ETHICS GUIDELINES FOR HUMAN BIOMEDICAL RESEARCH

(2021 REVISED EDITION)

BIOETHICS ADVISORY COMMITTEE
SINGAPORE

October 2021

ETHICS GUIDELINES FOR HUMAN BIOMEDICAL RESEARCH (2021 REVISED EDITION)

BIOETHICS ADVISORY COMMITTEE
SINGAPORE

October 2021

The Bioethics Advisory Committee, Singapore is an independent advisory committee that was established by the Government in December 2000 to address the ethical, legal and social issues arising from human biomedical research and its applications. The Bioethics Advisory Committee, Singapore studies emerging areas in human biomedical research and develops and recommends policies to the government as appropriate, with the aim of protecting the rights and welfare of individuals, while allowing the biomedical sciences to develop and realise its full potential for the benefit of mankind.

Published by

Bioethics Advisory Committee Secretariat
Regulatory Policy and Legislation Division
Ministry of Health
1 Maritime Square
#11-23, Harbourfront Centre
Singapore 099253

Printed in Singapore

Bioethics Advisory Committee (January 2020 to December 2021)

Patron
Dr Tony Tan Keng Yam
Honorary Patron and Distinguished Senior Fellow, Singapore Management University (SMU)
Former President of the Republic of Singapore

Emeritus Advisor
Professor Lim Pin
Emeritus Consultant, Division of Endocrinology, National University Hospital (NUH)
Professor of Medicine, National University of Singapore (NUS)

Chair
Mr Richard Magnus
Chief District Judge (Retired)

Deputy Chair
Professor Kon Oi Lian
Adjunct Professor, Duke-NUS Medical School

Members
Associate Professor Chin Jing Jih
Chairman, Medical Board, Tan Tock Seng Hospital (TTSH)
Senior Consultant, Department of Geriatric Medicine

Associate Professor Lim Tit Meng
Chief Executive, Science Centre Board (SCB)

Associate Professor Roy Joseph
Emeritus Consultant, Department of Neonatology, Khoo Teck Puat - National University Children's Medical Institute (KTP-NUCMI), NUH
Chairman, National Medical Ethics Committee (NMEC)

Dr Nazirudin Bin Mohd Nasir
Mufti, Office of the Mufti, Majlis Ugama Islam Singapura (MUIS)

Ms Chang Ai Lien
Health and Science Editor, The Straits Times

Mr Charles Lim Aeng Cheng
Principal Senior State Counsel, Legislation Division, Attorney-General's Chambers

Mr Gregory Vijayendran
Equity Partner, Rajah & Tann Singapore LLP
President, The Law Society of Singapore

Professor Lee Eng Hin
Emeritus Consultant, Division of Paediatric Orthopaedic Surgery, Department of Orthopaedic Surgery, NUH

Professor Patrick Tan Boon Ooi
Cancer and Stem Cell Biology Programme, Duke-NUS Medical School
Executive Director, Genome Institute of Singapore
Director, SingHealth Duke-NUS Institute of Precision Medicine (PRISM)

Professor Tan Sor Hoon
Professor of Philosophy, School of Social Sciences, Singapore Management University (SMU)

Professor Vineeta Sinha
Professor, Department of Sociology, Faculty of Arts and Social Sciences, NUS

Past Advisors on BAC's International Panel of Experts

Professor Bernard Lo (2000 – 2014)
President, Greenwall Foundation and Emeritus Professor of Medicine, University of California, San Francisco, United States of America

Professor Martin Bobrow (2000 – 2014)
Emeritus Fellow, University of Cambridge, United Kingdom

Professor Bartha Maria Knoppers (2003 – 2012)
Director, Centre of Genomics and Policy, Faculty of Medicine, Department of Human Genetics, McGill University, Canada

Dr Thomas H Murray (2005 – 2012)
Senior Research Scholar and President Emeritus, The Hastings Center, United States of America

Professor Onora O'Neill (2011 – 2013)
Baroness O'Neill of Bengarve
Emeritus Professor, University of Cambridge, United Kingdom

Professor Steven Hyman (2012 – 2017)
Director, Stanley Center for Psychiatric Research, Broad Institute, United States of America

Professor Peter Braude (2014 – 2021)
Emeritus Professor of Obstetrics and Gynaecology, King's College London

Dr Christine Grady (2014 – 2016)
Chief, Department of Bioethics, National Institutes of Health

Secretariat

Adj. Associate Professor (Dr) Raymond Chua Swee Boon

Dr Lee Wei Liang

Dr Tiong Wei Wei

Dr Durkeshwari Anbalagan-Raj

Mr Nicholas Wong

Mr Louis Peter Hor

Ms Toh Si Min

CONTENTS

FOREWORD **1**

EXECUTIVE SUMMARY **2**

PART I INTRODUCTION **10**

What is Human Biomedical Research? 11

The Legislative and Regulatory Framework of Human Biomedical Research in Singapore 13

PART II ETHICS GOVERNANCE OF HUMAN BIOMEDICAL RESEARCH **16**

General Ethical Principles that have Guided the BAC 16

Ethics Review of Human Biomedical Research in Singapore – The IRB System 20

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

Consent for Research Involving Persons Lacking Mental Capacity 27

Consent for Research Involving Vulnerable Persons Not Lacking Mental Capacity 28

Consent for Research Involving Patients 29

Consent for Research Involving Minors 30

Consent for Participants of Neuroscience Research 31

Waiver of Consent 32

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 **40**

Guidelines on Biobanking and Research Involving Human Biological Materials 41

PART VI HUMAN GENETIC RESEARCH **48**

Guidelines on Human Genetic Research 50

PART VII HUMAN STEM CELL RESEARCH **52**

Legislation 53

Ethical and Social Issues 54

Guidelines on Human Stem Cell Research 57

GLOSSARY **59**

BIBLIOGRAPHY **61**

Annexe A Consultation Paper: Ethics Guidelines for Human Biomedical Research

Annexe B Consultation Paper Distribution List

Annexe C Written Responses Received During the Public Consultation

Foreword

The Bioethics Advisory Committee (BAC) held a 20th Anniversary Event in June 2021 to commemorate its 20 years of establishment. The event was a timely occasion to review the Committee's past work and recommendations that have been issued since 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. This continues to be the guiding impetus of the committee. In accordance with our mandate, the BAC has examined a wide range of topics with an overarching focus on human biomedical research.

In 2015, the BAC reviewed and consolidated its prior recommendations into a single volume – *Ethics Guidelines for Human Biomedical Research*. The objective of this publication was to be a one-stop resource for researchers and members of ethics committees, or any interested individual seeking guidance on best practices for the ethical conduct of human biomedical research in Singapore. We also reviewed the BAC's past recommendations and our positions, taking into account new scientific, regulatory and legal developments. This was done to ensure that we were up-to-date with both local practices and international best standards, and that the guidelines contained 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.

Over the last few years, as the biomedical sciences have further advanced, the research ethics infrastructure in Singapore has also developed rapidly. With major developments such as the enactment of the Human Biomedical Research Act in 2015, there have been substantial changes to the current legislation, guidelines or directives that govern the conduct of biomedical research in Singapore. Thus, many of the examples or references used in the 2015 version of the *Guidelines* have been superseded.

In light of these developments, the BAC undertook a review of the *Guidelines* in 2021 to ensure that it remains current. At the same time, we also took this opportunity to incorporate the recommendations from our latest reports on Neuroscience Research and Mitochondrial Genome Replacement Technology (MGRT). This would ensure that the revised 2021 version of the *Guidelines* continues to be a one-stop resource for researchers, research institutions and individuals involved in the ethics review seeking to conduct human biomedical research in Singapore.

I would like to express my gratitude to my committee members for their commitment and contribution to this vital review. I would also like to thank the members of the research community and the general public who have supported the work of the BAC over the last 20 years. I look forward to your continued support for the BAC in the years to come.

Chief District Judge (Ret.) Richard Magnus
Chair
Bioethics Advisory Committee
October 2021

EXECUTIVE SUMMARY

I. Introduction

1. The BAC's *Ethics Guidelines for Human Biomedical Research* was first published in 2015. In 2021, the BAC undertook a review of the *Guidelines* to update the publication. The *Ethics Guidelines for Human Biomedical Research (2021 Revised Edition)* seeks to consolidate the BAC's past reports and recommendations, reconcile apparent discrepancies, and clarify any uncertainties which may have emerged since the original reports were published.

2. The revised *Guidelines* is intended to serve as an ethical resource for researchers and members of ethics committees or institutional review boards (IRBs) and should be taken as definitive at the date of publication.

II. Ethics Governance of Human Biomedical Research

3. An IRB should review all human biomedical research and the composition of the IRB should include appropriate expertise with some lay representation to reinforce the objectivity and impartiality of the process. The composition of IRBs and other functional and operational details are provided for in the Human Biomedical Research Act 2015.

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. 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. They should be provided with information on the procedures for withdrawal and any possible implications or risks involved in withdrawing from the research during the consent-taking process. If there is a risk of them suffering direct harm as a result of their withdrawal, they should also be informed of any protocols for follow-up monitoring and management.

12. 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.

13. 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.

14. 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.

15. 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.

16. 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.

17. 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.

18. 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.

19. 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).

20. 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.

21. 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.

22. When conducting high-risk neuroscience research, researchers should take extra caution in ensuring the safety and welfare of research participants which may have an impact on the personal identity and autonomy of participants. In such cases, researchers should put in place appropriate safeguards during the consent-taking process to ensure that the individual autonomy of participants is respected.

IV. Personal Information in Research

23. 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.

24. 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'.

25. 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.

26. 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, 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.

27. If it is necessary to collect individually-identifiable information, under the Human Biomedical Research Act 2015, researchers have the duty to take all reasonable steps and safeguards to protect individually-identifiable information obtained for the purposes of human biomedical research.

28. 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.

29. 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.

30. 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 waiver will not adversely affect the safety and welfare 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.

31. 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

32. 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.

33. 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.

34. Under the Medical (Therapy, Education and Research) Act 1972, 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.

35. Research conducted in Singapore involving the use of human biological materials is required to comply with the relevant requirements stipulated in the Human Biomedical Research Act 2015 and Human Biomedical Research (Tissue Banking) Regulations 2019.

36. 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 1972.

37. The supply and use of human gametes and embryos are regulated under the Human Cloning and Other Prohibited Practices Act 2004. Researchers should also comply with the requirements stipulated in the Human Biomedical Research Act 2015 and its relevant subsidiary legislation.

38. Under the Human Biomedical Research Act 2015, written approval from the Director of Medical Services, in addition to IRB approval, must be obtained for all research involving human eggs or human embryos. This requirement extends to human biomedical research involving human-animal combination embryos, such as those created in-vitro by using human gametes and animal gametes.

39. 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.

40. 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.

41. 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.

42. 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.

43. 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.

44. 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.

45. 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.

46. 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.

47. 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.

48. 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

49. 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.

50. Participation in genetic research should be voluntary, whether directly or by contribution of biological materials or personal information.

51. 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.

52. 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.

53. The clinical practice of germline genetic modification (such as Mitochondrial Genome Replacement Technology) should not be permitted at this stage, until there is further evidence of the efficacy and safety of such techniques.

VII. Human Stem Cell Research

54. 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.

55. 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.

56. 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.

57. 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.

58. 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 ETHICS (2021 REVISED EDITION)

I. INTRODUCTION

1.1 The main purpose of the *Ethics Guidelines for Human Biomedical Research* (*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 focused on human biomedical research. This is captured in nine reports issued between 2002 and 2021. In 2011, the BAC reviewed its past reports, and consolidated them in the first edition of *Guidelines* which was published in 2015. In 2021, the BAC conducted a further review to update the *Guidelines* and incorporate the BAC's latest recommendations from reports published since 2015, and ensure that it remains an up-to-date ethics resource in Singapore.

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 that have emerged 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 nine BAC reports that form the basis of these *Guidelines* are 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);

(g) The *Human-Animal Combinations Report*. Human-Animal Combinations in Stem Cell Research (2010);

(h) The *Neuroethics Report*. Ethical, Legal, and Social Issues Arising from Neuroscience Research (2021); and

(i) The *MGRT Report*. Interim Report on the Ethical, Legal and Social Issues Arising from Mitochondrial Genome Replacement Technology (MGRT) (2021).

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.'[i] 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.[ii] 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;

---

[i] Office for Human Research Protections, 45 Code of Federal Regulations (2018), 46.102(l).

[ii] 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.

(b) The research will use or manipulate human biological materials (e.g. human cells, tissues, organs and body fluids);

(c) The research involves technology that aims to manipulate human biological materials;

(d) 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;

(e) 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

(f) 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.[iii]

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.

[iii] 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.

1.15 Most significantly, the Human Biomedical Research Act 2015 was passed by Parliament on 18 Aug 2015. The Act sets out a regulatory framework to ensure the responsible and ethical conduct of human biomedical research and human tissue banking activities in Singapore. Many of the BAC's recommendations on issues such as informed consent, the roles and responsibilities of IRBs, and collection and use of human biological materials were incorporated into the Act and subsidiary legislation.

Statutes and Subsidiary Legislation

1.16 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) Human Biomedical Research Act 2015 and its subsidiary legislation: This Act regulates the conduct of human biomedical research (including research institutions and institutional review boards), tissue banks and tissue banking activities; further regulates certain restricted human biomedical research; and prohibits certain types of human biomedical research and the commercial trading of human tissue.

(b) Medical (Therapy, Education and Research) Act 1972: This Act makes 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;

(c) Medicines (Clinical Trials) Regulations 2016 made under Section 18 of the Medicines Act 1975, which is an Act to make provisions with respect to medicinal products and medical advertisements and matters connected therewith;

(d) Health Products (Clinical Trials) Regulations 2016 made under Section 72 of the Health Products Act 2007: 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;

(e) Human Cloning and other Prohibited Practices Act 2004: 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) Mental Capacity Act 2008: 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'. For present purposes, these include decisions relating to consent to biomedical research and

donation of tissues. 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;

(g) Private Hospitals and Medical Clinics Act 1980 (will be repealed by the Healthcare Services Act): 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;

(h) Healthcare Services Act 2020: An Act to provide for the regulation of healthcare services and other connected or incidental matters, and to repeal the Private Hospitals and Medical Clinics Act;[iv]

(i) Personal Data Protection Act 2012: This Act governs the collection, use and disclosure of personal data, including for the purposes of research;

(j) Infectious Diseases Act 1976: An Act relating to quarantine and the prevention of infectious diseases. Section 59A of the Act relates to National Public Health Research;

(k) National Registry of Diseases Act 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;

(l) Animals and Birds Act 1965, Animals and Birds (Care and Use of Animals for Scientific Purposes) Rules: 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.

Guidelines / Directives

1.17 Relevant guidelines / directives are as follows:

(a) Health Sciences Authority (HSA), Guidance on Good Clinical Practice Compliance Inspection Framework, 2021;

(b) International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), ICH E6(R2) Good Clinical Practice Guideline, 2016;

(c) Ministry of Health (MOH), Guidance on Prohibition against Commercial Trading of Human Tissue, 2017;

[iv] The Healthcare Services Act 2020 was passed by the Singapore Parliament in Jan 2020 and its regulations are being progressively rolled out in three phases before the Private Hospitals and Medical Clinics Act (PHMCA) is repealed.

(d) MOH, Guide on the Requirement of Appropriate Consent for the Conduct of HBR and Handling of Human Tissue, 2019;

(e) MOH, Directive on the Use of Cell, Tissue and Gene Therapy Products Manufactured In-House by Healthcare Institutions, 2020;

(f) National Advisory Committee for Laboratory Animal Research, Guidelines on the Care and Use of Animals for Scientific Purposes, 2004. Administered by the National Parks Board's Animal & Veterinary Service and the National Advisory Committee on Laboratory Animal Research;

(g) Singapore Medical Council, Ethical Code and Ethical Guidelines, 2016; and

(h) Singapore Medical Council, SMC Handbook on Medical Ethics, 2016.

1.18 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. This was subsequently institutionalised through the Human Biomedical Research Act 2015. This system of ethics governance is discussed further in Part II of these Guidelines.

1.19 The BAC reports have all been accepted by the MOH as providing guidance on matters not covered by statute, subsidiary legislation, or otherwise.

1.20 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 Human Biomedical Research Act 2015 or any other related legislation.

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,[v] 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 Health-related Research Involving Humans (2016);

(e) The United Nations Educational Scientific and Cultural Organisation (UNESCO) Universal Declaration on the Human Genome and Human Rights (1997); and

(f) UNESCO Universal Declaration on Bioethics and Human Rights (2005).

General Ethical Principles that have Guided the BAC

2.3 A review of the six 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.

[v] 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. Autonomy can be broadly defined as the right of individuals to make decisions and take actions by themselves on what is good for them. The welfare and interests of individuals 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.

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.[vi] 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.[vii]

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.[viii] 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.

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

---

[vi] '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.

[vii] An example would be a research participant assigned to a placebo control group.

[viii] 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.

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 jurisdictions in the context of biomedical research.[ix] 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 better captures 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 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 (2010), developed by the 2nd World Conference on Research Integrity (WCRIF), 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.[x] This Statement was then used by WCRIF to develop subsequent guidance documents such as the Montreal Statement (2013), and the Amsterdam Agenda (2017).

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.

[ix] 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.

[x] The Statement is available at http://www.wcif.org/guidance/singapore-statement.

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 human biomedical research in Singapore is through the IRB system, which has been established by statute through the Human Biomedical Research Act 2015. Under the Act, all human biomedical research must be reviewed by an appointed IRB before it may proceed. The Act also sets out the functions, duties, composition and proceedings of IRBs.

2.19 In parallel, the Medicines (Clinical Trials) Regulations 2016 and Health Products (Clinical Trials) Regulations 2016 also require all proposals for pharmaceutical clinical trials to undergo an ethics review by an IRB. 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 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 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 or developed since the IRB system was implemented. These recommendations should be read in tandem with existing regulatory requirements listed in paragraph 1.16 to guide IRBs on best practices.

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.

2.39 Institutions should ensure that there is an arrangement for receiving feedback from research participants.

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. They should be provided with information on the procedures for withdrawal, and any possible implications or risks involved in withdrawing from the research. Researchers should also follow up and monitor participants for an appropriate period of time if there is a risk of direct harm arising from their withdrawal.

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. However, 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

3.13 The conduct of research for persons lacking mental capacity is governed by the Mental Capacity Act 2008 and the Human Biomedical Research Act 2015.

The Mental Capacity Act 2008

3.14 The Mental Capacity Act 2008 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.

3.15 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,[xi] 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

(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.

3.16 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).

[xi] 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.'

3.17 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.[xii] 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.[xiii] 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.

The Human Biomedical Research Act 2015

3.18 Section 7(1) of the Human Biomedical Research Act 2015 sets forth the conditions for taking appropriate consent from adults who lack mental capacity to participate in human biomedical research. Under the Act, researchers are only permitted to recruit such research subjects when there are reasonable grounds for believing that biomedical research of comparable effectiveness cannot be carried out without their participation (e.g. research involving treatment of mental illnesses).

3.19 When recruiting such research participants, appropriate consent must be obtained from an authorised deputy or donee (as defined by the Mental Capacity Act 2008) on the participant's behalf. Should there be no authorised deputy or donee available to give consent to the research on behalf of the participant, the Act also stipulates the persons from whom to obtain consent.[xiv]

Consent for Research Involving Vulnerable Persons Not Lacking Mental Capacity

3.20 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;

[xii] 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.

[xiii] 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.

[xiv] Section 7(1)b of the Human Biomedical Research Act 2015 states: 'where there is no donee or deputy who is authorised to give consent to the biomedical research on behalf of the adult, consent is obtained from any of the following persons in the order of priority stated, when persons in prior classes are not available, and in the absence of actual notice of contrary indications by the adult, or actual notice of opposition of a member of the same class or a prior class:
(i) the spouse;
(ii) an adult son or daughter;
(iii) either parent or a guardian;
(iv) an adult brother or sister;
(v) any other person named by the adult as someone to be consulted on the matter in question or on matters of that kind.'

(c) Patients, especially if the intending researcher is their attending physician; and

(d) Employees, junior collaborators, or students.

3.21 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 declining to contribute 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.

3.22 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.

3.23 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

3.24 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.

3.25 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

3.26 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.[xv] 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 3.17 above.

3.27 Participation in research without direct benefit should involve no more than minimal risk and not be contrary to the best interests of the minor. Where possible, research should be conducted in older children with sufficient understanding and intelligence to understand what is proposed in the research before involving younger children. In research involving minors as participants, in addition to seeking IRB approval for their research protocols, researchers should justify to IRBs why their research cannot be conducted in an older population.

3.28 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 be informed of the altruistic nature of his/her participation. Respect for a minor's developing autonomy is recognised by both the Human Biomedical Research Act 2015 and Medicines (Clinical Trials) Regulations 2016, which require *both* the minor who has sufficient understanding and a parent or guardian to consent to participation in a clinical trial.[xvi,xvii] Similarly, the common law will not subject a child with sufficient understanding to a non-therapeutic procedure against his/her will.[xviii]

Determining decision making capacity

3.29 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.[xix] 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 the

[xv] Children and Young Persons Act (Cap. 38), s.3A; Guardianship of Infants Act (Cap 122), s3

[xvi] Medicines (Clinical Trials) Regulations 2016, r.16(5).

[xvii] Human Biomedical Research Act 2015, s8.

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

[xix] 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.

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

Engagement

3.30 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.[xx] 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

3.31 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

3.32 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.

Consent for Participants of Neuroscience Research

3.33 Neuroscience is the study of the nervous system which includes the central nervous system that consists of the brain and spinal cord, and the peripheral nervous system that consists of all the nerves distributed throughout the body. Much of neuroscience research is aimed at understanding, preventing or treating disorders of the nervous system. This also includes the study of interventions to the human brain through a range of neurotechnologies. While such research has the potential to develop therapies to treat specific motor/behavioural symptoms or mental illnesses, they also have the potential to alter an individual's cognition, emotion, and even personality. Given that the human brain has the capacity to influence all our physiological processes of thought, emotion and behaviour, research on the human brain has implications beyond that of other organs or tissues.

3.34 In most instances of neuroscience research, especially for research involving the medical use of neurotechnologies, many of the ethical, legal and social issues raised are not exceptional and do not differ fundamentally from those found in most biomedical research. These concerns are sufficiently addressed by applying existing research ethics frameworks, including those that are described in these *Guidelines*, such as the taking of informed consent

[xx] 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.

and the recruitment of participants lacking mental capacity.

3.35 However, there are a few exceptional cases in neuroscience research which may require additional caution to ensure the safety and welfare of research participants. These cases involve the conduct of high-risk neuroscience research, such as sham brain surgeries or research that may have an impact on the personal identity and autonomy of participants. As an added precaution, researchers should inform participants during the consent taking process if there is a risk that the research could affect the participant's personal identity or autonomy. In such cases, researchers should put in place appropriate safeguards to respect the individual autonomy of participants. Such safeguards include proactively ascertaining the wishes of research participants in the event that they lose mental capacity over the course of the research protocol, or re-seeking consent to continue should they notice any personality changes in the participant.[xxi]

Waiver of Consent

3.36 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;

(d) Obtaining consent is not possible or practicable; and

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

3.37 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 time frame 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 Human Biomedical Research Act 2015 and Mental Capacity Act 2008, 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

3.38 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

[xxi] For more details on the cases of neuroscience research which will require additional safeguards, please see Recommendations 7 and 9 to 11 of the BAC's Neuroethics Report.

follow up on the matter with a medical practitioner.

3.39 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. The BAC is of the view that researchers have a duty to return clinically significant incidental findings, whether actionable or not,[xxii] to research participants who have requested to know. 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.

3.40 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.

3.41 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.

3.42 If a clinically significant finding is discovered, but the preference of the research participant for receiving such information is unknown, researchers must consider whether the potential harm of returning the incidental finding would outweigh the expected benefits. Researchers should seek expert advice and/or refer to their IRBs for advice on the appropriate handling of such information.

Guidelines on Consent

3.43 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.

3.44 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. They should be provided with information on the procedures for withdrawal and any possible implications or risks involved in withdrawing from the research during the consent-taking process.[xxiii] If there is a risk of them suffering direct harm as a result of their withdrawal, they should also be informed of any protocols for follow-up monitoring and management.

3.45 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;

xxii Incidental findings that are not curable or otherwise clinically actionable may still be considered to be clinically significant as participants could make lifestyle decisions they might otherwise not have.

xxiii Under s 14(3) of the Human Biomedical Research Act 2015 the withdrawal of consent in the circumstances specified in s 14(1) or (2)(b) does not affect the research information obtained before the consent is withdrawn and such information may still be retained and used for 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.

3.46 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.

3.47 Consent to participation in research should be documented in writing.

3.48 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.

3.49 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.

3.50 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.

3.51 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.

3.52 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.

3.53 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.

3.54 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.

3.55 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).

3.56 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.

3.57 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.

3.58 When conducting high-risk neuroscience research, researchers should take extra caution in ensuring the safety and welfare of research participants which may have an impact on the personal identity and autonomy of participants. In such cases, researchers should put in place appropriate safeguards during the consent-taking process to ensure that the individual autonomy of participants are respected.

IV. PERSONAL INFORMATION IN RESEARCH

4.1 Personal information is any identifiable information about an individual, living or deceased. 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 Under the Human Biomedical Research Act 2015, researchers have the duty to take all reasonable steps and safeguards to protect individually-identifiable information obtained for the purposes of human biomedical research.[xxiv]

[xxiv] Human Biomedical Research Act 2015, s27-29.

4.7 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.

4.8 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.[xxv] 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.

4.9 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 Sections 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.

4.10 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.

4.11 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 any individual, without IRB approval. Should an individual

[xxv] Personal Data Protection Commission, 'Advisory Guidelines on the Personal Data Protection Act for Selected Topics' (revised 9 Oct 2019), at para 3.37.

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.

4.12 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

4.13 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 in the records and safeguard the privacy of patients concerned.

4.14 Much valuable medical knowledge has resulted from the study of patients' medical records. 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.

4.15 In 2007, the BAC recommended in its *Personal Information Report* that IRBs should be legally empowered to waive patient consent requirements for research involving only the use of medical records, as long as patient privacy and confidentiality of medical information can be ensured.[xxvi] Further to the BAC's recommendations, the Human Biomedical Research Act 2015 now allows IRBs to waive the requirement for consent in specific situations as stipulated within its Fifth Schedule.[xxvii] These include the use of personal information for research without consent, provided that certain stringent conditions are satisfied.

Epidemiological and Public Health Research

4.16 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 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

[xxvi] See Recommendation 8 of the report.
[xxvii] See Section 13 and Fifth Schedule of the Human Biomedical Research Act 2015.

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 must be approved by an IRB. The conditions for a waiver of consent are provided in paragraph 3.36.

Guidelines on the Use of Personal Information in Research

4.17 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.

4.18 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.

4.19 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.

4.20 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.

4.21 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 waiver will not adversely affect the safety and welfare 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.

4.22 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 deceased 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 materials 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.[xxviii] 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,

[xxviii] 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.

discoveries or biological products. However, it is generally accepted that the human body or any parts of it, 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.[xxix] 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.

5.8 With the enactment of the Human Biomedical Research Act 2015, MOH has implemented a Human Tissue Framework to govern the use of human tissue in research. The objective of this regulatory framework is to protect the safety and welfare of tissue donors and prohibit commercial trading of human tissue. Research conducted in Singapore involving the use of human biological materials is required to comply with the relevant requirements stipulated in Part 6 of the Human Biomedical Research Act 2015 and Human Biomedical Research (Tissue Banking) Regulations 2019.

Guidelines on Biobanking and Research Involving Human Biological Materials

General

5.9 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.

5.10 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.

5.11 Donors of biological materials should not be offered any financial incentives for their donation, although reasonable reimbursement of expenses incurred may be given.

5.12 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.

[xxix] Medical Research Council, UK. *Human tissue and biological samples for use in research: Operational and Ethical Guidelines* (2014), page 8.

Consent in research with human biological materials

5.13 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.

5.14 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.

5.15 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.

5.16 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.

5.17 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.

5.18 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.

5.19 Under the Medical (Therapy, Education and Research) Act 1972, 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

5.20 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.

5.21 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.

5.22 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 1972.

5.23 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

5.24 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 2004 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.

5.25 The supply and use of human gametes and embryos are regulated under the Human Cloning and Other Prohibited Practices Act 2004. Researchers should also comply with the requirements stipulated in the Human Biomedical Research Act 2015 and its relevant subsidiary legislation.

5.26 Under the Human Biomedical Research Act 2015, written approval from the Director of Medical Services, in addition to IRB approval, must be obtained for all research involving human eggs or human embryos.[xxx] This requirement extends to human biomedical research involving human-animal combination embryos, such as those created in-vitro by using human gametes and animal gametes.

5.27 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.

5.28 For women undergoing fertility treatment, consent for the donation of surplus eggs 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 eggs or embryos for research. Donors should confirm in writing that they do not require the eggs or embryos for future use.

5.29 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.

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

5.31 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.

[xxx] See Human Biomedical Research (Restricted Research) Regulations 2017 and 4th Schedule of the Human Biomedical Research Act 2015.

5.32 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.[xxxi]

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 allowed to develop beyond 14 days *in vitro*.

5.34 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.

5.35 Human cytoplasmic hybrid embryos[xxxii] 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.

5.36 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

5.37 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.

5.38 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 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.

5.39 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.

[xxxi] See Section 10.2 of the MOH Licensing Terms and Conditions on Assisted Reproductive Services 2020.

[xxxii] 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.

Surplus Biological Materials from Research Projects

5.40 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.

5.41 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

5.42 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

5.43 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

5.44 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.[xxxiii] 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.

5.45 With the introduction of the Human Tissue Framework under the Human Biomedical Research Act 2015, MOH has also exempted legacy tissues which were removed from the donor's body and rendered non-identifiable prior to 1 November 2019 from the legal requirements of the HBRA. However, this exemption does not apply to legacy tissues which were collected for specific purposes.[xxxiv]

5.46 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[xxxv] 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.

[xxxiii] 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.'

[xxxiv] See Section 64(1) of the Human Biomedical Research Act 2015 for the types of legacy tissue that do not fall within this exemption.

[xxxv] For what constitutes sensitive research, see paragraphs 1.9 and 1.11.

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 possibility 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 to 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.[xxxvi] 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.[xxxvii] 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) Regulations[xxxviii] 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 the 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.[xxxix] In light of further international deliberations on germline modification techniques for the treatment of serious diseases, especially in the field of Mitochondrial Genome Replacement Technology (MGRT), a Review Group was appointed by the BAC to study these developments and review the BAC's existing position on the clinical practice of germline modification with a focus on MGRT.

6.7 In its 2021 MGRT Interim Report, the BAC maintained its position from its 2005 Genetics Report, concluded that it was premature to exempt MGRT from prohibition of clinical germline genetic modification, and recommended that the clinical application and in vivo research of MGRT in human subjects should not be permitted presently. A more definitive assessment would be better undertaken at a future date when there is greater certainty in the science, techniques, safety, and efficacy of MGRT.

6.8 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 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.

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

[xxxvii] 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.

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

[xxxix] The report states: 'We are of the view that the clinical practice of germline genetic modification should not be allowed at this time. Germline genetic modification is at present still experimental and will require substantial research to establish its feasibility and safety in clinical application. In addition, the potentially great impact on future generations presents serious ethical concerns.'

6.9 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.

6.10 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.

6.11 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

6.12 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.

6.13 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.

6.14 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.

6.15 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.

6.16 For clinical trials involving gene-based therapies, regulatory approval from HSA is required, in addition to ethics approval from an IRB.

6.17 The clinical practice of germline genetic modification (such as Mitochondrial Genome Replacement Technology) should not be permitted at this stage, until there is further evidence of the efficacy and safety of such techniques.

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 foetuses (*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 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.

7.5 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.

7.6 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.

7.7 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 dementia, diabetes and spinal cord injury. 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.

7.8 Over the years, the BAC has published several reports containing recommendations on the conduct of research involving the use of stem cells, such as its Stem Cell Report (2002), Egg Donation Report (2008), Human-Animal Combinations Report (2010), and Neuroethics Report (2021). Some of these areas are contentious because they involve techniques such as cloning technology that arouse unease or opposition among those who consider that science risks hubristically exceed its proper function, or think that human embryos and gametes are not proper materials for research. The recommendations in these reports have addressed some of the more controversial areas of biomedical research, namely, research involving the use of human embryonic stem cells; research with human eggs and embryos; research in which tissues or cellular components of humans and animals are combined; and research involving the use of cerebral organoids.

Legislation

7.9 In 2004, the Human Cloning and Other Prohibited Practices Act 2004 was enacted 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.

7.10 Stem cell research is now governed by the Human Biomedical Research Act 2015 in the same way as other forms of research except that stem cell research involving human gametes and embryos including human-animal combinations is subject to more stringent regulatory control. The Human Biomedical Research Act 2015 and Human Biomedical Research (Restricted Research) Regulations 2017 set out the requirements for the use of human gametes and embryos for research, including the use of human-animal combination gametes and embryos for research.

7.11 The Health Products (Clinical Trials) Regulations 2016 made under Section 72 of the Health Products Act 2007 set out the requirements for research involving the use of Cell, Tissue and Gene Therapy Products (CTGTP).

Ethical and Social Issues

Moral status of the human embryo

7.12 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.

7.13 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.

7.14 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

7.15 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

7.16 *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.

7.17 *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.

7.18 *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.

7.19 *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.

7.20 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.

7.21 *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 foetuses[xl], 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:[xli]

(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;

[xl] Ourednik V *et al.* Segregation of Human Neural Stem Cells in the Developing Primate Forebrain. *Science.* 293 (2001): 1820-1824.
[xli] Greene M *et al.* Moral Issues of Human-Non-Human Primate Neural Grafting. *Science*. 309 (2005): 385-386.

(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.

7.22 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.

Cerebral Organoids

7.23 Stem cells have also been used to derive organoids, three-dimensional tissue structures which mimic the architecture and function of mature organs that can assist in disease modelling, drug testing for precision medicine, or regenerative medicine. Common tissue types grown include gastrointestinal, eye and brain (cerebral organoids).

7.24 In recent years, scientists have been able to develop human cerebral midbrain-like organoids comprising distinct cell layers with functional dopamine producing neurons.[xlii] These findings show promise in developing a disease model to develop treatments for chronic brain diseases such as Parkinson's disease.

7.25 These 'mini brains' have been sensationalised in media reports that have raised both expectations and fears of the general public. However, such organoids generated to date have only reached the peak maturity and complexity of a prenatal state. Furthermore, even though pluripotent stem cells have the ability to differentiate into all cell types, their ability to self-organise into a specific temporal and spatial configuration is limited, and technological hurdles to develop functionally mature organs remain. Nevertheless, brain organoids are expected to become invaluable models for better understanding of the fundamental biology of brain development, function and disorders, as well as the development of personalised medicine for brain disorders. This is because brain organoids derived from individuals maintain the major characteristics of the developing brain with identical genetic information. Although brain organoid technology is still in its nascent stages, there may be a need to also ascertain the relevant ethical considerations for conducting such research in the long run.

7.26 However, at the current state of science, the BAC is of the view that research involving human cerebral organoids does not require any additional safeguards. Despite recent scientific developments in this area, the current state of cerebral organoid development does not pose any additional ethical, legal or social issues in human biomedical research. At this time, any in vitro research conducted in Singapore involving the use of human cerebral organoids is permissible, subject to the laws and regulations governing the use of stem cells in human

[xlii] Jo J *et al.* Midbrain-like Organoids from Human Pluripotent Stem Cells Contain Functional Dopaminergic and Neuromelanin-Producing Neurons. *Cell Stem Cell*. 19(2) (2016): 248–257.

biomedical research, and any in vivo use of such organoids would fall under the 'Restricted Research' category of the Human Biomedical Research Act 2015.

Guidelines on Human Stem Cell Research

7.27 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.[xliii]

7.28 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.

7.29 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.

7.30 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.

7.31 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.

7.32 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.

7.33 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.

[xliii] See Human Biomedical Research (Restricted Research) Regulations 2017 and 4th Schedule of the Human Biomedical Research Act 2015.

7.34 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.[xliv]

7.35 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.

[xliv] With effect from 1 March 2021, the use of cell, tissue, and gene therapy products in Singapore for therapeutic, preventive, palliative or diagnostic purposes is regulated under the Health Products (Cell, Tissue, and Gene Therapy Products) Regulations 2021.

GLOSSARY

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.

Central nervous system – Part of the nervous system consisting of the brain and spinal cord.

Cerebral organoids – Cerebral organoids are three-dimensional tissue structures derived from pluripotent stem cells which mimic the architecture and function of the brain. Human cerebral organoids have the potential to be used as models to study human brain development and disorders.

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.

Germline – The lineage of germ cells from which eggs and sperm are derived.

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.

Mental capacity – One's ability to make their own decisions, of which may be lowered if there is an impairment of one's cognitive abilities.

Peripheral nervous system – Part of the nervous system that exists outside of the brain and spinal cord.

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).

Sham Surgery – A faked surgical intervention that excludes the step(s) hypothesised to be therapeutically necessary. In clinical trials, it serves as an important control in assessing surgical interventions.

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 in collaboration with the World Health Organization. *International Ethical Guidelines for Health-related Research Involving Humans.* 2016.

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 Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), *ICH E6(R2) Good Clinical Practice Guideline,* 2016.

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.

Jo J *et al.* Midbrain-like Organoids from Human Pluripotent Stem Cells Contain Functional Dopaminergic and Neuromelanin-Producing Neurons. *Cell Stem Cell*. 19(2) (2016): 248–257.

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 (2011) 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*. 2010.

Singapore. Animals and Birds Act 1965.

Singapore. Children and Young Persons Act 2001.

Singapore. Guardianship of Infants Act 1985.

Singapore. Health Products Act 2007.

Singapore. Health Products (Clinical Trials) Regulations 2016.

Singapore. Healthcare Services Act 2020.

Singapore. Human Biomedical Research Act 2015.

Singapore. Human Biomedical Research (Restricted Research) Regulations 2017.

Singapore. Human Biomedical Research (Tissue Banking) Regulations 2019.

Singapore. Human Cloning and other Prohibited Practices Act 2004.

Singapore. Infectious Diseases Act 1976.

Singapore. Medical (Therapy, Education and Research) Act 1972.

Singapore. Medicines (Clinical Trials) Regulations 2016.

Singapore. Medicines Act 1975.

Singapore. Mental Capacity Act 2008.

Singapore. National Registry of Diseases Act 2007.

Singapore. Personal Data Protection Act 2012.

Singapore. Private Hospitals and Medical Clinics Act 1980.

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. *Ethical, Legal, and Social Issues Arising from Neuroscience Research.* 2021.

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. *Interim Report on the Ethical, Legal and Social Issues Arising from Mitochondrial Genome Replacement Technology (MGRT).* 2021.

Singapore. Bioethics Advisory Committee. *Personal Information in Biomedical Research*. 2007.

Singapore. Bioethics Advisory Committee. *Research Involving Human Subjects: Guidelines for IRBs*. 2004.

Singapore. Health Sciences Authority. *Guidance on Good Clinical Practice Compliance Inspection Framework.* 2021.

Singapore. Ministry of Health. *Code of Ethical Practice in Human Biomedical Research*. 2009.

Singapore. Ministry of Health. *Directive on the Use of Cell, Tissue and Gene Therapy Products Manufactured In-House by Healthcare Institutions.* 2020.

Singapore. Ministry of Health. *Governance Framework for Human Biomedical Research.* December 2007.

Singapore. Ministry of Health. *Guidance on Prohibition against Commercial Trading of Human Tissue.* 2017.

Singapore. Ministry of Health. *Guide on the Requirement of Appropriate Consent for the Conduct of HBR and Handling of Human Tissue.* 2019.

Singapore. Ministry of Health. *Licensing Terms and Conditions on Assisted Reproduction Services.* 2020.

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 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. Personal Data Protection Commission. *Advisory Guidelines on the Personal Data Protection Act for Selected Topics.* Amended 2019.

Singapore. Singapore Medical Council. *Ethical Code and Ethical Guidelines*. 2016.

Singapore. Singapore Medical Council. *SMC Handbook on Medical Ethics*. 2016.

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*. 2014.

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. *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 Kingdom. 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.* 2014.

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 Nations Educational, Scientific and Cultural Organization. *Universal Declaration on the Human Genome and Human Rights.* 1997.

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 2018.

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.

ANNEXE A

CONSULTATION PAPER: ETHICS GUIDELINES FOR HUMAN BIOMEDICAL RESEARCH

Annexe A

ETHICS GUIDELINES FOR HUMAN BIOMEDICAL RESEARCH

FOR COMMENTS

BIOETHICS ADVISORY COMMITTEE

SINGAPORE

20 June 2012

ETHICS GUIDELINES FOR HUMAN BIOMEDICAL RESEARCH

I. INTRODUCTION

1.1 The main purpose of these Guidelines is to present an accessible and consolidated ethics resource for biomedical researchers and members of ethics committees or institutional review boards (IRBs), based on a review of the collected Reports and recommendations of the Bioethics Advisory Committee (BAC).

1.2 The BAC was formed in 2000. Its remit is to examine ethical, legal and social issues arising from research on human biology and behaviour and its applications; and to develop and recommend policies on such issues. The aim is 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. The BAC is a policy advisory body, not an executive body; hence it has no supervisory or regulatory power.

1.3 The work of the BAC since its inception has focussed on human biomedical research. This work is captured in seven Reports issued between 2002 and 2010, and continues. In 2011, the BAC reviewed these reports and prepared the Ethics Guidelines for Human Biomedical Research.

1.4 The views of the BAC presented in these Guidelines should be taken as definitive as of the date of publication. Our intention is to render it unnecessary for readers to consult the various BAC Reports in order to grasp the essentials of our position on the issues covered. These Guidelines seek to reconcile any apparent discrepancies and clarify any uncertainties emerging since the original reports were published. Some new material has been included. The Reports remain available as primary sources for those who may be interested.

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

(e) The *Human-Animal Combinations Report*. Human-Animal Combinations in Stem Cell Research (2010).

1.6 A further purpose of these Guidelines is to summarise the framework of legislative and regulatory provisions that determines ethics governance of biomedical research in Singapore.

Annexe A

It may be helpful to set out this framework as the BAC frequently receives enquiries about such matters, together with occasional requests for it to intervene or comment on issues.

What is Human Biomedical Research?

1.7 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.'[i] 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.

1.8 Biomedical research has been defined as research having as its purpose the enhancement or improvement of medical practice.[ii] This extends the scope of biomedical research beyond research that is clinical, and it could include research that does not use human subjects at all. Much fundamental research in physiology and other disciplines has the eventual goals of medicine as its ultimate aim. In a similar way, the goal of much bioengineering is ultimately medical, though this is not true of the foundation disciplines in engineering. For such 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 aim of furthering its goals.

1.9 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 or disorder of the human mind or body, and which entails the involvement of humans, human tissues or information derived from humans or human tissues.'*

1.10 The BAC takes the view that human biomedical research normally 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; or

(b) The research will use or manipulate human biological materials (e.g. human cells, tissues, organs and body fluids), including those which were previously acquired and stored; or

(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; or

---

[i] US Department of Health and Human Services, 45 CFR 46.102(d).

[ii] 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 (2008), 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.

1.11 The BAC is concerned with human biomedical research, 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 subjects 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.

1.12 The BAC also recognises that biomedical research could be more or less sensitive in character, where 'sensitivity' depends on societal considerations. For example, research that relied on sensitive information, such as about 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 it to clone a human being is widely seen as unacceptable. Research deemed sensitive would attract more exacting regulatory control, or could be prohibited.[iii]

1.13 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, for which the Health Sciences Authority (HSA) is the licensing authority.

1.14 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 a matter for journal editors, and the Singapore Medical Council as the authority for upholding the requirements of medical ethics in Singapore. Such publication does not necessarily require independent ethics review, as both medical ethics and the requirements of journal editors that informed consent be obtained offer safeguards against the improper publication of case reports.

The Legislative and Regulatory Framework of Human Biomedical Research in Singapore

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

Statutes and Subsidiary Legislation

1.16 Relevant statutes and subsidiary legislation are as follows. The list is not exhaustive, but covers all the principal sources of legislation impinging on 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

[iii] 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 3-5 and 11 of that Report.

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) Ministry of Health (MOH), Licensing Terms and Conditions on Assisted Reproduction Services (2011) imposed under Section 6(5) of the Private Hospitals and Medical Clinics Act (Cap. 248) (1999 Ed.), which is 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. Sections 9 and 10 of the Licensing Terms and Conditions relate to research;

(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 where decisions need to be made on behalf of persons lacking 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, on personal welfare and financial matters and substitute decision-making by attorneys or court-appointed 'deputies', and clarifies the position where no such formal process has been adopted. The Act 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; and

(i) Animals and Birds Act (Cap. 7) (revised 2002) , Animals and Birds (Care and Use of Animals for Scientific Purposes) Rules (Cap. 7, R 10); 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.

1.17 If and when passed, the Personal Data Protection Bill would govern the collection, use and disclosure of personal data, including for the purposes of research. The BAC recognises that revisions may be made to these Guidelines when the Bill is eventually passed, but it has taken into consideration the provisions provided in the draft Bill made public in March 2012.

Guidelines

1.18 Relevant guidelines are as follows:

(a) MOH, Singapore Guideline for Good Clinical Practice, 1998, Revised 1999;

(b) MOH, Governance Framework for Human Biomedical Research, 2007;

(c) MOH, Operational Guidelines for IRBs, 2007;

(d) MOH, Code of Ethical Practice in Human Biomedical Research, 2009;

(e) 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;

(f) National Medical Ethics Committee (NMEC),[iv] Recommendations On Clinical Trials: Update Focusing On Phase 1 Trials, 2007;

(g) NMEC, Ethical Guidelines for Gene Technology, 2001;

(h) NMEC, Ethical Guidelines on Research involving Human Subjects, 1997; and

(i) Singapore Medical Council, Ethical Code and Ethical Guidelines.

1.19 The ultimate responsibility for ethical governance of research lies with the individual researcher and the research institution. Since 1998, the MOH has therefore required all government and restructured hospitals to set up hospital ethics committees (or IRBs) for the ethics review of research involving human participants. From 2004, after the publication of the 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.

1.20 The BAC Reports have all been accepted by the MOH as providing guidance on matters not covered by statute, subsidiary legislation, or otherwise.

[iv] The NMEC is a committee established by MOH to provide guidance on ethical issues in medical practice.

1.21 As research should be appropriately conducted regardless of where it is done, the BAC Guidelines are applicable to all 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.

II. ETHICS GOVERNANCE OF BIOMEDICAL RESEARCH

2.1 It is now internationally recognised that biomedical research needs a system of ethics governance to provide guidance that the research is ethical, and to ensure that unethical research does not take place. Historically there were many examples of research that failed to meet elementary standards of respect for the care of participating subjects,[v] and even today such cases can be found. 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 exposed to conflicts of interest, for example when doctors wish to conduct research on their own patients, when commercial value or scientific prestige may attach to the outcome of research, or when findings may not support the hopes of those who provide funding.

2.2 Ethical 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. Moreover, it acts as a check that there is scientific value in the research.

2.3 It is also concerned with the integrity of the research process itself. Scientific research is self-correcting in the long run, since scientific reputations and scientific advances depend on the reliability of findings and the support of theories in the face of sceptical testing. However, the integrity of the research process can be affected if there is plagiarism, selectivity in the publication of results, or if the independence of scientists is undermined by their obligations to their employers or to the funders of their research.

2.4 As a consequence of such considerations there have been a number of international documents and declarations that form the foundations of ethical biomedical research governance as practised in major jurisdictions. They have also formed the basis for the ethical principles that have guided the BAC. Of these foundation documents and declarations the following are key:

(a) The Nuremberg Code (1947), reported in 1949;

(b) The Declaration of Helsinki: Ethical Principles for Research Involving Human Subjects (1964, Revised 2008);

(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

2.5 A review of the five foundation documents above reveals that participants need to be protected and their autonomy in matters of research participation recognised. Although these documents do not agree in every particular, they appear to be in accord in their fundamentals.

[v] The BAC used the term 'subject' in its earlier reports, but more recently has used the term 'participant'. The latter is increasingly used in many jurisdictions as it implicitly acknowledge the fact that research participants choose to participate, and should not be merely the passive subjects of research. These terms are however treated as interchangeable in these Guidelines.

Based on these, the BAC formulated five guiding principles reflecting their local application, first summarised in its Egg Donation Report. In particular, as enjoined by the UNESCO Declaration, the BAC expects researchers to be aware of and respect the cultural and religious diversity of Singapore society. The BAC also indicated that respect for individuals can be subordinate to the public interest in certain cases, as in some kinds of public health research.

2.6 The five principles the BAC endorses are as follows:

Respect for persons

2.7 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.[vi] 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; for safeguarding confidentiality; for protecting vulnerable participants; and it also requires a proper regard for religious and cultural diversity.

2.8 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 such as all citizens being equal under the law, or having rights to privacy and 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, in the last 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. An individual's autonomy can be curtailed under certain circumstances, such as when quarantined in disease epidemics.

Solidarity

2.9 The BAC earlier advocated a principle of reciprocity between the individual and the 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 individual and society. In biomedical research where there is minimal risk of harm to participants, 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 the public interest.

2.10 However, the underlying principle is perhaps better expressed as one of solidarity. The essential principle is not one of individual exchange, but of a wider vision in which a common interest is invoked as a reason for the subordination of individual interest to that of a group in specified circumstances. Expressing the idea as solidarity reflects the importance of general altruism as a basis for participation in biomedical research.

[vi] 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

2.11 The concept of justice as applied to research includes the general principle of fairness and equality under the law. This implies that access to the benefits of publicly funded 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.[vii] The concept of justice also implies that researchers and their institutions incur some responsibility for the welfare of participants and their possible compensation and treatment in the event of adverse outcomes arising 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.[viii]

2.12 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

2.13 The regulation of research should be in proportion to the possible threats to autonomy, individual welfare, or 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.[ix] 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 strictness of its regulation, should not be disproportional 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.

Sustainability

2.14 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 long term implications are unforeseeable and could possibly be harmful.

2.15 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

[vii] '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 a manifest injustice. It would also breach the principle of solidarity.

[viii] An obvious example would be a participant in a placebo control group.

[ix] 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 by Lord Clyde, in the words of Gubbay CJ (Zimbabwe), in which he said, *inter alia*, 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.

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

2.16 It may be noted that beneficence is not listed explicitly among the BAC's principles, though it is mentioned in this connection in some jurisdictions.[x] This is because beneficence (together with non-maleficence or the principle of 'do no harm') finds its main expression in medical treatment, deriving 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 mis-estimation – the fallacy of overestimating the benefits they may gain from participating in the research. Research is a process designed to yield a general contribution to 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 capture better 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.

2.17 It may be noted that the BAC principles do not include an explicit mention of research integrity. This is because the integrity of process in all aspects has to be a given for ethical governance of research, including judicial process and IRB decisions on research proposals. 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 the results can be regarded as a threat to research integrity. As can be seen from, for example, the Singapore Statement on Research Integrity put up by the 2nd World Conference on Research Integrity,[xi] research integrity is not a simple concept. Essentially it is thought of in terms of the following components:

(a) The trustworthiness of the research product, as manifest in attention to the details of the scientific process in ways that maximise objectivity and minimise bias or selectivity by researchers. Research should be reported in ways that allow others to replicate it and test the research conclusions;

(b) The ethics of the research environment, as manifest for instance in institutional practice, the regulation of research, the sensitivity of the research to the social context in which it occurs, and the measures taken to ensure that professional standards are respected; and

(c) The avoidance by researchers of any plagiarism or fabrication of data.

[x] 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.

[xi] More information on the World Conference on Research Integrity can be found at: http://www.singaporestatement.org/

2.18 The BAC's view is that research integrity is essential. To some extent the presumptive integrity of research, and of researchers, is already implicit in adherence to the general ethical principles outlined above, but its importance is made explicit wherever appropriate in these Guidelines.

2.19 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.

2.20 The principles given above are general in nature and fundamental to ethics governance of biomedical research involving human participants or the use of the biospecimens that they have contributed, and of information about persons obtained or derived from the research process. In practice these principles emerge in a number of more specific guidelines, considered below.

Ethics Review of Biomedical Research in Singapore – the IRB system

2.21 Ethics governance of research in Singapore has been established in statute for the specific case of 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 in turn requires that all proposals for pharmaceutical clinical trials be reviewed by independent ethics committees.

2.22 The HSA is the licensing authority for clinical trials. Since January 2006, researchers can make parallel submissions to both HSA and to their respective IRB. 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.

2.23 In 1997, the NMEC published a document titled 'Ethical Guidelines on Research Involving Human Subjects'. Accordingly, in 1998, the MOH required all government and restructured hospitals to establish ethics committees to review all research protocols involving human experimentation, whether pharmaceutical trials, trials of new medical devices, new clinical procedures, or any other kinds of clinical studies requiring the participation of human subjects or the use of human tissues or organs.

2.24 The focus of the research covered by all these provisions was primarily clinical, although the NMEC Guidelines clearly included epidemiological research. No explicit provision existed for biomedical research that involved human participants, or human cells or tissues, which was not clinical in orientation. It appeared to the BAC (in 2003) 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 hospitals and clinics. Moreover, such non-clinical research was at the time becoming more frequent, and researchers themselves felt a need for an internationally acceptable and clear standard of ethics governance to enable collaboration with researchers elsewhere, and to ensure that generally their work was undertaken within a recognised framework that stipulated the nature of acceptable practice and the boundaries that researchers should respect.

2.25 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 then current 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 to the best international standards and practice.

2.26 Much of the original analysis under (a) above is now history. The 2004 IRB Report was accepted by the government and as a result the present system of IRBs for institutions undertaking biomedical research with human subjects 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 of course the particulars often differ greatly.

2.27 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, given the principles of ethical research, in light of the facts and opinions available to the IRB.

2.28 In what follows there is an updated summary of the current position of the BAC with respect to the manner in which the ethical position of the BAC translates to IRB practice. There is discussion of some issues which may not have been clear in the original reports, or which have surfaced in the seven years during which the IRB system has been implemented.

Guidelines on Ethics Governance of Biomedical Research

Ethics Review

2.29 All human biomedical research as defined in paragraph 1.10 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, and so that there can be no room for any public perception that it is not independent of those who are required to submit to its review.

2.30 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 the 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.

2.31 A less formal process of review than that of a standard full review is permissible for research that involves minimal risk. The Chairperson, or other IRB delegate(s) may be empowered to conduct such expedited reviews.

2.32 In the case of exemption from review, there should be no likelihood of harm, for example, when irreversibly de-identified data is used. Researchers seeking exemption from review would need to make a request with an abbreviated protocol accordingly, and obtain endorsement from the IRB, before commencing the research.

Multi-Centre and Multi-National Research

2.33 For multi-centre research, a lead IRB could be designated. The choice of the lead IRB should be dictated by considerations such as the principal institution of affiliation of the Principal Investigator, the location where the greater part of the research is carried out, the expertise of the constituted IRB, or the location where the largest number of subjects is located. The lead IRB will play the main role in conducting a full ethics review, in coordinating the research programme, and in keeping other participating IRBs informed of any decisions or amendments, including those made during the whole research period.

2.34 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

2.35 Institutions, IRBs and members of IRBs, and researchers should take special care to avoid conflicts of interest, whether actual conflict, potential conflict, 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.

2.36 Should an IRB member have a personal interest in the research under review, that member should disqualify himself or herself from any consideration of the case by the IRB, and he or she should refrain from offering his or her opinion to the IRB on the particular research under review. The member should make full disclosure of such an actual, potential or apparent conflict of interest to the IRB.

2.37 Researchers should disclose any real, potential or perceived individual conflicts of interest, when submitting their research proposals to the IRB, as well as any institutional conflicts which they are aware of, that may have an impact on their research. The IRB shall then decide on the appropriate steps to manage the conflict.

2.38 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 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 source of funds. IRBs need to consider how best to avoid such threats to integrity when considering applications in which they might arise.

Annexe A

Responsibilities of Institutions

2.39 Institutions have the overall responsibility of ensuring the proper conduct of human biomedical research carried out on their premises or facilities; or by their employees or on their patients; or involving access to or use of human tissue collections, medical records or other personal information in their custody. They are also responsible for ensuring research integrity.

2.40 Every institution that conducts human biomedical research, or allows such research to be carried out on 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.

2.41 The institution should set up clear policies for the operation of IRBs. The composition of IRBs and specific operational details are provided in the MOH Operational Guidelines for Institutional Review Boards.[xii]

2.42 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.

2.43 Institutions should ensure that provisions are made to compensate or treat research participants for adverse consequences of their participation, where appropriate.

2.44 An institution must accept legal responsibility for the decisions of its IRB and must provide the IRB members with full indemnity against actions resulting from decisions made by those members in good faith in the course of their duties.

2.45 In view of the investment of time and effort in preparing for research, including the sourcing of funds, it would be proper for there to be in place some kind of mediation or appeals procedure, so that in the event that a research proposal is not approved by an IRB, the Principal Investigator has an opportunity to further justify the research, or if disagreement persists, to have available an appeal mechanism in which adjudication by some third party is possible. Institutions are responsible for ensuring that such a mechanism is in place.

Responsibilities of IRBs

2.46 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. The IRB is not expected to undertake the review itself, but has to be satisfied that it has been competently done;

(c) Evaluating the provisions for the consent process to ensure that valid consent that is appropriate for the study to be undertaken is obtained;

(d) The continuing review and oversight of the research projects approved by them;

[xii] Ministry of Health, *Singapore, Operational Guidelines for Institutional Review Boards.* 2007.

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

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

(g) Ensuring that there is an arrangement for receiving feedback from research participants.

2.47 IRBs should provide a fair hearing to those involved. If there are any doubts or difficulties with particular aspects of proposals, IRBs should clarify these in writing with the researchers, or in minuted face-to-face meetings between the IRB and researchers.

2.48 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

2.49 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.

2.50 Researchers should submit annual (or more frequent) progress reports as required by the IRBs, as well as project completion reports to their respective IRBs.

2.51 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.

2.52 Researchers should not alter or modify in any way (whether in formulation, dosage or timing) any drug or other clinical regimen without the approval of the attending physician and the IRB.

2.53 Researchers should conduct their research in a professional manner and with due regards 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.

2.54 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 part of biomedical research. Consent requirements exemplify the principle of respect for persons by acknowledging individuals' right to decide for themselves what is good for them. An IRB should evaluate the provision for consent whenever it considers a research proposal entailing work with human participants, or the use of biospecimens or identifiable personal information.

3.2 There is a distinction between the legal and ethical obligations arising on matters of consent. There are various situations where the law requires consent to be obtained, and where a procedure done without consent could be challenged in court. Legal requirements thus constrain what can or cannot be enforced concerning ethical obligations on consent. For instance, short of recommending a change in the law, it would not be possible to recommend waiving consent in any situation where the law sets some standard of consent. However, these Guidelines refer to ethical consent issues – what ought to be done in obtaining informed consent – and are to be understood as presuming observance of the law as it stands.

Voluntary and Informed Consent

3.3 Consent must be voluntary and informed.[xiii] Informed consent is not a matter of merely providing information, but requires that the person giving consent 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 to understand what consent is being asked for.

3.4 Consent taking entails providing sufficient relevant information and explaining it to prospective participants in ways that allow them to make an informed decision at an appropriate level of understanding. The requirements vary somewhat depending upon the nature of the research; whether involving tissue or genetic information; whether or not there may be clinically significant findings either directly or incidentally to the research; and also on the vulnerability or ability of the participant. Anything in the nature of the research which the participant may find sensitive should entail some corresponding sensitivity in taking 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[xiv] or inducement. Any payment in addition to expenses incurred, should not amount to an inducement; and

(c) Participants understand that they may withdraw from the research at any time without any explanation, and without penalty or prejudice to any treatment they may be receiving.

[xiii] Consent in law has to be consent with understanding to be valid, so the term 'informed consent' is technically redundant, but in lay parlance it serves to make clear that the need for consent should be a considered matter and not something to be taken for granted.

[xiv] Keeping research subjects in ignorance of a research hypothesis, or of which group they have been assigned to, does not amount to deception in the sense intended here. 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 matter. The important consideration is that subjects cannot be deceived as to the risks or benefits of the research, or such things as the affiliation of the researcher, the uses or value of the research, or their rights in respect of participation.

3.6 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 preferably in writing. Together with a conscientious approach to making sure the participant understands as far as possible what is proposed, this minimises the likelihood of later misunderstandings.

3.7 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 magnitude and probability of harm, the complexity of the information conveyed, and the setting where the information is given.

Specific and General Consent

3.8 *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 specified research project, or where his or her tissue or information is sought for such a project. There is no implication that such consent would extend to the use of the tissue or information that is collected for other subsequent research, unless this is requested, in which case the consent would be considered general.

3.9 A *general consent* may be taken for the storage and future use of tissue or personal information. This 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 general consent is sufficient, if previously given.

3.10 In any general consent for future research, donors may wish to impose some limits to the use of their tissue or information. If the donation is accepted, any such conditions must be observed. 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 tissue or information will be used only if the research is approved by an IRB.

The Mental Capacity Act

3.11 Under the Mental Capacity Act, decisions in matters affecting day-to-day living of a person lacking capacity may be taken by a proxy, such as a parent, caregiver or legal guardian, or a 'donee', who is a proxy appointed with a lasting power of attorney (LPA). The Act is silent with regards to whether or not next-of-kin can assume the responsibility for seeking and giving consent for medical treatment, including clinical trials. However, a donee who has been specifically given authority under the 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 conduct of clinical trials.

3.12 In making such decisions, the donee must follow the statutory principles under the Act, viz., act in the donor's best interests,[xv] have regard to the guidance in the Codes of Practice, 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 donee must be satisfied that:

[xv] With regard to best interests, Mental Capacity Act, section 6 (7) states: 'He [the proxy] 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.'

(a) The individual has previously indicated a willingness to participate; or

(b) Consent would, in the judgement of the donee, have been given had the individual (not being a child), been able to make an informed choice.

3.13 Legal protection is offered to any individual acting in connection with the care or treatment of a person lacking capacity, provided certain requirements, 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).

3.14 It should be stressed that biomedical research other than clinical trials research is not covered under the Act. A donee or other proxy is obligated under the Act to put the best interests of the participant first, yet participation in research is not usually a benefit to the participant. Consequently, consenting to participation in research on behalf of a non-competent person cannot be defended as in the person's best interest if no clinical trial is involved.

Consent Involving Vulnerable Persons

3.15 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 might be considered vulnerable. Such participants include:

(a) Adults with diminished mental powers (such as the intellectually disabled or patients with dementia or others who lack mental capacity as defined in the Mental Capacity Act) or because they are incapacitated through accident, injury or illness;

(b) Those whose autonomy might be prejudiced by being under the influence of, or the control of, or obligated to, third parties; and

(c) Infants or children. In the case of under-aged research participants issues of consent primarily involve parent or guardians.

Consent from Vulnerable Persons not Lacking Capacity

3.16 Vulnerable adult research participants not only include those who are of diminished capacity, but also those whose autonomy might be prejudiced by being under the influence of, or the control of, or obligated to, third parties. Potentially vulnerable participants might include, but are not limited to:

(a) Prisoners;

(b) Serving uniformed personnel, especially junior ranks;

(c) Patients, especially if the intending researcher is their attending physician; and

(d) Employees, junior collaborators, or students.

3.17 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 tissue for research. Thus consent among uniformed personnel, for example, should not be taken by a senior officer, and preferably not by uniformed personnel at all.

3.18 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.

3.19 A further issue of vulnerability arises in societies where social proxy arrangements are widespread, for example, where a village headman might be felt to have 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 from Patients

3.20 It is important to note differences between a patient's consent for 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 treatment is strongly indicated. Because research, by contrast, is not designed to confer benefit for the research participant (although it may sometimes do so), there are thus usually no personal benefits against which to balance risks. The benefit is general and the consent of the participant fundamentally altruistic in character. High levels of risk thus become very unacceptable, and even low levels are to be avoided as far as possible.

3.21 Consent for treatment should therefore be clearly separated from consent for participating 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 Children

3.22 Children present certain consent issues if involved in research, and they are categorised as a vulnerable class of research participants. In some jurisdictions a distinction is made between consent and assent, such that if parents consent, research can proceed provided children assent, i.e. agree. The assent of a child is not comparable to the informed consent of an adult. It is perhaps better regarded as a mechanism for engaging the child in the research process, in such a way as to respect the child's right to object, and to entitle them to as reasonable an explanation as may be reasonable, consistent with the child's level of understanding, but without an implication that the child is giving informed consent.[xvi] In clinical research that has a reasonable expectation of benefitting a child, the research might be allowed to proceed even without the child's assent, if the parents give consent, but in general, researchers should respect refusal by a child. Because, in Singapore, there is no

[xvi] For a discussion on the meaning of assent in research see Wilfond, BS & Diekema, DS. Engaging children in genomics research: decoding the meaning of assent in research, *Genetics in Medicine* (2012), 14 (4): 437-443.

clear legal standing for assent as a procedure – unlike the case of consent – the BAC retains the use of the term consent for children as well as adults, but on the understanding that a child's consent can be informed only to the extent that is reasonable given the child's age, and that a combination of parental and child consent is the normal requirement. The older the child and the more mature his or her understanding, the more important it is to engage them in ways that respect their level of understanding and their right to refuse.

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.

3.24 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.

3.25 Under the Medicines (Clinical Trials) Regulations, consent for participation in clinical trials must be obtained from the parent, guardian or legal representative of an individual below the age of 21.

3.26 The BAC is of the view that for research involving individuals less than 21 years of age and presenting more than minimal risk, such as those with invasive procedures, consent from parents should be obtained, in addition to consent from the child. For research that does not involve more than minimal risk, such as surveys, IRBs should be able to waive parental consent.

Waiver of Consent

3.27 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;

(e) Individual privacy and confidentiality of the personal information are assured; and

(f) In the event that clinically significant findings are discovered, affected individuals who have indicated their wish to know will be informed in a timely manner, if reasonably possible.

3.28 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 available to give consent. 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, with patient consent being 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).[xvii]

Clinically Significant Incidental Findings

3.29 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 clinically important 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 the matter with a medical practitioner.

3.30 Research participants should be given the choice of whether to be informed about such findings, prior to the commencement of the research, if the research is such that there is some reasonable possibility that incidental findings may occur. 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.

3.31 Communication of clinically significant findings to research participants could be directly by the researcher, or through a healthcare provider or other party authorised to receive the information and in a better position to advise and discuss the implications of the findings.

3.32 Communication of clinically significant incidental findings to biological relatives should be encouraged. This, including the question of who will do it and taking into account the participant's preference, should be discussed and agreed upon at the time of obtaining consent

3.33 Parents who have indicated a wish to know, should be informed of clinically significant research results 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 clinically significant incidental findings are uncovered.

Guidelines on Consent

3.34 Consent for participation in research must be voluntary. There should be no coercion or undue influence. Participants may be reimbursed for legitimate expenses, such as cost of transport and child care services, and actual loss of earnings. Any additional payment to be given, whether monetary or in kind, should not amount to an inducement.

3.35 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.

3.36 Prospective research participants or authorised third parties 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;

[xvii] This contingency has been considered by the UK MRC Ethics Guide: *Medical research involving adults who cannot consent*, 2007 (section 4.3).

(b) Any entailed risks and benefits to them, and how any such risks are to be managed and minimised;

(c) The safeguards for protecting their privacy and confidentiality of their personal information;

(d) Any reimbursement or other 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 human tissue research, genetic research, and stem cell research in these Guidelines.

3.37 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 the result, prior to the commencement of the research. Participants should also have an opportunity to express their preferences about the sharing of such information with biological relatives, or others.

3.38 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.

3.39 Consent to participation in research should be documented in writing.

3.40 Consent could be *specific* to a particular research project, or *general* for the storage and future use of tissue or personal information. In any general consent, donors should be allowed to impose some limits to the use of their tissue or 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.

3.41 For research involving vulnerable adults not lacking capacity (for example, prisoners, serving 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 tissue 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.

3.42 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.

3.43 While local customs should be respected when conducting research in places where social proxy arrangements are widespread, individual consent from prospective participant is nevertheless essential.

3.44 For research involving individuals less than 21 years of age and presenting more than minimal risk, such as those involving invasive procedures, consent from parents should be obtained, in addition to consent from the child. Researchers should respect a child's right to refuse to participate in research, and their entitlement to such explanation as may be reasonable, consistent with the child's level of understanding. For research that does not involve more than minimal risk, such as surveys, IRBs should be able to decide to waive parental consent.

3.45 Clinical research that has a reasonable expectation of benefitting a child might be allowed to proceed even without the child's consent, if the parents give consent.

3.46 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;

(e) Individual privacy and confidentiality of the personal information are assured; and

(f) In the event that clinically significant findings are discovered, affected individuals who have indicated their wish to know will be informed in a timely manner, if reasonably possible.

3.47 For valuable 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, with patient consent being 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 from the study).

Annexe A

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, as a function of use and context.

4.2 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 be such that it was in a sense created by the researcher, who by his or her procedures and interventions may have created the information – for instance a measure of memory, or an assessment of genetic potential – that might otherwise have been unknown. The 'gift' model for the altruistic donation of tissue for research might therefore be 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 safeguards. 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'.

4.3 In particular, it is often valuable, and customary, to retain research data, which may include personal information, 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 participant privacy must be maintained.

4.4 Personal information used in research may be obtained through various sources, such as through interviewing or testing individuals, information submitted to registries or databases, and information provided or obtained during the course of medical diagnosis or treatment. Such data may be stored as physical records, as in medical records, or stored electronically, and managed by healthcare institutions, research institutions, and government and non-government registries. Data that are routinely collected or submitted to registries, public and private agencies may be immensely valuable for biomedical research. To enhance its value, it may be necessary to link records of individuals from multiple databases.

4.5 Personal information in research may be identified or de-identified. *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 whereby the identity of the individual is not known. If it is de-identified through a 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.

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 early as possible. 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 tissues collected in cohort or follow-up studies, where a large amount of data are collected for analysis, it should be managed as reversibly de-identified data. In the re-identification of reversibly de-identified data, the management of the key to any code or encryption can and sometimes should be separated from the management of the data. This distinction is recognised in the Personal Data Protection Bill, which recognises 'data intermediaries'. A data intermediary is an organisation which processes personal data on behalf of another organisation, but does not include an employee of that other organisation. As a data intermediary merely serves as a processor of the personal data, it will be subject only 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. It is therefore possible for data to be shared and used as de-identified data, without a breach of 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 a name 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.

4.8 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 confidentiality. Therefore, research which relies exclusively on the secondary use of irreversibly de-identified information or human tissue 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.

4.9 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.

4.10 The data collected by researchers may or may not be sensitive, depending on the research, but researchers have a proportionate duty to maintain proper 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 accrues to them 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.

Annexe A

Use of Medical Records for Research

4.11 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 as physical records or electronic 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 (both physical and electronic) are under a legal and ethical obligation to observe the confidentiality of the information on the records and to safeguard the privacy of patients concerned.

4.12 Much valuable medical knowledge has, however, resulted from the study of patients' medical records. Thus, 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.

4.13 Healthcare institutions should also inform patients that their medical records may sometimes be used for research and explain the reasons for such research. They should reassure patients that all research will require the approval of an IRB, that there are safeguards to protect their privacy and the confidentiality of their medical information and that the institution will answer any questions patients may have.

Epidemiological and Public Health Research

4.14 The use of personal information in public health and epidemiological research can lead to clashes between public and private interests. Ideally, consent should be 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, where information may have been collected routinely by law. Such use is of tremendous value in epidemiological and public health research, which is ultimately for 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. Waiver of consent is discussed above at paragraphs 3.27 and 3.28.

Guidelines on the Use of Personal Information in Research

4.15 All research involving identifiable personal information must be reviewed by an IRB. 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 informationThe 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 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;

(e) Individual privacy and confidentiality of the personal information are assured; and

(f) In the event that clinically significant findings are discovered, affected individuals who have indicated their wish to know will be informed in a timely manner, if reasonably possible.

4.20 Personal health information obtained or used for research purposes should not be released 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. HUMAN TISSUE RESEARCH AND BIOBANKING

5.1 The term 'human tissue' refers to any kind of human biological material from living or dead individuals. It includes blood and other body fluids and their derivatives, as well as solid body tissues, organs, foetuses, gametes and embryos, and is a valuable resource for biomedical research. Even tissue that has been stored for many years may be useful. The ethical issues concerning the use of human tissue for research relate to the collection, storage, access, and actual usage of the tissue (the purpose of the research); and to the use of information generated from research. Such information, may be central to the research or incidental, and may also have health implications for tissue donors or for their genetic relatives, and relevance for their employers or insurers.

5.2 Tissues 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 tissue, consequent to a clinical procedure. They may also be identified or de-identified.

5.3 Human tissue banks are repositories, where human biospecimens taken for clinical or research use are stored. Tissue banks can be set up specifically for research, but many tissue banks exist primarily for clinical use in transplantation. Clinical tissue repositories, which consist of samples, such as blood or a tumour that has been surgically removed, that have been collected and used for clinical diagnosis, are also potentially useful for research. Some such repositories consist of accumulated and archived biospecimens that may have been acquired over a period of many years and can be described as legacy tissues.

5.4 Biobanks are collections of human biospecimens that are linked to personal information, which may include medical information of individuals from whom the specimens originate. The individuals may or may not be identifiable by the biobank. They may be created for research purposes or be part of a clinical service, such as a health screening programme. As they consist of biospecimens and data systematically collected from a large number of individuals, they are very valuable for research that may lead to better understanding of diseases.

5.5 Many countries, including Singapore, 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 biospecimens collected.

5.6 It is unclear whether a person, or a body corporate, can legally own human tissue samples or whether an individual can have any property rights over his or her tissue after it is contributed for research. 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. For this reason, the term of custodianship has been used to refer to the relationship of tissue banks to the tissues they contain.[xviii] 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 tissue for use in research should thus be considered as an altruistic gift. An altruistic donor does not retain rights in the donated tissue, or an intellectual property right in any commercially valuable development arising from the research, and donations should be made and accepted on that understanding.

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

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

Guidelines on Human Tissue Research and Biobanking

General

5.8 All research involving human tissue, whether identified or de-identified, should be reviewed by an IRB, and approved before it commences.

5.9 It is essential to protect the privacy of tissue donors and the confidentiality of their personal information, including personal information given by donors about individuals who are not themselves donors. All the requirements for the use of personal information in research in Part IV of these Guidelines will apply.

5.10 Donors 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, as these vary considerably amongst various religions and cultures, especially when whole cadavers or gross organ parts are involved.

Consent in research with human tissues

5.12 Informed consent must be obtained from the donor or the legal guardian or proxy (or the next-of-kin if the donor has died), before any tissue is used for research. If there is intention for storage and future use of the tissue for research, consent should also be obtained.

5.13 Consent may be general or specific. General consent is consent that does not limit the use of the tissue for any particular research project. It includes consent for future use of the tissue or information generated from the research using the tissue, without a requirement for re-consent. In a general consent, the donor may seek to limit the uses to which the tissue and any information derived from research with the tissue are put; any such limits must be respected, and it is for the researcher and IRB to decide if they disqualify the use of the tissue or the related information in any given project.

5.14 Specific consent is consent for a particular research project. In the event where there is surplus tissue from this project, a fresh consent would be needed, if consent has not been given for any future research.

5.15 When consent is sought, donors of biospecimens for research should be provided with sufficient information, explained appropriately, to make an informed decision. Such information should include:

(a) The purpose or intention of the research, and any risks or benefits to them;

(b) The type and amount of tissue to be collected, and the procedures and risks involved in taking it;

(c) That the tissue will be considered a gift and they will not have the right to any commercial gain from the research;

(d) Whether the tissue may be stored and used for future research, and for how long;

(e) The potential types of research for which the tissue may be used;

(f) Any possibility of being re-contacted for future research;

(g) Whether the tissue sample will be identified and the applicable privacy and confidentiality safeguards;

(h) The safeguards for protecting their privacy and the confidentiality of their personal information; and

(i) That it is possible for them to withdraw consent from the research, as long as the specimens have not 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 tissue was collected (unless the re-consent requirement is waived by an IRB);

(b) If the tissue was collected when the individual was a child, such that consent from a parent or guardian was required, and there is ongoing contact. Once the child attains the age of 21, his or her consent should be obtained if research is to be conducted on the previously collected tissue or information related to this tissue specimen. In the event re-contact is not practicable, the IRB should have the discretion to determine whether or not the stored material or information can be used without re-consent; and

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

5.17 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 are 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

5.18 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 material for research.

5.19 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. Provisions for ensuring that where possible an attending physician should not also seek consent for research participation from a patient apply in this situation.

5.20 Consent for the use of foetal tissue for research could be obtained from either parent, as indicated in the Medical (Therapy, Education and Research) Act.

5.21 Any intention to propagate foetal cells and/or to transplant these cells into a human recipient should be disclosed when consent is sought.

Human Gametes and Embryos

5.22 The creation of human embryos specifically for research can only be justified when there is strong scientific merit and potential medical benefit from such research. Under the Human Cloning and Other Prohibited Practices Act, 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, is prohibited. Commercial trading in human eggs, human sperm and human embryos is also not allowed.

5.23 The use of human gametes or embryos for research is governed by the requirements of the law, as given in the MOH's 2011 Licensing Terms and Conditions on Assisted Reproduction Services imposed under Section 6(5) of the Private Hospitals and Medical Clinics Act and by the Human Cloning and Other Prohibited Practices Act (Cap. 131B).

5.24 Under the Licensing Terms and Conditions on Assisted Reproduction Services, 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.

5.25 Consent from the donors must be obtained before any gametes or embryos are to be used for research. Individuals from whom the gametes or embryos are derived, should be provided with sufficient information to make an informed decision and be given at least a week to decide.

5.26 For women undergoing fertility treatment, consent for the donation of 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 and embryos for research. Donors should confirm in writing that they do not require the oocytes or embryos for future use.

5.27 As the process of donating eggs for research is time-consuming, invasive and associated with a certain degree of discomfort and risks, women wishing to donate eggs specifically for research i.e. who are not also undergoing any 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.

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

5.29 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 additional payment to be given, whether monetary or in kind, should not amount to an inducement. If complications occur as a direct and proximate result of the donation, the donor should be provided with prompt and full medical care. The cost of this provision is the responsibility of the researchers and their institutions.

5.30 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.

5.31 No human embryos created for research, including human cytoplasmic hybrid embryos[xix] and other embryos created through any form of cloning technology, should be allowed to develop beyond 14 days *in vitro*.

5.32 No human embryo created for research, including any human cytoplasmic embryo or other embryo created through any form of cloning technology, should be implanted into the body of any human or animal.

5.33 Research involving human germline modification for purposes other than the prevention or treatment of serious genetic conditions should not be allowed.

5.34 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 Tissues from Clinical Procedures

5.35 Tissues, such as blood, biopsy samples or even whole organs, may be left over after clinical procedures, which may be therapeutic or diagnostic. Such tissues can be very useful for research. However, when tissue is being taken primarily for a therapeutic or diagnostic purpose, this purpose must be fulfilled before any surplus tissue may be used for research.

5.36 Every effort should be made to obtain consent for the use of surplus tissue for research. As the primary objective for removing such specimens is clinical, consent for the clinical procedure should be separate from the consent for the use of left over tissues for research. To avoid any conflict of interest and to 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

[xix] 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.

the research. In the case that 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 will not affect the quality of care that will be given to them.

5.37 If consent could not be obtained for the use of surplus tissue 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 biospecimens. Healthcare institutions should inform patients that there is a possibility that their surplus biospecimens 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.

5.38 It is current practice to use patients' biospecimens that are surplus to clinical requirements for validating laboratory tests or for purposes of clinical audit without consent of the originators and without IRB approval, if the specimens are irreversibly de-identified. Although this practice is ethically acceptable, since it is not possible for individuals to be identified, it is good practice for healthcare institutions to inform patients that there is a possibility that their surplus biospecimens may be used for such purposes, for example, by displaying a notice to that effect.

Surplus Tissues from Research Projects

5.39 Tissues that are collected for a specific research project may remain after the project is completed. Such tissues can be stored for future research if consent for storage and future research use has been obtained from the donors.

5.40 Consent need not be re-taken if IRBs are satisfied that subsequent use of the tissue for research is covered by the initial consent. If the subsequent research use of the tissue 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 research may progress without re-consent.

Imported Tissues

5.41 When the tissues to be used for research are imported, the researcher should obtain written assurance from the source authority that the samples have been ethically and legally obtained. The test of ethical acceptability should be the criteria that would have applied had the tissue 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 specimens from the bank. As custodians of the biospecimens, 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 biospecimens;

(b) 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 biospecimens;

(c) That all research involving the biospecimens is approved by an IRB, and also by MOH in certain cases, such as when the biospecimens are human gametes or embryos;

(d) Keeping proper records of all uses of the biospecimens;

(e) Proper disposal of the biospecimens 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 have been 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, they are also tissues collected before the publication of the BAC's recommendations on human tissue research on 12 November 2002.[xx] It is important that procedures are in place that allow the use of this material for research, as it is a valuable resource to be preserved and made use of.

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 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.

[xx] '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.' BAC Tissue Report, paragraph 9.1, page 28.

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. The study may involve research participants directly and specifically, or it may involve stored tissue samples or personal information from medical records or other databases. It may involve the study of a specific gene, or multiple genes, or gene-environment interactions, or the entire genome, for example 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 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 biospecimens and associated biodata. These allow detailed long-term genetic studies to take place. Technological advances have 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 biospecimens, genome sequencing, data analysis, and, possibly, the use of the biospecimens and data for future research projects that may not be known when the biospecimens are taken. In addition, the data may also be submitted to easily accessible scientific databases, to facilitate research. Thus, the implications for 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 a research culture of relatively 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) Participants may 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. Parties should be clear in advance as to when the obligation of the researcher ceases; 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 germ-line genetic modification being the most contentious. Any intervention that alters the germ-line 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 have laws that prohibit germline modification. With emerging assisted reproductive

techniques such as ooplasmic transfer, pronuclear transfer and maternal spindle transfer, to prevent the transmission of mitochondrial disease, the Nuffield Council on Bioethics conducted a public consultation early this year. The Council recently published a report, which explores the ethical issues concerning the possible use of such treatments in future.[xxi] 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, but a continuing debate on these issues is important. The Human Fertilisation & Embryology Authority (HFEA), which licenses and monitors all fertility clinics and research involving human embryos in the UK, will take a lead in continuing the debate by launching a public consultation in September 2012, and report its findings in Spring 2013. The clinical use of such techniques is currently prohibited in the UK. In its 2005 Genetics Report, the BAC had similarly recommended that the clinical practice of germ-line modification be prohibited and its position remains, pending evidence from research that clinical procedures to prevent or eliminate serious genetic disorders has been proven effective.

6.5 Genetic research can also be viewed to 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 the research. Thus pharmacogenomics depends on the presumption that optimal drug treatments may be tailored to the genetic makeup of the patient, or a subset of patients, for example classified by ethnic group. For this and other reasons, economic exploitation has been the subject of some controversy, and it is correspondingly important that all parties to research be well aware of the implications.

6.6 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.

6.7 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, as well as when considering genetic diseases, 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 relative ease with which the individual human genome can now be comprehensively analysed has created a situation in which incidental findings of genetic conditions or susceptibility might become easy to obtain, and in which the sheer volume of genetic detail available for large-scale genomic studies 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;

[xxi] The report *Novel techniques for the prevention of mitochondrial DNA disorders: an ethical review* was published in June 2012.

(d) Genetic information has predictive power, predicting 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 not be something a person wishes to know; and

(e) Genetic information may be of interest to others, such as relatives, who may also be affected, and insurers and employers.

6.8 For all these reasons, there has been a tendency to regard genetic research as somehow sensitive in much the same way as medical records are regarded as sensitive, because the information yielded by the research ought to be considered as private to the individual since its implications might be considerable, and because respect for the body is an important aspect of autonomy. In some cases, of course, genetic information is actual medical information, but in other cases it is just raw data that can be interpreted to yield a particular kind of personal information. The BAC is not of the view that genetic information is always and inherently special or exceptional. The BAC considered issues arising from the use of personal information generally in its Personal Information Report and in Part IV of these Guidelines.

Guidelines on Human Genetic Research

6.9 All human genetic research should be reviewed by an IRB and approved before it commences.

6.10 Participation in genetic research should be voluntary, whether directly or by contribution of biospecimens or personal information, and all the requirements of voluntary informed consent in Part III will apply. The requirements for the procurement and use of human tissue and personal information for such research in Parts IV and V respectively, will also apply.

6.11 When clinically significant findings are discovered in any genetic research, researchers should ensure that affected participants are informed, if they have indicated their desire to know.

6.12 In whole-genome research, participants should be provided with as much detailed information as possible that is specific to such research, during the consent process. They should be provided with information on mechanisms for data security, and an explanation on the nature of whole-genome research, with its 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 be practical limitations on withdrawal from research. Participants should be informed of these limitations and the implications of their withdrawal.

6.13 Approval from MOH is required for research involving germ-line modification. Such research is only allowed for purposes of preventing or treating serious genetic conditions.

6.14 For clinical trials involving gene-based therapies, approval from HSA is required.

VII. HUMAN STEM CELL RESEARCH

7.1 Stem cells are unspecialised cells that have the potential to develop into specialised cell types. They may be derived from early embryos (*embryonic stem cells*), or from the germ cells of foetuses (*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 the 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 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 into the understanding of 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 disease, 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 covered what is 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 feel 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;

(b) *Human-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; and

(c) *Transgenic animals*, which 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.

7.7 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.

7.8 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

7.9 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). It limits the development of a human embryo that is created by a 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.

7.10 The MOH's Licensing Terms and Conditions 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.

7.11 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-man trials and trials of cell- and tissue-based therapeutic products.

Ethical and Social Issues

Moral status of the human embryo

7.12 The main controversial issue 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 end, the view is that it is a mass of cells, no different from any other biological material used for research.

7.13 After public consultation, the BAC adopted an intermediate position, whereby a human embryo is considered as having 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, as at around day 14, the primitive streak appears, signaling 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. This remains the BAC position on this issue.

7.14 With the increasing possibility of alternative means of generating pluripotent stem cells, such as induced pluripotent stem cells, it is increasingly less likely that cloning technology would be used for the creation of embryos. The BAC welcomes such diversity in research methodologies, but regards 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

7.15 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 about any unforeseen problems for those born as a result of the technology.

Human-Animal Combinations

7.16 *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 likely harms and benefits.

7.17 *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.

7.18 *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.

7.19 *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 read into 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 are not to 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.

7.20 The BAC's view is that the problem of slippery slopes, 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 challenge to the fundamental values, beliefs and practices that underlie society, and only when the key ethical issues arising from research involving human-animal combinations have been considered in each case.

7.21 *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 foetuses[xxii], which offers an in-principle possibility of a degree of humanisation of the resulting brain. In this case, six relevant factors have been suggested[xxiii] for the guidance of ethics committees, namely:

(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;

[xxii] Ourednik V *et al.* Segregation of Human Neural Stem Cells in the Developing Primate Forebrain. *Science.* 293 (2001): 1820-1824.
[xxiii] Greene M *et al.* Moral Issues of Human-Non-Human Primate Neural Grafting. *Science*. 309 (2005): 385-386.

(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.

7.22 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

7.23 Human stem cell research that is ethically uncontentious, 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 be reviewed 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.

7.24 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 for the procurement of human tissues generally for research.

7.25 IRBs reviewing proposals involving human stem cells should ensure that all proposals have been reviewed and approved by a scientific committee, and that the biological materials to be used have been obtained ethically, with appropriate consent, and without any inducement or coercion, especially when vulnerable people are involved.

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 non-human 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*.

7.30 No human cytoplasmic embryo should be implanted into the body of any human or animal.

7.31 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 product, 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.

7.32 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.

Annexe A

Bibliography

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

Bioethics Advisory Committee. *Donation of Human Eggs for Research*. Singapore, 2008.

Bioethics Advisory Committee. *Ethical, Legal and Social Issues in Human Stem Cell Research, Reproductive and Therapeutic Cloning*. Singapore, 2002.

Bioethics Advisory Committee. *Genetic Testing and Genetic Research*. Singapore, 2005.

Bioethics Advisory Committee. *Human-Animal Combinations in Stem Cell Research*. Singapore, 2010.

Bioethics Advisory Committee. *Human Tissue Research*. Singapore, 2002.

Bioethics Advisory Committee. *Personal Information in Biomedical Research*. Singapore, 2007.

Bioethics Advisory Committee. *Research Involving Human Subjects: Guidelines for IRBs*. Singapore, 2004.

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.

Council for International Organizations of Medical Sciences/World Health Organization. *International Ethical Guidelines for Biomedical Research Involving Human Subjects*. Geneva: CIOMS, 2002.

Department of Health and Human Services. The Belmont Report: *Ethical Principles and Guidelines for the Protection of Human Subjects of Research*. United States of America, 1979.

Department of Health and Human Services. *Protection of Human Subjects*, Title 45 Code of Federal Regulations, Part 46, 102(d). United States of America, 1980.

Greene M and 21 others. 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.

Health Products Act (Cap. 122D). Singapore, 2008.

Human Cloning and other Prohibited Practices Act (Cap. 131B). Singapore, 2005.

Human Fertilisation and Embryology Act 2008. United Kingdom: HMSO.

Human Tissue Act 2004. United Kingdom: HMSO.

Infectious Diseases Act (Cap. 137). Singapore, Amended 2010.

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 (2008) page 211.

Medical (Therapy, Education and Research) Act (Cap. 175). Singapore, amended 2010.

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

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

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

Medicines Act (Cap. 176). Singapore, 1985.

Mental Capacity Act 2005. United Kingdom: HMSO.

Mental Capacity Act. Singapore, 2010.

Ministry of Health. *Code of Ethical Practice in Human Biomedical Research*. Singapore, 2009.

Ministry of Health. *Governance Framework for Human Biomedical Research*. Singapore, December 2007.

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

Ministry of Health. *Licensing Terms and Conditions on Assisted Reproduction Services*. Singapore, 2011.

Ministry of Health. *Operational Guidelines for Institutional Review Boards*. Singapore, December 2007.

Ministry of Information and the Arts. Public Consultation Paper on *Proposed Data Protection Bill*. Singapore, 2012.

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

National Health and Medical Research Council, *National Statement on Ethical Conduct in Human Research*. Australia, 2007.

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

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

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

Annexe A

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

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

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

Ourednik V and 10 others. Segregation of Human Neural Stem Cells in the Developing Primate Forebrain. *Science*. 293 (2001): 1820-1824.

Personal Data Protection Bill. Singapore, 2012.

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

Singapore Medical Council. *Ethical Code and Ethical Guidelines* (nd).

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

Wilfond BS and Diekema DS. Engaging children in genomics research: decoding the meaning of assent in research, *Genetics in Medicine*.14 (2012): 437-443.

World Medical Association. *Declaration of Helsinki:Ethical Principles for Medical Research Involving Human Subjects* (revised 2008).

List of Abbreviations

BAC	Bioethics Advisory Committee
HFEA	Human Fertilisation and Embryology Authority
HSA	Health Sciences Authority
IRB	Institutional Review Board
LPA	Lasting Power of Attorney
MOH	Ministry of Health
NMEC	National Medical Ethics Committee
SGGCP	Singapore Guideline for Good Clinical Practice
UNESCO	United Nations Educational, Scientific and Cultural Organization

ANNEXE B

CONSULTATION PAPER DISTRIBUTION LIST

Annexe B

Distribution List for Consultation Paper on
"Ethics Guidelines for Human Biomedical Research – for comments"
(Public Consultation Period: 20 June 2012 to 15 August 2012)

1. Academy of Medicine
2. Agency for Integrated Care
3. Alice Lee Centre for Nursing Studies
4. Alzheimer's Disease Association
5. Association of Muslim Professionals
6. Autism Association (Singapore)
7. Bioinformatics Institute
8. Biomedical Research Council
9. Bioprocessing Technology Institute
10. Buddhist Fellowship
11. Cardiovascular Research Institute
12. The Catholic Medical Guild of Singapore
13. Changi General Hospital
14. College of Family Physicians Singapore
15. Defence Medical & Environmental Research Institute @ DSO National Laboratories
16. Department of Biological Sciences, National University of Singapore
17. Duke-NUS Graduate Medical School
18. ES Cell International
19. Experimental Therapeutics Centre
20. Genome Institute of Singapore
21. Graduates' Christian Fellowship (Singapore)
22. Health Sciences Authority
23. Hindu Advisory Board
24. Institute of Bioengineering and Nanotechnology
25. Institute of Medical Biology
26. Institute of Mental Health
27. Institute of Molecular and Cell Biology
28. Inter-Religious Organisation Singapore
29. Jewish Welfare Board
30. John Hopkins Singapore International Medical Centre
31. Khoo Teck Puat Hospital
32. KK Women's and Children's Hospital
33. Khoo Teck Puat - National University Children's Medical Institute
34. Law Reform Committee, Singapore Academy of Law
35. The Law Society of Singapore
36. Majlis Ugama Islam Singapura (Islamic Religious Council of Singapore)
37. Muscular Dystrophy Association Singapore
38. Nanyang Polytechnic
39. Nanyang Technological University
40. National Arthritis Foundation
41. National Cancer Centre
42. National Council of Churches of Singapore
43. National Council of Social Service
44. National Dental Centre
45. National Healthcare Group
46. National Heart Centre

Annexe B

47. National Neuroscience Institute
48. National Skin Centre
49. National University Cancer Institute, Singapore
50. Ngee Ann Polytechnic
51. NUHS Research Office
52. Parkway Hospitals Singapore
53. The Parsi Zoroastrian Association of Singapore
54. Raffles Hospital
55. Republic Polytechnic
56. Saw Swee Hock School of Public Health, National University of Singapore
57. Sikh Advisory Board
58. SIM University
59. Singapore Association For Mental Health
60. Singapore Bioimaging Consortium
61. Singapore Buddhist Federation
62. Singapore Cancer Society
63. Singapore Children's Society
64. Singapore Chinese Buddhist Association
65. Singapore Clinical Research Institute
66. Singapore Epilepsy Foundation
67. Singapore Eye Research Institute
68. Singapore General Hospital
69. Singapore Health Services
70. Singapore Heart Foundation
71. Singapore Immunology Network
72. Singapore Institute for Clinical Sciences
73. Singapore Management University
74. Singapore Medical Association
75. Singapore Medical Council
76. Singapore National Stroke Association
77. Singapore Nurses Association
78. Singapore Nursing Board
79. Singapore Polytechnic
80. Singapore Sports Council
81. Singapore Taoist Federation
82. SingHealth Polyclinics
83. The Spiritual Assembly of the Bahá'ís of Singapore
84. Tan Tock Seng Hospital
85. Taoist Mission (Singapore)
86. Temasek Laboratories
87. Temasek Polytechnic
88. Yong Loo Lin School of Medicine, National University of Singapore

ANNEXE C

WRITTEN RESPONSES RECEIVED DURING THE PUBLIC CONSULTATION

Annexe C

Written Responses Received During the Public Consultation on Ethics Guidelines for Human Biomedical Research

Organisations / Institutions

1. Alice Lee Centre for Nursing Studies
2. Buddhist Fellowship
3. Cancer Science Institute of Singapore
4. Catholic Medical Guild of Singapore
5. Humanist Society (Singapore)
6. Lily-NUS Centre for Clinical Pharmacology
7. School of Public Health, National University of Singapore
8. SingHealth Tissue Repository
9. The Law Society of Singapore

Individuals

10. Mr Benjamin Gaw and Ms Keow Mei Yen
11. Member of the Public (1)
12. Member of the Public (2)

1. Alice Lee Centre for Nursing Studies

14 August 2012

Many thanks for the draft Ethics Guidelines for Human Biomedical Research.

We welcome the Guidelines and are very supportive to its recommendations. We believe this document will be a valuable resource for researchers in our department. We are pleased to see that an appeal mechanisms has been implemented for those who have proposals rejected. The variability in review process and opinion makes this a valuable inclusion.

We also noted the concerns raised regarding monetary coercion of participants. We support that every effort should be made to resist 'tempting' participation in research via monetary incentives (other than reasonable loss of time and costs).

Warmest regards

Professor Sally Chan
Professor and Head, Alice Lee Centre for Nursing Studies

Annexe C

2. Buddhist Fellowship

26 July 2012

A Buddhist's muse on the ethics of human biomedical research

That only constant in life is that it ever changes. Our parents' lives would seem rather different from ours, let along life 2600 years ago. Human biomedical research did not exist back in the Buddha's time, but neither did most of the things we take for granted in our lives in the 21st century. The beauty of the Dhamma is its timelessness. This guide to leading a life with wisdom, love and compassion through right thoughts and right actions remain true and valid even as the context and nuance of life changes.

A lay Buddhist aspires to a life grounded in the 5 precepts.

- to refrain from killing and harming others, physically or mentally,
- to refrain from taking anything not belonging to us
- to refrain from sexual misconduct
- to refrain from false speech
- to refrain from intoxicating agents

Some of the ethical questions raised in human biomedical research include;

- Usage of foetal tissues and human embryos
- Genetic Intervention esp. gene therapy to alter our genetic makeup
- Human stem cell research
- Status of the human embryo

I will address these questions as a human being first, with full humility and recognition of my many own imperfections. I shall be guided by my understanding of the Buddha Dhamma. I shall also wear many caps; a doctor, a scientist, a father, a son and a husband, and a sick person to be; as I try to provide a humanistic answer. I cannot speak as the voice of the Buddhist community but as a member of the Buddhist Community. I would invite people to disagree with me, and to invoke the spirit of Ehipassiko. I shall frame my answers according to the moral and ethical questions that are commonly debated on.

Are we harming anyone?

Human beings begin life when a sperm fertilises an human egg cell. This results in a Zygote which has half its DNA from the father and the other half from the mother. The unicellular Zygote then gets implanted in a mother's womb and divides into a multi-cellular organism. It is called an embryo at this stage. These early cells are pleuri-potential, meaning that they can differentiate into different cells, for e.g. heart cells, blood cells, brain cells, skin cells, bone cells etc. At 5 weeks, the embryo's heart, brain and spinal cord starts to form but does not reach maturity until After 8 weeks, the embryo becomes a foetus. A foetus starts feeling pain around 20 weeks. By 26 weeks, most organs are fully formed but will continue to mature until the time of birth.

The million dollar question is when does life begin? Many people, including many Buddhists take that at the point of conception, i.e. when the Zygote is formed. This is point may make sense for those who believe in a permanent, unchanging soul.

I do not believe in a permanent self or soul. `I' represent a consciousness or mental energy that resides within a brain that is supported by a physical body for its biological needs. This consciousness can only exist when there is a sufficiently mature brain which consists of brain cells, other neural tissues and nerve fibres.

Yes, I accept that a Zygote is `alive' from conception but a person only comes into existence when there is a consciousness within the foetus, which is after 8 weeks gestation. However I do not know when that exact point is. With consciousness, there comes thought processes and thinking. Biologically, this occurs as electrical activity within the brain. Thus, there can be no consciousness without a brain. Our body is just a physical vehicle and our brain a mental vehicle during this life. Most doctors will accept that a brain dead person is just a physical body with no consciousness or mind.

Hence an embryo or an early foetus is not yet a human being. Using an embryo or early foetus for biomedical research is using human cells that have yet to mature to become a human being. Hence no human lives are sacrificed in this type of research. Sacrificing a late foetus for research is a different matter all together. By the time consciousness exists within a brain, that foetus has become a human being, a baby. However, I do not have the answer as to when the brain is sufficiently mature to accept a consciousness, and hence I am unable to precisely define what's early or late. 8 weeks gestation is definitely early whilst 26 weeks and beyond is definitely late but I do not know the cut off.

Cloning

Going by the concept that `me' consist of a physical energy within a body together with mental energy (consciousness) within a brain, I have no firm objections towards cloning. Cloning will result in another being that is genetically identical to the `cloned' creature. If ever a human being is cloned, he or she will be an exact genetic copy to the cloned person. However it is impossible to clone consciousness. The new person will look and maybe even sound the same as the cloned person. However his consciousness will be very different as a consciousness can only reside in one brain at a time.

Cross species genetic exchange

Currently a lot of research is going on, incorporating human genes into animal genes. The most important thing here is to have the right motivation for this research to be helpful to other humans and living beings in the future. Care is needed to prevent harm in these animals, especially in not creating animals with genetic features that are harmful to their life or causes pain to them. A line has to be drawn in genetic transfer going the other way from animals to humans. We do not know what kind of human beings will emerge if we try and in corporate animal DNA into humans. The potential for harm is very high and this is best avoided.

Playing God

The question of `playing God' is probably viewed by most Buddhists very differently from adherents of the Abrahamic faiths. Buddhists reject the concept of fate or destiny in the conventional sense, i.e. that your life journey and outcome is already predetermined by an omnipotent creator and that you should just be grateful and be completely submissive to what has already been planned for you. Buddhists believe that many forces will mould our lives, and one of these powerful forces is our karma.

Karma to me is basically about cause and effect. For every action, there will be a reaction or consequence. Positive or negative, that would be dependent on our intent and the circumstances surrounding that action. Plant a mango seed and you get a mango tree. Yes, but only if you have planted it somewhere suitable, fertile soil, with readily available sunlight and water, and protected from people or animals trodding on it whilst young.

Every action, every movement, we are creating more karma to ripen in the future. In the current moment, our circumstances have been determined by what we have done in the past. Karma sets the scene but what happens next is also largely dependent on what we chose to do. As human beings, we always have a choice, albeit the choices available to us may be influence by our past karma.

If we are taken ill, we have a choice to do the right things to get better or to allow ourselves to succumb to our illness. Even a simple sore throat, if not managed properly can sometimes lead to a serious pneumonia. If that is then not treated with the appropriate antibiotics and medical care, it is possible to die from that. So, we seek medical help when we fall sick. Break your leg, we will see a surgeon to fix it. That is common sense and that is what Buddhists are expected to do. We don't see it as a punishment from God and accept that the leg needs to remain broken, because that is our destiny.

And yet, with certain `nasty' illnesses like Alzheimer's or Parkinson's come along, the attitude from many people can be very different. Because a cure does not yet exist although medications exist to help with symptom control and to slow the progression, some may take the attitude that it is your destiny or that this is a test from God. Gene therapy and stem cell therapy may one day convert these illnesses into chronic but well managed diseases and possibly even cure some affected patients. The concept that if we accept these treatments, we or the doctors are then playing God; is alien to most Buddhists.

After all, as Buddhists, are encouraged to `play God' in our lives. We are always striving to improve our lives and lives of others around us. We are always striving to make this world a better place for all beings. We have the power to change things for the better, to reduce suffering for ourselves and others. We have the power to receive medical help if we are taken ill. Obviously, all these actions should always be tempered by being mindful that our actions do not harm ourselves and others.

For those who say that using Gene therapy or stem cell therapy, we are changing or modulating our genetic makeup, which is something that God has given us, and hence bringing on the playing God questioning. The question then is when are we allowed to play God and when are we not allowed to. If we get cancer, would seeking surgery or chemotherapy constitute playing God, especially since it is

now well recognised that most cancers occur as an interplay of our genetic susceptibility and environmental factors. Most people have vastly different thresholds on what constitute `playing God'. Who then decides who is right and who is wrong? If you decides that treating a certain illness a certain way equates `playing God', others should respect your decision to accept your illness as destiny and not seek medical help but it would be unjust for you to impose your beliefs on others.

Going back to Karma, I also believe that whilst getting a `nasty' illness may be a manifestation of some of your negative karma; being born and living in a country with healthcare system that is able to provide the right treatment, and importantly as well, your own ability to fund the treatment or getting help from donations, should be seen as ripening of some of your positive karma to offset the negative karma. At the end of the day, one still has the choice whether or not to proceed with the treatment.

The question about what treatment the government should fund i.e. when and what to `play God' with is a question on a different level that would be influenced by social, cultural, economic and political factors. Many karmic forces from many different people involved here!! We must not forget that in many undeveloped countries, millions of people are dying from `simple' infections, dying from causes of death that we no longer see in our prosperous and developed country. Leave these people to their destiny? I say, we should `play God' more and not less and help alleviate suffering in the world.

Bearing a child to facilitate gene therapy or stem cell therapy for an existing child

One hotly debated topic is that of parents conceiving and bearing another child with the hope that unborn child carries the `good' gene to facilitate gene therapy to an existing child's `bad' genes. Parents have always had their own agenda and motivation about starting a family and the number of children to have. Farming families may choose to have many children to ensure sufficient labour to work the fields later on. Not too long ago, when infant and childhood mortality is high due to disease, malnutrition and accidents, many parents chose to have as many children as possible to increase the chances that some of these children will survive into adulthood to look after them when they themselves grow old and frail. Some couple have children to save a marriage.

Who are we then to judge the motivations of parents who chose to have another child in order to save the life of a current child. Isn't their motivation about love and lessening the suffering of others. On whether this new child will be loved as much as the one saved, that is what everyone would hope for but will not be for us to decide. Karmic links may decide on this. Ultimately, for the new child, wouldn't it be wonderful that he or she was created to save another live?

Status of the human embryo

Many of the human embryo s used in research as donated by couples on fertility treatment. These embryos a surplus to requirement and would be disposed off otherwise. Hence human embryos used for research are the ones `saved' from destruction. At the same time these embryos are not yet

human beings albeit they having the potential to be one. Until these embryos develop fully into human beings, the is no reason to confer on them the same rights as human beings.

With metta,

Ho Eu Chin 26th July 2012

on behalf of Buddhist Fellowship

Angie Monkgeld.

President

#848 10738

3. Cancer Science Institute of Singapore

2 August 2012

I have no major comments to this document except for the following:

Section 3.32 states that 'communication of clinically significant incidental findings to biological relatives should be encouraged....'. This concept is further reinforced in section 3.37, which states that 'participants should also have the opportunity to express their preferences about the sharing of such information with biological relatives.'

I am not sure why such a statement is required. Is it to facilitate disclosure of clinically significant incidental findings to family members in the event that the subject is deceased (particularly for genetic information)? For practical purpose, it should be noted that almost all informed consent documents do not have this provision for the patient to indicate whether to and who to share clinically significant incidental findings. How does the BAC expect the researchers to carry out this recommendation?

With regard to genetic information, from the medical point of view, it will be ideal that all affected family members of an index patient who is found with a genetic mutation be informed as they are at risk. However, it should be noted that in reality, this does not always happen for various reasons. I run a cancer genetics clinic and test patients for hereditary cancer syndromes. When a patient is found with a deleterious mutation, we strongly encourage the patient to share the information with siblings, who have 50% chance of carrying the same mutation. Not all patients are willing to share the information.

Similarly, not all cancer-free siblings are pleased to be told of the information (many would rather not know). If a cancer-free family member wants to know but the index patient refuses to share the information, the treating physician will be breaching patient confidentiality if he/she divulges the information, even if the information does benefit the family member. I am uncertain if the law will protect the physician if he chooses beneficence for the family member against respecting patient confidentiality. These are highly sensitive issues, and I am not sure that it is fair for a researcher to have to deal with communicating clinically significant incidental findings to family members, who did not directly participate in the research.

A more practical approach would be for the researcher to communicate the information to the patient, refer the patient to an appropriate clinical facility for further management, and stress that the information should be shared with family members – but the patient must be the one initiating the sharing, not the physician/researcher.

Regards,

Dr Lee Soo Chin
Cancer Science Institute of Singapore

Annexe C

4. Catholic Medical Guild of Singapore

15 August 2012

15th August 2012

Response to the Bioethics Advisory Committee's Ethical Guidelines for Human Biomedical Research by the Catholic Medical Guild of Singapore 15th August 2012

Dear Members of the BAC,

The Catholic Medical Guild of Singapore appreciates your efforts at presenting "an accessible and consolidated ethics resource" in the form of your latest guidelines for human biomedical research. However, we would like to make the following comments to further strengthen the guidelines in line with the BAC's intent of improving the ethical standards of biomedical research in Singapore.

First of all, we think that **beneficence be included as one of the core principles of biomedical research.**

In sections 2.5 – 2.16, the guidelines has notably left out beneficence as a core principle, giving the reason that beneficence

"finds its main expression in medical treatment, deriving 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."

First of all, we think that **beneficence be included as one of the core principles of biomedical research.**

In sections 2.5 – 2.16, the guidelines has notably left out beneficence as a core principle, giving the reason that beneficence

"finds its main expression in medical treatment, deriving 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."

It however goes on to concede that, "research is a process designed to yield a general contribution to knowledge, which is practically useful or theoretically important, and is therefore a public good". Yet, the guidelines does not consider this the same as beneficence, opting instead to lump "the essential aspects of beneficence and non-maleficence" under the principle of "respect for persons", which includes "respecting (individuals') right to make their own decisions without being coerced, misled, or kept in ignorance, which the BAC refers to as autonomy".

We think that the guidelines could be further strengthened here in two regards:

(1) The first is that while it is true that research participants are not patients and that they often do not "benefit" in the same sense that patients "benefit" from their therapeutic relationship with their doctors, it is not true that they do not benefit at all. Most research participants participate in research because of altruistic motives. By doing so, they do benefit from a sense of satisfaction and fulfillment in participating in something that may lead to the good of society in the future. This fact is not something that should be discounted. Furthermore, just because they do not benefit in the same way as patients do does not mean that the principle of beneficence should be taken away. Indeed, as the guidelines themselves suggest, biomedical research is in itself a "public good". As such, even if not mentioned, the principle of beneficence is already foundational in every act of research because research is ultimately done for the benefit of other individuals in society. To remove beneficence as a principle of biomedical research is to remove the ultimate purpose of research all together.

(2) The second area that the guidelines might be improved upon concerns the co-opting of the principles of beneficence and autonomy within the single principle of respect for persons.

The principles of autonomy and beneficence are clear and distinct philosophical entities that have been described extensively by scholars and doctors all over the world.[1] While it is true that protecting the autonomy and rights of the individual are often good in itself, there are times when autonomy contradicts and conflicts with beneficence. For example, if a person states that he is suffering from a terminal illness and asks for a doctor to assist in his suicide, the principle of autonomy would support his "right" to die, whereas the principle of beneficence would protect the "good" of not ending his life prematurely. As such, while there is a need for a "respect for persons" and their autonomy, rights and interests, there must also be a co-guiding principle of beneficence to protect the good, welfare and safety of society and the individuals in it. It is thus a fallacy to lump them together.

As such, may we suggest that the principle of beneficence be included among the principles of biomedical research. Below is a suggested formulation of how the principle could be worded:

[1] Please refer to Tom Beauchamp and James Childress. Principles of Biomedical Ethics. New York, Oxford: OUP 2009 for a full treatment of the principles of autonomy and beneficence, in which it is shown that they are clearly different entities.

The Catholic Medical Guild of Singapore
55 Waterloo Street #09-03 Catholic Welfare Centre Singapore 187594
Website: www.cmg.org.sg Email: cmgsingapore@yahoo.com.sg

Annexe C

"Beneficence as a principle is concerned not only with the good of the individuals participating in research but more so, also involves the good of society as a whole. While it is true that research participants do not benefit from the goods of the therapeutic relationship in the same way that patients benefit from seeing a doctor for a medical condition, these participants often benefit from being able to contribute to the good of society. Through their altruistic participation, they often receive a sense of satisfaction and fulfillment, which results whenever someone participates in some public good. Most importantly, beneficence is the foundational principle of all biomedical research since all research, is ultimately aimed at achieving results that can be used for the good of others in society in the future.

Our second comment refers to the BAC's examination of **the moral status of the human embryo.** In Sections 7.12 and 7.13, it states that

"The main controversial issue 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 fertilization, while at the other end, the view is that it is a mass of cells, no different from any other biological material used for research. After public consultation, the BAC adopted an intermediate position, whereby a human embryo is considered as having 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, as at around day 14, the primitive streak appears, signaling 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. This remains the BAC position on this issue."

In doing so, we think that the BAC has tried to act moderately in a situation in which moderation cannot be applied. This is not a political decision in which one decides based on how many votes one has, nor is it a statistical decision in which one can give the mean

The Catholic Medical Guild of Singapore
55 Waterloo Street #09-03 Catholic Welfare Centre Singapore 187594
Website: www.cmg.org.sg Email: cmgsingapore@yahoo.com.sg

or the mode as the final answer. This is a moral decision that needs careful thought and deliberation, and no unethical action should be allowed until the process has been carefully and completely debated.

The scientific literature is clear that human life begins from the moment of conception, or in the case of cloned embryos derived from somatic cell nuclear transfer, at the point where the nucleus has been incorporated into the enucleated ovum. We are of the opinion that, from this very beginning of life, "the human being is to be respected and treated as a person" and "from that same moment his rights as a person must be recognized, among which in the first place is the inviolable right of every innocent human being to life."[2]

Thus, even if some should still question the moral status of the embryo, the fact remains that this view is not shared by those who consider the embryo as a distinct human entity that is fully deserving of human dignity and of a right to life.

In criminal law, if there is reasonable doubt that a person did not commit the crime, then the prosecution cannot convict that person. So long as there is reasonable doubt that the embryo may indeed be a human being, shouldn't the killing of these embryos be considered morally unacceptable until all doubt has been properly reviewed and removed? As such, **we do not condone the use and destruction of human embryos in biomedical research and call for an immediate moratorium on the use of human embryos in such research.**

Yours Sincerely,

Dr Colin Ong, Deputy Master

Dr John Hui, Immediate Past Master

The Catholic Medical Guild of Singapore

[2] Congregation for the Doctrine of the Faith, Instruction on Respect for Human Life in its Origin and on the Dignity of Procreation *Donum Vitae* (22 February 1987), I, No. 1: *AAS* 80 (1988), 79.

The Catholic Medical Guild of Singapore
55 Waterloo Street #09-03 Catholic Welfare Centre Singapore 187594
Website: www.cmg.org.sg Email: cmgsingapore@yahoo.com.sg

Annexe C

5. Humanist Society (Singapore)

13 August 2012

To: Bioethics Advisory Committee, Singapore
We, the Humanist Society (Singapore), a registered society representing the non-religious in Singapore, would like to express our support for the draft "Ethics Guidelines for Human Biomedical Research".

We believe that research is vital to understanding nature and holds great potential for extending human lifespans and improving quality of life. In particular, we agree with the committee's stand that stem cell research should not be prohibited, but instead regulated with guidelines based on our current understanding of Science.

Yours sincerely,
Humanist Society (Singapore)
Guided by reason, informed by evidence, driven by compassion

6. Lily-NUS Centre for Clinical Pharmacology

16 and 21 August 2012

Greetings,

I am responding to the call for comments from the BAC on the proposed Draft Guidelines for Human Biomedical Research. Please allow me a short introduction. I am Dr Danny Soon, and currently the Managing Director of the Lilly-NUS Centre for Clinical Pharmacology, located at MD11 in NUS. We have been in operation for 14 years, and have conducted over 130 studies, in the field of clinical pharmacology research, including first-in-man, biopharmaceutics and experimental medicine studies. These studies are conducted in healthy volunteers, in the majority. According to HSA statistics, clinical pharmacology studies and Phase 1 studies, which overlap significantly, form 17% and 25% of all trials approved in 2011.

There is one clause that I would like to seek clarification from the BAC.

v. ***Compensation / payment to research participants.*** *. It has always been a fundamental principle that participation in research should be voluntary. There should be no coercion or undue influence on a prospective volunteer. In this connection, it is important to avoid financial inducement to participate in research. Participants may be reimbursed for legitimate expenses, such as the cost of transport and child care services, and actual loss of earnings. Reimbursement and any additional payment to be given, whether monetary or in kind, should not amount to an inducement. Donation of tissue for research, however, is considered an altruistic gift and there should be no payment of any kind, except in the case of donation of human eggs for research by healthy volunteers, as the process required to obtain the eggs is invasive and carries a health risk.*

Participation in our studies is always entirely voluntary. However, it is common and customary, in Singapore and in other geographies where healthy volunteer studies are conducted, that research subjects are paid for their time on the study. The principle applied in formulating an appropriate payment quantum is predicated on a 'minimum wage' approach, sometimes known as the 'wage payment' model (*Dickert N, Grady C. N Engl J Med. 1999 Jul 15;341(3):198-203. What's the price of a research subject? Approaches to payment for research participation.*) In this model, a research subject is paid a pre-determined stipend, in accordance with the duration of his participation in the study. This payment is submitted to the Ethical Review Board for approval, and provided to the subject at the time of informed consent for entry into a study. It should be noted that such payments are fixed, and not based on reimbursement of the subject's expenses or loss of earnings. I seek clarification from the committee as to whether it is their intent to disallow such payments.

I do feel the BAC's position on this need to be clarified to researchers and IRBs. As to the question as to whether nonpatient volunteer research in general will suffer impact if 'loss of time' payments were discontinued, I think the answer is self-evident. One needs to be circumspect when using terms such as 'vulnerable persons' and 'risky research'. It needs to be clear that the vast majority of healthy volunteer research subjects in our experience, are educated and with gainful employment. We have our own safeguards to prevent subjects from overvolunteering in Lilly studies, and if the concern is around a small minority of the economically disadvantaged who may look upon these payments as a major source of income, then for further protection, I have proposed in the past that some form of central tracking of nonpatient research volunteers be administered by a coordinating body. Such a system already exists in the UK:
<http://www.tops.org.uk/site/cms/contentChapterView.asp?chapter=1>.

Annexe C

On the question of risk, it also needs to be clear to payment to volunteers are calculated mainly on the time spent on study, with degree of discomfort factored in if appropriate. There is no payment on the basis of 'risk' incurred. Further, any discussion of 'risk' is not complete without consideration of risk mitigation. In the phase 1 clinical protocols that are put forth to the IRB and HSA, a large measure of clinical monitoring is often in place. Also, not clinical pharmacology research is in novel therapeutics.

Last, I am quite concerned that there was not more of an effort to engage with stakeholders on this discussion. I was only made aware of the proposed changes when I chanced upon it in a press report, and a couple of investigators in other institutions I spoke with who conduct healthy volunteer research, were not aware of these proposals at all. I would urge a nuanced approach to this matter from the BAC.

Sincerely,

Dr Danny Soon
Managing Director & Principal Investigator
Lily-NUS Centre for Clinical Pharmacology, Singapore

7. School of Public Health, National University of Singapore

11 July 2012

I would like to reiterate the following points for BAC's consideration:

1. Para 1.10

The current definition of human biomedical research is very much disease focused and patient-centric. There is an increasing body of biomedical research that focuses on health seeking behaviour, knowledge, attitudes and practices of both patients and "normal" healthy individuals. In addition, clinical research requires "normal" subjects as a comparison group; etiological research using cohort studies starts with recruiting healthy subjects. A simple definition would encompass all research that involve human subjects/tissues/information with the aim of disease treatment, prevention and health promotion. I would like to propose that the following sentence be added the existing definition:

"…..derived from humans or human tissues. Research on normal subjects and populations is also included in this definition."

1. Paras 4.7, 4.14

The proposed Personal Data Protection Bill recognises the role of "data intermediaries" or "Trusted Third Parties" (TTPs). TTPs are fairly common in many non-biomedical sectors but need to be "popularized" in the biomedical sectors. With an efficient and trustworthy TTP, data owners and research subjects can have greater confidence that their reversibly de-identified data are well protected. Propose adding a short para after 4.7:

"The use of 'data intermediaries' in the form of a 'Trusted Third Party' should be encouraged especially when data are kept in a reversibly de-identified form. Record linkages via TTP provide greater confidence to data owners and research participants that their data are adequately protected. Ideally for Singapore, either a single or a few large TTPs with the ability to conduct audits on the storage and use of reversibly de-identified data."

Happy to provide further clarifications if required.

Best regards

Professor Chia Kee Seng
Dean, School of Public Health

Annexe C

8. SingHealth Tissue Repository

13 August 2012

Background

a. Incidental research findings (IF) are not limited to the disease area under study. A researcher looking into biomarkers for cancer may find that a sample of blood from a supposedly healthy volunteer actually shows hyperglycaemia whilst another researcher studying genetic predisposition for diabetes may instead discover that a patient sample shows *BRCA1* mutation, which carries a high risk of breast and ovarian cancers.

b. High-throughput interrogation of alterations at the genomic level is now widely performed, using donated patient samples removed during surgery. These samples are banked in research tissue biobanks or repositories, of which the two largest collections reside in the NUHS Tissue Repository and the SingHealth Tissue Repository (STR).

c. Tissue repositories ensure that samples are collected ethically and legally. Processed and annotated samples with de-identified patient information are then distributed to Principal Investigators (PIs) after approval by an oversight or tissue access committee.

d. Despite its noble intentions, the proposal currently under consideration by the Singapore Bioethics Advisory Committee (BAC) relating to the return of IF[i] raises significant ethical and in particular, legal concerns.

BAC's existing recommendations

2.1 The BAC has previously recommended that tissue donations for use in research should be treated as outright gifts. As such, there is no obligation for researchers or tissue bankers to return research data nor should donors expect such benefits arising from the donation:

"Donations of tissue samples for use in research should be treated as outright gifts. Donors should not be paid any financial incentives for the donation….. As a corollary of this principle, donors should not expect any personal or direct benefit from the donation of tissue, including information of any medical condition or predisposition or likelihood of such discovered in the course of research on the sample. Likewise, researchers and tissue bankers should not be under any obligation to disclose such information to the donors, unless they have agreed to do so in advance of the donation." (para 13.1.1.8, Consultation Paper: "Human Tissue Research", Singapore Bioethics Advisory Committee, 27 Feb 2002)

2.2 The policies and SOPs of the STR have been formulated following these recommendations and we use a donation model for the acquisition of patient samples. It has been made clear to our donors that they will not receive any material benefits including any patient-specific data emerging from the research. The current proposal under consideration would be a complete deviation from the BAC's previous position and recommendations.

---

[i] '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 the result, prior to the commencement of the research. Participants should also have an opportunity to express their preferences about the sharing of such information with biological relatives, or others.' (para 3.37, proposed "Ethics guidelines for Human Biomedical Research", Singapore Bioethics Advisory Committee, 20 June 2012, pg.27)

2.3 Nevertheless, I recognize that the position of the BAC might have shifted somewhat on this issue. In the subsequent publication on genetic testing, the BAC made a recommendation that appeared to run contrary to its previous guidelines as mentioned above:

'Human genetic research is not conducted with the aim of providing research participants with specific information about their genetic status or health. However, if there is a possibility that the research may yield individual data of clinical significance, the research participant should be informed of this possibility and whether he or she would receive such information if so desired, prior to participation in the research.' (para 46, Genetic testing and genetic research, Singapore Bioethics Advisory Committee, Nov 2005, pg 7)

STR position: Return of research findings is not feasible

3.1 Return of research findings to donors is not feasible for the following reasons:

3.11 Unacceptable liabilities for biobanks. A large biobank like STR distributes up to thousands of samples a year to numerous researchers. A biobank has no means to monitor the research output of all these researchers and it is unlikely that PIs will allow the biobank access their research data. As tissue samples are donated to the biobank which subsequently distributes them, would the biobank be held jointly liable if a researcher fails to declare and return significant IF? The amount of data emanating from genomic research is colossal. Would the researcher/biobank be held liable if a significant IF has surfaced from the research but is not picked up by the PI who is studying a different question? The proposed policy will impose unacceptably high legal risks for the biobank and will threaten its very existence and the success of Singapore's biomedical initiative.

3.12 Danger of inaccurate data disclosure. A research laboratory is designed to uncover novel data and research assays are not conducted in a standardised manner as with an accredited service laboratory. The finding of a significant mutation may subsequently be found to be erroneous, giving rise to unnecessary distress and patient concerns. In extreme circumstances, the patient might have taken steps to distribute his properties and manage his financial affairs differently had he known that the research data were inaccurate. It will be crucial to emphasize that the IF is preliminary and needs to be confirmed in an accredited laboratory but it does not take away the distress and damage it might have caused in the interim. There is also the question as to who is financially liable for performing the confirmatory assays in an accredited laboratory.

3.13 Absolute need for anonymization which precludes follow-up studies. To protect patient confidentiality, biobanks de-identify or anonymize tissue samples.

3.14 Bioresources are only released to researchers after all identifiable patient information (ID) has been detached from the sample, which is then given a random code. In this process of **de-identification**, the biobank functions as the trusted third party who holds the link between the patient's identity and the code. This allows for valuable follow-up clinical data to be collected, de-identified and provided to the researcher whilst protecting patient confidentiality.

3.15 Alternatively, the link between the patient's ID and the sample code can be irreversibly destroyed in the process of **anonymization**. Obviously, this precludes the collection of crucial clinical information such as the response to chemotherapy and survival data.

3.16 Some biobanks will provide de-identified samples for researchers who require follow-up data but anonymize samples for studies that do not require such information.

3.17 If researchers and biobanks have an obligation to return IF, one possible consequence is that biobanks will completely anonymize all patient samples. This will render it impossible to return IF and thereby protect the researcher from legal liabilities, but will also impede important and valuable scientific research.

3.18 Patient autonomy and the need for genetic counselling. Some patients cannot handle the devastating news that they suffer from a mutation that will result in breast cancer or early dementia. For example, patients have jumped off buildings immediately after receiving news that they have HIV infection. Inheritance of a mutation like BRCA1 also has implications for family members and the donor will be burdened with the responsibility of disclosure to relatives who may be affected. A patient may well NOT wish to receive data relating to significant genetic alterations. For this reason, the BAC has emphasized the need for pre- and post-test counselling in the context of genetic testing[ii]. If return of IF is necessary, one would assume that the same requirements for genetic counselling will apply as part of the consent procedures:

"*... When the tissue samples provided for clinical use are intended also for research, informed consent for the research is required in addition to the consent for taking the tissue for clinical use. Consent is also required if there is an intention to store the tissue for future use*." (para 4.4, Genetic testing and genetic research, Singapore Bioethics Advisory Committee, Nov 2005)

"The individual should be given appropriate genetic counselling and informed about the nature of the test and risks of the procedure (if any) before giving consent. Pre-test counselling is thus intrinsic to the process of consent-taking. (para 4.6, Genetic testing and genetic research, Singapore Bioethics Advisory Committee, Nov 2005)

One implication of the need to return IF is that there will be a need for pre- and post-test genetic counselling and there are simply insufficient resources and trained genetic counsellors for that matter.

3.19 No consensus on what constitutes significant incidental findings. The range of possible genetic and biochemical alterations that may emerge from tissue-based research are legion. Yet, it is near impossible to define which are sufficiently significant and should trigger a return of IF. A genetic predisposition towards low sperm count may not be significant to an 80-year-old single male but may well be very significant to the scion of a wealthy family. Placing on the researcher/biobank the duty to decide which of the numerous genetic alterations (which will include not only mutations but polymorphisms) to report will pose far too onerous a liability and may stop all human genomic research in its tracks. For that matter, it is impossible to conduct any meaningful genetic counselling when the implications of the IF can range from bilateral ovarian cancers at the age of 40 to a polymorphism that may render one less likely to win a marathon race.

[ii] 'An individual tested positive for a predisposition to developing a specific genetic condition has to decide whether this risk should be disclosed to other family members who may also be at risk of developing the same condition. The individual may be additionally burdened with considerations for the family members who may or may not be affected by the condition and their wish to know or not to know. Family members who are not affected by the genetic condition may nevertheless be affected psychologically (such as the condition of 'survivor guilt'). In view of these considerations, we emphasise the importance of pre- and post-test genetic counselling.' (para 4.25, Genetic testing and genetic research, Singapore Bioethics Advisory Committee, Nov 2005, pg.30)

Concluding remarks

4. Return of incidental research data is a hotly debated issue with many angles that need to be considered and for that reason, there is currently no consensus in the research community. Whilst I fully appreciate the arguments to return significant incidental findings, the implications may well sound the death knell for biobanks and human tissue research.

5. I take the position that, for the moment, the earlier BAC recommendations of Feb 2002 should stand. Research tissue samples should be acquired as donations or absolute gifts and the act of donation be separated from the research intention[iii]. Patient donors should not expect any material benefits in making the gift for the advancement of knowledge and the benefit of humankind in general. Similarly, biobanks and researchers should not have an obligation to return research results, incidental or otherwise to patient donors.

A/Prof Tan Soo Yong
Director, SingHealth Tissue Repository
Singapore Health Services

[iii] 'Another way of simplifying consent is to have a system in which consent is completely delinked from the research purpose. In this system, the donor makes an absolute gift of tissue to a specified tissue bank. But it is made clear to the donor that the consent to the gift is not to be linked to or conditional upon any particular approved research use or purpose. It is also made clear to the donor that research applications are handled and approved by an independent ethics review committee or body...' (para 8.8-8.9, Human Tissue Research, Bioethics Advisory Committee, Feb 2002, pg.11)

Annexe C

9. The Law Society of Singapore

15 August 2012

THE LAW SOCIETY OF SINGAPORE

The Law Society of Singapore
39 South Bridge Road S(058673)

t: +65 6538 2500 f: + 65 6533 5700
www.lawsociety.org.sg

Sender's Fax: 6530 5700
Sender's DID: 6530 0226
Sender's Email: represent@lawsoc.org.sg

Our Ref: LS/11/CLO.Gen(BAC)/12-01/AC
Your Ref:

15 August 2012

BY E-MAIL
E-Mail: contactus@bioethics-singapore.org
No. of pages: 8
(including this page)

Ms Charmaine Chan
Senior Executive
Secretariat
Bioethics Advisory Committee
11 Biopolis Way
#10-12 Helios
Singapore 138667

Dear Mdm

REQUEST FOR FEEDBACK ON THE BAC'S DRAFT ETHICS GUIDELINES FOR HUMAN BIOMEDICAL RESEARCH

We refer to your e-mail dated 13 July 2012 inviting the Law Society to provide its comments on the recommendations set out in the draft Ethics Guidelines entitled "Ethics Guidelines For Human Biomedical Research".

The Society appointed an ad hoc committee to review the draft Ethics Guidelines.

We are pleased to enclose our ad hoc committee's feedback on the matter for your consideration.

Thank you for giving the Society the opportunity to give our views on the matter.

Yours faithfully

Alvin Chen
Chief Legal Officer
Director, Representation and Law Reform

Enc.

COMMENTS ON THE BIOETHICS ADVISORY COMMITTEE'S DRAFT ETHICS GUIDELINES ON HUMAN BIOMEDICAL RESEARCH

Introduction

1. We have been appointed by the Law Society of Singapore to provide our inputs on the Bioethics Advisory Committee's Ethics Guidelines for Human Biomedical Research ("BAC Guidelines").

2. The members of this ad hoc committee are involved in advising and representing individuals and organizations within the healthcare industry, as part of their legal practice. Some of the members also sit as members of Institutional Review Boards (IRBs) that review clinical research proposals.

3. We are of the view that the BAC Guidelines in general provide a good summary of the ethical, legal and social issues arising from research on human biology and behaviour and its applications and the policies on such issues.

4. We set out below our comments on the following specific issues dealt with in the BAC Guidelines:-

    (a) Informed Consent from minors on turning 21
    (b) Clinically significant incidental findings
    (c) Human Tissue Research
    (d) Compensation/Payment to Research Participants

Annexe C

Informed Consent from minors on turning 21

5. Paras. 3.22 – 3.25 of the BAC Guidelines refers to 21 years being the age of majority. This is correct. However, it should also be noted that with effect from 1 March 2009, Section 35 of the Civil Law Act now provides that a minor who has attained the age of 18 years is regarded under law as having sufficient capacity to enter into contracts (except for certain types of contracts such as contracts for sale/purchase of any land etc). With this amendment, a minor between the ages of 18 to 21 years can now purchase investment products or enter into commercial contracts as long as it is one of the transactions stipulated in Section 35 of the Civil Law Act. This amendment does not affect the Medicines (Clinical Trials) Regulations where the age for consent for participation in clinical trials is still stipulated to be 21 years. It would therefore appear that although the law now regards those aged 18 to 21 as being sufficiently mature to understand the implications of entering into various contracts where the young person may undertake fairly onerous legal obligations and commitments, the Medicines (Clinical Trials) Regulations still regards the age for consent for participation in clinical trials as being 21 years.

6. Human biomedical research does however, extend beyond just "Clinical Trials" as defined under the Medicines (Clinical Trials) Regulations. There are also non-drug studies where it may be desirable to recruit minors. In terms of what constitutes valid and effective consent to medical treatment, it has been generally accepted under common law that minors who are "Gillick competent" can consent for themselves, so long as they have sufficient understanding of the information being conveyed and are mature enough to appreciate the risks involved. We agree with the observation made in para 3.20 that research by contrast, is not generally designed to confer benefit on the research participant and there are thus usually no personal benefits against which to balance risk. This could make the decision whether to

participate, a more difficult one for the young person to make, but on the other hand there is no reason why the ability of the mature minor to consent to participation in human biomedical research, should be discounted entirely, particularly where the risks posed to the subjects are low. The fact that our law has now been amended to allow those aged 18 to 21 years to enter into certain contracts, further strengthens the case that in the area of low risk biomedical research, the mature minors deserve to be treated as competent decision makers exercising their right to autonomy.

7. The distinction between "consent" and "assent" as referred to in the BAC Guidelines is sometimes unclear. For example, para 3.26 requires the consent of the parents "in addition to consent from the child". Para 3.22 provides that "in clinical research which has a reasonable expectation of benefitting a child, the research might be allowed to proceed even without the child's assent, if the parents give consent but in general, the researchers should respect refusal from a child". We find it difficult to see the difference between "consent" and "assent" as used in these paragraphs. It is also unclear whether there is a positive obligation to obtain the assent of a child (as opposed to silence) and in the face of a child's refusal, whether the researcher is still permitted to proceed. This is important as the range of ages under consideration is wide and the guidelines presently are vague on whether there is a positive obligation to seek the assent of, for example, a 17 year old and whether the researcher can proceed in spite of refusal from the child (but with the consent of the parents). At what point would the child's distress stemming from his or her refusal, make it clear that proceeding against the child's objections would simply be against the child's best interests, which after all is always the paramount consideration for all decisions being made for the child.

8. Para 3.26 does however suggest that there is a positive obligation to obtain the child's consent. But again, it does not specify whether research can

proceed where the child objects. We are of the view that in the case of research presenting more than minimal risk, the child's objection should be allowed to stand (save perhaps in special situations of specific waiver by IRBs) and given such weight that it could even override parental consent as it could be against the child's best interests to be subjected to the research under those circumstances.

9. It is proposed under para 5.16(b) that once the minor reaches 21 year, his or her consent should be obtained for the continued use of the previously collected tissue or information related to this tissue specimen. If we recognize that the minor had already meaningfully consented to the use of tissue or information related to the tissue specimen between the ages of 18 and 21 years, such a requirement would be unnecessary. It is worth noting that under the Medical (Therapy, Education and Research) Act, anyone aged 18 years or above may give all or any part of her or his body for research or for therapy. Why then, would that minor of 18 years or above be unable to provide consent for use of tissue samples? In this regard, the need for a formal consent to be provided should be limited to instances where the minor did not give prior consent to the use of the tissue specimen or was below the age of 18 years at the time when he or she was included in the study.

10. Alternatively, at such time when consent or assent is being obtained from the minor between the age of 18 and 21 years, the minor may be requested to state in the consent/assent whether they wish to be consulted again on the continued use of their tissue specimen when they turn 21 years.

11. A similar point for consideration is whether a formal consent is required for the minor's continued participation in the clinical trial when the minor reaches 21 years. Again if we regarded the minor as being capable of giving meaningful consent when he or she agreed to join the study at between the

age of 18 and 21 years, then there is no logical reason why the subject needs to be re-consented at age 21.

Waiver of Consent

12. Para 3.27 provides for the waiver of the consent by IRBs for certain research done in the public interest. One of the conditions to be met before such waiver may be considered is that individuals who have indicated their wish to know will be informed in a timely manner of clinically significant findings, if reasonably possible (para 3.27(f)). It is likely that in situations where waiver of the consent requirement is being contemplated, there will be no opportunity for individuals to indicate their wish to know of clinically significant findings. In this context, it may be more appropriate to provide that all individuals will be informed of clinically significant findings in a timely manner, if reasonably possible.

Clinically significant incidental findings

13. In para 3.30, there is a proposal that research participants be given a choice whether to be informed about clinically significant findings. If they choose to be informed, then the researchers would ensure that research participants are informed and advised to seek medical attention and confirmation of the research result in a clinical laboratory. This suggests that should the research participant choose not to be informed of clinically significant findings, the researcher may not need to inform the participant. We feel that ideally participants should be notified of clinically significant findings (incidental or otherwise) that would impact on the participant's health or well-being regardless whether they had opted to be informed or not. This is particularly so because at the time when the participants made the original choice, they

may not have fully contemplated how such findings could impact them, and how they might value such knowledge particularly as they age.

14. As an alternative, perhaps the Patient Informed Consent should provide that unless the participant informs the PI in writing that they do not wish to be notified of clinically significant findings, the PI will notify the participant of such findings. In other words, all participants will be told of clinically significant incidental findings unless they inform the PI in writing that they do not wish to receive such information on such findings. The other exception would be in situations where the subjects have agreed to the anonymization of tissue samples, such that contributors cannot subsequently be traced.

Human Tissue Research

15. In para 5.13, it is provided that the donor may seek to limit the use of the human tissue and any information derived from the research. We know that some researchers obtain a general consent from participants for use of their human tissue for research in general, even without specifying what type of future research may be done. We are of the view that participants should be meaningfully consulted regarding the use of the tissue samples such that participants can choose whether they would permit such tissue samples to be used for research in general, or for research that is related to the particular area of research for which consent was originally sought. In other words, participants should be given a specific choice to decide on the ambit of the use permitted. There should be a separate section to allow participants to indicate their choice and it should not be an "all or nothing" consent that is tied to the original purpose of the research study.

16. Further, if the participant decides that they do not wish for their tissues to be used for further research, whether related to the particular research in question or not, it should be provided in the Patient Informed Consent that

such tissue samples should be destroyed by the researcher. It is observed that such a provision is not uncommonly omitted in Patient Informed Consent forms.

17. We are in agreement with para 5.44 on the issue of how to deal with legacy tissues. Researchers should be told clearly how best to deal with legacy tissues as there is often uncertainty amongst researchers as to whether consent is required for use of such legacy tissues for all forms of research.

Compensation/Payment to Research Participants

18. In para 3.5, there is a reference to payment to research participants and how such payments may amount to coercion. We acknowledge that care must be exercised so that any payments do not present as an inducement to research participants. It should also be noted that inducement may not come in the form of payment but in the form of subsidising cost of medical treatments that participants would otherwise have to bear should they not participate in the clinical trial. Often the point of contention is to get researchers to cover tests that are directly related to the research. It is not often that we encounter circumstances where participants are given substantial coverage for the entire medical treatment. If this should occur, it should be recognized as a potential inducement to subjects to participate in research.

Thank you for giving us an opportunity to provide our inputs on the BAC Guidelines.

Submitted by: Ms Rebecca Chew
Ms Mak Wei Munn
Ms Audrey Chiang
Ms Kuah Boon Theng

Annexe C

10. Mr Benjamin Gaw & Ms Keow Mei Yen

15 August 2012

S/No.	Para No.	Subject Matter	Comment
			Consolidation of Reports
1.	1.4	With the Guidelines, it is the intention of the BAC to render it unnecessary for readers to consult the various BAC reports.	We agree that consolidation of BAC's previous Reports would be of great assistance to researchers and organisations as it would facilitate reference and adherence to the BAC Guidelines. However, given the need for brevity, there is concern that there may be certain important concepts or principles expressed in the earlier Reports which may not have been incorporated in these Guidelines. A sampling of what does not seem to have been incorporated in the Guidelines: (i) The portion on Genetic Testing in the Guidelines is covered in paras 6.1 to 6.13. However, the BAC report on Genetic Testing and Genetic Research ("**BAC Genetic Testing Guidelines**") spans 53 pages. Some content-specific items which appear very important in the BAC Genetic Testing Guidelines do not appear in the new Guidelines. These include: (i) a detailed explanation of what genetic testing is and what it can be used for (paragraphs 2.1 to 2.11); (ii) general and specific ethical considerations in genetic testing including the 20 recommendations given by the BAC with regards to how genetic testing should be conducted (paragraphs 4.1 to 4.80); and (iii) genetic counseling (paragraphs 4.81 to 4.89). The information set out in the Guidelines seem to provide a very broad summary of genetic testing and only appear to touch on the surface when it comes to content-specific information. (ii) The portion on Stem Cell research in the Guidelines is covered in paras 7.1 to 7.32. However the BAC Report on Human-Animal Combinations in Stem Cell Research ("**BAC Stem Cell Research Guidelines**") spans 34 pages. Similar to the BAC Genetic Testing Guidelines, the Guidelines does not include large portions of the BAC Stem Cell Research Guidelines. These include: (i) the detailed explanation on chimeras and hybrids as at out in paragraphs 2.1 to 2.15; (ii) the regulatory practices adopted by different countries set out at paragraphs 4.1 to 4.11; and (iii) the table of regulatory approaches adopted by different countries at pages 27 to 34 of the BAC Stem Cell Research Guidelines. (iii) Other omissions from the Guidelines include important principles such as the one stated in paragraph 8.7 of the Human Tissue Research Report "… *the governing common law principle that informs the letter of the law of both the Human Organ Transplant Act, and of the Medical (Treatment, Education and Research) Act: no person may enter into a contract for the sale of his body or any part thereof, including organs, tissue or blood. No person is under any compulsion to give. Nor is any person under an obligation to accept a gift*…".

S/No.	Para No.	Subject Matter	Comment
			Our view is that these background information can be very helpful in understanding the background and BAC's thinking in relation to the relevant guidelines and recommendations. We therefore suggest that the Guidelines be expressed as being complementary to the previous Reports, and to also include references to the previous Reports, where helpful, within the Guidelines. This will also aid readers to navigate the BAC's Reports. On another level, we also propose that there should be an effort in consolidating other relevant guidelines to human biomedical research. Particularly, we note that other than the BAC (which guidelines do not have the force of law), there are also a number of other guidelines issued by various bodies, including the Ministry of Health, the National Medical Ethics Committee, and the Singapore Medical Council. Whilst the guidelines issued by these bodies are presumably drafted with the specific target audience (such as the healthcare institutions licensed under the Private Hospitals and Medical Clinics Act ("**PHMC Act**") in the case of the MOH guidelines), there may be a need to review and to consider whether there are any inconsistencies or ambiguities amongst these various guidelines, as a plethora of guidelines can lead to confusion as to the applicable ethical codes. In particular (see our comments to paragraph 1.10 below), there are some noted differences between the MOH guidelines and these Guidelines.
2.	1.10	Definition of "Human Biomedical Research"	We note that the Guidelines have introduced a definition of "Human Biomedical Research" as follows: "*Human Biomedical Research refers to any research done for the ultimate purpose of studying, diagnosing, treating or preventing any disease, injury or disorder of the human mind or body, and which entails the involvement of humans, human tissues or information derived from humans or human tissue.*" On the other hand, the Ministry of Health has defined "Human Biomedical Research" in paragraph 2.2 at pages 1 of 19 of the *Operational Guidelines for Institutional Review Boards* ("**MOH IRB Operational Guidelines**") as "*any research on human subjects that involves*: *a. intervention on, interaction with, or observation of, humans;* *b. use or manipulation of any human biological derivative (e.g. human cells, tissues and body fluids), including those which were previously acquired and stored; and* *c. review, analysis and publication of previously compiled identifiable data for the purpose of studying, diagnosis, treating and/or preventing, any ailment, injury or adverse condition of the human mind or body."* From a quick comparison of the two definitions, it can be seen that the BAC definition is broader as it includes research on any form of information derived from humans or human tissues (whether identifiable information or de-identified information), whereas the definition in the MOH IRB Operational Guidelines appears to be limited only to identifiable data. Of course, the difference could be deliberate in that research using de-identified information derived from humans may be deemed less sensitive and thus should not fall within the MOH IRB Operational Guidelines. However, as noted above, it will be helpful if a study be undertaken to consider if some of these guidelines can be consolidated as well, to avoid creating any unnecessary or unwanted confusion.
3.	1.17	Applicable statutes and subsidiary legislation	The BAC may wish to consider if there should be reference to the Human Organ Transplant Act.

Annexe C

S/No.	Para No.	Subject Matter	Comment
4.	1.19	Relevant Guidelines	The BAC may wish to consider if there should be reference to MOH's Licensing Terms and Conditions on Assisted Reproduction Services issued by the Director of Medical Services on 26 April 2011 ("**2011 AR Licensing Terms**"). Section 9 of the 2011 AR Licensing Terms contain terms and conditions on the conduct of research, and Section 10 contains the conditions in relation to human-animal combinations.
5.	1.22	Application of BAC Guidelines	We note that the BAC Guidelines are intended to apply to research whether privately or publicly funded. We agree with the position taken by the BAC but are however concerned as to how the BAC Guidelines would in reality be implemented. Where research facilities are licensed under the PHMC, the application of the BAC Guidelines may be facilitated by way of a suitable licence condition under the BAC (although we are uncertain if there is indeed such blanket requirement currently). However, privately funded research laboratories (which do not carry out clinical services) would not fall to be regulated under the PHMC, and with the BAC Guidelines not having the force of law, there would be great concerns as to whether the BAC Guidelines would have sufficient reach to research carried out by privately-funded research laboratories.
6.	2.7 to 2.20	BAC General Ethical Principles	We note that the BAC has formulated the following five guiding principles: (a) Respect for persons (b) Solidarity (c) Justice (d) Proportionality (e) Sustainability We agree with the principles enunciated, but however, note that the principles governing human biomedical research as enunciated by the Ministry of Health although largely similar, are not identical to the BAC principles: See Section 3 of the MOH IRB Operational Guidelines, which specifically lists Beneficence as one of three fundamental principles. Again, such differences may lead to a possible conflict in implementation, particularly where the IRBs may be guided by principles which are differently articulated. In reality though, the ethical principles are not in and of themselves clear and distinct and each principle may embody concepts or shades of the other principles. Further, these principles would be distilled into specific guidelines, and there may be therefore be little or any difference in implementation. Nonetheless, as mentioned above, there may now be an increased need for a consolidated approach to regulating human biomedical research to ensure comity and consistency in approaches.
			Institutional Review Boards
7.	2.45	Appeal Mechanism	We agree with the setting up of an appeal mechanism. However, we suggest that the implementation of such appeal mechanisms not be the responsibility of the Institution (given that the IRB acts for and on behalf of the Institution). One important point of consideration in establishing an appeal process is the need to consider whether the decision of the IRB is akin to that of a public administrative body, and therefore subject to the principles of administrative law and public law.

S/No.	Para No.	Subject Matter	Comment
			In any event, we suggest that, given that the IRBs are constituted pursuant to the directions of the MOH under the PHMC, any appeal against the decision of the IRB should be escalated beyond the Institution, and to the Director of Medical Services, who may be empowered to constituted a panel of experts to consider the appeal. The introduction of an elevated appeal process would be helpful to provide assurance that there is impartiality in the appeal process as it is easy for allegations of conflicts of interest if the Institution were to review the decision of the IRB (since the IRB acts for and on behalf of the Institution).
8.	3 & 4	Roles and responsibilities of the Institutional Review Board ("**IRB**")	We also note that there appears to be increased roles and responsibilities placed on the IRB under these Guidelines. For example: (i) at paragraph 3.18, in the case of vulnerable persons not lacking capacity and when it is not possible for consent to be taken by an independent third party, the IRB may now give directions for consent to be taken by the researchers so long as there are provisions to manage the conflict of interest and sufficient safeguards to protect the welfare and interests of the participant. (ii) at paragraph 3.21, if the researcher is also the physician, the IRB may give directions for consent to be taken by the researcher as long as there are provisions to manage conflict of interest situations. (iii) at paragraph 3.26, IRBs should be able to waive parental consent in research that does not involve more than minimal risk. (iv) at paragraph 3.27, IRBs may consider a waiver of the consent requirement for research done in the public interest. (v) at paragraph 3.28, giving the IRBs the power in some cases to authorise research with regards to patients who are subject to the provisions of the Mental Capacity Act. (vi) at paragraph 3.47, giving the IRBs the ability the power to authorise research for valuable research involving recruitment of highly compromised patients who are unable to give consent and for whom no proxy is available to give consent. (vii) at paragraphs 4.12 and 4.18, the IRB is tasked to formulate formal procedures in consultation with the institution with regards to the release of medical records and other personal information. (viii) at paragraph 4.16, the IRB is tasked with the responsibility of considering the suitability of the extent and means of the With the increased roles and responsibilities on the IRB, the onus on the Institutions would also increase to ensure that there is proper training provided for members of the IRBs. It may well then be that there is a greater need to have a properly defined appeals mechanism.
			Consent Involving Children
9.	3.22	Consent v Assent	We are generally not in favour of introducing a concept of either assent or consent of children below the age of majority. As noted under the Guidelines, "*in Singapore, there is no clear legal standing for assent as a procedure…*". Such a procedure may therefore be confusing to a researcher who is tasked toobtain such assent. In the case of consent from children, it is similarly submitted that such a concept may not be that clear under Singapore law. Whilst common law recognises the concept of "Gillick" competency, there does not appear to be very clear guidelines for consent by minors for participation in clinical trials or research involving human subjects, since, as is noted in the BAC's general principles, there may not be actual benefit to the child in consenting to the trial, as opposed to consent for treatment.

Annexe C

S/No.	Para No.	Subject Matter	Comment
			Further, Regulation 11 of the Medicines (Clinical Trials) Regulations ("**Clinical Trials Regulations**") provides that that a person under the age of 21 shall not be a subject in a clinical trial unless consent is obtained from the subject's parent, guardian or legal representative. There is no corresponding requirement for consent (or assent) to be obtained for the trial. Whilst we do not advocate that consent or assent be a requirement, we agree that it is important that proper explanation be given to the child and that the IRB should ensure that such a requirement is set out in the protocol and the form of informed consent to provide that whilst ultimately it is the parent, guardian or legal representative who gives the consent, efforts should be made by the researcher to involve the child in the informed consent, but it should stop short of requiring consent or assent.
10.	3.44 and 3.45	Consent from child in addition to consent from parent for research	We also note that the BAC has recommended that for research on subjects below 21 years and involving more than minimal risks, such as those with invasive procedures, consent from parents should be obtained, in addition to consent from the child. However, for research on subjects below 21 years that does not involve more than minimum risk, the IRB should be able to waive parental consent. The Guidelines however are silent as to whether child consent is still required, and the implication may be that whilst the IRB may be able to waive the need for parental consent, the consent from the child may still be required. We also note that under paragraph 3.45, clinical research that has a reasonable expectation of benefiting a child might be allowed to proceed even without the child's consent, if the parents give consent. We have two suggestions: (a) First, we suggest that the Guidelines make clear that such waivers by the IRB in paragraph 3.44 can only apply in the case where the research is not regulated under the Clinical Trials Regulations. Otherwise, an anomaly may arise in a case where there may be a clinical trial which may not involve more than minimal risks (i.e. a non-invasive clinical trial), and IRB may waive a requirement for parental consent, which is required under Clinical Trials Regulations.
			(b) Secondly, on the assumption that consent of the child is a requirement in all research involving children (we have advocated above that there should not be such a requirement), we suggest that it should be the consent of the child that is waivable, rather than parental consent. Otherwise, there may an inadvertent displacement of the authority of the parent over the child, where the child may agree to participate, but where the parent may not. For example, it is likely that a parent would still need to be involved in the child's participation in the research (such as arranging for the parent to be present for the research or tests to be carried out, etc). The parent's wishes should be respected in such a case. This position would also be consistent with the position articulated in paragraph 3.45 and therefore does not run the risk of creating many different layer of consents (for invasive research, for non-invasive research, and for clinical research). As important as it is to take into consideration the views of the minor who will be subject to the research, an approach requiring both consent from the minor and parent may pose a potential problem in situations where the parent consents to the research and the minor does not. In the event of a deadlock, would the parents' decision trump that of the minor, and if so, what purpose would there be in having both the minor and parent give consent to the research?

S/No.	Para No.	Subject Matter	Comment
			Use of Personal Information
11.	4.12, 4.13 and 4.18	Use of Medical Records for Research	We note that the BAC has recommended that appropriate access be given to suitably qualified professionals for the purpose of research. We note that the BAC Guidelines are silent on whether there is a need to obtain consent from patients before the release of such medical information. Whilst the BAC does advocate that the Healthcare Institutions and the IRBs formulate clear procedures for the release of such medical records and other personal information, we suggest that the Guidelines should make clear that all such access must be subject to IRB approval (similar to the need to obtain IRB approvals for other forms of research and which would be in line with paragraph 4.15 of the Guidelines).
			Tissue Banking
12.	5.8	Guidelines on Human Tissue Research	We note that the Guidelines provide that all research involving human tissue, whether identified or de-identified, should be reviewed by an IRB and approved before it commences. At present, we understand that tissue banks are required to be licensed under the PHMC Act. We note that under the Guidelines for Healthcare Institutions promulgated pursuant to Regulation 4 of the Private Hospitals and Medical Clinics Regulations ("**PHMC Regulations**"), the term "Tissue Banking" is defined as "*the activities of donor screening, procurement, processing, storage and distribution of human tissue intended for transplantation into a human*". The term "tissue bank" or "tissue banking" does not appear to be defined in the PHMC Act or the PHMC Regulations. Accordingly, it is not clear if it is only tissue banks that deal with organs for transplantation (and not tissue banks in general (or biobanks for that matter)) that would need to be regulated under the PHMC Act. The question thus arises as to whether a private tissue bank dealing with tissue banking only for purposes of research and not for transplantation would necessarily fall within the jurisdiction or purview of a hospital's IRB. If it does not, then the requirement that all research involving human tissue be approved by an IRB may be hard to be implemented in practice.
13.	5.41	Imported Tissue	We also note that the Guidelines require researchers to obtain written assurance from the source authority when dealing with imported human samples that the samples have been ethically and legally obtained, and that the test of ethical acceptability would seemingly be the Singapore ethical standards. We suggest that this requirement be removed. We understand that typically, tissue imported from overseas laboratories and institutions are usually done by way of Material Transfer Agreements, and such samples are usually provided on an "AS IS, WHERE IS" basis. Accordingly, it would be an uphill task to require these overseas laboratories to provide written assurance of any form that the samples have been ethically obtained according to their ethical standards. Furthermore, it appears that the applicable ethical standards are that of Singapore. Given that these are foreign laboratories, it is hard to conceive that the foreign laboratories would be prepared to give any such assurances at all.

Annexe C

11. Member of the Public (1)

27 July 2012

From the press report and brief look at the provisions related to children, I am deeply concerned about the waiver for consent for persons under 21 years if the risk equates with minimal risk. I think this is far too lax a standard.

(1) The concept of "minimal risk" is poorly defined in current ethical guidelines in Singapore, and elsewhere. More importantly, empirical research has indicated that leaving the matter to IRB "judgment" is simply to invite significant variation of interpretation of what amounts to minimal risk. The indications in the proposed guidelines are simply insufficient considering the potential gravity of the issues involved.

(2) Secondly, parental consent is not relevant simply because of various risks involved in the research, but also out of basic respect for parental responsibility and the implications participation might have on the child's daily routines and so forth. None of this seems to be appreciated by para. 3.26 and I fear that it may open the door to unwise waivers. One possible additional caveat to the waiver should be that the research could not reasonably be undertaken if parental consent were insisted upon, and this would be detrimental to the public health interest or the general public interest. I understand that this is already the view taken by some local IRBs.

(3) In short, more detailed guidelines are necessary on such an important issue as waiver of parental consent, which the law considers as a first line of defence in protection of a child's interests.

Finally, I have written in some detail on these issues in the context of minors and biomedical research. I attach these articles if they have not already been referred to, and might be of some use to the BAC. The relevant portions in the Singapore Academy of Law Journal article are 44- 50.

---

12. Member of the Public (2)

21 and 29 July 2012

Summary of Main Revisions

"The BAC recognises this importance and is of the view that research institutions have a responsibility to ensure that the requirements of research integrity are observed. The BAC has recommended that there be an appeal mechanism, to allow the Principal Investigator to make an appeal for reconsideration of their proposals if they are not approved by an IRB. Institutions would be responsible for ensuring that such a mechanism is in place."

Question: Drawing along the same parallels, property agents in Singapore used to be unlicensed and if they misconduct themselves, it is up to the companies to decide their own disciplinary action. Sometimes, these companies mete out different standards of punishment such as dismissal, suspension or a written warning letter. In addition, the so-called 'disciplinary committee' usually consist of a more senior staff who will have the unfeterred sole decision to do what he/she prefers while the rest will usually be the silent majority.

After several complaints from members of public, a new statutory board Council for Estate Agencies was set up to hear grievances and allow them to investigate complaints while at the same time, help be a bridge of communication and to increase public trust between consumers and property agents.

They also help to standardise the system by having a demerit point systems for each property agent so that the process will be clear and transparent.

IRBs in Singapore usually consist of members who have full time day jobs. Quite a lot of them may not have enough training or time to fully assess the merits of each projects.

Research institutions are may not be truly capable of having a good IRB in place. Having a centralised IRB with full time staff with adequate training allows more transparency and accountability while at the same time, maps out the common similarities between researchers and research participants. Moreover, it disallows researchers and PIs from shopping around any research institution in Singapore.

For example, HSA Singapore already regulates and enforces clinical trials in Singapore and metes out punitive action to manufacturers or importers of poorly made medical devices or harmful pharmaceuticals. In UK, HRA Health Research Authority was set up in 2011 Dec to look into this issue.

HRA UK allows the blowing of whistle from research participants but at the same time, it helps gather patient advocacy groups as a one-stop service so that research institutions can forward to having a more cohesive adequately informed patient advocacy groups rather than having to hunt or source for research participants. May I know if there is a consideration along this line?

In your ethical guidelines that "3.17 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 tissue for research."

Annexe C

My working place needs many research participants who serve as control groups. As a result, many researchers need to 'advertise' around and ask if their friends, families or spouses are willing to donate their time for research purposes. Many fear reprisals. Even when there was an assurance that it is not true, there were rumours that it could turn up in other ways such as a delay in promotion, or lower bonuses or getting marked down or denied opportunities later.

In reality, it is quite difficult to even get independent third parties. Presently, many researchers already have difficulties to get people to be the controls for their research. To get independent third parties will be an additional obstacle. It is necessary but in reality, it will be hard to implement on the ground level.

In addition, many researchers are not even familiar with the various Acts and ethical guidelines proposed by BAC. Especially for visiting investigators, genuine safety lapses may occur as they may not be well-versed in the guidelines. Unless they are forced to attend some courses in this area, it is likely that they may not know what the boundaries are until they are scrutinised by their IRBs or have infringed the guidelines.

Having a one-stop centre may help solve this problem. This one-stop centre could oversee all the research institutions. This one-stop centre could help to disseminate information to researchers and research participants and form a bridge of understanding while at the same time, enforce the guidelines in the research. All guidelines or Acts will not achieve its full effect if there is no concerted effort to implement or enforce it through a single body.

In addition, this one-stop centre could be the independent third parties. Many research participants are scattered all over and a researcher will usually have difficulty finding suitable candidates.

For example, the CHIP trial in 2008- (http://www.chip.sg/) "CHloroquine for Influenza Prevention" - is a new drug trial in which chloroquine, a simple and well-known medicine, might prevent flu. It was advertised widely in the press which costs more than S$10K to have a coverage in Straits Times. This money could have been saved if there was a one-stop centre to help disseminate the information through their established network.
