POLICY REQUIREMENTS, PROCEDURES AND GUIDELINES FOR THE CONDUCT AND REVIEW OF HUMAN GENETIC RESEARCH IN MALAWI

[Sections 18 & 48 of the S&T Act No.16 of 2003]

National Health Sciences Research Committee

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1.0 INTRODUCTION

The benefits of human genetics research in promoting the health of mankind cannot be over-emphasised. For example, genetics research enhances the understanding of how genes and environmental factors interact to influence the health of individuals and communities. Gene localization and identification studies would be helpful in identifying genes in individuals or communities that cause or contribute to a disease/disorder or a trait. These types of studies including genetic screening and diagnostic studies have both the public health and therapeutic advantages to the participating individuals and communities. Thus, research in genetics has the potential to generate scientific knowledge that could improve the health of individuals and communities.

However, research in human genetics is internationally recognized as an area in biomedical research that poses greater concern for ethical, political, religious and cultural sensitivities and controversies than any other area in biomedical research involving humans. While genetic science and technology offers some benefits, it also has potential for risks of various harms not only for the individuals or communities that are participating in a genetic study but also families, populations and a country as a whole. Ethically and politically, genetic information (more than any other health information) could have harmful social consequences for individuals and countries when used in contexts such as employment, insurance and immigration. For example, cases have been reported of people with asymptomatic genetic predisposition who were excluded from employment or insurance and denied immigration status (Emanuel, EJ *et al*., 2003). Other risks of harm associated with genetics research include potential for stigmatisation and discrimination of certain individuals, families, tribes and societies besides psychosocial impacts all arising from use and careless disclosure of genetic information. As genetic research also involves family members, some family members may prefer not to be given genetic information that might provide knowledge of future health or health risks. In addition, other family members who are not blood relatives, such as partners and spouses, may have an interest in the genetic information because

of concerns about the health of the offspring. While potential risks of harm arising from genetic research could be several, the Government of Malawi does not prohibit the conduct of genetic research but requires concerned researchers and stakeholders to not only clearly articulate sound rationale/justification for the conduct of such studies but also to properly define steps and strategies of how they would obviate the risks of harm. It is important to note that Government of Malawi through "*The Government Policy Measures for the Improvement of Health Research Co-ordination in Malawi (2005)"* designated genetics research as one of the areas under studies of national interest because of the greater magnitude of the ethical, safety and political implications associated with such studies.

In establishing these requirements, great effort was carefully taken to critically review peer- reviewed and published literature on genetics research ethics and regulatory requirement. The application of such review was analytically contextualized into the Malawi setting. In addition, a number of relevant international conventions and declarations on the conduct of health research including the 2005 Universal Declaration on Bioethics and Human Rights as well as the Government of Malawi 2005 Policy Measures on the Improvement of Health Research Co-ordination and the 2003 Government of Malawi Communiqué to the UN on Malawi's Position on Human Cloning provided an integrated national framework in benchmarking the policy requirements, procedures and guidelines contained herein. These requirements apply to all researchers and stakeholders involved in human genetics related research to be conducted in Malawi. They, however, represent the minimum standards in the ethical and regulatory governance of genetics research in Malawi, and stakeholders are, therefore, required to adhere to them. These policy requirements, procedures and guidelines are lawfully made and enforced by **Sections 18 (1) and 48 of the Science and Technology Act No.16 of 2003.**

2.0 GENETIC RESEARCH GOVERNANCE STRUCTURE

2.1 Review Structure

The 2005 Government Policy Measures for the Improvement of Health Research Co-ordination in Malawi stipulates that any genetic research proposed for implementation in Malawi shall be reviewed by the National Health Sciences Research Committee (NHSRC) irrespective of the affiliation of the principal investigators (PIs) and collaborators for the said research. The NHSRC shall have the discretion of either, by itself reviewing the submitted genetic research protocol, or appointing a special *ad hoc* committee to conduct the review on its behalf. Such an *ad hoc* committee shall be responsible to the NHSRC. In the case of a review done by the *ad hoc* committee, feedback of decision to the applicant/PI shall be done by the Secretariat of the NHSRC. The appointment of such an ad hoc committee shall be done by the chairman of the NHSRC. Relevance of expertise, policy and regulatory experience and key stakeholder representation shall be the most important considerations. At a minimum, the ad hoc committee shall include **Chairman of the NHSRC; representative of the National Commission for Science and Technology; Ministry of Health; National Health Sciences Research Committee; College of Medicine Research and Ethics Committee; and any individual(s) with special expertise in the area of the proposed research**. This *ad hoc* committee shall monitor the study through to its conclusion.

2.2 Secretariat of the *Ad Hoc* Committee

Any *ad hoc* committee appointed for the purpose described in 2.1 shall be serviced by the Secretariat of the NHSRC.

2.3 Format and Submission of Protocols

All protocols shall be prepared in the required format of the NHSRC which is contained in the Procedures and Guidelines for the Conduct of Health Research in Malawi (2007) and shall be submitted for review in accordance with the application procedures which are available at the secretariat. **However, investigators shall be required to clearly state in their protocols the permissible category (or a combination thereof) under**

which a particular study is falling. The permissible categories appear in section 3.2 below.

3.0 SCOPE AND CATEGORISATION OF PERMISSIBLE AREAS OF GENETIC RESEARCH IN MALAWI

3.1 Scope

While medical genetics concerns the clinical decision made by a medical doctor to use genetic technology for the benefit of his or her patient, public health genetics is concerned with the systematic application of human genetic technologies to identify, prevent or ameliorate genetic conditions in whole populations or communities. Genetic testing, therefore, involves the decision to test an individual patient, while genetic screening involves a decision to systematically test a discrete population. While being cognisant of the on-going international debate and controversies in human genetics research, Malawi, while carefully informed by a series of stakeholder consultations at a national level, adopted her own policy and regulatory position on human genetics research that fits her own context. The policy and regulatory position is to promote only human genetics research which serves a clear medical and/or public health goal and utility. Only scientifically and ethically sound genetics research studies with clearly defined therapeutic and public health value shall be permissible for review, approval and implementation in Malawi, provided that all the minimum requirements for safeguards and considerations as set under section **4.0 below** are adhered to. As is the case in any health related research involving humans, ethical principles of *respect for persons; beneficence and justice* shall be the framework of principles within which researchers are expected to conduct their proposed genetics research. Review and approval of such studies by the NHSRC shall occur within this framework. Protocols of these studies shall be reviewed against all the important considerations and elements specific to research in genetics as described in sections **4.0 and 5.0 below**. Genetics studies that smack of elements akin to eugenic activities are not allowed in Malawi and must be avoided. In addition, the NHSRC shall expect researchers to design studies in the permissible areas that are in tandem with the National Health Research Agenda in Malawi.

3.2. Categories of Genetic Research

Research in human genetics is generally classified into three main categories, namely: gene localization and identification studies; genetic screening and diagnostic studies; and gene therapy studies. Because of differences in these categories, protocols of studies under each of them attract specific elements of review. These categories are briefly outlined below.

3.2.1 **Gene Localization and Identification Studies:** The intention of these studies is to identify genes that cause or contribute to a disease or trait. Done typically by first finding the approximate chromosomal position of the gene (termed gene-mapping), and then by determining the identity of the gene.

3.2.2 **Genetic Screening and Diagnostic Studies:** These studies include population based genetic research studies and protocols aimed at identification, among apparently healthy individuals, of those who are sufficiently at risk of a specific disorder or of those who are at risk of being a carrier of a gene that causes a genetic disease/disorder to justify a subsequent diagnostic test or procedure. These studies are also concerned with genetic testing protocols on individuals at different levels that would include clinical phenotyping; chromosomal analyses; metabolite level analyses; polypeptide or protein level analyses; and DNA level analyses for genetic mutations, susceptibilities and disorders.

3.2.3 **Gene Therapy Studies:** These include studies aimed at introducing genetic material into patients to treat a genetically inherited or acquired disorder.

3.3 Permissible Areas and Forms

Permissible areas and forms of genetic research studies are those with **a clear therapeutic and/or public health value** that fall under any of the three categories of research in genetics or a combination thereof which have satisfied the requirements, procedures and guidelines as well as specific elements of review as described in **sections 4.0 and 5.0.** These shall also include areas and forms **not** mentioned as

examples under the section of non-permissible areas and those that the NHSRC has not determined as being non permissible at any given time.

3.4 Non Permissible Areas and Forms

The following non permissible areas/forms of genetics research only serve as examples. The NHSRC has the ultimate authority to determine from time to time other non permissible areas and forms besides the ones listed hereunder.

3.4.1 Research in Human reproductive cloning
3.4.2 Any research related to human germ line genetic engineering
3.4.3 Research involving the creation of human embryos for research or therapeutic purposes
3.4.4 Human genetic enhancement studies aimed at promoting socially desirable personal characteristics
3.4.5 Genetic screening and testing for genetic disorders/diseases that manifest later in life
3.4.6 Genetic screening and testing for conditions/diseases for which there is no possible and suitable interventions
3.4.7 All forms of studies and testing aimed at collecting and storing human biological samples for future unspecified genetic research/analyses including any scientific retrospective genetic analyses
3.4.8 Plans, attempts and requests for obtaining human biological/genetic material for future research
3.4.9 Any studies or scientific intentions that do not serve the therapeutic and public health goal for the people of Malawi

4.0 REQUIREMENTS, PROCEDURES AND GUIDELINES

The scientific and ethical design of any research in human genetics serving a clearly defined therapeutic and/or public health goal that has been proposed for implementation in Malawi shall incorporate the following requirements, procedures and guidelines in relation to a specific study in the defined categories and permissible areas and forms as outlined above;

4.1 Consent in Genetic Research

The traditional paradigm for research ethics requires an autonomous individual to make an informed choice/consent about participation in research. However, genetics

research and genetic information are by nature about families. For ethical reasons and success of the study, where a protocol calls for family members to inform relatives about the study, the researchers must undertake to obtain an informed written permission from the family members. However, each individual participant has the right to make an informed written consent to participate or not. To make an informed and educated consent, the consent form or information sheet must include statements on what is being studied and why; details about study procedures, known risks, discomforts, and benefits; and alternatives to participation besides what is specifically described in the tables of schema of NHSRC review as applicable to each permissible category of genetic research.

4.2 Genetic Counseling

On recruitment, potential participants should be counseled about the possible consequences, implications and psychosocial impacts for the proposed research and disclosure of tests results. The research protocol must provide for counseling and support services to the participants before enrolment begins and when contemplating to disclose research results to the participants. Counseling and disclosure of tests results must be provided by health professionals who have appropriate training, skills and experience. Researchers shall adhere to the related requirement as further described under **section 4.6.**

4.3 Genetic Testing and the Availability of Therapy or Prevention Strategies

Where safe and effective therapy or prevention strategies exist that have been accepted as standard of care and standard practice, providing the information necessary for patients or participants to make appropriate choices is in the best interests of the participants. Where there is no therapy, and prevention strategies are unknown or unproven, **genetic testing is unethical and is herein prohibited as such research cannot offer a therapeutic and/or public health value.**

4.4 Validity of the Protocol

A research design that leads to false conclusions is unethical because actions based upon those conclusions may have adverse consequences. Research that lacks validity also raises ethical issues of justice, if scarce resources are wasted. Researchers, should, therefore, ensure that the design of the study has taken into consideration all factors avoid those that would render the study invalid. Such design elements include (among others): appropriate inclusion criteria, sample size to give a proper statistical power, appropriateness of the study design in relation to the title and objectives of the study. Proper justification for including narrow group of potential subjects like in pedigree studies must also be given.

4.5 Sensitivity and Specificity of the Test and the Uncertainty of Clinical Prediction

Receiving accurate information on the anticipated predictive value of a testing or screening protocol is important for the NHSRC for a number of reasons. The accuracy of the results and their consequent usefulness to participants will be a determining factor in the investigator's and NHSRC consideration of whether individual tests results should be disclosed to the participants. In undertaking the risk-benefit analysis, the NHSRC shall weigh the scientific, clinical and public health usefulness of the test or screen. **The predictive value shall be cardinal in making these considerations. Thus, the NHSRC expects the researcher to indicate how frequently a result is expected to be falsely negative or falsely positive and the impact that this will have on the participant receiving the results**. Higher reliability and accuracy of the screening and diagnostic tests and any associated confirmatory tests in terms of providing the positive and negative predictive values is extremely paramount in genetic research. Therefore, researchers are expected to include in their protocols, the acceptable cut-offs of the values of the tests against those of any gold standard, to show the reliability of the tests and confidence that the NHSRC may place in such tests and their results as such would minimize potential for making erroneous and harmful disclosure of test results to the participants.

The NHSRC, therefore, expects and requires the researcher to thoroughly explore in the protocol the role of false positives and false negatives in the context of the importance of the results and the existence of confirmatory testing as such would provide further relevance on:

- how results should be handled (i.e.; what steps should be taken with a positive test result; what steps should be taken with a negative test result; and what steps should be taken when the result is equivocal)
- deciding to repeat the test if there is an additional diagnostic tool that can be employed in order to confirm **the accuracy** of the testing process.

4.6 Obligation to Disclose or not to Disclose Results

The principle of respect of persons is often tempered by the principle of beneficence: the decision to disclose test results must involve a consideration of the risks and benefits of disclosure. The NHSRC takes a middle view of these principles where investigator's obligation to disclose the test results to participants is regarded as a mechanism for realizing and promoting the therapeutic and public health advantage of the research study. However, the participant has a right and choice to consent to the disclosure of the results while taking into consideration requirements as described under sections on genetic counseling; protocol validity; sensitivity and specificity of the tests; and the uncertainty of clinical prediction**.** The NHSRC shall require a protocol to properly take into account all these requirements in meeting the obligation to disclose or not to disclose.

4.7 Privacy and Confidentiality

Genetic information about individuals is highly sensitive and requires that investigators take great care in handling it. The NHSRC or its *ad hoc* committee expects the investigator and/or the sponsor of the study to describe in detail how the privacy of participating individuals, communities, tribes will be protected and how the confidentiality of obtained information will be maintained. Thus, the consent form or information sheet shall be required to include explicit descriptions of the type and

scope of genetic information that will be collected and used in the proposed research study as well as whether, when and how participants will be informed of the results of the genetic analysis including outcomes not currently contemplated that may have implications for an individual participant.

In order to properly achieve the therapeutic and/or public health value and depending on the nature of the research study, a protocol must specify whether genetic information or genetic material, and any other information derived from studying the genetic material will be stored in code-identified or anonymous form.

4.8 Stigma and Discrimination

Genetic information, more than any other health information, has harmful social consequences for individuals and families when used in contexts such as employment, insurance and immigration. As cited earlier, cases have been reported elsewhere of people with asymptomatic genetic predisposition who were excluded from employment or insurance. The NHSRC, therefore, requires the researcher to demonstrate how best the protection of confidentiality of genetic data of these individuals or families will be maintained in a manner that does not lead to divulsion into the public domain and consequently lead to the adoption of discriminatory and exclusionary practices.

4.9 Risks and Safety Concerns and Strategies for Obviating Risks

Genetic research studies in all the categories outlined above have specific risks which researchers are required to fully describe in a protocol and provide strategies for obviating them. The specific risks vary with categories and proposed methods or techniques of genetic research. The risks which must be described are not limited to the following ones;

4.9.1 Gene therapy studies require a clear and detailed description of any strategies for delivering genes to cells. The genes are delivered through what is termed gene delivery vehicles or vectors. Whatever the gene delivery strategies and gene delivery vehicles/vectors, there are risks and safety concerns that are associated

with each of the chosen strategy and vector. The NHSRC shall require the investigator to honestly describe all the potential risks and safety concerns associated with the chosen gene delivery strategy and vector and as a whole risks and safety issues of the proposed gene therapy study (i.e. risks to the individual or to society).

4.9.2 Having described such risks, the NHSRC shall require the investigator to provide precautionary measures that will be taken to obviate and mitigate such risks.

4.9.3 There is no single set of risks associated with or applicable to gene therapy studies. The risks vary with the technique used to transfer the genetic material into the research participant's body. For example, the following risks are possible risks that are associated with gene therapy studies: *contamination during vector preparation; certain delivery systems triggering a significant immune response that would in turn disrupt or interfere with treatment efficacy; potential for some viral vectors including retrovirus and adeno-associated virus permanently incorporating into the research subject's genetic material which in turn may disrupt important host gene or may activate oncogenes.*

4.9.4 Gene localization and identification studies as well as screening and diagnostic studies have their own risks of harm too. Some of which are summed up in the NHSRC schema for protocol review. The NHSRC shall require protocols under all these categories to contain a detailed description of all possible risks and strategies for obviating them.

4.10 Capacity Building, Collaboration and Affiliation

4.10.1 As a strict and fundamental requirement, all foreign based researchers intending to conduct genetics research in Malawi are required to:

- be affiliated to local research related institutions/departments. The affiliating institutions' roles shall be to aide such researchers to conduct research in Malawi according to the applicable regulatory requirements

and to foster meaningful local capacity building arrangements. In considering affiliation, appropriate fees and memoranda of understanding shall be required depending on procedures and policies of the affiliating local institutions.

- enter into meaningful collaborative arrangements with investigators/researchers of a local research related institution to which they shall have been affiliated. In particular, NHSRC shall require the participation of local collaborators/co-investigators of the affiliating/collaborating institution that have requisite qualifications that are commensurate with the nature of the proposed study.

4.10.2 The NHSRC shall require evidence of such affiliation arrangements. The NHSRC shall also require a protocol that clearly describes **meaningful collaborative and capacity building activities with roles of every collaborator clearly defined**. Testing and analysis shall primarily be required to be done in Malawi. Researchers, collaborators and the affiliating institution shall ensure that the research project has the appropriate technology for testing and analysis. All the technology that shall have been transferred into Malawi to fulfill the objectives of a research study shall be the property of the local affiliating institution. The requirement and guidance under **section 4.12** applies to only very exceptional circumstance. Such a circumstance shall, however, be reviewed and approved by the NHSRC.

4.11 Statement on the Therapeutic and Public Health Value of the Research

In line with the Malawi policy position on genetics research as outlined above, the NHSRC shall require the protocol to have a clear statement that defines the scope of the envisaged therapeutic and/or public health value of the proposed research. Depending on the nature and category under which the proposed research falls, such a statement shall include a description of the proven and acceptable standard of care and practice and/or prevention strategies planned to be administered to the participants in tandem with the requirement as defined in **section 4.3**.

4.12 Material Transfer Agreement and Ownership of Genetic Material

4.12.1 While it is a strictest requirement that genetic analyses must be done locally, there may be restricted circumstances and reasons (for example, to expedite a timely therapeutic cause) where there might be a justifiable need to do such analyses/tests beyond the Malawi borders. Such circumstances would necessitate the transfer/exportation of biological/genetic material, subject to the provisions of any national relevant law. In which case, the researcher shall be required to apply for such a transfer under a material transfer agreement that shall be reviewed, approved and signed for by the NHSRC, provided that the researcher shall provide satisfactory description of how privacy and confidentiality of the individuals and communities as well as safety of such materials will be maintained. Storage period of such materials shall not exceed initial period of five years.

4.12.2 A researcher must not transfer genetic material and related information to another research group locally and internationally unless:

- The researcher and the other research group are collaborating on a research study that has been approved by the NHSRC; and

- The genetic material and information is provided in a form that ensures that participants can not be identified, and that the research group must undertake to hold the material and related information in such a manner that there is no reduction in the protection of the privacy of the participants or of the confidentiality of the information, subject to the guidance provided in sections **4.12.1; 4.12.3; 4.12.4; 4.12.5 and 4.12.6**.

4.12.3 The quality of the technology/equipment or laboratory facilities and personnel where the diagnostic or confirmatory genetic tests will be performed is so

fundamental in providing the credibility of the results. Tests results are only as good as the equipment and the personnel involved. Participants in genetic research and the NHSRC must know whether those results are in any way limited or compromised. Thus, for ethical and quality assurance reasons, the NHSRC shall require the investigator to provide a certificate of accreditation and good laboratory practice for a laboratory providing genetic test results to which the genetic material has been transferred/exported to for the purpose defined under section **4.12.1**.

4.12.4 Any human biological/genetic material that may have been transferred/exported as specified under section **4.12.1** is the property of the Ministry of Health of the Government of Malawi represented by a local affiliating and collaborating institution. The Government of Malawi through the Ministry of Health requires investigators to send back such samples after analysis and the cost of shipment back to Malawi shall be borne by the research group/institution that initially requested the transfer/exportation. All such materials on return shall be accessioned into the **National Public Health Reference Laboratory** in Malawi or any other laboratory that shall be designated in advance by the Ministry of Health.

4.12.5 The National Commission for Science and Technology shall subsequently charge a fee on any approved study in respect of the collection and transfer/exportation of biological samples including the genetic material beyond the Malawi borders in accordance with the regulations of the Science and Technology Fund. The investigator shall make payment of this fee directly to the Commission.

4.12.6 In accessing, collecting and transferring human biological samples/tissues for research purposes, the NHSRC shall require researchers to satisfy the provisions of any relevant national statute including the **Penal Code, Anatomy Act, Health Act and Public Health Act.**

4.13 Disclosure of Interest

The investigator, sponsor and all collaborators are required to provide a statement of disclosure of interest in the research study.

4.14 Prohibition of Commercial Exploitation of Human Biological/Genetic Materials

Any form of commercial exploitation of human biological/genetic materials collected in Malawi **is strictly prohibited**.

5.0 SCHEMA/ELEMENTS OF REVIEW OF GENETIC RESEARCH

The NHSRC will take into consideration all the requirements and guidelines as outlined above in reviewing protocols. In addition, the NHSRC shall review the protocols in terms of the specific elements that are applicable to each type of the three categories of research in genetics. These elements are presented in form of specific questions under each of the sections of a protocol format. These questions are summed up as a schema for the NHSRC review of a protocol. In reviewing protocols falling under Gene Localisation and Identification Studies, the NHSRC will use the schema presented in **Table 1** while **Table 2** schema will be used in reviewing protocols falling under Genetic Screening and Diagnostic Studies. In reviewing protocols that fall under Gene Therapy Studies, the schema in **Table 3** will be used. The NHSRC may use a combination of the schemas or parts thereof in reviewing a protocol, should a protocol be of a study that falls under a combination of the pre-classified categories of genetics research. The investigator is, therefore, expected to address the requirements, procedures and guidelines as well as the specific elements for review contained herein in light of their applicability to the proposed study under a given permissible area of research in genetics. These tables appear in appendix **one.**

6.0 SOURCE DOCUMENTS/REFERENCES

A number of source materials were used in drafting these guidelines. The full list of all source materials appears in **appendix two**.

APPENDIX ONE: SCHEMA FOR REVIEW OF PROTOCOLS ACCORDING TO CATEGORY OF RESEARCH IN GENETICS

Table 1: Schema of review of gene localization and identification studies

{Questions marked with an asterisk refer to issues of particular relevance in genetics protocols}

BACKGROUND AND JUSTIFICATION

What questions does the research address? Has the investigator demonstrated that the research has scientific and medical/therapeutic or public health value? How does the proposed study relate to previous work, if any? Does it provide a rational continuation of this work?

RESEARCH DESIGN

Is the scientific method to be employed valid? Has it been used previously, and if so, how has it been assessed? What quality controls are built into the method?

Is the planned statistical analysis appropriate (i.e., is it likely to provide valid and unbiased answers to the study question)?

*If a full genome scan is planned,
Does the sample size provide sufficient power to identify one or more loci with a reasonable degree of certainty?
Are population-specific allele frequencies already known? If not, how will they be determined?

*If the trait to be mapped is complex, will robust nonparametric methods of analysis (which do not necessarily require a Mendelian model) be used first?
If not, is there good justification for this?

*If the study is a case-control study, are the cases and controls carefully matched for ethnicity?

*Is there adequate consideration and/or statistical correction for multiple comparisons (which may number in the hundreds for genome scans), and is the procedure to be used described clearly?

PROCEDURES

What procedures are involved in the study (e.g., medical examinations, blood draws, tissue/tumor donation, questionnaires, interviews, etc.)?How often? How much time will they take?

Are all of the procedures in this study required to answer the research question? Can any be eliminated?

Will the data/DNA be destroyed at any point according to the requirement on the initial storage period? Will identifiers be maintained with the stored data/DNA for the initial allowable storage period?

*Will subjects be asked to allow investigators to contact them in the future for more information about “nonparticipating “family members, if need be)?
*Are the procedures for maintaining confidentiality of data/records/database information specified clearly (e.g., encryption, use of unique identifiers, sequestering of records, security measures)?

SUBJECT SELECTION

How is the study population defined? Does it include affected and/or unaffected individuals, related or unrelated? Are healthy controls included?

Have the eligibility criteria been justified? Do they strike a defensible balance between scientific validity and generalizability (i.e., is the study population sufficiently restricted to yield interpretable results without being unduly restrictive)?

How are subjects to be recruited? Will they be reasonably compensated?

If so, in what form will be the compensation? Is the nature of the compensation or reimbursement reasonably appropriate?

*If the study involves families, how will family members be recruited? By the proband? By the health worker? By investigators directly?
*Will the proposed recruitment process place undue pressure on other members to participate?
*Might recruitment itself “inflict” unwanted information about risk status on family members?

Are adequate procedures in place to protect the interests of these people?

*Does the protocol involve “nonparticipating” family members about whom subjects will provide personal/medical information?

*Does the protocol include incompetent subjects (young children or incompetent adults) Is there a valid alternative to their participation in this protocol?
If not, have provisions been made for assent and/or proxy consent?
*Does the protocol involve other vulnerable populations (e.g., patients with Alzheimer disease or psychosis who have periods of fluctuating competence)? Have their special needs been taken into account?

RISKS AND BENEFITS

Is the importance of the research question sufficient to justify risks associated with the procedures specific to the proposed research?
Have risks been minimized to the extent possible?

*Will participation in the protocol result in any benefit to subjects? Will the results have any predictive value for subjects in terms of life or health choices (e.g., marriage, reproductive choices, choice of employment, medical treatment, disease prevention)?
*Are instances of nonpaternity or incest likely to be uncovered by the research? How will these be handled (e.g., disclosure of the possibility in consent materials, withdrawal of the samples from the research)?
*Will the knowledge gained by the subjects about their current or future health or their carrier status pose additional risks to them, such as risks to insurability, employability, immigration, paternity suits, or social stigma? Have adequate provisions been made for privacy and confidentiality of subject information, including for “nonparticipating subjects”?
*Could the research result in stereotyping or stigmatizing a particular community or cultural group?

Have investigators taken steps to approach the group involved and solicit comments where appropriate?

*Will a family pedigree be published? Will the method or occasions of publication or presentation of findings contain the potential for identifying family members?
If so, how will the confidentiality be maintained?

INFORMATION TO SUBJECTS

Does the information to be provided to prospective subjects adequately inform them of what is being studied and why, details about study procedures, known risks and benefits as well as uncertainties about risks and benefits, and alternatives to participation?

*If there is no individual benefit to subjects, has this been disclosed?

*Have subjects been told of their right to withdraw from the research without penalty or loss of benefits to which they are otherwise entitled? Have they been advised of any consequences of withdrawal?

Are there any limitations on the ability of subjects to withdraw their data or DNA samples?

If so, has this been adequately disclosed?

*Is it clear to subjects what information will be revealed to whom and under what circumstances (e.g., participants may learn about other family members risk status)?
*Will subjects be informed of any special risks associated with the study (e.g., changes in family relationships, risks to privacy, confidentiality, insurability, employability, immigration status, paternity suits, and educational opportunities)?
*Will the general study results be made available to subjects?
*If no immediately useful or interpretable information of relevance to subjects is likely to result from the study, has this been adequately explained?
*If information that is clinically relevant to subjects is likely to result, will counseling by an experienced health worker or genetic counselors be made available?
*Have subjects been given the option of individually choosing not to receive their study results?
*Could other clinically relevant information be uncovered during the study? If so, how will it be disclosed to subjects? Who will disclose it (e.g., investigators, experienced health worker or genetic counselors, the family physician)?

Will there be any costs associated with participating (including the cost of genetic counseling or psycho/social counseling) that are not covered by the investigator or the institution? If so, has this been disclosed?

Table 2: Schema for Review of Diagnostic and Screening Protocols

{Questions marked with an asterisk refer to issues of particular relevance in genetics protocols}.

BACKGROUND AND JUSTIFICATION

What questions does the research address? Has the investigator demonstrated that the research has scientific and medical/therapeutic or public health value?

How does the proposed study relate to previous work, if any? Have any innovative aspects been adequately justified?

*If the study concerns a diagnostic test, in what (clinical or other) situations will this test be helpful?

RESEARCH DESIGN

Is the scientific method to be employed valid? Has it been used previously? And if so, how has it been assessed? What quality controls are built into the method?

Is the planned statistical analysis appropriate (i.e., is it likely to provide valid answers to the study questions)?

*For diagnostic studies, how is the condition (or risk thereof) currently diagnosed? Will the new diagnostic strategy be compared with the best available standard test/gold standard?

*What is known about the nature and frequency of genetic polymorphisms related to the study condition?
If the study is a diagnostic protocol: How does the existence of polymorphisms affect the ability to define risk thresholds (cut-offs)?

If the study is a screening protocol: How does the frequency of polymorphisms affect the feasibility of population screening?

*Is it likely that other genes are required for full trait expression?
*If subjects will be informed of the test results, does the study design provide for an adequate assessment of the psychosocial impact of genetic testing?

PROCEDURES

What research-specific procedures are involved in the study (e.g. physical examinations, blood tests, tissue/tumor donation, questionnaires, interviews, etc)? How many? How often? How much time will they take? Are they all required to answer the research question?

*If long-term follow up is required, over what period of time will this take place?
*What are the procedures for maintaining privacy and confidentiality of information on data/DNA? (e.g., use of identifiers, limitation on access, duration of storage not exceeding initial required period of five years?

*Are adequate procedures in place for maintaining security and confidentiality of data/records/database information specified clearly (e.g., encryption, use of unique identifiers, sequestering of records)?

SUBJECT SELECTION

*How is the study population defined?
If the study is a diagnostic protocol: Does it include affected and/or unaffected individuals, related or unrelated?

If the study is a screening protocol: How is the population at risk defined and why was it chosen? (General population? Targeted population – prenatal, newborns, young children, adolescents, adults, at-risk population?)

Have the eligibility criteria been justified? Do they strike a defensible balance between scientific validity and generalizability (i.e., is the study population sufficiently, but not unduly, restricted so as to yield interpretable results)?

How are subjects to be recruited? If compensation/remuneration is provided, is the amount or nature appropriate?

*Does the protocol target members of an indigenous or other identifiable community? Have appropriate measures been included to take account of this fact (e.g., approaching community leaders, soliciting collaboration where appropriate)?

*Does the protocol include or target newborns or other young children? If so, is the study condition one that manifests or requires initiation of preventive measures in childhood? Have provisions been made for children's assent, where appropriate, and consent of the parents/guardians?

*Does the protocol include or target adolescent subjects? If so, is the study condition one which has implications for health at this age? For reproductive planning? Have provisions been made for counseling taking account of any special needs of subjects in this age group?

*Does the protocol include incompetent adults? Is there a valid alternative to their participation? If not, have provisions been made for assent, where appropriate, and/or proxy consent?

If children or incompetent adults are included in the protocol, is there any conflict of interest between the research subjects and the parent/guardian giving consent? If so, how will the subjects' interests be protected?

*Does the protocol involve other vulnerable populations (e.g., patients with Alzheimer disease or psychosis who have periods of fluctuating competence)? Have their special needs been taken into account?

RISKS AND BENEFITS

Is the importance of the research question sufficient to justify the research-specific risks? Have risks to subjects been minimized?

*Will participation in the study result in any benefit to subjects? Will the results be informative for participants in terms of life or health choices?

*Will knowledge gained by the subjects about their current or future health or their carrier status pose additional risks to them, such as risks to insurability, employability, immigration, paternity suits, educational opportunities, or social stigma? Have adequate provisions been made for privacy and confidentiality of subject information?

*Could the research result in stereotyping or stigmatizing a particular community or cultural group? What steps will be taken to obviate this?

Have investigators taken steps to approach the group involved and solicit comments where appropriate?

*Is psychological support required for those determined to be at risk? How will it be provided?

INFORMATION TO SUBJECTS

Does the information to be provided to prospective subjects adequately inform them of what is being studied and why; details about study procedures, known risks, discomforts, and benefits; and alternatives to participation?

*Will subjects be adequately informed if the study objective is to assess unknown risks?

*Will subjects be adequately informed of any limitations of the test/screen results as a predictor of clinical risk?

*Will subjects be informed of any special risks associated with the study (e.g., risks to privacy, confidentiality, insurability, immigration status, paternity suits, educational opportunities, or social stigma)?

*If no immediately useful or interpretable information of relevance to subjects is likely to result from the study, will this be disclosed adequately to subjects in advance of their participation?

*Will subjects be told of their right to withdraw from the research without penalty or loss of benefits? Will they be advised of any consequences of, or limitations on, withdrawal, including withdrawal of data or DNA samples?

Will the general study results be made available to subjects?

*Could other clinically relevant information be uncovered during the study? Who will disclose it (investigator, experienced health worker or genetic counselor?)

*Will genetic counselors or experienced health worker be available to transmit relevant information to subjects?

*Will subjects be given the opportunity not to receive their test results?

*Will there be any monetary costs to the subject associated with participation (including the cost of counseling)?

Table 3: Schema of Review of Gene Therapy Studies/Gene Transfer

BACKGROUND AND JUSTIFICATION

- Why is this disease a good candidate for gene transfer or gene therapy?
- What previous work has been done, including studies of animals and cultured cell models? Does the work demonstrate effective gene delivery? How does the proposed study relate to previous work?
- Is the disease course sufficiently predictable to allow for meaningful assessment of the results of the treatment proposed?
- What level of gene expression is presumed to be required to achieve the desired effect?
- Given responses to the above questions, is there a sufficient justification for the investigator to proceed at this point to a clinical trial?

RESEARCH DESIGN

- What are the objectives of the proposed study (e.g., establishing feasibility or relative safety of the gene transfer, determining a safe dose range, demonstrating proof of principle, etc.)?
- Is the goal of the study to ameliorate or cure disease?
- What is the target tissue for gene transfer (e.g., bone marrow cells, skeletal muscle cells, respiratory epithelial cells, central nervous system tissue, etc.)?
- What method(s) (e.g., direct injection, inhalation, *ex vivo genetic modification with injection of modified cells) and reagent(s) - e.g* vectors based on retroviruses, adeno-associated viruses, herpes viruses) will be employed for gene delivery? What is the rationale for their use? Are other methods or reagents known that are more appropriate with regard to efficacy, safety, and stability?

- How will the investigator determine the proportion of cells that acquires and expresses the added DNA?
- How will the investigator determine if the product is biologically active?
- Is the planned statistical treatment appropriate (i.e., is it likely to provide valid answers to the study question)?
- Is it reasonable to expect that the research design proposed will meet the investigator's objectives?

PROCEDURES

- What research-specific procedures and research-specific investigations are required by the study over and above those that would be required for patients receiving standard clinical care (e.g., physical examinations, venous or arterial blood tests, collection of target cells, imaging procedures, irradiation, chemotherapy, direct injection of vector, reinjection of genetically modified cells, organ or tissue transplantation, surgery, tissue/tumor donation, questionnaires, interviews)?

- Is long term follow-up appropriate or essential for this protocol? If long term follow-up is proposed, is there justification for the number of visits and the length of time required? Is such follow-up feasible in the case of this protocol (e.g., have provisions been made for subjects who are mobile or move to other geographical areas, is adequate funding available for such follow-up)?

- Are all of the research-specific procedures necessary? In combination with data collected in the course of clinical care, is it reasonable to expect that the information produced by this study will be sufficient to answer the research question?

CONFIDENTIALITY

- Are the practical steps for maintaining confidentiality of data /records/ database information clearly specified and adequate (e.g., encryption, use of unique identifiers, sequestering of records, security measures)?

SUBJECT SELECTION

- How has the study population been defined?

- Has an adequate rationale been provided for each eligibility criterion (e.g., safety considerations, definition of disease, avoidance of additional concurrent therapies, administrative considerations)? Do they strike a defensible balance between scientific validity and generalizability (i.e., is the study population sufficiently, but not unduly, restricted so as to yield interpretable results)?

- How will the subjects be recruited? If a cohort of eligible patients exists, how will selection be made amongst them? If several trials exist for which the same patients are eligible, how will this be presented to prospective subjects?

- Does the definition of the research population reflect appropriate scientific, clinical, and ethical norms? In recruiting and negotiating with potential subjects, have the norms of nondiscrimination been respected?

RISKS, DISCOMFORTS, AND BENEFITS

- What risks and discomforts are associated with the research-specific procedures and investigations (e.g., surgery, chemotherapy, radiation, bone marrow transplantation)? Have they been minimized?

- If a virus-mediated gene transfer is proposed, what is the potential for the presence of a replication-competent or pathological virus or other form of contaminants? How sensitive are the tests to detect such viruses or contaminants? What level of viral presence or other form of contamination would be tolerable in this protocol?

- Has the possibility of vertical transmission (i.e., gene insertion into germ cells or a fetus) or horizontal transmission (e.g., to family members or health care staff) been considered? What measures have been taken to minimize the risks of this transmission? Are other measures possible? If transmission were to occur, what would be the consequences?

- What are the risks for the vector to activate an oncogene or to inactivate a tumor suppressor gene leading to vector-related malignancy?

- Are the risks and discomforts of the study justified given the potential benefit to subjects and the scientific importance of the research?

INFORMATION TO SUBJECTS

Have prospective participants been adequately informed of the following?

- What is being studied and why, given details about study procedures, known or potential risks, discomforts and benefits, and alternatives to participation;

- Their rights: (a) to information on an ongoing basis, confidentiality with regard to their participation and handling of their data, and the right to consult with others before making a decision whether to participate; and (b) to withdraw from the study without penalty or loss of benefits, as well as of any health consequences of withdrawal for themselves or their immediate contacts, or limitations on withdrawal, if any;

- Any special issues related to this gene therapy trial, such as uncertainty associated with short and long term risks and benefits; and

- Disclosure of investigator's or sponsor's interest in the research.

Have prospective participants been provided this information in simple language, using translation where necessary, with answers to their questions, referral to other sources of information, and adequate time to make up their minds whether to participate?

If there is no individual benefit from participation in the research, has this been appropriately disclosed?

Will the general study results be made available to subjects?

Do all the elements of the consent process combine to allow subjects a full opportunity to make an informed choice?

APPENDIX TWO: SOURCE MATERIALS

CIOMS in collaboration with WHO,Geneva, 2002

Declaration of Helsinki, October 2000

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Government of the Republic of Malawi. The 2005 Policy Measures for the Improvement of Health Research Co-ordination in Malawi

Government of the Republic of South Africa. Ethics in Health Research: Principles, Structures and Processes: Research Ethics Guidelines, 2004

Indian Council of Medical Research. Ethical Guidelines for Biobanking in India, November, 2006

Justine Burley and John Harris. A Companion to Genethics, 2002, Blackwell Publishing

Kathleen Cranley Glass, Charles Weijer, Roberta M. Palmour, Stanley H. Shapiro, Trudo Lemmens, and Karen Lebacqz. *Structuring the Review of Human Genetics*

Protocols: Gene Localisation and Identification Studies. IRB: A Review of Human Subjects Research 18, no.4 (1996): 1-9

Kathleen Cranley Glass, Charles Weijer, Trudo Lemmens, Roberta M. Palmour, and Stanley H. Shapiro. *Structuring the Review of Human Genetics Protocols Part II: Diagnostic and Screening Studies*. IRB: A Review of Human Subjects Research 19, nos, 3 and 4 (1997): 1-11,13.

Kathleen Cranley Glass, Charles Weijer, Denis Cournoyer, Trudo Lemmens, Roberta M. Palmour, Stanley H. Shapiro, and Benjamin Freedman. *Structuring the Review of Human Genetics Protocols Part III: Gene Therapy Studies*. IRB: A Review of Human Subjects Research 21, no.2 (1999): 1-9

The Belmont Report: Ethical Principles and Guidelines for the Protection of Human subjects of Research,Wahington DC, 1979

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UNESCO. *Universal Declaration on Bioethics and Human Rights, 2005*, France