

ANNEX A

**CONSULTATION PAPER:
ETHICS GUIDELINES FOR HUMAN BIOMEDICAL
RESEARCH**

ETHICS GUIDELINES FOR HUMAN BIOMEDICAL RESEARCH

FOR COMMENTS

BIOETHICS ADVISORY COMMITTEE

SINGAPORE

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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. 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.”¹ Although the observations and clinical experiences of medical practitioners and others have been vital in the history of medicine, the systematic scientific foundations are also essential. While good medical practice entails far more than the mechanical application of science, good biomedical research is fundamental to its success, and is a safeguard against unsubstantiated or harmful claims. Biomedical research in general is thus regarded by the BAC as a public good.

1.8 Biomedical research has been defined as research having as its purpose the enhancement or improvement of medical practice.² This extends the scope of biomedical research beyond research that is clinical, and it could include research that does not use human 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:

¹ US Department of Health and Human Services, 45 CFR 46.102(d).

² Levine, RJ. The Nature, Scope, and Justification of Clinical Research. In Emanuel, EJ *et al.* (Eds.) *The Oxford textbook of clinical research ethics*. Oxford: OUP (2008), page 211.

- (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
 - (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.³
- 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.

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

- 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 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) (2005Ed.): 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),⁴ 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.

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.

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

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,⁵ 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);

⁵ 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 acknowledges 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.

- (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. 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.⁶ Their welfare and interests are to be protected, especially when their autonomy is impaired or lacking. This principle mandates the need for informed consent to participation in research; respect for privacy; 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

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

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.

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.⁷ 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.⁸

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

⁸ An obvious example would be a participant in a placebo control group.

- 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.⁹ It appeals to moderation and good sense in the determination of prohibited actions and the avoidance of micro-management and over-determination. The risk in any acceptable programme of research, and the 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 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

⁹ See for example the discussion of proportionality in Harris, B. *Disciplinary and Regulatory Proceedings*, 6th Ed. London: Wiley & Sons (2011). The essential legal burden on the court was stated 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.

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

2.16 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.¹⁰ 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.

Research Integrity

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,¹¹ research integrity is not a simple concept. Essentially it is thought of in terms of the following components:

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

¹¹ More information on the World Conference on Research Integrity can be found at: <http://www.singaporestatement.org/>

- (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.
- 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 entitled “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.

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.¹²
- 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;

¹² Ministry of Health, Singapore, *Operational Guidelines for Institutional Review Boards*. 2007.

- (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;
 - (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.¹³ 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

¹³ 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.

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, deception¹⁴ 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.

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.

¹⁴ 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.

- 3.9 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,¹⁵ 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:
- (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

¹⁵ 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.”

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.¹⁶ 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 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

¹⁶ 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.

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).¹⁷

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

¹⁷ This contingency has been considered by the UK MRC Ethics Guide: *Medical research involving adults who cannot consent*, 2007 (section 4.3).

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;
 - (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).

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.

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 information. The principle of proportionality applies, such that the level of care and urgency regarding de-identification and data protection should be consistent with the sensitivity of the data. IRBs should consider the suitability of the extent and means of the de-identification in proportion to the risk.
- 4.17 Researchers should safeguard all information used and derived in research and take adequate measures to prevent inadvertent identification of individuals. Should an individual be identified inadvertently from de-identified information, the confidentiality and privacy rights of this individual should not be regarded as abrogated by such identification, and steps should be taken to reinstate and secure them.
- 4.18 Healthcare institutions should ensure that clear formal procedures are laid down for the release of medical records and other personal information for research, and to formulate these procedures in consultation with their IRBs.
- 4.19 IRBs may waive the consent requirement for the use of personal information for epidemiological or public health research, or the use of medical records for research, if they are satisfied that the following conditions are met:

- (a) The research is justified and poses no more than minimal risk to 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, fetuses, 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.¹⁸ 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.

- 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.

¹⁸ Medical Research Council, UK. *Human tissue and biological samples for use in research: Operational and Ethical Guidelines* (2005), paragraph 2.1.

- 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 *mutatis mutandis* 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 *in vitro* 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 embryos¹⁹ 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 the research. In the case that the researcher is also the attending physician, the IRB may give directions for the

¹⁹ 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.

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 2002.²⁰ 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.

²⁰ "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.²¹ 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.

²¹ The report *Novel techniques for the prevention of mitochondrial DNA disorders: an ethical review* was published in June 2012.

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;
- (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 fetuses²², which offers an in-principle possibility of a degree of humanisation of the resulting brain. In this case, six relevant factors have been suggested²³ 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;
- (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) *he 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.

²² Ourednik V *et al.* Segregation of Human Neural Stem Cells in the Developing Primate Forebrain. *Science*. 293 (2001): 1820-1824.

²³ Greene M *et al.* Moral Issues of Human-Non-Human Primate Neural Grafting. *Science*. 309 (2005): 385-386.

- 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.

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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