

RESEARCH INVOLVING HUMAN SUBJECTS

GUIDELINES FOR IRBs

PART A: INTRODUCTION AND CURRENT FRAMEWORK

SECTION I: INTRODUCTION

1. Introduction

About these Guidelines

- 1.1. The Bioethics Advisory Committee (BAC) was appointed by the Cabinet to examine the potential ethical, legal and social issues arising from research in the biomedical sciences in Singapore, and to recommend policies to the Life Sciences Ministerial Committee.
- 1.2. These Guidelines are issued by the BAC and were prepared by the Human Genetics Subcommittee (HGS). The members of the HGS are detailed in Annexe A.
- 1.3. These Guidelines are the third of a series of recommendations submitted to the Government by the BAC. The first set of recommendations issued by the BAC dealt with human embryonic stem cell research and cloning. These recommendations were issued in a Report entitled “Ethical, Legal and Social Issues in Human Stem Cell Research, Reproductive and Therapeutic Cloning” (“Human Stem Cell Report”) in June 2002. The second set of recommendations dealt with issues arising from human tissue banking and human tissue research and was issued in a Report entitled “Human Tissue Research” (“Human Tissue Research Report”) in November 2002.

- 1.4. These Guidelines were shaped and informed by feedback and suggestions received by the BAC on a Consultation Paper entitled “Advancing the Framework of Ethics Governance for Human Research” released on 16 September 2003 to 37 bodies concerned with the ethics governance of human biomedical research. The Consultation Paper is set out in Annexe B, the 37 bodies are listed in Annexe C and the responses to the Consultation Paper are set out in Annexe D. Annexe E is a summary of the dialogue session with the hospital ethics committees or institutional review boards (IRBs), which was held on 7 November 2003.
- 1.5. Where common ground is covered in these Guidelines and the earlier Reports issued by the BAC, it should be understood that the more particular and specific recommendations made in the earlier two Reports in relation to human embryonic stem cell research, human cloning and human tissue research should prevail.

Objectives

- 1.6. Our objectives in advancing these Guidelines are:
 - (a) To review the current system of ethics governance of human biomedical research in Singapore, with particular focus on the processes and procedures;
 - (b) To advance recommendations and operational guidelines on the constitution and role of ethics committees or IRBs in the process of ethics governance of human biomedical research; and
 - (c) To provide guidance in Singapore for the promotion of ethically responsible human biomedical research conforming to the best international standards and practice.

SECTION II: THE CURRENT FRAMEWORK

2. The Current Framework

The Background

- 2.1. In Singapore and other technologically advanced societies, advances in biomedical technology and knowledge have been the main foundation for the vast improvement in health, life expectancy and the quality of life of the general population. These advances represent some of the principal achievements in the modern history of the human race. In the main, such advances in biomedical knowledge have been beneficial and are considered to be research conducted in good faith for the benefit of humankind.
- 2.2. Events during World War II, however, gave rise to concerns that research conducted on human subjects should be subject to agreed ethical norms. The Nuremberg Code¹ was born out of these concerns and represents the first universally accepted code spelling out the minimum content of the ethical norms governing the conduct of research on human subjects.
- 2.3. These ethical norms were given full consideration and description in the World Medical Association's Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects,² which since its adoption by the 18th World Medical Association General Assembly at Helsinki, Finland, has become universally accepted as the core body of ethical norms governing human research.
- 2.4. The principal theme of the Helsinki Declaration is that the life, health, privacy and dignity of the human subject in biomedical research are the first considerations before all others. To this end, the Helsinki Declaration advocates safeguards such as the principle of freely given informed consent of the human subject and the need for rigorous scientific assessment of the risks to the human subject in relation to the benefit sought to be gained from the research.
- 2.5. One of the basic principles enunciated in the Declaration of Helsinki is spelt out in Article 13. This provides that the "design and performance of

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

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

each experimental procedure involving human subjects should be clearly formulated in an experimental protocol” and that this protocol should be submitted to an independent ethics review committee for “consideration, comment, guidance, and where appropriate, approval.”

- 2.6. The basic principles of the Declaration of Helsinki have been long accepted by the medical community in Singapore and by other medical communities in the great majority of nations. In Singapore, the need for ethics committees or IRBs and the requirement for the ethics review of research proposals involving human subjects have long been an accepted and integral part of biomedical research in the institutional setting.
- 2.7. The principles of the Declaration of Helsinki today find expression in regulatory standards and practice guidelines governing various aspects of clinical research such as those contained in the Medicines (Clinical Trials) Regulations, promulgated pursuant to Section 74 of the Medicines Act (Cap. 176), the “Singapore Guideline for Good Clinical Practice” (SGGCP) and the “Ethical Guidelines on Research Involving Human Subjects” (NMEC Guidelines) issued in August 1997 by the National Medical Ethics Committee (NMEC). We discuss these regulatory standards and practice guidelines in detail below.

Pharmaceutical Trials in Singapore

- 2.8. In Singapore, pharmaceutical trials involving the testing of drugs on human subjects are regulated by the Health Sciences Authority (HSA). The HSA regulates the conduct of pharmaceutical trials under the Medicines Act and the Medicines (Clinical Trials) Regulations (2000, Revised Edition). Under the Medicines Act, these pharmaceutical or drug trials are known as “clinical trials”.
- 2.9. The system of regulation requires that sponsors and researchers conducting pharmaceutical trials obtain both ethics and regulatory approval before initiating a study.
- 2.10. The current approval system is sequential. Approval from the HSA is sought only after the relevant hospital ethics committee has approved an application. Regulatory approval is provided in the form of a Clinical Trial Certificate issued by the HSA to the applicant.
- 2.11. The HSA, in deciding the regulatory approval for a pharmaceutical trial, consults an expert advisory committee known as the Medical Clinical Research Committee (MCRC). The MCRC is an “independent body constituted of medical members, whose responsibility is to ensure the

protection of the rights, safety and well-being of human subjects involved in a trial ... and documenting informed consent of the trial subjects” (Section 1.37 of the SGGCP). It currently comprises five members, all of whom are clinical specialists.

- 2.12. In this way, pharmaceutical trials are subject to ethics review at more than one level.
- 2.13. Additionally, pharmaceutical trials are also required to conform to the SGGCP issued by the MOH in 1998. The SGGCP is a set of guidelines adapted from the 1996 “Guideline for Good Clinical Practice” of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH GCP Guideline), which is the international gold standard for conduct of pharmaceutical trials. Accordingly, the SGGCP reflects best international practice in its approach to the governance of pharmaceutical trials. Since 1998, the SGGCP has been incorporated by reference in Regulation 21 of the Medicines (Clinical Trials) Regulations. Sponsors and researchers in pharmaceutical trials are required by law to comply with the SGGCP unless specifically exempted under the Medicines (Clinical Trials) Regulations.
- 2.14. The SGGCP sets out in detail a framework for the ethics governance of pharmaceutical trials. The SGGCP begins its statement of applicable principles by declaring that “[c]linical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki” (Section 2.1).
- 2.15. Section 1.12 of the SGGCP treats the terms “clinical trial” and “clinical study” as being synonymous, and defines them as being any “investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy.”
- 2.16. The SGGCP sets out detailed guidelines as to the roles and duties of researchers and sponsors in a pharmaceutical trial, and lays down requirements such as monitoring procedures, audits and other matters to be included in trial protocols.
- 2.17. Of note are the provisions in Part 3 of the SGGCP requiring all pharmaceutical trials to be reviewed and approved by the hospital ethics committees concerned and the MCRC of the HSA before a Clinical Trial

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

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

Human Biomedical Research other than Pharmaceutical Trials

The Ethics Governance of Human Biomedical Research other than Pharmaceutical Trials

- 2.19. While the ethics governance of pharmaceutical trials in Singapore is comprehensively and appropriately regulated by statutory rules and practice guidelines, the picture for the ethics governance of human biomedical research other than pharmaceutical trials is less clear.
- 2.20. Currently, there is no statutory scheme for the ethics governance of human biomedical research apart from pharmaceutical trials. In Section III, we define and explain “Human Biomedical Research”.
- 2.21. Indirectly, however, the MOH has long exercised jurisdiction over, and given informal ethical guidance on, human biomedical research carried out in hospitals, clinics and clinical laboratories in its role as the statutory regulator under the Private Hospitals and Medical Clinics Act.
- 2.22. In January 1994, the MOH set up the NMEC, a national-level policy advisory body, to “assist the medical profession in addressing ethical issues in medical practice and to ensure a high standard of ethical practice in Singapore.”³
- 2.23. One of the objectives of establishing the NMEC was to “identify and study ethical issues relating to medical practice and research in Singapore and to provide an ethical framework for medical practitioners to carry out their duties and responsibilities.”⁴

³ “National Medical Ethics Committee: A Review of Activities, 1994-1997” published in 1998, page 1

⁴ Ibid.

- 2.24. Several sets of ethics guidelines were issued by the NMEC and adopted by the MOH. In the sphere of ethics governance of human biomedical research, the most significant of these ethics guidelines is the NMEC Guidelines.
- 2.25. In a written directive dated 25 June 1998 (Directive), the MOH required all government and restructured hospitals to set up hospital ethics committees (if they had not already done so) for the ethics governance of research involving human subjects. Before 1998, the practice of reviewing research proposals involving human subjects by hospital and medical institution ethics committees in Singapore was not governed by any formal rules or directives.

- 2.26. We quote from the Directive:

“The National Medical Ethics Committee has recommended that:

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

The Ministry has accepted these recommendations.”

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

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

The Future of Human Biomedical Research

- 2.30. Until recently, the vast majority of human biomedical research (whether pharmaceutical trials or research other than pharmaceutical trials) were carried out by researchers who were medical practitioners registered under the Medical Registration Act (Cap. 174), in government medical institutions directly controlled by the MOH or in hospitals and medical clinics licensed under the Private Hospitals and Medical Clinics Act. In all of these cases, the competent supervisory authority was the MOH.
- 2.31. In recent years, however, the development of the biomedical industry in Singapore has led to an increasing proportion of human biomedical research other than pharmaceutical trials. In 2002, for example, hospital ethics committees of the five main restructured hospitals reviewed nearly three times as many applications for such research as they did for pharmaceutical trials.
- 2.32. Human biomedical research increasingly tends to be institution-driven, rather than being researcher-driven (the traditional model assumed in the current regulatory regime). Institution-driven pharmaceutical trials received by the HSA now outnumber researcher-driven pharmaceutical trials.
- 2.33. Concomitantly, an increasing proportion of human biomedical research is now conducted outside the traditional paradigm assumed by the current regulatory environment: many research projects are now led by researchers who, although being qualified and competent for the research proposed by them, are not medical practitioners registered under the Medical Registration Act, or by researchers who work in or for entities not subject to the regulatory jurisdiction of the MOH. Such entities include companies and other commercial entities in the biomedical industry, research institutes and statutory agencies with an interest in the biomedical industry.

- 2.34. The vast majority of these new players in the field of human biomedical research in Singapore are keenly aware of the need for proper ethics governance. Most researchers are anxious to conform to internationally accepted standards for ethics governance. In many cases, researchers are involved as collaborators in multinational or multi-centre (or both) biomedical research projects.
- 2.35. With the development of the biomedical sector in Singapore, new avenues of biomedical inquiry are rapidly emerging. The traditional categorisation of research for ethics governance, which separates research into pharmaceutical trials and non-pharmaceutical trials, is becoming irrelevant and obsolete. Some new kinds of research may blur the border between these two categories. New kinds of biomedical research include trials of medical devices, experimental therapeutic procedures (which may or may not involve drugs), new modes of non-drug treatment and new diagnostic methods. Other increasingly important research includes epidemiological or population studies (which may or may not require invasive interaction with human subjects), genetic screening, genetic research and research that involves no direct interaction with human subjects but only access to their medical, personal or genetic information.