

PART B: HUMAN BIOMEDICAL RESEARCH

SECTION III: HUMAN BIOMEDICAL RESEARCH

3. Human Biomedical Research

Defining Human Biomedical Research

- 3.1. In this section, we consider what kinds of human biomedical research ought to be subject to the framework of ethics governance that we recommend in these Guidelines.
- 3.2. In keeping with our terms of reference, we consider only such human biomedical research that involves an interaction (whether direct or otherwise) with a human subject or human biological material, and therefore exclude any human biomedical research in relation to:
 - (a) Genetically modified organisms;
 - (b) Animals and their treatment; and
 - (c) Economic, sociological and other studies in the disciplines of the humanities and social sciences.
- 3.3. Human biomedical research is a term capable of a very broad definition. In our review of the approaches taken by national ethics bodies or agencies in other countries, we have found that there is considerable variation in what is to be included in the definition of human biomedical research coming within the purview of institutional ethics review bodies. For example, in some jurisdictions, ethics committees are required to review proposals for sociological research or humanities-based research if they involve human subjects, while in other jurisdictions this requirement does not apply.
- 3.4. Currently, there is no international agreement on the exact scope of human biomedical research that should be subject to IRB review. But that is not to say that there is no agreement at all on what should be subject to IRB review. Clearly, there is universal and unanimous agreement in all reputable research communities that research involving direct physical interference or interaction with human subjects, and where such direct physical interference or interaction may result in death, injury or other physical or emotional harm to the research subject, must be subject to proper IRB review. These core values and principles are captured in international documents such as the Nuremberg Code, the Declaration of Helsinki and the ICH GCP Guideline.

- 3.5. At the edge of this core of certainty, however, international consensus is still in a state of development. Increasingly, human experimentation and human biomedical research have moved away from direct physical interference or interaction with human subjects themselves, towards research conducted largely on cell lines, tissues or other bodily samples given by human donors, and on medical information derived from patients and other human subjects.
- 3.6. Increasingly, it is the case that there is no direct physical contact at all between the researchers and the human subjects. In such circumstances, there is no possibility of physical injury or harm befalling the human research subjects. In these situations, the ethical, legal and social concerns centre not on the possibility of physical injury or harm but on the larger penumbra of *indirect* harms to the patient or donor such as the breach of the patient's or donor's expectation of confidentiality of his medical information, or his expectation that his tissue should not be used for research without his consent.
- 3.7. It is therefore appropriate that a fundamental distinction be made between:
- (a) Direct Human Biomedical Research. This comprises any kind of human biomedical research that involves any direct interference or interaction with the physical body of a human subject, and that involves a concomitant risk of physical injury or harm, however remote or minor. A research programme which involves the administration of any drug (whether it is for the purpose of testing the effects or efficacy of the drug, or whether it is a means for establishing any other objective of the research programme), the trial or use of a medical device on a human subject, or any test of a human subject's physiological, emotional or mental responses (not being tests conducted for diagnostic purposes with a view to the therapeutic management of a patient) all qualify as Direct Human Biomedical Research; and
 - (b) Indirect Human Biomedical Research. This comprises any research (not qualifying as Direct Human Biomedical Research) involving human subjects, human tissue, or medical, personal or genetic information relating to both identifiable and anonymous individuals, undertaken with a view to generating data about medical, genetic or biological processes, diseases or conditions in human subjects, or of human physiology or about the safety, efficacy, effect or function of any device, drug, diagnostic, surgical or therapeutic procedure (whether invasive, observational or otherwise) in human subjects whether as one of the objectives or the sole objective, of the research study, trial or activity, and which research, study, trial or activity has

the potential to affect the safety, health, welfare, dignity or privacy of the human subjects involved in the study, or of the donors of human tissue or information used in the research, or of the family members of any of the human subjects or donors thereof, or to which such medical, personal or genetic information relates.

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

Ethics Review of Direct Human Biomedical Research

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

Ethics Review of Indirect Human Biomedical Research

- 3.10. There is currently no international consensus on what kind of Indirect Human Biomedical Research needs to be formally reviewed by an IRB. Laws, social attitudes and concerns, and ethical formulations vary from jurisdiction to jurisdiction.
- 3.11. Subject to the recommendations set out in our earlier Reports (the Human Stem Cell Report and the Human Tissue Research Report), we recommend that every research institute have clear policies for the ethics review (full, exempted or expedited review) of all categories of research involving Indirect Human Biomedical Research, as set out below.

Exempted Review and Expedited Review of Human Biomedical Research

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

Exempted Review

- 3.13. Exempted Review should in general only be permitted for categories that are widely accepted by the community as being eligible for Exempted Review.
- 3.14. There can be no hard and fast rule dictating which categories of Human Biomedical Research ought to be allowed exemption from review, and which categories ought to undergo full review. Each institution should determine for itself, after due deliberation and consultation with its IRB, the categories of Human Biomedical Research that could be exempted from ethics review. The most important consideration is that there should be no likelihood of harm to the research subject.
- 3.15. In general, we suggest that categories for Exempted Review should be drawn from categories of Indirect Human Biomedical Research. By way of illustration, the following categories of Indirect Human Biomedical Research could be considered for Exempted Review, taking into account current practice:
 - (a) Writing up or reporting of individual patients' clinical results by the patients' doctors, provided that the patients' consent for procedures and interventions in clinical management have been obtained and the patients' privacy protected, for example, the review of a clinical programme that includes demographic, clinical and outcome parameters, which are useful in the audit of the programme; or the review of a procedure or treatment (a surgical technique or drug treatment outcome) by a physician or surgeon, where the choice of the drug or technique is based on the clinical judgment of the physician or surgeon and on best practices and not on any randomisation procedure. Researchers who are not the attending physicians in the programme but wish to have access to such information should send their proposals to the IRB in the usual way;
 - (b) Research using appropriately designed data escrow or other arrangements in which personal or other identity information is securely withheld from researchers by a third party provider of information, there being no possibility of researchers by themselves being able to trace or reconstruct significant information on the identity of subject donor;
 - (c) Research using established commercially available cell lines or commercially available anonymous DNAs, RNAs and fixed tissues; and

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

Expedited Review

- 3.16. Some categories of research programmes may be permitted a less formal process of review than that of a standard full review. For example, the Chairperson or other IRB delegate(s) (the reviewer) may be empowered to conduct Expedited Review.
- 3.17. The same principles and general considerations set out above in relation to the categories of Human Biomedical Research that qualifies for Exempted Review also apply to IRBs' determination of categories permitted Expedited Review. Research qualifying for Expedited Review should present no more than minimal risks to research subjects.
- 3.18. By way of illustration, the following categories of Human Biomedical Research could be considered for Expedited Review, taking into account current practice:
 - (a) Minor changes to previously approved research;
 - (b) Annual reviews of previously approved research in which there has been little or no change in the on-going research;
 - (c) The analysis of patients' information without interacting with the patients. Researchers may be allowed access to medical records only if the IRB is satisfied that there is potential scientific / medical benefit of the research and that the researchers will take appropriate measures to protect the privacy of the individuals;
 - (d) The local portion (at the level of specific institutions) of a multi-centre or multinational research programme that has already received a full review and approval by the lead IRB (as elaborated in paragraphs 5.49 to 5.56 of this Report); and
 - (e) Research involving human tissues from tissue banks. IRBs must be satisfied that the tissues are obtained from a reliable source in which consent has been obtained for the tissues to be used for research and that the donor's privacy is protected.

Stem Cell Lines

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

Cadaveric, Foetal and Legacy Tissues

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

Therapy versus Research

- 3.21. In Section 2.2.1 of the NMEC Guidelines, it is stated that:

“Human research can be broadly defined as studies which generate data about human subjects which go beyond what is needed for the individual’s well-being. The primary purpose of research activity is the generation of new information or the testing of a hypothesis. The fact that some benefit may result from the activity does not alter its status as “research”. Defined in this manner, human research includes not only studies which involve human subjects directly, but also epidemiological surveys and reviews of patient records, for purposes not related to the patient’s immediate health care needs”.

- 3.22. In its Guidelines, the NMEC also considered the relationship and distinction between research and therapy. It held that when “an activity is undertaken with the sole intention of benefiting the patient, the activity may be considered to be part of “therapy”. The progressive modification of methods of diagnosis and treatment in the light of experience is a normal feature of medical practice and should not be considered as research. There could be potential conflicts between research (intended to generate new information) and therapy (intended to benefit the individual patient directly). Their resolution rests on the integrity of the physician /

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

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

Legal Considerations

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

Savings

- 3.27. We make clear that nothing in these Guidelines is intended to supplant the recommendations that we have made in the Human Stem Cell Report and the Human Tissue Research Report, and that the recommendations contained in these Guidelines are intended to supplement those advanced in our first two Reports.

Exceptional Situations

- 3.28. We note that there may be some exceptional circumstances in which it may be ethically acceptable to abbreviate or temporarily suspend the usual

ethics review procedures and requirements, provided that all the applicable legislative and regulatory requirements are satisfied. We have in mind situations of national security or emergency health situations, in which urgent research may have to be carried out to avert harm to national security or for the urgent protection or treatment of whole populations at risk. In such cases, it should be permissible for IRBs in consultation with the proper authorities such as the MOH, to formulate and lay down written guidelines for the exemption or expedited review of defined classes or types of such emergency or urgent research in the national interest.

- 3.29. We also exclude from ethics review procedures and requirements all clinical audit and quality assurance activities, which require the institution to review patients' information and are conducted for the sole purpose of improving the quality of patient care within that institution.
- 3.30. We therefore recommend that all Human Biomedical Research as defined in this section, save for the exceptions expressly provided above, be subject to review and approval by and to the continued supervision of an IRB in accordance with the principles discussed in Section IV.