

# Informed Consent Template and Guidelines on the Ethical Practice in Human Genetics and Human Genomic Research; Initiatives of the Universiti Sains Malaysia

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## Abstract

Malaysia is advancing and nearly on pace with the international scientific community in human genetics and human genomics research. However, this research poses unique challenges. Although Malaysia already regulates medical genetic services, these regulations are insufficient for coping with the ethical issues emerging from recent genomic technologies. The Universiti Sains Malaysia recently created in-house guidelines and an informed consent template for genetic and genomic research. This article presents these guidelines and the informed consent template and discusses the justification and the background of the initiative. We also propose recommendations pertaining to local social studies and regulatory arrangements.

**Keywords:** ethical, guidelines, informed consent, human genetics, human genomic, Malaysia

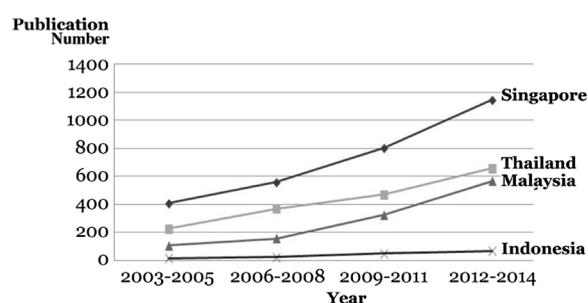
## Introduction

Figure 1 shows the number of publications for four South-East Asian countries per year since 2003, the year when the Human Genome Project was completed. Singapore, Thailand and Malaysia lead, with Singapore in first place. Figure 1 also indicates that since 2009, Malaysia has probably shown the sharpest increase in the number of publications per year when compared with Thailand and Singapore.

Figure 2 shows the proportion of the cumulative publication number from each country as of December 2014. Malaysia contributed 19%, which is a fair amount compared with Thailand's contribution of 28% and Singapore's 48%.

As a whole, the Malaysian research community is nearly on pace with other countries in human genetics and human genomics advancement.

Notably, the Malaysian Medical Council issued guidelines in 2006 that focused on genetic medical services (1). This important document



**Figure 1:** A line chart comparing the number of publications per year over a 12-year period since the completion of The Human Genome Project in 2003, which are indexed in PubMed ([www.ncbi.nlm.nih.gov/pubmed](http://www.ncbi.nlm.nih.gov/pubmed)) and from leading countries in Southeast Asia. The data were obtained for each country using the search expression ((human genetics) OR human genomics) AND "Country" [Affiliation] AND "YYYY/MM/DD" [Date – Publication].

provides guidance to health care providers, especially medical doctors, in Malaysia to address ethical and social issues in genetic medical services and genetic testing.

As a general statement, the guideline's foreword stated that the objective is to ensure "...that registered medical practitioners are fully aware of the codes of professional medical practice,..."(1).

The MMC Guidelines also outlined provisions relating to research, the banking of DNA specimens and the management of existing patient registries relating to medical genetic services.

However, at its initiation, the purpose of genetic research differs significantly from genetic services. Genetic services are generally intended to provide information to patients based on individual medical indication. Genetic research, on the other hand, is initiated to collect genetic/genomic data to fulfill the objective of the research.

The two may be intertwined. Genetic services may accumulate data in a clinical registry that could have research value. Genetic services may also retain DNA samples in a biobank, which could be utilised in later research. On the other hand, genetic research may obtain information which has clinical significance to individual research participants.

It is a reasonable assumption that research provisions in the MMC guidelines were intended for when the initial intention of genetic services changes into a research intention. It is therefore necessary to formulate an independent guideline that focuses on human genetic and genomic

research that also addresses cases in which genetic research uncovers information that has clinical significance to individual research participants.

Additionally, genomic sequencing and various technologies with the capacity to identify large amounts of genomic data at a reasonable cost in a relatively short period of time have created a unique range of ethical and social issues. Despite the existence of the MMC Guidelines, there is not yet a comprehensive guideline that focuses on the practice of genetics and genomic research and addresses the impact of newer genomic technologies. Such a guideline would provide important information to a much larger research community beyond medical doctors and other healthcare providers.

With the aim of formulating a more comprehensive guideline, the Universiti Sains Malaysia (USM) Human Research Ethics Committee (HREC) created an in-house guideline for the practice of genetic and genomic research at the University and provided a template informed consent form for such research. USM-HREC has recently been recognised by the Forum for Ethical Review Committees in the Asian and Western Pacific Region (FERCAP) as compliant with internationally accepted standards for ethics review of biomedical research.

### USM Guidelines on Ethical Issues in Whole Genome/Genetic Studies (The Guidelines)

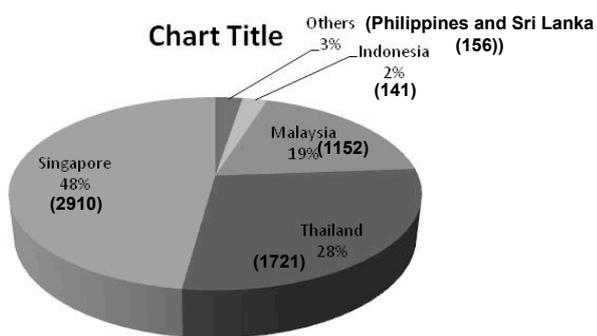
The Guidelines are divided into six chapters: definitions, general issues, consent, sample/data storage and withdrawal from research, disclosure of results, and public data release. One of the authors (THS) was invited to share the guidelines during the FERCAP Annual International Conference 2013 in Denpasar (Indonesia) (2).

#### Chapter 1 – Definitions

For the purposes of this guideline, the following terms are defined as:

- (i) Genetics: the study of heredity (3).
- (ii) Genomics: the study of the genome, its action (3), and related techniques (4).

Note: The World Health Organization (WHO) has emphasised that "the main difference between genetics and genomics is that genetics scrutinises the functioning and composition of a single gene whereas genomics addresses all genes and their inter-relationships in order to identify their combined influence on the growth and development of the organisms" (5).



**Figure 2:** A pie chart showing the proportion of the total number of publications from countries in Southeast Asia from 2003 - 2014. The data were obtained from the PubMed (www.ncbi.nlm.nih.gov/pubmed) using the search expression ((human genetics) OR human genomics) AND "Country"[Affiliation].

- (iii) Research: a process seeking to obtain generalisable knowledge.
- (iv) Clinical Service: the provision of health care services to patients based on clinical indications.
- (v) Data: Information about heritable or non-heritable characteristics of individuals obtained by the analysis of nucleic acids or by other scientific analysis (6).
- (vi) Consent: Any freely given specific, informed and express agreement by an individual to have his or her data collected, processed, used and stored (6).
- (vii) Samples: Any sample of biological material (for example, blood, skin and bone cells or blood plasma) that contains nucleic acids and the characteristic genetic make-up of an individual (6).
- (viii) Genetic counseling: A procedure to explain the possible implications of the findings of genetic testing or screening, its advantages and risks and, when applicable, to assist the individual in the long-term handling of the consequences; the procedure takes place before and after genetic testing and screening (6).

#### Chapter 2 – General Issues

1. Researchers are required to provide genetic counseling based on signed informed consent regarding the disclosure of research results and incidental findings.
2. Whenever applicable, genetic counseling should be incorporated into the research methodology and budget.
3. The involvement of genetic counselors should be highlighted within the research team OR included as part of the professional services.
4. With regard to genetic counseling, researchers are advised to refer to the Genetic Counseling section in the Malaysian Medical Council Guidelines (1).
5. Researchers are required to keep all samples and data that identify particular individuals confidential.
6. Researchers are required to inform participants about how their sample and data are kept (whether and how their samples and data will remain anonymous).
7. Researchers are required to inform participants that their genetic data may concern family members and members of their community because they may share genetic material.
8. Researchers are required to inform

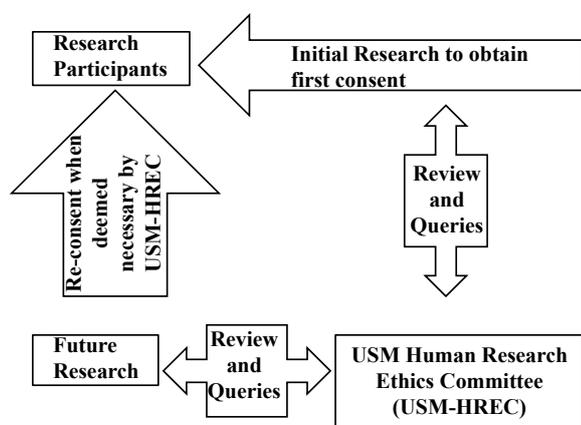
- participants about limitations in confidentiality efforts as well as situations of reportable conditions (such as HIV status) and the risks associated with the possible loss of privacy.
- 9. In the event that research and clinical services combine or overlap, clinical services must be prioritised.
- 10. Researchers are required to determine whether certain research results are clinically meaningful for the participants' and related family members' health and whether such results are worthy of disclosure.
- 11. Researchers are required to provide the option for participants to be informed about the research results.
- 12. Even in cases where researchers determine that disclosure is not necessary, participants retain the utmost right to retrieve their data. If participants' data are retrieved, researchers must provide sufficient information about their data disclosure decisions.
- 13. Research methodology is of the utmost importance in the context of the ethical conduct of research.
- 14. Researchers are required to ensure the accuracy, reliability, quality and security of the data and the processing of biological samples.
- 15. The Ethics Committee reserves the rights and responsibilities to assess study viability and provide pertinent recommendations.

#### Chapter 3 – Consent

16. Informed consent should involve a process of providing adequate information to potential research participants prior to their enrollment in a research study. Informed consent should not be undertaken merely for the purpose of collecting the required signatures of potential participants.
17. The informed consent process should consider the competence of research participants, the amount and the accuracy of information, and the ability of participants to understand the information. The process should also reflect participants' voluntariness and the active authorisation of the consent.
18. The informed consent document must be signed by prospective participants prior to enrollment in the study.
19. The informed consent form must include (but is not limited to) information on the

topic of the research, the names of the researchers involved, the proposed study procedure, the purpose of the study, the risks, possible benefits, incidental findings, the disclosure of research results, questions, confidentiality, the nature of likely future research activities, withdrawal from the study and signature pages.

20. Whenever applicable, information on associated commercialisation activities should also be included,
21. The scope of the consent must be well understood by researchers, research participants and the ethics review committee.
22. Because participants' data and samples are retained by researchers, the consent process should consider governance structure and mechanisms for evaluating future research protocols (Figure 3).
23. Ethical clearance is valid for only the research study for which ethical approval is granted. If researchers wish to use the same data and samples for a different study, fresh ethical approval must be



**Figure 3:** Guidelines; Governance Structure of Consent Procedure (Adapted from Caulfield et al. (9)). This figure illustrates the governance of consent in the use of nucleic acid samples. Researchers involved in initial research may differ from or be the same researchers involved in future research. Future research may use samples obtained from the initial research provided there is approval from the ethics committee. Depending on the ethics committee, re-consent may be required for the future research.

obtained. Whenever deemed necessary by the ethics committee, re-consent may be required (e.g., when the proposal deviates significantly from what was stated in the initial consent).

#### Chapter 4 – Sample/Data Storage and Withdrawal from Research

24. Participants' biological samples and data will be kept by researchers for the duration specified in the informed consent. Upon participants' consent, however, researchers may keep the sample and data for a longer duration. Researchers are responsible for an adequate storage system to ensure privacy protection.
25. Withdrawal from genetic/whole-genome studies is accomplished by sample destruction and data elimination as much as possible.
26. Researchers are required to inform participants of their rights upon withdrawal from research as well as limitations in the data elimination effort.
27. Researchers are required to inform participants about the mechanism for withdrawal.
28. If participants wish to withdraw, they can do so by contacting the Principal Investigator.
29. Although primary responsibility for proper withdrawal lies with the respective researcher, the ethics committee reserves the right to supervise the process.
30. Subsequent to sample destruction and data elimination, researchers must officially inform both the participant and the ethics committee.

#### Chapter 5 – Disclosure of Results

31. Researchers are required to determine whether study results (incidental or otherwise) meet the criteria for disclosure to individual participants. This determination is subject to approval by the ethics committee.
32. If researchers decide to disclose study results to individual participants, informed consent must include the expected time frame of the disclosure.
33. Sufficiently qualified professionals should be involved in the identification and disclosure of study results to ensure a correct understanding and interpretation of the information. Shared study results should be scientifically valid, confirmed

- and have significant implications for the health and well-being of the subject.
34. When applicable, the disclosure of study results should be incorporated into the research methodology and the budget.
  35. The involvement of related professionals for this purpose should be highlighted within the research team OR included as part of professional services.
  36. Researchers are required to inform participants of the option of receiving study results (incidental or otherwise) where knowledge for interpreting the results is currently available.
  37. Researchers are required to provide participants with the option to be re-contacted with study results (incidental or otherwise), where knowledge for interpreting the results is currently unavailable but may be available in the future.
  38. When applicable, plans to disclose or not to disclose other significant non-health related data (such as incidental findings of non-paternity) should be included in the study design and stated in the informed consent.
  39. The disclosure of results should be implemented in accordance with genetic counseling processes and principles.

#### Chapter 6 - Public Data Release

40. The use of public funds, resources and samples for research requires the return of the benefit to society at large when public data release of the research results is beneficial to the general public.
41. Researchers are required to provide a public data release policy in their study design/research methodology.

Example language [whenever applicable]:

*As a community resource project, the 1000 Genomes Project publicly releases data on a regular basis [or specify if the data will be stored in a database, specify what database]. The database is freely available to the public, thus enabling retrieval of the data by anyone [specify whether the database requires paid access]. However, there will be no personal identifiers submitted to the database. Once data are submitted to the database, it will not be possible to retract the data in the case of participant withdrawal. The sequencing centers release the raw reads to the Sequence Read Archive (SRA).*

*The Data Processing Group, Analysis Group, and Data Coordinating Center (DCC) release alignments, re-calibrated error rates, and SNP calls for individual samples. Data that pass the quality filters are the most visible, but data that do not pass quality filters are also available. When the Structural Variation Group has developed its methods, the structural variant calls on individual samples will be released. Eventually, the Project will release haplotypes and imputed variant calls. Data formats and analysis software developed by the Project will also be made publicly available. Data formats and analysis software developed by the Project will also be made publicly available. (Adapted from <http://www.1000genomes.org/data#DataReleasePolicy>)*

42. The data release policy must include (but is not limited to) the rationale and justification for the proposed data release policy, the database location of the data release, public coverage of the database, the implications of withdrawal, and the types and nature of the data to be released.
43. Informed consent must disclose the implications of the public data release to research participants, which includes issues associated with family members and relevant groups/populations, the likely finality of the release process and the implications that the release may have on privacy and the future right to withdraw.
44. Public Data Release policy is subject to approval by the ethics committee.
45. Researchers are required to comply with the DNA Act of 2009 (7) and inform the participants of the risk that, in the case that the participant becomes a crime suspect, the police may collect data from the researchers.

#### International perspectives

Although some variations were observed, the USM Guidelines considered the relevant provisions of other similar guidelines or recommendations internationally, such as the Bioethics Advisory Committee of Singapore (8), the UNESCO International Declaration on Human Genetics Data (6), the Consensus Statement on Research Ethics Recommendations for Whole- Genome Research (9), the WHO Consultant Reports on Review of Ethical Issues in Medical Genetics, the European Society of Human Genetics recommendations (ESHG) (11) and the

American College of Medical Genetics (ACMG) guidelines (12).

Given the high probability that the same samples and data will be used in future research, we adapted published recommendations regarding the governance structure and mechanisms for considering future research protocols (9). Consistent with this approach, the USM Human Research Ethics Committee adopted a policy regarding the use of human DNA that requires new ethical approval for the future use of samples and data and the possibility that re-consent may be required, depending on the possible benefit and/or harm from findings of the future use. This aspect, however, may be different from the WHO proposal on guiding the practice (10) where it suggested that “*A blanket informed consent...is the most efficient approach*”. Notably, the same statement appeared in the Malaysian Medical Council guidelines (1).

There seems to be some variation with regard to incidental findings. Similar to the standpoint of ESHG (11), our informed consent template includes a place where participants can indicate whether they wish to be informed of incidental findings. The ACMG (12) strongly encourages the disclosure of “medically actionable” incidental findings.

However, the ESHG recommendations (11) and ACMG guidelines (12) were intended for the clinical setting where diagnostic purposes and patients’ interests were initially sought. The context may be different with our guidelines because the original intention was the achievement of research objectives. Nevertheless, it is of our opinion that both contexts shall not prevail over or negate personal interests over clinically relevant incidental findings.

### **USM Informed Consent for Whole-Genome/Genetic Studies: Policy and Template**

We also formulated an informed consent template to help researchers build their own informed consent that is tailored to their specific research needs (<http://jepem.kk.usm.my/index.php/forms>). Even if the research is not genomic in nature, we found several clauses that may be useful to researchers.

### **Conclusion and Recommendations**

Herein, we have described our in-house guidelines for the ethical practice of human genetics and genomics research as well as an informed consent template for such studies. As

with any similar guidelines, this document should always consider local social and cultural factors. Thus, both (the guidelines and the informed consent template) are “living” documents that should accommodate the aspirations of the Malaysian public and the genetic and genomic research community. In this regard, research on the perceptions and attitudes of the Malaysian public and the research community on relevant issues are important and timely.

It has been widely discussed that genetic information is prone to abuse by third parties, leading to discriminatory treatment and loss of privacy, particularly by insurers and employers. Although this discrimination has not significantly materialised (13), it is worthwhile to explore the extent to which the Malaysian public perceives threats of discrimination arising from sharing their genetic or genomic information. Such perceptions may hinder participation in genetic research as well as consent to undergo medically necessary genetic testing. Similarly, it is timely to explore whether Malaysia has sufficient legal protections to guard against such potential discrimination.

Additionally, several regulatory arrangements are needed. A Regulation on Material and Data Transfer Agreement (MTA/DTA) is needed to facilitate collaborative research that involves the transfer of human biological specimens and data, including nucleic acids. MTA/DTA provide assurance that the rights and obligations of all collaborating parties pertaining to the specimens and data are protected, whether a dispute relates to intellectual property rights, the ownership of the specimens and data, publication rights, security and privacy concerns, scientific usage of the specimens and data, quality of the specimens and data, informed consent, usage of previous data and archived specimens, or disclosure of results to partner institutions and to individual donors of specimens. Recently, an International Charter of principles for sharing bio-specimens and data were published (14).

Finally, given the unique ethical challenges and the increasing research volume, it is time for the Malaysian scientific community to agree on a national guideline for research in human genetics and human genomics.

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### Authors' Contributions

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Critical revision of the article for important intellectual content: ZZH, NHO, HVR

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