available to give consent, and subject to the treatment of the patient remaining the priority, IRBs may authorise the research if it involves no more than minimal risk. Consent must be sought, directly or from a proxy, as soon as is practicable. The patient or proxy shall have every right to withdraw or decline with retrospective effect (which will require removing earlier collected data or biological material from the study).
19. Where there is a possibility that the research may yield clinically significant incidental findings, participants should be allowed to decide whether or not to be informed of such findings, during the consent-taking process.
20. If a clinically significant finding is discovered, but the preference of the research participant for receiving such information is unknown, researchers should refer to their IRBs for advice on the appropriate handling of such information.

IV. Personal Information in Research

21. All biomedical research involving personal information, whether identified or de-identified, should be reviewed by an IRB and approved, or granted an exemption from review, before it commences. IRBs should have the discretion to decide whether specific consent is required or general consent is sufficient for the particular project.
22. It is not practicable to give research participants a right to view, amend, delete or otherwise control data they have provided for research purposes. Information created through research should be managed in ways that respect the need to observe confidentiality and care in use. It should remain in the care of and for the use of the researcher, subject to ethics governance procedures, rather than being treated as the continued property of the research participant or 'donor'.
23. Personal information used for research should be de-identified as early as possible, and stored and managed as de-identified information. The principle of proportionality applies, such that the level of care and urgency regarding de-identification and data protection should be consistent with the sensitivity of the data. IRBs should consider the suitability of the extent and means of the de-identification in proportion to the risk.
24. To maximise the value of data and biological materials collected in cohort or follow-up studies, where a large amount of data is collected for analysis, it should be managed as reversibly de-identified data. Under the Personal Data Protection Act 2012 (PDPA), an organisation that collects and de-identifies personal data for processing and storage is still considered to hold personal data if it retains the ability to re-identify the data. Thus, in the re-identification of reversibly de-identified data, the management of the key to any code or encryption can and generally should be separated from the management of the data.
25. Should an individual be identified inadvertently from de-identified information, the confidentiality and privacy rights of this individual should not be regarded as abrogated by such identification, and steps should be taken to reinstate and secure them.
26. Healthcare institutions should ensure that clear formal procedures are laid down for the release of medical records and other personal information for research, and to formulate these procedures in consultation with their IRBs.
27. IRBs may waive the consent requirement for the use of personal information for epidemiological or public health research, or the use of medical records for research, if they are satisfied that the following conditions are met:
 - (a) The research is justified and poses no more than minimal risk to individuals concerned;
 - (b) The research could not practicably proceed without the waiver;
 - (c) Obtaining consent is not possible or practicable; and

(d) Individual privacy and confidentiality of the personal information are assured.

28. Research information may not be definitive, and research participants are entitled to expect that their data will not be used for purposes other than those for which they have given consent. Thus, such information should not be disclosed to any third party, including employers or insurance companies.

V. Biobanking and Research Involving Human Biological Materials

29. Informed consent must be obtained before any human biological materials are taken for use in research. If the materials are intended for storage and future use in research, consent should also be obtained for this purpose.

30. Re-consent is required in the following situations:

(a) When the proposed research is not covered by the consent that was given when the biological materials were collected (unless the re-consent requirement is waived by an IRB);

(b) If the biological material was collected from a minor below 21 years of age, who did not at the time of collection possess decision-making capacity and therefore did not personally, or jointly together with his/her parent, consent to the donation. In the event that re-consent is not practicable, the IRB should generally have the discretion to waive the requirement in accordance with the relevant criteria for waiver of consent, where appropriate; or

(c) For research deemed to be sensitive, such as that involving human eggs and embryos, or human-animal combinations.

31. Under the Medical (Therapy, Education and Research) Act, any person who is not mentally disordered and who is 18 years of age or above may give all or any part of his or her body for research or for therapy. The gift will take effect upon death. Legally authorised relatives of deceased individuals (which include still-born infants and foetuses) may also give all or part of the deceased person for research after or immediately before death.

32. For research using foetal tissues, consent for the termination of pregnancy should be separate from the consent for obtaining foetal tissue or any tissue related to the pregnancy for research. Where possible, an attending physician should not also seek consent for research participation from a patient in this situation. Consent for the use of foetal tissue for research could be obtained from either parent, as provided for in the Medical (Therapy, Education and Research) Act.

33. Specific and personal consent from the donors must be obtained before any gametes or embryos are to be used for research. Potential donors should be provided with sufficient information to make an informed decision and be given at least a week to decide.

34. For women undergoing fertility treatment, consent for the donation of surplus oocytes or embryos for research should be separate from the consent for treatment. The treating physician should not also be the researcher seeking consent for the donation of oocytes or embryos for research. Donors should confirm in writing that they do not require the oocytes or embryos for future use.
35. Women wishing to donate eggs specifically for research must be interviewed by an independent panel. The panel must be satisfied that they are of sound mind, clearly understand the nature and consequences of the donation, and have freely given explicit consent, without any inducement, coercion or undue influence.
36. If complications occur as a direct and proximate result of the egg donation, the donor should be provided with prompt and full medical care. This provision is the responsibility of the researchers and their institutions.
37. Trans-species fertilisation involving human gametes is not allowed for the purpose of reproduction unless done to assess or diagnose sub-fertility, in which case, the resultant hybrid must be terminated at the two-cell stage, and must have written approval from the Director of Medical Services.
38. Human embryos created for research through *in vitro* fertilisation of human eggs by human sperm, or created through any form of cloning technology, should not be allowed to develop beyond 14 days *in vitro*, or to be implanted into the body of any human or animal.
39. Human cytoplasmic hybrid embryos created for research should not be allowed to develop beyond 14 days *in vitro*, or to be implanted into the body of any human or animal.
40. Every effort should be made to obtain consent for the use of surplus biological materials for research. As the primary objective for removing such materials is clinical, consent for the clinical procedure should be separate from the consent for the use of left over materials for research. Consent for research should only be taken after consent has been given for any clinical procedure and it should be taken by a different person. If this is not possible, the IRB may give directions for the consent to be taken by the researcher-physician so long as there are provisions to manage the conflict of interest and sufficient safeguards to protect the welfare and interests of the patient.
41. If consent could not be obtained for the use of surplus biological materials for research, IRBs should have the discretion to waive the consent requirement if the patient is not identifiable, since the research protocol would not have influenced the procedures used in obtaining the biological materials. Healthcare institutions should inform patients that there is a possibility that their surplus biological materials may be used for research.
42. Proposed research with legacy tissue should undergo IRB review. IRBs may waive the consent requirement for the use of legacy tissues for non-sensitive research under the following conditions:

- (a) If the tissues are irreversibly de-identified and there is thus no possibility of re-identifying the individuals who have contributed the tissues; or
- (b) If the tissues are identifiable but it is impossible or impracticable to seek consent from the individuals who have contributed the tissues. In this case, IRBs should ensure that adequate measures are in place to protect the privacy of the donors and the confidentiality of any personal information associated with the tissues.

VI. Human Genetic Research

- 43. All human genetic research should be reviewed by an IRB and approved before it commences. A written approval from the MOH is also required if the research involves human eggs and embryos.
- 44. Participation in genetic research should be voluntary, whether directly or by contribution of biological materials or personal information.
- 45. When clinically significant findings are discovered in the course of any genetic research, researchers should ensure that affected participants are informed, if they have indicated their desire to know.
- 46. In whole-genome research, participants should be provided with as much detailed information as possible that is specific to such research, during the consent taking process. They should be informed of the mechanisms for data security, and given an explanation on the nature of whole-genome research, highlighting the difficulty in guaranteeing their anonymity with complete certainty. As the dissemination of information in whole-genome research is likely to be rapid and wide, there will also be practical limitations on withdrawal from such research. Participants should be informed of these limitations and the implications of their withdrawal.

VII. Human Stem Cell Research

- 47. Human stem cell research that is not ethically contentious, such as research using established pluripotent stem cell lines and confined to cell culture or research that involves routine and standard research practice with laboratory animals, should be exempted from review. All other human stem cell research should undergo full or expedited review by an IRB. Approval from MOH must also be obtained if the research involves the use of human eggs, human embryos, or human-animal combinations.
- 48. In human-animal combinations research involving live animals or resulting in the creation of live animals, the IRB should also ensure that the proposal has been approved by the Institutional Animal Care and Use Committee, whose remit covers the welfare of laboratory animals.
- 49. Where human embryonic stem cells, induced pluripotent stem cells, or any other kind of pluripotent stem cells are introduced into animals at any stage of development, particular attention should be paid to the need to avoid the creation of entities in which human sentience or consciousness might be expected to occur.

50. Animals into which human embryonic stem cells, induced pluripotent stem cells, or any other kind of pluripotent stem cells have been introduced should not be allowed to breed.

51. If the research involves introducing human embryonic stem cells or any pluripotent cells, or products derived from these cells, into humans, or any novel applications of any stem cells that are outside the scope of established standards of medical care, it should be conducted in accordance with the requirements and standards of a clinical trial for cell-based products, as specified by the HSA, and approval from HSA must be obtained. IRBs must ensure that:
 - (a) The proposal is reviewed and approved by a scientific review committee with the relevant expertise;
 - (b) There is strong evidence of the safety and efficacy of the cells from pre-clinical studies;
 - (c) The research participants have been provided with sufficient information, in particular information on the nature and risks of the research, and the source of the cells, so that their values and beliefs are respected; and
 - (d) Appropriate and informed consent has been obtained, without any inducement, coercion or undue influence.

ETHICS GUIDELINES FOR HUMAN BIOMEDICAL RESEARCH**I. INTRODUCTION**

- 1.1 The main purpose of these *Guidelines* is to present an accessible and updated ethics resource for researchers and members of ethics committees or institutional review boards (IRBs), based on a review of the previous reports and recommendations of the Bioethics Advisory Committee (BAC).
- 1.2 The BAC was formed in 2000 to examine the ethical, legal and social issues arising from research on human biology and behaviour, and its applications. The Committee develops and recommends policies on such issues, with the aim of protecting the rights and welfare of individuals, while allowing the biomedical sciences to develop and realise their full potential for the benefit of humankind.
- 1.3 The work of the BAC since its inception has focussed on human biomedical research. This is captured in seven reports issued between 2002 and 2010. In 2011, the BAC reviewed its past reports, and prepared these for consolidation in the *Ethics Guidelines for Human Biomedical Research*.
- 1.4 The views of the BAC presented in these *Guidelines* should be taken as definitive as at the date of publication. These *Guidelines* seek to reconcile any apparent discrepancies and clarify any uncertainties emerging since the original reports were published. Some new material has also been included. The original reports remain available as primary sources of information.
- 1.5 The seven BAC reports that form the basis of these *Guidelines* are referred to throughout as follows:
 - (a) The *Stem Cell Report*. Ethical, Legal and Social Issues in Human Stem Cell Research, Reproductive and Therapeutic Cloning (2002);
 - (b) The *Tissue Report*. Human Tissue Research (2002);
 - (c) The *IRB Report*. Research Involving Human Subjects: Guidelines for IRBs (2004);
 - (d) The *Genetics Report*. Genetic Testing and Genetic Research (2005);
 - (e) The *Personal Information Report*. Personal Information in Biomedical Research (2007);
 - (f) The *Egg Donation Report*. Donation of Human Eggs for Research (2008); and
 - (g) The *Human-Animal Combinations Report*. Human-Animal Combinations in Stem Cell Research (2010).

What is Human Biomedical Research?

- 1.6 Biomedical research is important because it is a basic prerequisite for evidence-based medicine. Research, in this context, means “a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalisable knowledge.”¹ Although the observations and clinical experiences of medical practitioners and others have been vital in the history of medicine, the systematic scientific foundations are also essential. While good medical practice entails far more than the mechanical application of science, good biomedical research is fundamental to its success, and is a safeguard against unsubstantiated or harmful claims. Biomedical research in general is thus regarded by the BAC as a public good.
- 1.7 Biomedical research has been defined as research having as its purpose the enhancement or improvement of medical practice.² This extends the scope of biomedical research beyond research that is clinical, and it could include research that does not use human participants at all. Much fundamental research in physiology and other disciplines has the goals of medicine as its ultimate aim. In a similar way, the goal of much bioengineering research is ultimately medical, though this is not true of the foundational disciplines in engineering. For these reasons, it is difficult to provide a single definition that covers all obvious examples of research that have a clearly medical goal, while not becoming over-inclusive with respect to basic research that might ultimately be important for medicine but is not done with the primary aim of furthering its goals.
- 1.8 The BAC therefore adopts the following definition of human biomedical research:

Human Biomedical Research refers to any research done for the ultimate purpose of studying, diagnosing, treating or preventing, any disease, injury, disorder, or condition of the human mind or body, and which entails the involvement of humans, human biological materials or information derived from humans or human biological materials. Also included is research on human physiological processes.

- 1.9 The BAC takes the view that human biomedical research usually needs to be regulated because one or more of the following conditions will inevitably apply to any proposed human biomedical research:
- (a) The research involves intervention with respect to, interaction with, or observation of one or more human participants;
 - (b) The research will use or manipulate human biological materials (e.g. human cells, tissues, organs and body fluids);
 - (c) The research entails the systematic review, analysis, use or publication of previously compiled identifiable (identified or reversibly de-identified) medical or personal information or biodata;

¹ Office for Human Research Protections, 45 Code of Federal Regulations 46.102(d).

² Levine, RJ. The Nature, Scope, and Justification of Clinical Research. In Emanuel, EJ *et al.* (Eds.) *The Oxford Textbook of Clinical Research Ethics*. Oxford: OUP (2011), page 211.

- (d) The research topic is sufficiently sensitive to likely raise questions of public acceptability or public policy (e.g. research on human embryos or human-animal combinations); or
 - (e) The research could be considered sensitive by virtue of the nature of the personal information it proposes to gather.
- 1.10 The BAC is concerned with human biomedical research, and not with the wider issues of research with human participants generally. It does not seek to determine the extent to which ethics governance for the protection of human participants should be extended to research that is not biomedical, though this is clearly a matter of importance and public interest. It does, however, cover economic, sociological and other research in the humanities and social sciences whenever this research fits the above definition of human biomedical research.
- 1.11 The BAC also recognises that human biomedical research could be more or less sensitive in character, where ‘sensitivity’ depends on societal considerations. For example, research that relies on sensitive information, such as participants’ sexual practices or psychiatric history, would *ipso facto* be regarded as sensitive research. Similarly, research on cloning technology would generally be considered sensitive simply because the idea of using the technology it generates to clone a human being is widely seen as unacceptable. Research deemed sensitive would attract more exacting regulatory control, or could be prohibited.³
- 1.12 Human biomedical research can be basic and far removed from the likelihood of immediate application, or it can be explicitly clinical and therapeutic in character. Clinical research includes clinical trials, which are regulated by the Health Sciences Authority (HSA) in Singapore.
- 1.13 There is a long tradition in medicine of medical practitioners publishing clinical case reports based on their own cases, and these reports have often been a valuable source of learning in the profession. The BAC is of the view that the publication of case reports not amounting to a systematic programme of research is under the purview of journal editors and the Singapore Medical Council, as the latter is the authority for upholding the requirements of professional medical ethics and conduct in Singapore. Such publication does not necessarily require independent ethics review, as both medical ethics and conduct, and the requirements of journal editors that informed consent be obtained, offer safeguards against the improper publication of case reports.

³ The sensitivity of research with human embryonic stem cells, or with cloning technology, is manifestly sensitive in the sense that the morality and acceptability of such research is disputed. For this reason, the BAC had in its Stem Cell Report, recommended a strict regulatory regime, especially for the creation of human embryos specifically for research, and additionally recommended a ‘conscience clause’ allowing conscientious objection to participation in any manner in human stem cell research. See Recommendations 3 to 5 and 11 of that Report.

The Legislative and Regulatory Framework of Human Biomedical Research in Singapore

1.14 All research in Singapore, like any other activity, is bound by the laws of Singapore, comprising a combination of statute and case law. A number of statutes and regulations made under them are relevant to the conduct of human biomedical research.

Statutes and Subsidiary Legislation

1.15 Relevant statutes and subsidiary legislation are as follows. The list is not exhaustive, but covers all the principal sources of legislation impinging on human biomedical research practice:

- (a) Medicines (Clinical Trials) Regulations (Cap. 176, Rg 3) made under Sections 18 and 74 of the Medicines Act (Cap. 176) (1985 Ed.), which is an Act to make provisions with respect to medicinal products and medical advertisements and matters connected therewith;
- (b) Health Products Act (Cap. 122D) (2008 Ed.): An Act to regulate the manufacture, import, supply, presentation and advertisement of health products and of active ingredients used in the manufacture of health products and provide for matters connected therewith;
- (c) Private Hospitals and Medical Clinics Act (Cap. 248) (1999 Ed.): An Act to provide for the control, licensing and inspection of private hospitals, medical clinics, clinical laboratories and healthcare establishments, and for purposes connected therewith;
- (d) Medical (Therapy, Education and Research) Act (Cap. 175) (1985 Ed.) (amended vide Act 4/2010): This is an Act to make provision for the use of the bodies of deceased persons or parts thereof for purposes of medical or dental education, research, advancement of medical or dental science, therapy and transplantation, and for other purposes connected therewith;
- (e) Human Cloning and other Prohibited Practices Act (Cap. 131B) (2005 Ed.): An Act to prohibit the placing of a human embryo clone in the body of a human or an animal and certain other practices associated with reproductive technology;
- (f) National Registry of Diseases Act (Cap. 201) (2007 Ed.) (amended vide Act 56/2007): An Act to establish the National Registry of Diseases and to provide for the compilation of information on the incidence of certain diseases for use as a basis for the direction of programmes for disease prevention and control, and for purposes connected therewith. This Act regulates the release of data from disease registries for public health and research purposes;
- (g) Infectious Diseases Act (Cap 137) (amended 2010): An Act relating to quarantine and the prevention of infectious diseases. Section 59A of the Act relates to National Public Health Research;

- (h) Mental Capacity Act (Cap. 177A) (revised 2010): This Act reformed the law governing decisions made on behalf of persons lacking decision-making capacity. The Act governs decision-making on behalf of persons lacking capacity in specified conditions, both where they lose mental capacity at some point in their lives (for example as a result of dementia or brain injury) and where the incapacitating condition has been present since birth. It covers a wide range of decisions relating to personal welfare and financial matters, and substitute decision-making by attorneys or court-appointed “deputies”. The Act also clarifies the position where no such formal process has been adopted, and provides recourse, where necessary, to the High Court which has power to deal with personal welfare and financial decisions on behalf of persons lacking capacity;
- (i) Animals and Birds Act (Cap. 7), Animals and Birds (Care and Use of Animals for Scientific Purposes) Rules (Cap. 7, R 10) (revised 2007): An Act for preventing the introduction into, and the spreading within, Singapore of diseases of animals, birds or fish; for the control of the movement of animals, birds or fish into, within and from Singapore; for the prevention of cruelty to animals, birds or fish; for measures pertaining to the general welfare and improvement of animals, birds or fish in Singapore and for purposes incidental thereto; Regulations under this Act govern the use of laboratory animals for research.
- (j) Personal Data Protection Act (Act 26 of 2012): This Act governs the collection, use and disclosure of personal data, including for the purposes of research.

Guidelines / Directives

1.16 Relevant guidelines / directives are as follows:

- (a) Ministry of Health (MOH), Singapore Guideline for Good Clinical Practice, 1998, Revised 1999;
- (b) MOH, Governance Framework for Human Biomedical Research, 2007;
- (c) MOH, Operational Guidelines for Institutional Review Boards, 2007;
- (d) MOH, Code of Ethical Practice in Human Biomedical Research, 2009;
- (e) MOH, Licensing Terms and Conditions (LTC) on Assisted Reproduction (AR) Services (2011). Sections 9 and 10 of the Licensing Terms and Conditions relate to research;
- (f) National Advisory Committee for Laboratory Animal Research, Guidelines on the Care and Use of Animals for Scientific Purposes, 2004. Administered by the Agri-Food and Veterinary Authority of Singapore and the National Advisory Committee on Laboratory Animal Research;

- (g) National Medical Ethics Committee (NMEC),⁴ Recommendations On Clinical Trials: Update Focusing On Phase 1 Trials, 2007;
 - (h) NMEC, Ethical Guidelines for Gene Technology, 2001;
 - (i) NMEC, Ethical Guidelines on Research involving Human Subjects, 1997; and
 - (j) Singapore Medical Council, Ethical Code and Ethical Guidelines.
- 1.17 The ultimate responsibility for ethical governance of research lies with research institutions. Since 1998, the MOH has required all government and restructured hospitals to set up hospital ethics committees for the ethics review of research involving human participants. After the publication of the 2004 BAC IRB Report, this system of ethics review was further strengthened, with appropriately constituted IRBs, and researchers bound by the procedures and rules laid down by the applicable IRB. The system of ethics governance is discussed further in Part II of these Guidelines.
- 1.18 The BAC reports have all been accepted by the MOH as providing guidance on matters not covered by statute, subsidiary legislation, or otherwise.
- 1.19 As research should be appropriately conducted regardless of where it is done, the BAC *Guidelines* are applicable to all human biomedical research whether privately or publicly funded, and whether or not carried out in an institution under the direct jurisdiction of the MOH pursuant to the Private Hospitals and Medical Clinics Act.

⁴ The NMEC is a committee established by the MOH to provide guidance on ethical issues in medical practice.

II. ETHICS GOVERNANCE OF HUMAN BIOMEDICAL RESEARCH

- 2.1 It is now internationally recognised that a system of ethics governance is necessary to provide guidance for human biomedical research, protect the interests of human research participants and to ensure that unethical research does not take place. Historically, there were many examples of research that failed to meet basic standards of respect for participating human subjects,⁵ and such cases continue to recur. In addition, there are many wider ethical issues consequent on the internationalisation of research, with accompanying questions of equity in the carrying of risks and the sharing of benefits. Furthermore, researchers and their institutions can be subject to conflicts of interest, for example, when doctors wish to conduct research on their own patients, when commercial value or scientific prestige may be attached to the outcomes of research, or when findings may not support the hopes of those who provide funding.
- 2.2 Ethics governance of research seeks to ensure the protection and assurance of the safety, health, dignity, welfare and privacy of research participants, and to safeguard against unethical practices. There have been a number of international documents and declarations that form the foundation of ethical biomedical research governance as practised in major research jurisdictions. They have also formed the basis for the ethical principles that have guided the BAC. The following foundational documents and declarations are key:
- (a) The Nuremberg Code (1949);
 - (b) The World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects (1964, revised 2013);
 - (c) The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research (1979);
 - (d) The International Ethical Guidelines for Biomedical Research Involving Human Subjects (2002); and
 - (e) The United Nations Educational Scientific and Cultural Organisation (UNESCO) Universal Declaration on Bioethics and Human Rights (2005).

General Ethical Principles that have Guided the BAC

- 2.3 A review of the five foundational documents above reveals that participants need to be protected and their autonomy in matters of research participation recognised. Although these documents do not agree on every particular matter, they appear to be in accord in their fundamentals. Based on these, the BAC has formulated the following five guiding principles reflecting their local application, first summarised in its Egg Donation Report.

⁵ The BAC used the term “subject” in its earlier reports, but more recently has used the term “participant”. The latter is preferred as it implicitly acknowledges that research participants choose to participate, and should not be merely the passive subjects of research.

Respect for persons

- 2.4 Individuals are to be respected as human beings and treated accordingly. This includes respecting their right to make their own decisions without being coerced, misled, or kept in ignorance, which the BAC refers to as autonomy.⁶ Their welfare and interests are to be protected, especially when their autonomy is impaired or lacking. This principle mandates the need for informed consent to participation in research, respect for privacy, safeguarding confidentiality, and minimising harm to research participants. It also requires a proper regard for religious and cultural diversity.
- 2.5 This principle integrates with many other aspects of life in societies that could be described as free or self-regulating (democratic) rather than totalitarian or highly communitarian (hierarchical). Ideals of this democratic society include all citizens being equal under the law, or having rights to privacy in the management of their affairs, to the enjoyment of security and public health and safety, with rights over their own bodies, and many others. All of these, in the final analysis, come down to the principle that individuals should be accorded certain basic rights or entitlements arising from their existence in society. These entitlements exist notwithstanding individual differences in endowment of race, character, gender or talent, and without requirement that individuals justify them. However, an individual's autonomy can be curtailed under certain circumstances, for the public good, such as when quarantined during disease epidemics.

Solidarity

- 2.6 The BAC earlier advocated a principle of reciprocity between the individual and wider society, as a way to capture the well-established idea that there is some measure of mutual obligation that regulates the relationship between the two. However, the underlying principle is perhaps better expressed as solidarity. The essential principle is not one of individual exchange, but of a wider vision in which common interest is invoked as a reason for the subordination of individual interest to that of a group in specified circumstances. Solidarity reflects the importance of general altruism as a basis for participation in biomedical research.
- 2.7 In biomedical research, agreed social benefits – considered as a public good – carry an implication that, if accepted, they inherently reflect an in-principle willingness to consider participation in research of the kind yielding the accepted benefits. This means that there is a balance to be struck between the interests of the public and the rights of individual participants; and that incompatible and irreconcilable ethical perspectives should be resolved with some regard to public interest. The BAC is therefore of the view that that certain rights such as informed consent, derived from the principle of respect for individuals, may be subordinate to the public interest based on the principle of solidarity. However, this should only be permitted in certain minimal risk research such as public health and epidemiological research, and subject to appropriate safeguards.

⁶ NMEC similarly referred to autonomy as “the right of individuals to decide for themselves what is good for them.” Paragraph 2.3.1, *Ethical Guidelines on Research Involving Human Subjects* (1997).

Justice

- 2.8 The concept of justice as applied to research includes the general principle of fairness and equality under the law. This concept implies that access to the benefits of research, and the burden of supporting it, should be equitably shared in society. It should not, for example, be considered ethical to exempt a class of otherwise suitable patients from participation in research by virtue of economic status.⁷ The concept of justice also implies that researchers and their institutions incur some responsibility for the welfare of participants, and their compensation and treatment in the event an adverse outcome results directly from their participation. It mandates careful consideration of the arrangements in place for ancillary care or follow-up in the case of research participants located in regions that may be resource-poor relative to the initiating country. Moreover, in the event research yields an immediate benefit that could apply to one of the participants in the research, justice would dictate that the benefit be offered.⁸
- 2.9 Although it is easy to defend the generic idea of justice as fundamental to the proper functioning of any society, both justifying and implementing a specific conception of justice is difficult, since research may entail compromises between competing interests. What different parties in a disagreement see as fair may depend upon widely different assumptions.

Proportionality

- 2.10 The regulation of research should be in proportion to the possible threats to autonomy, individual welfare, or the public good. Proportionality is fundamental to the administration of any system of regulation or governance, not just in bioethics or research, and has legal standing as such. A robust formulation of the principle is that interference with individuals should not exceed what is needed to achieve necessary regulation.⁹ It appeals to moderation and good sense in the determination of prohibited actions and the avoidance of micro-management and over-determination. The risk in any acceptable programme of research, and the stringency of its regulation, should not be disproportionate to any anticipated benefits. Proportionality is a counterweight to an excessive reliance on absolute principles in the determination of ethical decisions, which is in any case often impracticable in multicultural contexts.

⁷ “For example, during the 19th and early 20th centuries the burdens of serving as research subjects fell largely upon poor ward patients, while the benefits of improved medical care flowed primarily to private patients.” *Belmont Report*, Part B(3), given as an example of manifest injustice. It would also breach the principle of solidarity.

⁸ An example would be a research participant assigned to a placebo control group.

⁹ See for example the discussion of proportionality in Harris, B. *Disciplinary and Regulatory Proceedings*, 6th Ed. London: Wiley & Sons (2011). The essential legal burden on the court was stated in *de Freitas v. The Permanent Secretary of Ministry of Agriculture, Fisheries, Lands and Housing* [1998] by Lord Clyde, that in deciding if a limitation imposed by an act, rule or decision is arbitrary or excessive, i.e. disproportionate, the court should ask itself “whether: (i) the legislative objective is sufficiently important to justify limiting a fundamental right; (ii) the measures designed to meet the legislative objective are rationally connected to it; and (iii) the means used to impair the right or freedom are no more than is necessary to accomplish the objective.” <http://www.bailii.org/uk/cases/UKPC/1998/30.html> at section 25.

Sustainability

- 2.11 The research process should be sustainable, in the sense that it should not jeopardise or prejudice the welfare of later generations. For example, research leading to permanent change to the human genome might not be considered ethical, even if immediately beneficial, on the grounds that the unforeseeable, potentially harmful long term implications outweigh the immediate benefits of the research.
- 2.12 The wider idea of sustainability has become an important aspect of contemporary thinking with increasing realisation of the finite nature of the earth and consequent need for thought regarding its sustainability and general viability. There may be debates over such things as the nature or extent of global climate change and the reserves of natural resources, but few would deny the need to consider these issues in terms of a responsibility to the future. The principle may be taken narrowly as relating to the welfare of humans in the future, which is the sense in which it is perhaps most relevant to biomedical research, but it can also be taken broadly in the field of bioethics, where it supports arguments for the conservation of nature and the minimisation of resource depletion for the good of the planet as a whole.

Other considerations

Beneficence

- 2.13 It may be noted that beneficence is not listed explicitly among the BAC's principles, though it is mentioned in some jurisdictions¹⁰ and the NMEC's Ethical Guidelines on Research Involving Human Subjects (1997). This is because beneficence (together with non-maleficence or the principle of 'do no harm') finds its main expression in medical treatment, and is derived from the Hippocratic Oath. It expresses the first duty of the physician – to treat the patient. In research, however, the participants may not be patients, and even if they are, there is often no direct benefit for the patient from participation in the research. Indeed, it is necessary to ensure patients participating in research are not victims of therapeutic misconception, or mis-estimation – the fallacy of overestimating the benefits they may gain from participating in the research. Research is a process designed to yield a contribution to generalisable knowledge, which is practically useful or theoretically important, and is therefore a public good. This is not the same as beneficence. Indeed, many researchers would argue that a spirit of intellectual curiosity often impels valid research that is difficult to evaluate in any practical way. The importance of respect for persons seems to us to better capture the essential aspects of beneficence and non-maleficence insofar as these concepts apply to research participants, and we have thus framed the principle of respect for persons as, in effect, incorporating them.

Research Integrity

- 2.14 Research integrity is the term used to refer to the integrity or validity of the research process. Anything which undermines the objectivity of the research and the validity of

¹⁰ In the US, for example, the regulatory requirements of minimising risks to participants and ensuring that the risks are acceptable in light of the anticipated benefits have been grounded in beneficence as a basic ethical principle in the Belmont Report, which subsumes non-maleficence under beneficence.

the results can be regarded as a threat to research integrity; for example, if there is plagiarism, selectivity in the publication of results, or if the independence of researchers is undermined by their obligations to their employers or to the funders of their research.

- 2.15 The BAC's view is that research integrity is essential. It is not a simple concept, but to some extent, the presumptive integrity of research and of researchers is already implicit in adherence to the BAC's general ethical principles outlined above, and its importance is made explicit wherever appropriate in these *Guidelines*. Further guidance is available in the Singapore Statement on Research Integrity, developed by the 2nd World Conference on Research Integrity, which was the first international effort to encourage the development of unified policies, guidelines and codes of conduct, with the long-term goal of fostering greater integrity in research globally.¹¹
- 2.16 The BAC is also of the view that research institutions have a responsibility to ensure that the requirements of research integrity are observed, and IRBs have a responsibility to check that research integrity, as well as research merit, has been considered.
- 2.17 The principles described above are general in nature and fundamental to ethics governance of biomedical research involving human participants, the use of the biological materials that they have contributed, and information about persons obtained or derived from the research process. In practice, these principles are engaged in a number of specific guidelines, considered below.

Ethics Review of Human Biomedical Research in Singapore – The IRB System

- 2.18 Ethics governance of research in Singapore has been established by statute for clinical trials. The Medicines Act 1975 (Chapter 176, Sections 18 and 74) and Medicines (Clinical Trials) (Amendment) Regulations 1998, require that all clinical trials be conducted in accordance with the Singapore Guideline for Good Clinical Practice (SGGCP), which is adapted from the International Conference on Harmonisation Tripartite Guideline E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95). The SGGCP requires that all proposals for pharmaceutical clinical trials be reviewed by independent ethics committees.
- 2.19 The HSA is the regulatory authority for clinical trials. Since January 2006, researchers can make parallel submissions to both HSA and to their respective IRBs. The regulatory approval from HSA, in the form of a Clinical Trial Certificate, is issued independently of ethics approval. Researchers are to initiate their studies only when both regulatory and ethics approvals have been obtained.
- 2.20 In 1998, based on the recommendations of the NMEC's Ethical Guidelines on Research Involving Human Subjects (1997), the MOH required all government and restructured hospitals to establish hospital ethics committees to review all research protocols involving human experimentation, whether pharmaceutical trials, trials of

¹¹ The Statement is available at <http://www.singaporestatement.org/>.

new medical devices, new clinical procedures, or any other kinds of clinical studies requiring the participation of human subjects or the use of human biological materials.

- 2.21 The focus of the research covered by these legislative provisions and guidelines was primarily clinical, although the NMEC Guidelines clearly included epidemiological research. No explicit provision existed for biomedical research that involved human participants, or human biological materials, which was not clinical in orientation. In 2003, the BAC thought it was timely to consider the ethical issues that might arise in basic research, since it could involve researchers who, not being medical practitioners, are not bound by obligations to patients, and could involve institutions other than healthcare establishments. Moreover, such non-clinical research was at the time becoming more frequent, and researchers felt a need for an internationally acceptable and clear standard of ethics governance to enable collaboration with researchers elsewhere. They also wanted to ensure that their work was generally undertaken within a recognised framework that stipulated the nature of acceptable practice and the boundaries that collaborators elsewhere should also respect.
- 2.22 The BAC therefore issued a Consultation Paper in September 2003. Following receipt of comments on this Paper and a dialogue session with IRB representatives, the BAC published a report in November 2004, containing a number of recommendations or guidelines, with the following objectives:
- (a) To review the existing system of ethics governance in human biomedical research in Singapore;
 - (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 for the promotion of ethically responsible human biomedical research in conformity with the best international standards and practices.
- 2.23 Much of the original analysis under 2.22(a) is now history. The IRB Report was accepted by the government and as a result, the present system of IRB review for institutions undertaking biomedical research with human participants was put in place. In some cases, IRB review has been extended and adapted to cover research that is not biomedical, since the basic principles captured in the report have proved applicable in large measure to research with human participants generally, though the particulars often differ greatly.
- 2.24 An IRB review is a means to ethical governance of biomedical research. It follows that an IRB is not merely implementing procedural rules in which contingencies are specified in advance, but is intended to be a forum in which the ethics of a research proposal can be discussed and an independent decision made, in accordance with the principles of ethical research and in light of the facts and expert opinions available to the IRB.
- 2.25 What follows is an updated summary of the current position of the BAC with respect to the manner in which the BAC's recommendations translate into IRB practice.

There is discussion of some issues which may not have been clear in the original reports, or which have surfaced in the decade since the IRB system was implemented.

Guidelines on Ethics Governance of Human Biomedical Research

Ethics Review

- 2.26 All human biomedical research as defined in paragraph 1.8 should be reviewed by a properly constituted IRB. The composition of an IRB should combine appropriate expertise with some lay representation to reinforce the objectivity and impartiality of the process, so that there can be no room for any public perception that it is not independent of those who are required to submit research for its review.
- 2.27 The level of detail required in a research protocol submitted for an IRB review should vary in proportion to the identifiable risk or sensitivity of the research. IRBs may conduct either *full* or *expedited reviews*, or grant *exemptions from ethics review*. Each institution should determine for itself, after due deliberation and consultation with its IRB, the categories of research that could be expedited or exempted from ethics review. Such research must present no more than minimal risks to research participants, where minimal risk refers to an anticipated level of harm and discomfort that is no greater than that ordinarily encountered in daily life, or during the performance of routine educational, physical, or psychological tasks.
- 2.28 A less formal process of review than that of a standard full review is permissible for research that involves no more than minimal risk to research participants. The Chairperson or other IRB delegate(s) may be empowered to conduct such expedited reviews.
- 2.29 In the case of exemption from review, there must be no likelihood of harm to research participants, for example, when irreversibly de-identified data or commercialised human cell lines are used. Researchers seeking exemption from review would accordingly need to make a request with an abbreviated protocol, and obtain endorsement from the IRB before commencing the research. The Chairperson or other IRB delegate(s) may be empowered to grant such exemptions.

Multi-Centre and Multi-National Research

- 2.30 For multi-centre research, a lead IRB could be designated. The choice of the lead IRB should be dictated by considerations such as the primary institution of affiliation of the principal investigator, the location where the greater part of the research is carried out, the expertise of the IRBs, or the place where the largest number of participants is located. The lead IRB will play the main role in conducting a full ethics review, in coordinating the research programme, and in keeping the other participating IRBs informed of any decisions or amendments, including those made during the entire research period.
- 2.31 For multi-national research, the local portion should be subject to review by the IRB of the local partner institution(s), and the local IRB(s) should have a final say on matters affecting local participants.

Conflicts of Interest

- 2.32 Institutions, IRBs, members of IRBs and researchers should take special care to avoid conflicts of interest, whether actual, potential, or only the appearance of conflict. Institutions should develop policies and procedures to identify, eliminate, minimise or manage conflicts of interest that may affect research.
- 2.33 Should an IRB member have a personal interest in the research under review, that member should disqualify him- or herself from any consideration of the case, and he or she should refrain from offering his or her opinion to the IRB on the particular research under review. The member should make full disclosure of such an actual, potential or apparent conflict of interest to the IRB.
- 2.34 Researchers should disclose any actual, potential or perceived individual conflicts of interest, when submitting their research proposals to the IRB, as well as any institutional conflicts that they are aware of and may have an impact on their research. The IRB shall then decide on the appropriate steps to manage the conflict.
- 2.35 Threats to research integrity could arise when there is a conflict of interest between those who commission and fund research (including commercial organisations) and those who carry it out (the researchers). Routine checks and balances ensuring the integrity of the research process have been developed in universities and other research institutions with a commitment to research. When research is recruited to the service of commercial or institutional interests, researchers may be in a difficult position if their results are inconsistent with the expectations or hopes of their funders. IRBs need to consider how best to avoid such threats to integrity when considering applications in which they might arise.

Responsibilities of Institutions

- 2.36 Institutions have the overall responsibility of ensuring the proper conduct of human biomedical research carried out in their premises or facilities; or by their employees or on their patients; or involving access to or use of human biological materials, medical records or other personal information in their custody. They are also responsible for ensuring research integrity.
- 2.37 Every institution that conducts human biomedical research, or allows such research to be carried out in its premises, should establish and maintain an appropriately constituted and effective IRB, or ensure that its research staff have access to an IRB at another institution.
- 2.38 Institutions should set up clear policies for the operation of their IRBs. The composition of IRBs and specific operational details are provided for in the MOH Operational Guidelines for Institutional Review Boards.¹²
- 2.39 Institutions should ensure that there is an arrangement for receiving feedback from research participants.

¹² MOH, *Operational Guidelines for Institutional Review Boards*. 2007.

- 2.40 It is the responsibility of institutions to provide adequate resources, including resources for the training and education of IRB members, and administrative support for the IRBs to discharge their responsibilities in an effective and timely manner.
- 2.41 Institutions should ensure that provisions are made to treat and compensate research participants for the adverse consequences resulting directly from their participation, where appropriate.
- 2.42 An institution must accept legal responsibility for the decisions of its IRB and must provide the IRB members with a full indemnity for actions resulting from decisions made by those members in good faith in the course of discharging their duties.
- 2.43 In view of the investment of time and effort in preparing for research, including the sourcing of funds, it would be proper to have some kind of re-evaluation or appeal procedure in the event that a research proposal is not approved by an IRB. The principal investigator should then have an opportunity to further justify the research, or if disagreement persists, to make available an appeal mechanism in which adjudication by a third party is possible. Institutions are responsible for ensuring that such a mechanism is put in place. Appeals should be considered by another committee, whose members should not include any member of the IRB that initially reviewed the proposal. This committee must be able to exercise independent judgement, free from bias or a conflict of interests.

Responsibilities of IRBs

- 2.44 The functions of an IRB include the following:
- (a) The ethics review and approval of proposed human biomedical research projects;
 - (b) Ensuring that research proposals have been scientifically evaluated and have scientific merit, as it would be unethical to subject human participants to any risk or research that is so poorly designed that it could not yield generalisable knowledge. The IRB is not expected to undertake such scientific review itself;
 - (c) Evaluating the provisions for the consent process to ensure that valid consent that is appropriate to the proposed research is obtained;
 - (d) The continuing ethics review of the research projects approved by them, through requiring submissions of annual or more regular progress reports from researchers;
 - (e) Reporting to their respective institutions any unusual or unexpected events arising from the research; and
 - (f) Providing feedback to and maintaining dialogue about applicable standards with their constituent researchers.
- 2.45 IRBs should provide a fair hearing to those involved. If there are any doubts or difficulties with particular aspects of the proposals, IRBs should clarify these in

writing with the researchers, or in minuted face-to-face meetings between the IRB and researchers.

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

Responsibilities of Researchers

- 2.47 Researchers are responsible for ensuring that their research is conducted with integrity and complies with all relevant laws and other regulatory obligations and requirements, including the conditions laid down by the IRB that approved their project. They should not vary their approved research without prior IRB agreement, unless the deviations are necessary to eliminate immediate hazards to participants, or when the changes involve only logistical or administrative aspects of the research.
- 2.48 Researchers should submit annual (or more frequent) progress reports as required by the IRBs, as well as project completion reports to their respective IRBs.
- 2.49 Reports of adverse events arising from the research should be submitted to the respective IRBs within 15 days of their occurrence. However, serious adverse events, such as those resulting in death or a life-threatening situation, or requiring hospitalisation of any research participant, should be reported immediately.
- 2.50 Researchers should not alter or modify in any way (whether in formulation, dosage or timing) any drug or other clinical regimen of a patient-participant, without the approval of the attending physician and the IRB.
- 2.51 Researchers should conduct their research in a professional manner and with due regard to applicable conventions and expectations with respect to the obtaining and managing of research data, the disclosure of conflicts of interest, and the reporting of the research.
- 2.52 When any clinically significant findings are discovered in the process of research, researchers should ensure that research participants are informed, if they have indicated their desire to know.

III. Consent

- 3.1 Consent is a vital component of ethical biomedical research. Consent requirements exemplify the principle of respect for persons by acknowledging the right of individuals to decide for themselves what is good for them. An IRB should evaluate the provisions for obtaining consent whenever it considers a research proposal entailing work with human participants, the use of human biological materials or identifiable personal information.
- 3.2 There is a distinction between the legal and ethical obligations relating to consent. There are various situations where the law requires consent to be obtained, and where a research procedure done without consent could be subsequently challenged in court. Legal requirements thus constrain what can or cannot be enforced concerning ethical obligations in obtaining an individual's consent. However, these *Guidelines* refer to consent issues as a matter of ethics – what ought to be done in obtaining informed consent – and are to be understood as presuming compliance with the law as it stands.

Voluntary and Informed Consent

- 3.3 Consent must be voluntary and informed. Informed consent is not merely providing information, but requires that the person consenting does so with adequate understanding. The language, occasion and manner of explanation, the level of detail offered, and the process by which the consent is taken, should all be aimed at helping the potential research participant understand what consent is being asked for.
- 3.4 Obtaining the consent of prospective participants entails providing sufficient relevant information and explaining it in ways that allow them to make an informed decision with an appropriate level of understanding. The requirements vary somewhat depending on the nature of the research, such as whether the research involves biological materials or genetic information, and the likelihood of discovering clinically significant findings either directly or incidentally to the research. The consent process will also depend on the vulnerability of the participant. Anything in the nature of the research which the participant may find morally or culturally sensitive should entail some corresponding sensitivity in obtaining consent.
- 3.5 Therefore, valid consent should require that:
- (a) Research participants understand what is proposed, the nature of any entailed risks and benefits to them, and how any such risks are to be managed and minimised. This is particularly important in clinical research where new therapies are involved;
 - (b) There is no coercion, deception or inducement. Any reimbursement for expenses incurred in relation to the research, whether monetary or in kind, should not amount to an inducement; and
 - (c) Participants understand that they may withdraw from the research at any time without needing to provide any explanation or justification, and without penalty or prejudice to any treatment they may be receiving.

- 3.6 Keeping research participants in ignorance of a research hypothesis, or of which intervention group they have been assigned to, does not amount to deception in the sense mentioned in paragraph 3.5(b). It is well recognised that the requirements of research may be inconsistent with full disclosure of the research purpose or hypothesis to intended participants, and there are procedures for managing this. However, the need to keep participants ignorant of a research hypothesis should be disclosed and justified to the satisfaction of an IRB. The important consideration is that participants cannot be deceived or kept ignorant of the material aspects of research participation that they would need to understand in order to make an informed decision whether to participate. Such matters would include the risks or benefits of the research (including, where applicable, randomisation), the affiliations of the researcher(s), the uses or value of the research, or their rights in respect of participation. Finally, it is best ethical practice to highlight to the participant the fact that, for methodological reasons, not all information concerning the research hypothesis and protocol will be revealed. A research participant who is uncomfortable with this should not be enrolled.
- 3.7 Nevertheless, one of the problems with taking consent is that however conscientiously it is done, one cannot be sure of the actual understanding of the participant. Consequently, it is desirable that consent be explicit and written, rather than implicit, which means that it should be expressly stated by the participant (or where appropriate, his or her legally authorised representative), preferably in writing. Together with a conscientious approach to ensure the participant understands as far as possible what is proposed, this minimises the likelihood of future misunderstanding.
- 3.8 Prospective participants should be given adequate time to decide whether or not to participate in the research and the opportunity to clarify any doubts that they may have. The time required will depend on factors such as the ethically contentious nature of the research, the magnitude and probability of harm, the complexity of the information conveyed, and the setting where the information is given.

Specific and General Consent

- 3.9 *Specific consent* is consent for a particular research project, analogous to consent for a specific medical treatment. It refers to the case where a participant is recruited for participation in a specific research project, or where his or her biological materials or personal information is sought for a specific project. There is no implication that such consent would extend to the use of the biological materials or personal information that is collected for other subsequent research, unless this is requested, in which case the consent would be considered as a general consent.
- 3.10 A *general consent* may be taken for the storage and future use of biological materials or personal information for research. This consent would allow such use without the need for re-consent. IRBs should have the discretion to decide, when considering a research proposal, whether specific consent is required, or if a previously given general consent is sufficient.
- 3.11 In any general consent for future research, donors may wish to impose some limits to the use of their biological materials or personal information. If the donation is accepted, any such conditions must be respected. If the conditions are unacceptable or

impractical, the donation should be declined. In general, the intention should be to seek a completely general consent without restriction, given that the biological materials or personal information will be used only if the research is approved by an IRB.

Consent Involving Vulnerable Persons

- 3.12 While it is usual to treat the individual as an autonomous agent for purposes of taking consent, provision has to be made when considering research participants who are vulnerable. Such participants include:
- (a) Persons lacking mental capacity (such as the intellectually disabled, people who are incapacitated through accident, injury or illness, and others as defined in the Mental Capacity Act);
 - (b) Those whose autonomy might be prejudiced by being under the influence of, or the control of, or obligated to, third parties; and
 - (c) Minors.

Consent for Research Involving Persons Lacking Mental Capacity

The Mental Capacity Act

- 3.13 The Mental Capacity Act lays down the general framework under which decisions can be made on behalf of a person lacking capacity. As the Act states in Section 13(7) that treatment includes the conduct of a clinical trial, a deputy appointed by the court under the Act, or a donee who has been expressly given authority under a Lasting Power of Attorney (LPA) to give or refuse consent to the carrying out or continuation of medical treatment by a health care provider, may also decide on the person's participation in clinical trials. But this is subject to the restrictions in Sections 13(8) and 25(3)(c), on both a deputy and a donee, concerning life-sustaining treatment or treatment necessary to prevent a serious deterioration in the patient's condition.
- 3.14 In making such decisions on personal welfare, the deputy or the donee must follow the statutory principles under the Act, viz., act in the incapacitated person's (i.e. donor's) best interests,¹³ have regard to the guidance in the Code of Practice of the Act, carry out the donor's instructions and make decisions within the scope of authority specified in the LPA. To give consent for the person lacking capacity to participate in clinical trials, the deputy or the donee must be satisfied that:
- (a) The incapacitated individual has previously indicated a willingness to participate; or

¹³ With regard to best interests, Mental Capacity Act, section 6(7) states: "He [the deputy or donee] must consider, so far as is reasonably ascertainable –

- (a) the person's past and present wishes and feelings (and, in particular, any relevant written statement made by him when he had capacity);
- (b) the beliefs and values that would be likely to influence his decision if he had capacity; and
- (c) the other factors that he would be likely to consider if he were able to do so."

- (b) Consent would, in the judgement of the deputy or donee, have been given had the incapacitated individual (not being a child), been able to make an informed choice.
- 3.15 Legal protection is offered to any individual acting in connection with the care or treatment of a person lacking capacity, provided certain requirements, as set out in Section 7(1) of the Act, are met. However, this statutory immunity does not apply to clinical trials, by virtue of an express exclusion in Section 7(3).
- 3.16 It should be stressed that biomedical research other than clinical trials is not expressly provided for or mentioned under the Act, unlike the specific provision made for research in the UK Mental Capacity Act 2005. A deputy or donee is obligated under the Act to make decisions on behalf of a potential participant in his best interests, yet participation in research, particularly non-clinical studies, does not usually benefit the participant directly. While an incapacitated person's best interests would generally require that there be some direct benefit from the participation in research, the common law has not always interpreted the best interests test so narrowly.¹⁴ International guidelines on biomedical research also envisage the permissibility of research participation for incapacitated adults where (a) the research is intended to promote the health of the group represented by the potential participant, (b) the research cannot be conducted with participants who can give informed consent, and (c) the research participation entails only minimal risk or burden.¹⁵ It may thus be ethical for a court deputy or donee of a lasting power of attorney to enrol an incapacitated adult in minimal risk research where this is consistent with the incapacitated person's beliefs and values, and not contrary to the person's present wishes and feelings.

Consent for Research Involving Vulnerable Persons Not Lacking Mental Capacity

- 3.17 Vulnerable research participants not only include those who are lacking mental capacity, but also those whose autonomy might be prejudiced by being under the influence or control of, or by being obligated to, third parties. Potentially vulnerable participants might include, but are not limited to:
- (a) Prisoners;
 - (b) Uniformed personnel, especially junior ranks;
 - (c) Patients, especially if the intending researcher is their attending physician; and
 - (d) Employees, junior collaborators, or students.

¹⁴ For example, the courts have permitted a simple paternity blood test for a child where this was not clearly against the interests of the child, notwithstanding there was no direct benefit to the child: *S v S* [1972] AC 24 (House of Lords). Nothing in the Mental Capacity Act (Chap 177A) expressly overrules the common law, except by necessary implication.

¹⁵ World Medical Association, *Declaration of Helsinki* (rev. 2013), article 28; Council for International Organizations of Medical Sciences, *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (2002), Articles 9 and 15.

- 3.18 In such cases, consent should be taken by independent third parties, whenever possible, and prospective participants reassured that they have nothing to fear in declining research participation or in contributing biological materials or personal information for research. Thus, consent from uniformed personnel, for example, should not be taken by a senior officer, and preferably not by uniformed personnel.
- 3.19 When it is not possible for consent to be taken by an independent third party, the IRB may give directions for the consent to be taken by the researcher so long as there are provisions to manage the conflict of interest and sufficient safeguards to protect the welfare and interests of the participant.
- 3.20 A further issue of vulnerability arises in societies where social proxy arrangements are widespread, for example, where a village headman might be thought to have the authority to give consent on behalf of a village, or a husband on behalf of a wife. Not all societies treat their individual members as autonomous. This can become an issue if researchers based in Singapore seek to conduct research in places where social proxy arrangements are widespread. In such cases, while local customs are to be respected, they cannot supersede a requirement for individual consent.

Consent for Research Involving Patients

- 3.21 It is important to note the differences between a patient's consent for medical treatment and an individual's consent for participating in research. The main difference is that in giving consent for treatment, a patient is accepting a proposed action that is intended for his or her benefit, and thus, needs to balance any risks or undesired consequences (such as side effects) against the benefit(s) sought. These risks may be substantial, but may be acceptable to the patient if no better treatment is available and some benefit is strongly indicated. Because research, by contrast, is not generally intended to confer benefit on the research participant (although it may sometimes do so), there are thus usually no personal benefits against which to balance risks. The benefits derived are generally for society as a public good, and the consent of the participant is fundamentally altruistic in character. High levels of risk thus become unacceptable, and any risks to the participants should be minimised. A therapeutic misconception may also occur when potential patient-participants fail to appreciate the difference between research and treatment, and believe that research participation is nonetheless offered to promote their medical interests.
- 3.22 Consent for treatment should therefore be clearly separated from consent for participation in research. When a researcher is also the attending physician, the researcher-physician should be aware of a potential conflict of interest and of the fact that his or her patients may feel obliged to give consent. Ideally, the consent for research should be taken by an independent third person, though this is not always possible. In such situations, the IRB may give directions for the consent to be taken by the researcher-physician so long as there are provisions to manage the conflict of interest and sufficient safeguards to protect the welfare and interests of the patient.

Consent for Research Involving Minors

Respect for the developing autonomy of minors

- 3.23 In Singapore, under the common law, the age of majority is 21 years. This age is generally taken as the age at which a person is considered an adult and thus able to make all decisions for oneself. The category of minors thus spans a wide range, from children of tender years who lack any capacity to give consent, to young persons who have acquired the capacity to understand and make decisions on research participation. Parents generally have the authority to make decisions on behalf of minors, and this would include research participation. However, the welfare and best interests of the child or young person is the paramount consideration and parents must discharge their responsibilities to promote these.¹⁶ Unless research participation offers direct benefit to the minor, the authority of parents or guardians to consent to research without direct benefit is constrained in a similar fashion to proxy decisions for incapacitated adults as discussed in para. 3.16 above. Participation in research without direct benefit should involve no more than minimal risk and not be contrary to the best interests of the minor.
- 3.24 It is nevertheless ethically important to give due respect to the developing capacity of minors to be involved in, and make their own decisions about research participation. This consideration is reinforced in the case of research without direct benefit, where the minor should appreciate its altruistic nature. Respect for a minor's developing autonomy is thus recognised by the Medicines (Clinical Trials) Regulations, which require *both* the minor who has sufficient understanding and a parent or guardian to consent to participation in a clinical trial.¹⁷ Similarly, the common law will not subject a child with sufficient understanding to a non-therapeutic procedure against his/her will.¹⁸

Determining decision making capacity

- 3.25 In order to give a valid consent, the minor must have sufficient maturity and intelligence to understand the relevant information relating to the proposed research, and use that information to arrive at a reasoned decision. This capacity is, however, not easily linked to fixed ages, as it varies from minor to minor, and depends on the nature and complexity of the research. None of the current legal age thresholds bear immediate relevance to determining when a minor develops sufficient decision-making capacity to consent to *research* participation, although children between the ages of 12-14 may acquire near adult decision-making capacity.¹⁹ We therefore recommend that IRBs set suitable age thresholds for obtaining minors' consent based on the relevant minors' developmental abilities, the context of the particular research protocol and the complexity of its procedures and risks. However, if researchers hold a reasonable doubt whether a particular minor possesses capacity to give consent, or if

¹⁶ Children and Young Persons Act (Cap. 38), s.3A; Guardianship of Infants Act (Cap 122), s.3

¹⁷ Medicines (Clinical Trials) Regulations, r.11(2).

¹⁸ *S v S* [1972] AC 24 at 45 (House of Lords).

¹⁹ Working Party of the Royal College of Paediatrics and Child Health, "Guidance on clinical research involving infants, children and young people: an update for researchers and research ethics committees" *Arch Dis Child* 2014 Oct; 99(10): 887-91.

the research risks involved are significantly greater than minimal, it would be prudent to assess capacity on an individual basis before enrolment.

Engagement

3.26 For minors who lack sufficient decision-making capacity, it is still important to engage them as far as their intellectual abilities permit. This may involve, for example, explaining the nature of the research procedures and dealing with the minor's concerns. Engagement serves to minimise the potential risks associated with participation, such as any distress experienced while undergoing research procedures.²⁰ In every instance, including the obtaining of consent, IRBs and researchers should ensure that such engagement or explanation should be communicated effectively with age appropriate language and methods, and appropriately documented.

Summary

3.27 The BAC is thus of the view that for research involving minors with decision-making capacity, consent from *both* the minor and a parent should be obtained; such a minor's refusal of consent should be respected. Apart from this, it is still important to engage the minor in ways that respect his or her current level of understanding. Parents or guardians of minors lacking decision-making capacity are authorised to consent to their participation in research that involves no more than minimal risk and is not contrary to their best interests.

Waiver of Parental Consent

3.28 For research that does not involve more than minimal risk, such as surveys seeking information relating only to the minor, the BAC is of the view that IRBs should be able to waive parental consent for minors who have decision-making capacity, where there is otherwise no prohibition by law and parental consent is not a reasonable requirement for the protection of the minor's interests.

Waiver of Consent

3.29 IRBs may consider a waiver of the consent requirement for research done in the public interest, typically in epidemiological or public health research carried out with medical records or with data from national registries, when the following conditions are met:

- (a) The research is justified and poses no more than minimal risk to research participants;
- (b) The waiver will not adversely affect the welfare and interests of research participants;
- (c) The research could not practicably proceed without the waiver;

²⁰ This is addressed by the concept of assent in some jurisdictions like the US. However, as assent is a procedure that lacks clear legal recognition in Singapore, and may be confused with consent to research, it is best to focus on engagement with the minor participant.

- (d) Obtaining consent is not possible or practicable; and
 - (e) Individual privacy and confidentiality of the personal information are assured.
- 3.30 Exceptionally, valuable research might require the recruitment of highly compromised patients, such as accident trauma victims, who are unable to give consent and for whom no proxy is practically available to give consent within the timeframe required for the research procedures to be administered. In such cases, always subject to the treatment of the patient remaining the priority, and subject to the provisions of the Mental Capacity Act, it may be appropriate for an IRB to authorise the research, if it involves no more than minimal risk. Consent must be sought, directly or from a proxy, as soon as is practicable, and with the clear understanding that a patient shall have every right to withdraw or decline with retrospective effect (which will require removing earlier collected data from the study).

Clinically Significant Incidental Findings

- 3.31 A clinically significant incidental finding occurs when, in the course of research done for some other purposes, a finding is made that has a clear implication for the health of the participant to whom it relates. Research findings are by their nature provisional and not definitive. Where research data suggests the presence of a clinical condition that would require a confirmation and possible treatment, there is some duty on the part of the researcher to ensure that the research participant is informed of the possible condition with advice to follow up on the matter with a medical practitioner.
- 3.32 If there is reasonable possibility that incidental findings may occur in a research, research participants should be given the choice of whether to be informed about such findings, during the consent-taking process, prior to the commencement of the research. Researchers should ensure that research participants, who so choose, are informed and advised to seek medical attention and confirmation of the research result in a clinical laboratory.
- 3.33 Communication of clinically significant findings to research participants could be done directly by the researcher, or through a healthcare provider or other party authorised to receive the information, and who is appropriately qualified and in a better position to advise and discuss the implications of the findings.
- 3.34 Parents who have indicated a wish to know, should be informed of clinically significant incidental findings affecting their children's health, when they are discovered. Upon reaching the age of 21 and if the research is still on-going, the individuals concerned will then be in a position to make their own decisions regarding whether or not to be contacted in the event that such findings are uncovered.
- 3.35 If a clinically significant finding is discovered, but the preference of the research participant for receiving such information is unknown, researchers should refer to their IRBs for advice on the appropriate handling of such information.

Guidelines on Consent

- 3.36 Consent for participation in research must be voluntary. There should be no coercion or undue influence. Participants may be reimbursed for legitimate expenses. Any other payment, whether monetary or in kind, should not amount to an inducement, and should be approved by an IRB.
- 3.37 Participants should be allowed to withdraw from the research at any time without any explanation, and without penalty or prejudice to any treatment they may be receiving.
- 3.38 Prospective research participants or legally authorised representatives should be provided with sufficient information in an understandable form and appropriate manner, to enable them to make an informed decision. Such information include:
- (a) The nature and purpose of the research;
 - (b) Any entailed risks and benefits to them, and how such risks are to be managed and minimised;
 - (c) The safeguards for protecting their privacy and confidentiality of their personal information;
 - (d) Any payment for participation in the research;
 - (e) The procedures and implications for withdrawal from the research; and
 - (f) Any other information specific to the type of research, as given in the parts on research involving human biological materials, genetic research and stem cell research in these Guidelines.
- 3.39 Prospective participants should be given adequate time to decide whether or not to participate in the research and the opportunity to clarify any doubts that they may have.
- 3.40 Consent to participation in research should be documented in writing.
- 3.41 Consent could be specific to a particular research project, or general for the storage and future use of biological materials or personal information. In any general consent, donors should be allowed to impose some limits to the use of their biological materials or personal information. IRBs should have the discretion to decide, when considering a research proposal, whether specific consent is required or general consent is sufficient, if previously given.
- 3.42 For research involving vulnerable persons not lacking mental capacity (for example, prisoners, uniformed personnel, and employees), consent should be taken by independent third parties, whenever possible. Prospective participants should be reassured that they have nothing to fear in declining research participation or in contributing biological materials for research. When it is not possible for consent to be taken by an independent third party, the IRB may give directions for the consent to

- be taken by the researcher so long as there are provisions to manage the conflict of interest and sufficient safeguards to protect the welfare and interests of the participant.
- 3.43 For research involving patients, consent for participating in research should be clearly separated from consent for treatment. When a researcher is also the attending physician, the consent for research should ideally be taken by an independent third person. If it is not possible, IRBs may give directions for the consent to be taken by the researcher-physician so long as there are provisions to manage the conflict of interest and sufficient safeguards to protect the welfare and interests of the patient.
- 3.44 While local customs should be respected when conducting research in places where social proxy arrangements are widespread, individual consent from the prospective participant is nevertheless essential.
- 3.45 For research involving minors with decision-making capacity, consent from both the minor and a parent should be obtained; such a minor's refusal of consent should be respected. Apart from this, it is still important to engage the minor in ways that respect his or her current level of understanding. Parents or guardians of minors lacking decision-making capacity are authorised to consent to their participation in research that involves no more than minimal risk and is not contrary to their best interests.
- 3.46 For research that does not involve more than minimal risk, such as surveys seeking information relating only to the minor, IRBs should be able to waive parental consent for minors who have decision-making capacity, where there is otherwise no prohibition by law and parental consent is not a reasonable requirement for the protection of the minor's interests.
- 3.47 IRBs may consider a waiver of the consent requirement for research done in the public interest, typically epidemiological or public health research carried out with medical records or with data from national registries, when the following conditions are met:
- (a) The research is justified and poses no more than minimal risk to research participants;
 - (b) The waiver will not adversely affect the welfare and interests of research participants;
 - (c) The research could not practicably proceed without the waiver;
 - (d) Obtaining consent is not possible or practicable; and
 - (e) Individual privacy and confidentiality of the personal information are assured.
- 3.48 For research involving recruitment of highly compromised patients who are unable to give consent and for whom no proxy is available to give consent, subject to the treatment of the patient remaining the priority, IRBs may authorise the research, if it involves no more than minimal risk. Consent must be sought, directly or from a proxy, as soon as is practicable. The patient or proxy shall have every right to

withdraw or decline with retrospective effect (which will require removing earlier collected data or biological material from the study).

- 3.49 Where there is a possibility that the research may yield clinically significant incidental findings, participants should be allowed to decide whether or not to be informed of such findings, during the consent-taking process, prior to the commencement of the research.
- 3.50 If a clinically significant finding is discovered, but the preference of the research participant for receiving such information is unknown, researchers should refer to their IRBs for advice on the appropriate handling of such information.

IV. PERSONAL INFORMATION IN RESEARCH

- 4.1 Personal information is any identifiable information about an individual, living or dead. It not only includes personal particulars, but also details of medical conditions, as well as information disclosed or derived in the process of healthcare management. In the research context, it will include any information collected, used or generated as part of the research process. Personal information varies widely in its sensitivity, depending on its use and context.
- 4.2 Personal information may be identified or de-identified when used in research. *Identified information* is information where identifying particulars are included, such that the identity of the individual is known, for example, in a medical record. *De-identified information* is information relating to an individual where the identity of that individual is not known. If it is de-identified through reversible means, such as the use of a coding system or encryption, it is described as *reversibly de-identified information*. If it is permanently stripped of all identifying details, it is referred to as *irreversibly de-identified information*. Thus identifiable information includes identified information and reversibly de-identified information.
- 4.3 Personal information used in research may be obtained through various sources, such as through interviewing or testing individuals, from the course of medical diagnosis or treatment, analysis of biological materials contributed for research, and registries or databases. Such data may be stored electronically or as physical records, and managed by healthcare or research institutions, or government or non-government registries. Data that are routinely collected or submitted to national registries may be immensely valuable for human biomedical research. To enhance its value, it may be necessary to link the records of individuals from multiple databases.
- 4.4 In research, information can be used in many unforeseen ways, and it is not practicable to give research participants a right to view, amend, delete or otherwise control data they have provided for research purposes. Moreover, the information may have been, in a sense, created by the researcher through his or her observation and interventions – for instance a measure of memory, or an assessment of genetic potential, which might otherwise have been unknown. Information created through research should be managed in ways that respect the need to observe confidentiality and care in use. It should remain in the care of and for the use of the researcher, subject to ethics governance procedures; rather than being treated as the continued property of the research participant or ‘donor’.
- 4.5 Research data, which may include personal information, should be retained for future use, re-analysis, or re-investigation in the light of fresh developments. Many journals also require that research data be made available to other researchers who wish to replicate and build upon a publication. Thus, destruction of research data is discouraged but the protection of participants’ privacy must be maintained.

Protection of Personal Information

- 4.6 Protecting the privacy of research participants and the confidentiality of their personal information obtained or derived from research is based on the principle of respect for

persons. Thus, personal information should be stored and managed in ways that provide proper security and confidentiality. While a researcher collecting data from consenting individuals will know their identities, such information should be stored and managed as de-identified information as soon as is practicable. The principle of proportionality applies, such that the level of care and urgency regarding de-identification and data protection should be consistent with the sensitivity of the data.

- 4.7 To maximise the value of data and biological materials collected in cohort or follow-up studies, where a large amount of data is collected for analysis, it should be managed as reversibly de-identified data. Under the Personal Data Protection Act 2012 (PDPA), an organisation that collects and de-identifies personal data for processing and storage is still considered to hold personal data if it retains the ability to re-identify the data.²¹ Thus, in the re-identification of reversibly de-identified data, the management of the key to any code or encryption can and generally should be separated from the management of the data.
- 4.8 This separation is recognised in the PDPA, which provides for “data intermediaries”. A data intermediary is defined in the Act as “an organisation which processes personal data on behalf of another organisation but does not include an employee of that other organisation”, where processing includes recording, holding, organising, adapting or altering, retrieving, combining, transmitting, and erasing or destroying of the data. A data intermediary is subject to the requirements pertaining to the safeguarding of personal data in respect of personal data processed on behalf of another organisation pursuant to a contract which is evidenced or made in writing, with the exception of obligations relating to the protection and retention of personal data under ss. 24 and 25 of the PDPA respectively. It is therefore possible for organisations to share and use such de-identified data for research, while protecting privacy and confidentiality. There are also systems in which data in more than one data set can be linked and compared, without the identity of the participants being known to the researchers. This is invaluable in certain kinds of public health and epidemiological research. Reversible de-identification also allows the retrieval of personal information if re-contact is needed, which may be important in cases where clinically significant incidental findings are discovered, or when consent is needed for further research not covered by the original consent obtained.
- 4.9 When the link between the participant and their data is permanently severed, the data is considered irreversibly de-identified. All that exists is a data set. Provided that there is no reasonable means to re-identify the individual from the nature of the data content, it ceases to attract as strong a case for the protection of privacy and confidentiality. Therefore, research which relies exclusively on the secondary use of irreversibly de-identified information or human biological material may qualify for exemption from ethics review, so long as the processes of data linkage or recording or dissemination of results will not generate identifiable information, and no attempt is made to re-identify the individual.

²¹ Personal Data Protection Commission, “Advisory Guidelines on the Personal Data Protection Act for Selected Topics” (11 Sep 2014), at para. 3.18.

- 4.10 Given rapid technological advances that may allow re-identification through comparison of multiple de-identified data sets, it is no longer possible to promise absolute anonymity under all circumstances. However, researchers are expected to take proper security safeguards with all data. When provided with de-identified information for research, they should refrain from attempting to identify an individual, without IRB approval. Should an individual be identified inadvertently from de-identified information, the confidentiality and privacy rights of this individual should not be regarded as abrogated by such identification, and steps should be taken to reinstate and secure them.
- 4.11 The data collected by researchers may or may not be sensitive in nature, but researchers have a proportionate duty to maintain privacy and confidentiality. Under the principle of autonomy and respect for persons, healthcare practitioners and researchers alike have certain duties regarding the protection of confidential personal information that they collect or generate in the course of their work, whether or not such information forms or originally formed part of a medical record. This implies that storage and security of data should be secured in proportion to its sensitivity.

Use of Medical Records for Research

- 4.12 Medical information and data collected or generated in the process of diagnosing and managing a person's health condition form the individual's medical records. These records may be stored electronically or as physical records. Most people regard their medical details as private and a matter for them and their physicians alone. Doctors are expected to respect the principle of medical confidentiality, as set out in the Ethical Code and Ethical Guidelines of the Singapore Medical Council. In a healthcare institution, all personnel who handle medical records are under legal and ethical obligation to observe the confidentiality of the information on the records and to safeguard the privacy of patients concerned.
- 4.13 Much valuable medical knowledge has resulted from the study of patients' medical records. Further to the BAC's recommendations in its 2005 Personal Information Report, the PDPA now affords an exemption under the Third Schedule allowing an organisation to use personal information for research without consent, provided that certain stringent conditions are satisfied.²² In addition, the BAC is of the view that although the primary responsibility for access to medical records should remain with medical practitioners, appropriate access could be given to suitably qualified professionals for the purpose of research. Healthcare institutions should ensure that clear formal procedures are laid down for the release of medical records and other personal information for research, and to formulate these procedures in consultation with their IRBs.

Epidemiological and Public Health Research

- 4.14 The use of personal information in public health and epidemiological research can lead to a clash between public and private interests. Ideally, consent should be

²² See Personal Data Protection Act, Third Schedule, paragraphs 1(i) and 2. Where such personal information is disclosed to a third party, the requirements in the Fourth Schedule, paragraphs 1(q) and 4 apply.

obtained for all research involving personal information. However, this may not be practicable in certain situations; for example, the use of information (including linkages from multiple databases) from any national or disease registry for research, where information may have been collected routinely by law. Such use is of tremendous value in epidemiological and public health research, which is ultimately a public good. As there is minimal risk of harm to individuals, it is ethically justifiable to waive the consent requirement for the use of personal information for epidemiological and public health research, provided there are adequate measures to protect individual privacy and the confidentiality of the information. In most cases, reversibly de-identified information could be used. Such research has to be approved by an IRB. The conditions for a waiver of consent are provided in paragraph 3.29.

Guidelines on the Use of Personal Information in Research

- 4.15 All biomedical research involving personal information, whether identified or de-identified should be reviewed by an IRB, and approved, or granted an exemption from review, before it commences. IRBs should have the discretion to decide whether specific consent is required or general consent is sufficient for the particular project.
- 4.16 Personal information used for research should be de-identified as early as possible, and stored and managed as de-identified information. The principle of proportionality applies, such that the level of care and urgency regarding de-identification and data protection should be consistent with the sensitivity of the data. IRBs should consider the suitability of the extent and means of the de-identification in proportion to the risk.
- 4.17 Researchers should safeguard all information used and derived in research, and take adequate measures to prevent inadvertent identification of individuals. Should an individual be identified inadvertently from de-identified information, the confidentiality and privacy rights of this individual should not be regarded as abrogated by such identification, and steps should be taken to reinstate and secure them.
- 4.18 Healthcare institutions should ensure that clear formal procedures are laid down for the release of medical records and other personal information for research, and to formulate these procedures in consultation with their IRBs.
- 4.19 IRBs may waive the consent requirement for the use of personal information for epidemiological or public health research, or the use of medical records for research, if they are satisfied that the following conditions are met:
 - (a) The research is justified and poses no more than minimal risk to individuals concerned;
 - (b) The research could not practicably proceed without the waiver;
 - (c) Obtaining consent is not possible or practicable; and
 - (d) Individual privacy and confidentiality of the personal information are assured.

- 4.20 Personal health information derived from research should not be disclosed or used for other purposes. Research information may not be definitive, and research participants are entitled to expect that their data will not be used for purposes other than those for which they have given consent. Thus, such information should not be disclosed to any third party, including employers or insurance companies.

V. BIOBANKING AND RESEARCH INVOLVING HUMAN BIOLOGICAL MATERIALS

- 5.1 Human biological materials are a valuable resource in biomedical research. These materials could be obtained from living or dead persons, or foetuses. It includes blood and other body fluids, solid body tissues and organs, gametes and embryos, as well as their derivatives. Even biological materials that have been stored for many years may be useful. The ethical issues concerning the use of human biological materials for research relate to the collection, storage, access, and use of these materials; and to the use of personal information generated from research using these materials. Such information may be of central importance to the research or merely incidental, may also have health implications for the donors of biological materials or their genetic relatives, and be of relevance to their employers or insurers.
- 5.2 Biological materials for research may be newly obtained specifically for the purpose of research or they may come from pre-existing stored specimens. They may be specifically requested for research or they may be surplus from a clinical procedure. They may also be identified or de-identified.
- 5.3 Human biological materials taken for clinical or research use may be stored in repositories called tissue banks. Tissue banks may be set up specifically for research, but many exist primarily for clinical use in transplantation. Clinical tissue repositories, which consist of samples that have been collected and used for clinical diagnosis, such as blood or tumours that have been surgically removed, are also potentially useful for research. Some repositories consist of accumulated and archived biological materials that have been acquired over a period of many years without specific or adequate donor consent for research use. These collections are referred to as legacy tissues.
- 5.4 Biobanks are collections of human biological materials that are linked to personal information, which may include medical information of individuals from whom the biological material originate. The individuals may or may not be identifiable by the biobank. Biobanks may be created for research purposes or be part of a clinical service, such as a health screening programme. As they consist of biological materials and data systematically collected from a large number of individuals, they are very valuable for research that may lead to a better understanding of diseases.
- 5.5 Many countries have created tissue banks and biobanks, some of which are national while others are institution-based. Several initiatives have also involved international collaborations. For such initiatives, all parties involved should agree to a common set of ethical guidelines and standards for the collection, storage, use and disposal of the biological materials collected.
- 5.6 It is still uncertain in Singapore whether a person, or a body corporate, can legally own human biological materials or whether the donor can have any property rights over his or her biological materials after it is contributed for research. However, there is gradual international legal recognition that individuals have at least some property

type rights of control in respect of their excised tissues.²³ The question of ownership applies not only to the physical forms of human biological materials but also to their derivatives - whether in the form of data, discoveries or biological products. However, it is generally accepted that the human body or any of its parts, should not be used as a means for financial gain. The donation of biological materials for use in research should thus be considered as an altruistic gift. An altruistic donor does not have intellectual property rights in any commercially valuable development arising from the research, and donations should be made and accepted on that understanding. Also, tissue banks and biobanks have been referred to as custodians of the biological materials that they are responsible for.²⁴ The 'gift' model for the altruistic donation of biological materials for research is also appropriate for the provision and management of research data, as this would allow it to be shared or re-analysed in other contexts or for other research purposes, subject to appropriate safeguards.

- 5.7 As the use of human biological material is critical for biomedical research, both the public and research participants should have confidence that the biological materials that they contribute are handled and used sensitively and responsibly. Researchers should always ensure that the collection and use of human biological materials will not compromise the safety, welfare and interests of donors, which should be of paramount consideration.

Guidelines on Biobanking and Research Involving Human Biological Materials

General

- 5.8 All research involving human biological materials, whether identified or de-identified, should be reviewed and approved by an IRB, or granted an exemption from review, before it commences.
- 5.9 It is essential to protect the privacy and confidentiality of donors of biological materials and their personal information, as well as personal information given by donors about others. All the requirements for the use of personal information in research in Part IV of these *Guidelines* should be observed.
- 5.10 Donors of biological materials should not be offered any financial incentives for their donation, although reasonable reimbursement of expenses incurred may be given.
- 5.11 Researchers and those managing tissue banks and biobanks need to be sensitive to religious and cultural perspectives and traditions relating to human tissue. These vary considerably amongst various religions and cultures, especially when whole cadavers or gross organ parts are involved.

²³ See for e.g., *Jonathan Yearworth v. North Bristol NHS Trust* [2009] 3 WLR 118, where the English Court of Appeal held that patients who stored their gametes in a hospital storage facility retained an ownership interest in the stored tissue. The patients possessed some rights to control the use of the stored tissue, and could sue for damages arising from the destruction of the stored tissue as a result of the hospital's negligence.

²⁴ Medical Research Council, UK. *Human tissue and biological samples for use in research: Operational and Ethical Guidelines* (2005), paragraph 2.1.

Consent in research with human biological materials

- 5.12 Informed consent must be obtained before any biological materials are taken for use in research. If the materials are intended for storage and future use in research, consent should also be obtained for this purpose.
- 5.13 Consent may be general or specific. General consent is consent that does not limit the use of the biological materials to any particular research project. It includes consent for storage and future use of the biological materials or personal information generated from the research using these materials, without a requirement for re-consent. In providing a general consent, the donor may restrict the use of the biological materials and any related information. Any such limits must be respected, and it is for the researcher and IRB to decide if the use of the biological materials or the related information in any given project should be excluded.
- 5.14 Specific consent is consent for a particular research project. In the event there are surplus biological materials from this project, a fresh consent would be needed if consent had not been given earlier for any future research. Specific and personal consent should be obtained if the biological materials, or information derived from research with the materials, are to be used in research deemed to be sensitive.
- 5.15 When consent is sought, donors of biological materials should be provided with sufficient information, explained appropriately, to make an informed decision. Such information should include:
- (a) The purpose of the research, and any risks or benefits to them;
 - (b) The type and amount of biological materials to be collected, and the procedures and risks involved in taking it;
 - (c) That the biological materials will be considered a gift and donors will not have any right or claim to any share in the commercial gain derived from the research;
 - (d) Whether the biological materials may be stored and used for future research, and for how long;
 - (e) The potential types of research for which the biological materials may be used;
 - (f) Whether there is any possibility of being re-contacted for future research, or to be informed about clinically significant incidental findings, if they so wish;
 - (g) Whether the biological materials will be identified and the applicable privacy and confidentiality safeguards for personal information derived from research involving the materials; and
 - (h) That it is possible for donors to withdraw consent from the research, as long as the biological materials have not yet been used, and in any case without prejudice to any treatment they may be undergoing, and of the procedures and implications of the withdrawal.

- 5.16 Re-consent is required in the following situations:
- (a) When the proposed research is not covered by the consent that was given when the biological materials were collected (unless the re-consent requirement is waived by an IRB);
 - (b) If the biological material was collected from a minor below 21 years of age, who did not at the time of collection possess decision-making capacity and therefore did not personally, or jointly together with his/her parent, consent to the donation. Once the minor attains the age of 21, his or her consent should be obtained if research is to be conducted on the previously collected material or personal information related to the sample, or at the least notified of his or her right to withdraw the biological material from research or storage for research. In the event that re-consent is not practicable, the IRB should generally have the discretion to waive the requirement in accordance with the relevant criteria for waiver of consent, where appropriate; or
 - (c) For research deemed to be sensitive, such as that involving human eggs and embryos, or human-animal combinations.
- 5.17 When any clinically significant findings are discovered in the process of research using human biological materials, researchers should ensure that donors of these materials are informed, if they have indicated their desire to know of such findings.
- 5.18 Under the Medical (Therapy, Education and Research) Act, any person who is not mentally disordered and who is 18 years of age or above may give all or any part of his or her body for research or for therapy. The gift will take effect upon death. Legally authorised relatives of deceased individuals (which include still-born infants and foetuses) may also give all or part of the deceased person for research after or immediately before death, if there is no actual notice of contrary indications by the deceased person, or actual notice of opposition of another legally authorised person of the same or prior class.

Foetal Tissues

- 5.19 Foetal tissues include membranes, amniotic fluid, placenta and umbilical cord. Foetal tissues for research should only be taken from dead or non-viable foetuses. Abortion should not be induced for the purpose of obtaining materials for research.
- 5.20 Consent for the termination of pregnancy should be separate from the consent for obtaining foetal tissue or any tissue related to the pregnancy for research. Where possible, an attending physician should not also seek consent for research participation from a patient in this situation.
- 5.21 Consent for the use of foetal tissue for research could be obtained from either parent, as provided in the Medical (Therapy, Education and Research) Act.
- 5.22 Any research intention to propagate foetal cells *in vitro* and/or to transplant these cells into a human recipient should be disclosed when consent is sought.

Human Gametes and Embryos

- 5.23 The creation of human embryos specifically for research can only be justified when there is strong scientific merit in and potential medical benefit from such research. The Human Cloning and Other Prohibited Practices Act prohibits the development of a human embryo created other than by fertilisation of human egg by human sperm, for a period of more than 14 days, excluding any period when the development of the embryo is suspended. Commercial trading in human eggs, human sperm and human embryos is also prohibited.
- 5.24 The supply and use of human gametes and embryos is governed by the Human Cloning and Other Prohibited Practices Act (Cap. 131B). Researchers should also comply with the requirements stipulated in MOH's 2011 Licensing Terms and Conditions (LTC) on Assisted Reproduction (AR) Services imposed under Section 6(5) of the Private Hospitals and Medical Clinics Act.
- 5.25 Under the LTC,²⁵ written approval from the Director of Medical Services must be obtained for all research involving human embryos and human oocytes (including those obtained from excised ovarian tissue). This requirement extends to human-animal combination gametes or embryos, which are those containing both human and animal genetic or non-genetic material and includes an embryo created by the fertilisation of human and animal gametes.
- 5.26 Specific and personal consent from the donors must be obtained before any gametes or embryos are to be used for research. Potential donors should be provided with sufficient information to make an informed decision and be given at least a week to decide.
- 5.27 For women undergoing fertility treatment, consent for the donation of surplus oocytes or embryos for research should be separate from the consent for treatment. The treating physician should not also be the researcher seeking consent for the donation of oocytes or embryos for research. Donors should confirm in writing that they do not require the oocytes or embryos for future use.
- 5.28 As the process of donating eggs for research is time-consuming, invasive and associated with a certain degree of discomfort and risk, women wishing to donate eggs specifically for research i.e. those who are not undergoing fertility treatment, must be interviewed by an independent panel. The panel must be satisfied that they are of sound mind, clearly understand the nature and consequences of the donation, and have freely given explicit consent, without any inducement, coercion or undue influence.
- 5.29 All egg donors should be informed if their eggs will be used to create embryos, including human-animal combination embryos, which will be destroyed in the process of research, and if any derived cells from the embryos so created will be kept for future research or possible clinical use. They should be assured that any embryos

²⁵ At paragraphs 9.1-9.11.

created for research will not be implanted or allowed to develop *in vitro* beyond 14 days.

- 5.30 Donors of eggs obtained specifically for research, and not as a result of clinical treatment, may be reimbursed for legitimate expenses incurred, such as cost of transport and childcare services, and actual loss of earnings, as a result of the procedures required to obtain the eggs. Any other payment, whether monetary or in kind, should not amount to an inducement and should be approved by an IRB. If complications occur as a direct and proximate result of the donation, the donor should be provided with prompt and full medical care. This provision is the responsibility of the researchers and their institutions.
- 5.31 Trans-species fertilisation involving human gametes is not allowed for the purpose of reproduction unless done to assess or diagnose sub-fertility, in which case, the resultant hybrid must be terminated at the two-cell stage, and in any case must have written approval from the Director of Medical Services.
- 5.32 Human embryos created for research through *in vitro* fertilisation of human eggs by human sperm, or created through any form of cloning technology, should not be allowed to develop beyond 14 days *in vitro*.
- 5.33 Human embryos created for research through *in vitro* fertilisation of human eggs by human sperm, or created through any form of cloning technology, should not be implanted into the body of any human or animal.
- 5.34 Human cytoplasmic hybrid embryos²⁶ created for research should not be allowed to develop beyond 14 days *in vitro*, or to be implanted into the body of any human or animal.
- 5.35 No one should be under a duty to participate in any manner of research involving human gametes or embryos, including human-animal combination embryos, to which he or she has a conscientious objection.

Surplus Biological Materials from Clinical Procedures

- 5.36 Biological materials, such as blood, biopsy samples or even whole organs, may be left over after clinical procedures that may be therapeutic or diagnostic in nature. Such materials can be very useful for research. However, when these materials are being taken primarily for a therapeutic or diagnostic purpose, this purpose must be fulfilled before any surplus materials may be used for research.
- 5.37 Every effort should be made to obtain consent for the use of surplus biological materials for research. As the primary objective for removing such materials is clinical, consent for the clinical procedure should be separate from the consent for the use of left over materials for research. To avoid any conflict of interest and to

²⁶ A human cytoplasmic hybrid embryo is an embryo that is created by the fusion of the nucleus of a human somatic cell with that of an enucleated animal ovum. The nuclear DNA is human. The mitochondrial DNA and ooplasm are of predominantly animal origin. It is not known if human cytoplasmic hybrid embryos are viable, and it is not considered ethical to determine viability by allowing development to proceed.

safeguard the patient's welfare, consent for research should only be taken after consent has been given for any clinical procedure and it should be taken by a different person. Ideally, the attending physician should obtain the consent for the diagnostic or therapeutic procedure, while the researcher should seek consent for the research. If this is not possible when the researcher is also the attending physician, the IRB may give directions for the consent to be taken by the researcher-physician so long as there are provisions to manage the conflict of interest and sufficient safeguards to protect the welfare and interests of the patient. Patients should be assured that refusal to consent for research will not affect the quality of care that will be given to them.

- 5.38 If consent could not be obtained for the use of surplus biological materials for research, IRBs should have the discretion to waive the consent requirement if the patient is not identifiable, since the research protocol would not have influenced the procedures used in obtaining the biological materials. Healthcare institutions should inform patients that there is a possibility that their surplus biological materials may be used for research, and assure them that only research with the necessary safeguards in place will be allowed to proceed after approval from an IRB.

Surplus Biological Materials from Research Projects

- 5.39 Biological materials that are collected for a specific research project may subsist after the project is completed. Such materials can be stored for future research if consent for storage and future research use had been obtained from the donors.
- 5.40 Consent need not be re-taken if IRBs are satisfied that subsequent use of the biological materials for research is covered by the initial consent, unless the research is deemed sensitive, in which case specific and personal consent is required. If the subsequent use is not covered by the initial consent, and re-contact is not possible or practicable, IRBs should have the discretion to determine whether or not the materials can be used without re-consent.

Imported Biological Materials

- 5.41 When imported biological materials are to be used for research, the researcher should obtain written assurance from the source authority that the materials have been ethically and legally obtained. The test of ethical acceptability should be the criteria that would have applied had the biological materials been obtained in Singapore and not imported, and the researcher and IRB should be satisfied that this test has been met in substance.

Biobanks

- 5.42 Institutions that maintain tissue banks or biobanks for research should have in place transparent and appropriate systems and standards for the proper ethical, legal and operational governance of research using biological materials from the bank. As custodians of the biological materials, they are responsible not only for the general maintenance of the biobank, but also for ensuring the following:
- (a) That appropriate consent has been obtained for the storage and use of the biological materials;

- (b) That all research involving the biological materials is approved by an IRB, and also by MOH where relevant, before the materials are handed over to the researcher(s);
- (c) Protection of the privacy of the donors and of any other individuals whose identity or personal particulars to which such information may relate, and the confidentiality of personal information associated with the biological materials;
- (d) Keeping proper records of all uses of the biological materials;
- (e) Proper disposal of the biological materials when no longer needed; and
- (f) Any training necessary to ensure the implementation of the above requirements.

Legacy Tissues

- 5.43 Legacy tissues are tissues that were previously collected without specific or adequate consent for research, and where it may be impossible or impractical to trace the donors (if living) for consent. For practical purposes, in relation to researchers on whom the BAC's guidelines are professionally authoritative, they are generally tissues collected before the endorsement by MOH of the BAC's recommendations on human tissue research via its directive dated 1 December 2006.²⁷ It is important that procedures are in place to allow the use of legacy tissues for research, as it is a valuable resource to be preserved and used for research.
- 5.44 Proposed research with legacy tissue should undergo IRB review. IRBs may waive the consent requirement for the use of legacy tissues for non-sensitive research²⁸ under the following conditions:
- (a) If the tissues are irreversibly de-identified and there is thus no possibility of re-identifying the individuals who have contributed the tissues; or
 - (b) If the tissues are identifiable but it is impossible or impracticable to seek consent from the individuals who have contributed the tissues. In this case, IRBs should ensure that adequate measures are in place to protect the privacy of the donors and the confidentiality of any personal information associated with the tissues.

²⁷ BAC Tissue Report, paragraph 9.1, page 28: "A special difficulty ...is posed by the existence of large collections of tissue samples accumulated over many years for which no specific or adequate consent for research investigations has been obtained. In the vast majority of the cases, the original donors can no longer be reliably traced for consent to research, or such tracing may no longer be practicable or socially acceptable.... We refer to these collections as legacy tissue collections."

²⁸ For what constitutes sensitive research, see paragraphs 1.9 and 1.11 above.

VI. HUMAN GENETIC RESEARCH

- 6.1 Human genetic research is the study of genes, their functions, how they are associated with health and disease, and how genetic and environmental factors influence health. This research may involve participants directly or indirectly through the use of their biological materials or personal information from medical records or other databases. It may involve the study of a specific gene, multiple genes, gene-environment interactions, or the entire genome in seeking to establish associations between genomic variants and diseases or specific traits.
- 6.2 With the completion of the human genome project in 2003, genetic research has progressed more rapidly than ever before. There is an increasing interest in population-based research to study the genetic susceptibility of diseases, with numerous biobanks set up all over the world to store biological materials and associated biodata. These allow detailed long-term genetic studies to take place. Technological advances have also led to an increase in pre-clinical and clinical trials of gene-based therapies in recent years. Gene transfer in combination with stem cell therapy is also being studied in more detail. In addition, whole human genome sequencing can now be done in a relatively short period and at a lower cost. All these advances, together with advances in information technology, have resulted in new ethical challenges in the conduct and governance of genetic research.
- 6.3 Whole-genome research is likely to continue to advance and intensify. It involves the collection of biological materials, genome sequencing, data analysis, and, possibly, the use of the biological materials and data for future research projects that may not be contemplated when the materials are taken. In addition, the data may also be submitted to easily accessible scientific databases in order to facilitate research. Thus, the implications of whole genome studies and the use of very large data sets of potentially or actually identifiable genetic information raise ethical concerns. Research using these data sets is often international and is facilitated by increasing acceptance of the concept of open access. Moreover, very extensive analysis can be performed by cross-referencing genomic data with demographic or other information. The possibility of inadvertent identification is thus higher than it would be with more restricted data and more limited analysis. Specifically, therefore:
- (a) Research participants may also need to be informed if and why whole-genome studies make it harder to guarantee their anonymity with complete certainty;
 - (b) Researchers may discover new patterns or relationships, and may feel there is considerable potential for detecting findings that may be suggestive or prove clinically significant in future. It should be made clear in advance as to when the obligation of the researcher to a research participant or tissue donor ceases in relation an incidental finding made during the conduct of research; and
 - (c) The potential commercial value of large-scale genomic studies makes issues of research integrity and data ownership especially important.
- 6.4 Genetic interventions also raise ethical and moral issues, with germline genetic modification being the most contentious. Any intervention that alters the germline of

an individual will lead to a change in the genetic makeup of that individual's descendants. At present, there is insufficient knowledge of the potential long-term consequences of such interventions, as they are still in the experimental stage. Many countries, such as Australia, Canada, and Finland therefore have laws that prohibit germline modification.

- 6.5 With the emergence of assisted reproductive techniques to prevent the transmission of mitochondrial disease, such as ooplasmic transfer, pronuclear transfer and maternal spindle transfer, the Nuffield Council on Bioethics (NCB) conducted a public consultation in early 2012, which explored the ethical issues concerning the possible use of such treatments in the future. It concluded that if these novel techniques are adequately proven to be acceptably safe and effective, it would be ethical for families to use them, if they choose to. However, a continuing debate on these issues is important.²⁹ Following this report, the Human Fertilisation & Embryology Authority (HFEA) also launched a public consultation, and it advised the Government that there was general public support for permitting mitochondrial replacement in the UK, so long as it is safe enough to offer in a treatment setting and is done so within a regulatory framework.³⁰ The Department of Health (DoH) held public consultations in early 2014 on its draft regulations that will allow the use of such techniques in patients for the prevention of serious mitochondrial disease. A scientific review by an expert panel convened by the HFEA published in June 2014 concluded that the evidence it has seen does not suggest the techniques unsafe. As a result, the UK Parliament passed the DoH's draft Human Fertilisation and Embryology (Mitochondrial Donation) Regulations³¹ in early 2015 to allow mitochondrial donation for prevention of serious mitochondrial diseases, with UK being the first country to do so.
- 6.6 In 2005 BAC Genetics Report, the Committee had recommended that the clinical practice of germline modification be prohibited, pending scientific evidence that techniques to prevent or eliminate serious genetic disorders have been proven effective. In light of recent international deliberations on germline modification techniques for the treatment of serious diseases, the BAC appointed a Germline Modification Working Group in October 2014 to review these developments and its current recommendations on the matter.
- 6.7 Information obtained from genetic research could be financially valuable. For example, research involving individuals who have genetic resistance to certain diseases, or whose genome might be found to contain genes relevant to understanding superior human athletic performance, could potentially be very valuable to researchers and institutions able to develop and commercially exploit such research findings. There is also much interest in pharmacogenomics, the aim of which is to create optimal drug treatments that are tailored to the genetic makeup of the patient, or a subset of patients, classified by (for example) ethnic group, in order to maximise

²⁹ Nuffield Council on Bioethics, *Novel Techniques for the Prevention of Mitochondrial DNA Disorders: an Ethical Review*, June 2012.

³⁰ The HFEA licenses and monitors all fertility clinics and research involving human embryos in the UK. Its report, *Mitochondria Replacement Consultation: Advice to Government*, was published in March 2013.

³¹ The National Archives, *Human Fertilisation and Embryology (Mitochondrial Donation) Regulations*, Available at: <http://www.legislation.gov.uk/ukdsi/2015/9780111125816/contents>.

efficacy and minimise adverse effects. For this and other reasons, economic exploitation has been the subject of some controversy, and it is correspondingly important that all research participants be well aware of the implications.

- 6.8 Genetic information refers to any information about the genetic makeup of an individual. It can be derived from genetic testing in either a clinical or research setting, or from any other sources, including details of an individual's family history of genetic diseases.
- 6.9 Genetic information is often seen as an exceptional kind of personal information. There are several reasons for this:
- (a) Genetic information is seen as a determining aspect of a person, yet many people are reluctant to countenance the role of genetic influences in considering human potential and conduct, lest it undermine the autonomy that we attribute to individuals;
 - (b) Genetic information can be socially sensitive because it can convey information about others. Even though an individual genome is unique, it may also provide information about family members. This can be highly sensitive, since genetic relatedness may not correspond to expected social relatedness. In particular, paternity information may be obtained through genetic testing;
 - (c) The increasing ease with which the individual human genome can now be completely sequenced has created a situation in which incidental findings of genetic conditions or susceptibility might become easy to obtain. The sheer volume of genetic detail available from large-scale genomic studies also raises issues of data protection and privacy, since much of the value of genetic information in research, as in medicine, depends upon linking findings to individuals and their characteristics;
 - (d) Genetic information may have predictive power for heritable disorders that develop later in life. Even when untreatable, knowledge of such disorders may still allow the individual to make decisions affecting their future, such as whether to refrain from having children. But it is not always the case that individuals wish to know the details of their own genetic makeup, and consequent prognosis in certain cases. Especially if there is no current prospect of treatment, information about potentially disabling genetic conditions, such as Huntington's disease, may be something a person would not wish to know; and
 - (e) Genetic information may be of interest to others, such as biological relatives, who may also be affected, insurers and employers.
- 6.10 For all these reasons, there has been a tendency to regard genetic research in some way sensitive because the information it yields is exceptional. Certainly, genetic information ought to be considered as private to the individual since its implications might be considerable, and because respect for persons is a key principle, but this requires precautions no different from other sensitive personal information that is not genetic in nature. In some cases, genetic information is actual medical information, but in other cases it is just raw data that has to be analysed and interpreted to yield

pertinent personal information. The BAC is therefore of the view that genetic information is not always and inherently special or exceptional, thereby requiring exceptional protection or precaution.

Guidelines on Human Genetic Research

- 6.11 All human genetic research should be reviewed by an IRB and approved before it commences. A written approval from the MOH is also required if the research involves human eggs and embryos.
- 6.12 Participation in genetic research should be voluntary, whether directly or by contribution of biological materials or personal information, and all the requirements of informed consent in Part III should be applied. The requirements for the procurement and use of personal information and human biological materials for such research in Parts IV and V respectively, are also applicable.
- 6.13 When clinically significant findings are discovered in the course of any genetic research, researchers should ensure that affected participants are informed, if they have indicated their desire to know.
- 6.14 In whole-genome research, participants should be provided with as much detailed information as possible that is specific to such research, during the consent taking process. They should be informed of the mechanisms for data security, and given an explanation on the nature of whole-genome research, highlighting the difficulty in guaranteeing their anonymity with complete certainty. As the dissemination of information in whole-genome research is likely to be rapid and wide, there will also be practical limitations on withdrawal from such research. Participants should be informed of these limitations and the implications of their withdrawal.
- 6.15 For clinical trials involving gene-based therapies, regulatory approval from HSA is required, in addition to ethics approval from an IRB.

VII. HUMAN STEM CELL RESEARCH

- 7.1 Stem cells are undifferentiated cells that have the potential to develop into specialised cell types. They may be derived from early embryos (*embryonic stem cells*), the germ cells of fetuses (*embryonic germ cells*) or from the human body at a later developmental stage (*somatic* or *adult stem cells*).
- 7.2 Since the discovery in 2007 that human skin cells can be reprogrammed into an embryonic state, research in this area has progressed rapidly. Researchers have been studying the characteristics of these reprogrammed cells, called *induced pluripotent stem cells*, creating disease models to further understand the pathophysiology of specific diseases, as well as creating patient-specific stem cells and finding ways to transform these stem cells into desired cells, which could then be used for treatment. Researchers are also trying to find more efficient ways to convert somatic cells directly into lineage-specific stem/progenitor cells, bypassing the intermediate pluripotent stage.
- 7.3 Stem cell research can be classified into two major categories:
- (a) Basic research to understand physiological cellular processes and disease mechanisms; and
 - (b) Research into new therapies, including pre-clinical and clinical trials involving stem cells or their derivatives.
- 7.4 The unique capacity of stem cells to develop into various specialised cell types makes them of potential use for the regeneration or reconstruction of diseased or injured tissue. Stem cell research may thus lead to new and better ways of treating serious and debilitating diseases such as Alzheimer's, diabetes and spinal cord injury. However, the derivation of pluripotent stem cells from human embryos, and the use of human-animal combinations in stem cell research are controversial and raise ethical, legal and social concerns that must be addressed.
- 7.5 In 2002, the BAC published its Stem Cell Report. Subsequently it published the Egg Donation Report (2008) and the Human-Animal Combinations Report (2010). Taken together these reports have addressed what are for some the most contentious areas of biomedical research, namely, research involving the use of human embryonic stem cells; research with human eggs and embryos; and research in which tissues or cellular components of humans and animals are combined. These are contentious because they involve techniques such as cloning technology that arouse unease or opposition among those who consider that science risks hubristically exceeding its proper function, or think that human embryos and gametes are not proper material for research.
- 7.6 Stem cell research may involve human-animal combinations, which is a term used to refer to any kind of living organism in which there is some mixing of human and animal material (genes, cells or tissues). It includes:

- (a) *Cytoplasmic hybrid embryos*, which are created by fusing human somatic cell nuclei with enucleated animal eggs. These embryos can be used to derive stem cells with human nuclear genetic material without the need to create human embryos or the use of human eggs; and
 - (b) *Animal chimeras*, which are created by injecting human stem cells, into animals at various stages of development to study stem cell integration and differentiation, to test the developmental potential of stem cells or their derivatives, to evaluate the potential usefulness and safety of transplanting human stem cells for clinical treatment or to study the possibility of growing human tissues and organs in animals for the transplantation into humans.
- 7.7 Transgenic animals are animals in which the genome has been modified to include human genes. They have been widely used in laboratory research into the understanding and treatment of diseases for many years. In its Human-Animal Combinations Report and in preparing these *Guidelines*, the BAC has not explicitly considered transgenic animals but insofar as these Guidelines are relevant they should apply. However, to the extent that research involves the use of transgenic mice or other small mammals in laboratory conditions, and subject to observance of provisions for laboratory animal welfare, the BAC does not foresee any ethical difficulty in the continued use of such animals.
- 7.8 The objectives of using human-animal combinations in stem cell research include:
- (a) To study stem cell integration and differentiation;
 - (b) To test the developmental potential of human stem cells or their derivatives;
 - (c) To evaluate the potential usefulness and safety of transplanting human stem cells for clinical treatment; and
 - (d) To study the possibility of growing human tissues and organs in animals for transplantation into humans.
- 7.9 The unique nature of stem cells also sometimes risks uncontrolled growth and differentiation whether used clinically, or in experiments involving animals. Thus research involving the use of human pluripotent stem cells requires particularly careful attention if it is to be ethically conducted and monitored.

Legislation

- 7.10 There is no specific legislation that governs stem cell research in Singapore. The Human Cloning and Other Prohibited Practices Act (Cap. 131B) was enacted in 2004 primarily to prohibit human reproductive cloning. This Act does not prohibit therapeutic cloning (research cloning), but it limits the development of a human embryo that is created by any process other than the fertilisation of a human egg by a human sperm, to not more than 14 days (excluding any period when the development of the embryo is suspended). It also prohibits the commercial trading of human gametes and embryos.

- 7.11 The MOH's LTC for AR Centres (2011) imposed under regulation 6(5) of the Private Hospitals and Medical Clinics Regulations (Cap 248, Rg 2), provides the requirements for the use of human gametes and embryos for research, including the use of human-animal combination gametes and embryos for research.
- 7.12 The Medicines (Clinical Trials) Regulations (Cap. 176, Rg 3) made under sections 18 and 74 of the Medicines Act (Cap. 176), govern all clinical trials, including first-in-human trials and trials of cell- and tissue-based therapeutic products.

Ethical and Social Issues

Moral status of the human embryo

- 7.13 The main controversy in embryonic stem cell research concerns the moral status of the human embryo, and arises from the fact that the human embryo is destroyed in the process of stem cell derivation. There is a wide spectrum of views concerning the human embryo. At one end, it is considered to be a human being from the time of fertilisation, while at the other, the view is that it is a mass of cells, no different from any other biological material used for research.
- 7.14 After public consultation, the BAC adopted an intermediate position, whereby a human embryo is considered to have the status of a potential human being, but not the same status as a living child or adult. As a measure of respect and protection for the human embryo, the BAC recommended that human embryonic stem cell research, including the creation of human embryos specifically for research, should be allowed only when there is strong scientific merit in and potential medical benefit from such research. In addition, only embryos less than 14 days old should be used for the derivation of stem cells. At around this threshold, the primitive streak appears, signalling the onset of cell differentiation and development of organ systems, including the nervous system. As for the use of surplus embryos donated from fertility treatment by consenting parents, the BAC was of the view that rather than allow them to perish, their use in research would serve a greater good. The BAC's position on this issue remains unchanged.
- 7.15 With the increasing possibility of alternative means of generating pluripotent stem cells, such as induced pluripotent stem cells, it is more likely that cloning technology would be less frequently used for the creation of embryos. The BAC welcomes such diversity in research methodologies, but continues to regard research cloning (or therapeutic cloning) as defensible under strict regulation, if the scientific question addressed cannot reasonably be investigated using other methods.

Cloning and Respect for Individuals

- 7.16 Respect for human dignity forms the basis for the prohibition of human reproductive cloning in many countries, including Singapore. In particular, there are serious concerns about the safety of the technology used for this purpose, and any unforeseen problems for those born as a result of the technology.

Human-Animal Combinations

- 7.17 *Repugnance.* Many people express repugnance or disgust at the idea of human-animal combinations, as human and animal tissues are not normally thought of as something that can or should be mixed. It is seen as unnatural. The BAC's position is that while feelings of repugnance cannot be ignored, the process of paying heed to them should involve an evaluation of actual or likely harms and benefits.
- 7.18 *Slippery slope arguments.* A concern is sometimes expressed that research with human-animal combinations risks a 'slippery slope' that will open the way to unacceptable research or applications. This was one reason for public concern over research cloning – it raised in the public mind the possibility of human reproductive cloning occurring if cloning techniques became widespread. The BAC takes the view that cases should be considered on their merits, and any danger of this kind should be considered when a case is reviewed.
- 7.19 *Human dignity* – maintaining a distinction between human and animals. There is and should be no intention, in research, to try and produce animals that have been rendered human in some important and essential mental, physical or existential characteristic. Human consciousness is the most fundamental of such characteristics. The BAC is of the view that acceptable research must preclude procedures that risk this consequence, and should certainly never have it as an explicit aim.
- 7.20 *The risk of hubris and 'playing God'.* The expression 'playing God' is often heard in connection with research or practice at the boundaries of medicine, and the exact meaning to be attributed to it may depend on the speaker. Religious critics may mean by it that interference with the process of creating and destroying life is interference with divine prerogative. In its secular form, this criticism can imply that we may suffer from scientific or ethical hubris, a pride in power that blinds us to limitations or unforeseen risks. Such concerns should not be lightly dismissed, but they are not without answers. Whatever we do will affect future generations. It is thus also 'playing God' if we prohibit research that might help patients.
- 7.21 The BAC's view is that the problem of slippery slope, hubris, and other ethical concerns discussed above present a powerful case for ethical and legal regulation, rather than a case for outright prohibition. Regulation is an assurance that change will be introduced without abrupt and radical challenges to the fundamental values, beliefs and practices in society, and only when the key ethical issues arising from research involving human-animal combinations have been considered in each case.
- 7.22 *The possibility of creating humanised animals.* Most of the concerns just discussed are related to the possibility of allowing actual independent living entities to develop from human-animal combinations. It seems to the BAC that the main ethical hazard lies in the possibility of inadvertently creating an animal with human characteristics, especially, but not exclusively, mental attributes. The risks can be seen most clearly in the specific case of human neural stem cells grafted into the brains of non-human

primate foetuses³², which offers an in-principle possibility of a degree of humanisation of the resulting brain. In this case, six relevant factors have been suggested for the guidance of ethics committees, namely:³³

- (a) *The proportion or ratio of human to animal cells in the animal's brain:* When the amount of human material is low, the likelihood of the animal acquiring something like human awareness as a result is correspondingly remote;
- (b) *The age of the animal:* The earlier in development, the greater the likely integration of transplanted cells, so human cells transplanted into animal embryos will probably result in greater likelihood of humanisation of the host animal's brain than implantation into a fully developed animal;
- (c) *The recipient species:* Species with a closer approximation to human neural organisation are more problematic, because the likelihood of human attributes occurring in another species is increased when the other species is biologically close;
- (d) *The brain size of the animal involved:* It is reasonable to suppose that animals with larger brains are more likely to be capable of an approximation to human consciousness in the event that they incorporate human neural cells;
- (e) *The site of integration of the human neural cells:* Integration into the parts of the brain which control cognitive functions is more likely to affect cognitive abilities than integration into other parts of the brain; and
- (f) *The presence of pathologies in the host animal:* It is possible that the humanising effect of transplanted human stem cells in an animal with a pathological condition might be greater than would be the case in a robust healthy organism. This is relevant if animal models of disease processes are used as a basis for trial approaches to treatment.

7.23 These factors and others need to be considered together and not in isolation, as they may combine or interact. The BAC is of the view that these or similar considerations should guide the deliberations of bodies in a position to permit or regulate research with human-animal combinations.

Guidelines on Human Stem Cell Research

7.24 Human stem cell research that is not ethically contentious, such as research using established pluripotent stem cell lines and confined to cell culture or research that involves routine and standard research practice with laboratory animals, should be exempted from review. All other human stem cell research should undergo full or expedited review by an IRB. Approval from MOH must also be obtained if the

³² Ourednik V *et al.* Segregation of Human Neural Stem Cells in the Developing Primate Forebrain. *Science*. 293 (2001): 1820-1824.

³³ Greene M *et al.* Moral Issues of Human-Non-Human Primate Neural Grafting. *Science*. 309 (2005): 385-386.

research involves the use of human eggs, human embryos, or human-animal combinations.³⁴

- 7.25 The procurement of biological materials (gametes, embryos, foetal tissue or somatic cells), including imported materials for stem cell research, should be in accordance with the guidelines provided in Part V.
- 7.26 In human-animal combinations research involving live animals or resulting in the creation of live animals, the IRB should also ensure that the proposal has been approved by the Institutional Animal Care and Use Committee, whose remit covers the welfare of laboratory animals.
- 7.27 Where human embryonic stem cells, induced pluripotent stem cells, or any other kind of pluripotent stem cells are introduced into animals at any stage of development, particular attention should be paid to the need to avoid the creation of entities in which human sentience or consciousness might be expected to occur.
- 7.28 Animals into which human embryonic stem cells, induced pluripotent stem cells, or any other kind of pluripotent stem cells have been introduced should not be allowed to breed.
- 7.29 Human cytoplasmic hybrid embryos should not be allowed to develop beyond 14 days *in vitro* or to be implanted into the body of any human or animal.
- 7.30 If the research involves introducing human embryonic stem cells or any pluripotent cells, or products derived from these cells, into humans, or any novel applications of any stem cells that are outside the scope of established standards of medical care, it should be conducted in accordance with the requirements and standards of a clinical trial for cell-based products, as specified by the HSA, and approval from HSA must be obtained. IRBs must ensure that:
- (e) The proposal is reviewed and approved by a scientific review committee with the relevant expertise;
 - (f) There is strong evidence of the safety and efficacy of the cells from pre-clinical studies;
 - (c) The research participants have been provided with sufficient information, in particular information on the nature and risks of the research, and the source of the cells, so that their values and beliefs are respected; and
 - (d) Appropriate and informed consent has been obtained, without any inducement, coercion or undue influence.

These recommendations do not apply to innovative or experimental uses of stem cells in clinical practice, which fall outside the remit of the BAC's terms of reference.³⁵

³⁴ MOH, *Licensing Terms and Conditions for Assisted Reproduction Centres* (2011) at paras. 9.1 and 10.3.

³⁵ The International Society for Stem Cell Research has issued recommendations for the clinical translation of stem cells, including innovative medical use of stem cells: *Guidelines for the Clinical Translation of Stem*.

- 7.31 No clinical or research personnel should be under a duty to conduct or assist in human embryonic stem cell or induced pluripotent stem cell research, or research involving human-animal combinations, to which they have a conscientious objection, nor should they be put at a disadvantage because of such objection.

GLOSSARY

Alzheimer's disease – A degenerative brain disorder common in the elderly, characterised by progressive deterioration of mental functions leading to impaired cognition and increased reliance on others for daily activities.

Assisted reproductive (AR) technologies – The use of clinical and laboratory techniques to increase the chances of conceiving a baby. An example is *in vitro* fertilization, or IVF.

Chimera – An organism whose body contains cells from another organism of the same or a different species.

Cytoplasmic hybrid embryo – An embryo created by the transfer of the nucleus of a somatic cell from one species into an egg of another species from which the nucleus has been removed.

Embryo – The earliest stage of development of an organism.

Embryonic germ cell – An unspecified cell derived from primordial reproductive cells of developing foetuses that is able to replicate itself indefinitely and develop into all types of cells.

Embryonic stem cell – An unspecialised cell derived from an embryo that is able to replicate itself indefinitely and develop into all types of cells.

Foetus – The stage of development of an organism beyond the embryo and before birth, when tissues and organs have started to differentiate.

Gamete – Sperm or egg.

Genome – The complete set of genetic information in an organism.

Huntington's disease – A neurodegenerative genetic disorder that causes the progressive breakdown of nerve cells in the brain and impacts the individual's movement, cognition and behaviour. The disease is caused by an autosomal dominant mutation.

Hybrid – An organism whose cells contain genetic material from organisms of different species.

In vitro fertilisation (IVF) – A clinical and laboratory procedure whereby the eggs and sperm from a couple are extracted and fertilised outside their bodies. Such a procedure is a form of assisted reproduction aimed at increasing the chances of a couple conceiving a baby.

Induced pluripotent stem cell – An adult somatic cell, such as a human skin cell, that has been reprogrammed (or induced) into an embryonic pluripotent state.

Institutional review board (IRB) – A committee appointed by an institution to review the ethical standards of biomedical research proposals.

Oocyte – An egg cell.

Pluripotent – The ability to differentiate into cells of the three germ layers in the body, namely the ectoderm, mesoderm and endoderm.

Reproductive cloning – Process of creating a genetically identical copy of a human being or animal.

Research cloning (also known as therapeutic cloning) – The use of cloning technology for research purposes that are directed towards a therapeutic goal, where genetically identical cells, tissues and organs may be used to treat the patient's disease(s).

Somatic or adult stem cells – An unspecialised cell, present in a tissue or organ, that is able to replicate itself and develop into specialised cell types of that tissue or organ, or into some other cell types.

Stem cell – An unspecialised cell that is able to replicate itself and develop into specialised cell types (such as a red blood cell, nerve, or heart cell).

Tissue – An aggregation of similar cells that perform a particular function.

BIBLIOGRAPHY

Australia. National Health and Medical Research Council, Australian Research Council, Australian Vice-Chancellor's Committee. *National Statement on Ethical Conduct in Human Research*. Updated 2009.

Australia. *Privacy Act 1988*. Amended 2012.

Australia. *Prohibition of Human Cloning for Reproduction Act 2002*. Amended 22 December 2008.

Australia. The Royal Children's Hospital Melbourne. *Understanding Consent in Research Involving Children: The Ethical Issues*. 2010.

Austria. *Reproductive Medicine Act*. 4 June 1992.

Beskow LM *et al.* Informed Consent for Population-Based Research Involving Genetics. *Journal of the American Medical Association*. 286(18): 2315-2321, 14 November 2001.

Brazil. *Law Number 8974*. 5 January 1995.

Canada. *Assisted Human Reproduction Act*. 2004.

Canada. Canadian Institutes of Health Research. *CIHR Best Practices for Protecting Privacy in Health Research*. September 2005.

Canada. Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, and Social Sciences and Humanities Research Council of Canada. *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans*. 2010.

Canada. *Personal Health Information Protection Act 2004*. Amended 2010.

China. Ministry of Health. *Guidelines on Human Assisted Reproductive Technologies*. July 2003.

Council for International Organizations of Medical Sciences in collaboration with the World Health Organization. *International Ethical Guidelines for Biomedical Research Involving Human Subjects*. 2002.

Council for International Organizations of Medical Sciences in collaboration with the World Health Organization. *International Ethical Guidelines for Epidemiological Studies*. February 2008.

Council for International Organizations of Medical Sciences. *The Declaration of Inuyama on Human Genome Mapping, Genetic Screening and Gene Therapy*. 1990.

Council of Europe. *Additional Protocol to the Convention on Human Rights and Biomedicine, Concerning Biomedical Research*. 2005.

Council of Europe. *Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine*. 4 April 1997.

Council of Europe. *Guide for Research Ethics Committee Members*. April 2012.

Council of Europe. *Recommendation No. R (97) 5 on the Protection of Medical Data*. 13 February 1997.

Council of Europe. *Recommendation Rec (2006) 4 of the Committee of Ministers to member states on research on biological materials of human origin*. 15 March 2006.

Denmark. *Act on a Biomedical Research Ethics Committee System and the Processing of Biomedical Research Projects*. 2009.

Denmark. *Act on Research Ethics Review of Health Research Projects*. 11 January 2012.

Denmark. Danish Council of Ethics. *Humans and Genetic Engineering in the New Millennium – How Are We Going to Get “Gen-Ethics” just in time?.* 1999.

Denmark. Danish National Committee on Biomedical Research Ethics. *Guidelines about Notification etc. Of a Biomedical Research Project to the Committee System on Biomedical Research Ethics*. 5 May 2011.

European Commission. *Opinion on Ethical Aspects of Clinical Research in Developing Countries*. 4 February 2003.

European Commission. Seventh Framework Programme. *Guidance for Applicants: Informed Consent*. (n.d.).

Finland. *Medical Research Act*. Revised 2010.

Finland. National Advisory Board on Health Care Ethics. *Perspectives on Medical Research Conducted on Children*. 2003.

France. *Civil Code*. 1994.

France. Comite Consultatif National d’Ethique. *Opinion on Gene Therapy*. 13 December 1990.

France. Comite Consultatif National d’Ethique. *Opinion on the Ethics of Research in the Sciences of Human Behaviour*. 14 October 1993.

Germany. *Act for Protection of Embryos - The Embryo Protection Act*. 13 December 1990.

Greece. National Bioethics Commission. *Template of Code of Research Ethics for Biological Sciences*. 2009.

Greene M *et al.* Moral Issues of Human-Non-Human Primate Neural Grafting. *Science*. 309 (2005): 385-386.

- Harris B. *Disciplinary and Regulatory Proceedings*. 6th Ed. London: Wiley & Sons, 2011.
- Human Genome Organisation. *Statement on Human Genomic Databases*. 2002.
- Human Genome Organisation. *Statement on The Principled Conduct of Genetics Research*. 21 March 1996.
- International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. *ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice*. 10 June 1996.
- International Society for Stem Cell Research. *Guidelines for the Conduct of Human Embryonic Stem Cell Research*. 21 December 2006.
- International Society for Stem Cell Research. *Guidelines for the Clinical Translation of Stem Cells*. 3 December 2008.
- Ireland. Irish Council for Bioethics. *Report on Human Biological Material: Recommendations for Collection, Use and Storage in Research*. 29 June 2005.
- Israel. Ministry of Health. *Guidelines for Clinical Trials in Human Subjects*. 2006.
- Israel. *The Prohibition of Genetic Intervention (Human Cloning and Genetic Manipulation of Reproductive Cells) Law Num. 5759/1999*. 29 December 1998.
- Italy. *Regulation of Medically Assisted Reproduction, Law n. 40*. 19 February 2004.
- Levine RJ. The Nature, Scope, and Justification of Clinical Research. In Emanuel, EJ et al. (Eds.) *The Oxford Textbook of Clinical Research Ethics*. Oxford: Oxford University Press (2008) page 211.
- Lithuania. *Law on Ethics of Biomedical Research*. Amended 15 November 2007.
- Malaysia. Ministry of Health, National Committee for Clinical Research. *Guideline on the Use of Human Biological Tissues for Research*. 31 October 2006.
- Malaysia. Ministry of Health, National Committee for Clinical Research. *Malaysian Guideline for Good Clinical Practice (Third Edition)*. 2011.
- National Heart, Lung, and Blood Institute Working Group. Ethical and Practical Guidelines for Reporting Genetic Research Results to Study Participants: Updated Guidelines from a National Heart, Lung, and Blood Institute Working Group. *Circulation Cardiovascular Genetics*. December 2010.
- Nepal. Nepal Health Research Council. *Guidelines for Institutional Review Committees for Health Research in Nepal*. 2005.
- Nepal. Nepal Health Research Council. *National Ethical Guidelines for Health Research in Nepal and Standard Operating Procedures*. February 2011.

Netherlands. Central Committee on Research Involving Human Subjects. *Manual for the Review of Medical Research Involving Human Subjects*. 2002.

Netherlands. *Embryos Act*. July 2002.

Netherlands. *Medical Research Involving Human Subjects Act*. 2000.

Netherlands. *Regulations on Medical Research Involving Human Subjects (Medical Research (Human Subjects)) Act*. Revised 1 March 2006.

New Delhi. Indian Council of Medical Research. *Ethical Guidelines for Biomedical Research on Human Participants*. 2006.

New Zealand. *Health Information Privacy Code 1994*. Amended December 2008.

New Zealand. Health Research Council. *Guidelines on Ethics in Health Research*. Revised 2005.

New Zealand. *Human Assisted Reproductive Technology Act*. 2004.

New Zealand. *Human Tissue Act*. 2008.

New Zealand. Ministry of Health. *Operational Standards for Ethics Committees*. Updated April 2006.

New Zealand. National Ethics Advisory Committee. *Ethical Guidelines for Intervention Studies*. Revised July 2012.

New Zealand. National Ethics Advisory Committee. *Ethical Guidelines for Observational Studies: Observational Research, Audits and Related Activities*. Revised July 2012.

New Zealand. *Privacy Act*. 1993.

Organisation for Economic Co-operation and Development. *OECD Guidelines on Human Biobanks and Genetic Research Databases*. 2009.

Ourednik V *et al.* Segregation of Human Neural Stem Cells in the Developing Primate Forebrain. *Science*. 293 (2001): 1820-1824.

Pakistan. National Bioethics Committee Pakistan. *Ethical Research Committee-Guidelines*. (n.d.).

Philippines. Philippine Council for Health Research and Development. *National Ethical Guidelines for Health Research*. 2006.

2nd World Conference on Research Integrity. *Singapore Statement on Research Integrity*. 22 September 2010.

Singapore. *Animals and Birds Act* (Cap. 7). Revised 2002.

- Singapore. Bioethics Advisory Committee. *Donation of Human Eggs for Research*. 2008.
- Singapore. Bioethics Advisory Committee. *Ethical, Legal and Social Issues in Human Stem Cell Research, Reproductive and Therapeutic Cloning*. 2002.
- Singapore. Bioethics Advisory Committee. *Genetic Testing and Genetic Research*. 2005.
- Singapore. Bioethics Advisory Committee. *Human-Animal Combinations in Stem Cell Research*. 2010.
- Singapore. Bioethics Advisory Committee. *Human Tissue Research*. 2002.
- Singapore. Bioethics Advisory Committee. *Personal Information in Biomedical Research*. 2007.
- Singapore. Bioethics Advisory Committee. *Research Involving Human Subjects: Guidelines for IRBs*. 2004.
- Singapore. *Children and Young Persons Act* (Cap. 38). Amended 2001.
- Singapore. *Guardianship of Infants Act* (Cap. 122). Amended 1985.
- Singapore. *Health Products Act* (Cap. 122D). 2008.
- Singapore. *Human Cloning and other Prohibited Practices Act* (Cap. 131B). 2005.
- Singapore. *Infectious Diseases Act* (Cap. 137). Amended 2010.
- Singapore. *Medical (Therapy, Education and Research) Act* (Cap. 175). Amended 2010.
- Singapore. *Medicines (Clinical Trials) Regulations* (Cap. 176). Amended 2000.
- Singapore. *Medicines Act* (Cap. 176). 1985.
- Singapore. *Mental Capacity Act* (Cap. 177A). Revised 2010.
- Singapore. Ministry of Health. *Code of Ethical Practice in Human Biomedical Research*. 2009.
- Singapore. Ministry of Health. *Governance Framework for Human Biomedical Research*. December 2007.
- Singapore. Ministry of Health. *Licensing Terms and Conditions on Assisted Reproduction Services*. 2011.
- Singapore. Ministry of Health. *Operational Guidelines for Institutional Review Boards*. December 2007.

Singapore. Ministry of Health. *Singapore Guideline for Good Clinical Practice*. Revised 1999.

Singapore. National Advisory Committee for Laboratory Animal Research. *Guidelines on the Care and Use of Animals for Scientific Purposes*. 2004.

Singapore. National Healthcare Group. *Investigator Manual: All that an Investigator Needs to Know*. August 2009.

Singapore. National Medical Ethics Committee. *Ethical Guidelines for Gene Technology*. 2001.

Singapore. National Medical Ethics Committee. *Ethical Guidelines on Research Involving Human Subjects*. 1997.

Singapore, National Medical Ethics Committee. *Recommendations on Clinical Trials: Update Focusing on Phase I Trials*. 2007.

Singapore. *National Registry of Diseases Act* (Cap. 201). Amended 2007.

Singapore. *Personal Data Protection Act* (No. 26). 2012.

Singapore. *Private Hospitals and Medical Clinics Act* (Cap. 248). 1999.

Singapore. Singapore Medical Council. *Ethical Code and Ethical Guidelines*. (n.d.).

South Africa. Health Professional Council of South Africa. *Confidentiality: Protecting and Providing Information*. May 2008.

South Africa. Health Professional Council of South Africa. *Guidelines on the Keeping of Patient Records*. 29 May 2007.

South Africa. *Human Tissue Act*. 1983.

South Africa. Medical Research Council. *Guidelines on Ethics for Medical Research – General Principles*. (n.d.).

South Korea. *Bioethics and Biosafety Act*. 1 January 2005.

Spain. *Law 14/2007*, of 3 July, on Biomedical Research.

Sweden. *Act concerning the Ethical Review of Research Involving Humans*. 5 June 2003.

Sweden. *Genetic Integrity Act*. 2006.

Sweden. Swedish Research Council. *Good Research Practice*. 2006.

Switzerland. Swiss National Advisory Commission on Biomedical Ethics. *Research Involving Children, Opinion No. 16/2009*. March 2009.

Uganda. Uganda National Council for Science and Technology. *National Guidelines for Research Involving Humans as Research Participants*. March 2007.

United Kingdom. *Access to Health Records Act*. 1990.

United Kingdom. Association of the British Pharmaceutical Industry. *Guidelines for Phase 1 Clinical Trials*. 2007.

United Kingdom. *Data Protection Act*. 1998.

United Kingdom. Department of Health, Royal College of General Practitioners, British Medical Association. *The Good Practice Guidelines for GP electronic patient records*. 2011.

United Kingdom. Department of Health. *Innovative Genetic Treatment to Prevent Mitochondrial Disease* (Press Release). 28 June 2013.

United Kingdom. England and Wales Court of Appeal (Civil Division): *Jonathan Yearworth & Ors v North Bristol NHS Trust* [2009] 3 Weekly Law Reports 118, 4 February 2009.

United Kingdom. General Medical Council. *Confidentiality*. 12 October 2009.

United Kingdom. General Medical Council. *Good Practice in Research and Consent to Research*. April 2010.

United Kingdom. House of Lords: *S (An Infant, by her Guardian ad Litem the Official Solicitor) v. S* [1972] Appeal Cases 24, 23 July 1970.

United Kingdom. *Human Fertilisation and Embryology Act*. 2008.

United Kingdom. Human Fertilisation and Embryology Authority. *Mitochondria Replacement Consultation: Advice to Government*. March 2013.

United Kingdom. Human Fertilisation and Embryology Authority. *Third Scientific Review of the Safety and Efficacy of Methods to Avoid Mitochondrial Disease through Assisted Conception: 2014 Update*. June 2014.

United Kingdom. *Human Fertilisation and Embryology (Mitochondrial Donation) Regulations*. 2015.

United Kingdom. Human Genetics Commission. *Inside Information: Balancing Interests in the Use of Personal Genetic Data*. 2002.

United Kingdom. *Human Tissue Act*. 2004.

United Kingdom. Human Tissue Authority. *Code of Practice 9: Research*. September 2009.

United Kingdom. Medical Research Council. *Ethics Guide: Medical Research Involving Adults who Cannot Consent*. 2007.

United Kingdom. Medical Research Council. *Ethics Guide: Medical Research Involving Children*. 2004.

United Kingdom. Medical Research Council. *Human Tissue and Biological Samples for Use in Research: Operational and Ethical Guidelines*. 2005.

United Kingdom. Medical Research Council. *MRC Operational and Ethical Guidelines: Human Tissue and Biological Samples for Use in Research Clarification following passage of the Human Tissue Act 2004*. 2005.

United Kingdom. Medical Research Council. *Personal Information in Medical Research*. 2002.

United Kingdom. *Mental Capacity Act*. 2005.

United Kingdom. National Children's Bureau Research Centre. *Guidelines for Research with Children and Young People*. March 2011.

United Kingdom. *National Health Service Act*. 2006.

United Kingdom. National Health Services, National Patient Safety Agency, National Research Ethics Service. *Information Sheets & Consent Forms: Guidance for Researchers & Reviewers*. March 2011.

United Kingdom. National Health Services, National Patient Safety Agency, National Research Ethics Service. *Standard Operating Procedures for Research Ethics Committees*. May 2010.

United Kingdom, Nuffield Council on Bioethics. *Novel Techniques for the Prevention of Mitochondrial DNA Disorders: An Ethical Review*. June 2012.

United Kingdom. Nuffield Council on Bioethics. *Report on Human Tissue: Ethical and Legal Issues*. April 1995.

United Kingdom. Nuffield Council on Bioethics. *The Ethics of Research Related to Healthcare in Developing Countries*. 2002.

United Kingdom. Royal College of Paediatrics and Child Health: Ethics Advisory Committee. *Guidelines for the Ethical Conduct of Medical Research Involving Children*. 2000.

United Kingdom. *The Health Service (Control of Patient Information) Regulations*. 2002.

United Kingdom. *The Medicines for Human Use (Clinical Trials) Regulations*. 2004.

United Kingdom. *UK Biobank Ethics and Governance Framework*. October 2007.

United Nations Educational, Scientific and Cultural Organisation. *Report of the IBC on Pre-implantation Genetic Diagnosis and Germ-line Intervention*. 24 April 2003.

United Nations Educational, Scientific and Cultural Organization. *Universal Declaration on Bioethics and Human Rights*. 2005.

United States of America. Office for Human Research Protections, Department of Health and Human Services. *Protection of Human Subjects, Title 45 Code of Federal Regulations, Part 46*. Revised 2009.

United States of America. National Bioethics Advisory Commission. *Research Involving Human Biological Materials: Ethical Issues and Policy Guidance*. August 1999.

United States of America. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research*. 1979.

United States of America. National Institutes of Health. *Guidelines for the Conduct of Research Involving Human Subjects at the National Institutes of Health*. August 2004.

United States of America. National Institutes of Health. *NIH Guidelines for Research Involving Recombinant DNA Molecules*. October 2011.

United States of America. *Nuremberg Code*. In: *Trials of War Criminals before the Nuremberg Military Tribunals under Control Council*. Law No. 10, Vol. 2: 181-182. 1949.

United States of America. Office for Civil Rights HIPAA Privacy. *Research*. 3 April 2003.

World Health Organization. *A Practical Guide for Health Researchers*. 2004.

World Health Organization. *Genetic Databases Assessing the Benefits and the Impact on Human and Patient Rights*. 2003.

World Health Organization. *Guideline for Obtaining Informed Consent for the Procurement and Use of Human Tissues, Cells and Fluids in Research*. 2003.

World Health Organization. *Handbook for Good Clinical Research Practice*. 2005.

World Health Organization. *Review of Ethical Issues in Medical Genetics*. 2003.

World Health Organization. *Standards and Operational Guidance for Ethics Review of Health-Related Research with Human Participants*. 2011.

World Medical Association. *Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects*. Revised 2013.

World Medical Association. *WMA Declaration on Ethical Considerations Regarding Health Databases*. October 2002.

