Guidance for the Design, Ethical Review, and Conduct of Genomic Research in Qatar

Ministry of Public Health

Department of Research

2017-2018

This policy has been approved by stakeholders in January 2018

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Introduction

Genomic research on humans has resulted in many benefits, both medical and non-medical. Through genomic research, we have discovered the pathophysiology of certain diseases. Similarly, we have learned about the specific genetic abnormalities that cause particular diseases. For others, we have discovered which gene variants protect against disease, which gene products are over or under expressed, and which gene variants modulate the likelihood of disease. We have been able to identify the cause of some rare diseases and provide a diagnosis for clinically similar conditions. In some cases, we can separate environmental and genetic causes of disease. Genomic research has even led to novel diagnostic techniques and treatments. As a result of genomics research, we are often able accurately diagnose diseases, identify gene variants associated with side effects to specific drugs, and select drugs that are likely to effectively treat cancer and other illnesses. Genomic research has also had benefits in social research by identifying patterns of migration, allowing individuals to better trace their family tree, and provide forensic evidence to further the ends of justice.

Genomic information collected in research has the potential to provide investigators with a greater understanding of the causes of and predisposition to a variety of diseases and conditions, which may lead to more effective methods of prediction, early diagnosis, treatment, and prevention. However, handling of genomic information presents emerging ethical and legal issues including, but not limited to, privacy and consent. As part of its commitment to facilitate research and protect human subjects, the Qatar Ministry of Public Health ("MOPH") wishes to make research institutions, investigators, and IRB members aware of specific ethical issues and policy implications of genomic research.

Purpose of the Genomic Policy

This document represents a set of guidelines targeted to provide practical assistance to investigators in the design and conduct of research and to Institutional Review Boards in the review and oversight of that research. This Policy document is meant to be used by investigators and institutions who wish to conduct genomic research involving human subjects. This policy is also meant to be used by IRBs during their review and on-going oversight of genomic research. This Policy will be reviewed and revised as needed or every three years.

Related Documents

As applicable, this Policy document should be read in coordination with the following MOPH policies, procedures, and guidelines:

- *"Guidance for the Use of Stored Data and Biological Specimens in Human Research."* This document assists investigators with understanding general parameters for whether review by an institutional review board ("IRB") or institutional ethics committee ("IEC") is required for research involving use of existing data or biological samples collected in the clinical setting or in prior research.
- *"Policies, Regulations and Guidelines for Research Involving Human Subjects."* This document outlines ethical guidelines, policies and regulations that should be followed in Qatar in conducting research involving human subjects.
- *"Guidance for the Use of Stored Data and Biological Specimens in Human Research."* This document provides policy and procedures to access and conduct research on data and biological samples provided by volunteers to the Qatar Biobank.

Risks of Genomic Research

Risk is a chance that harm may occur. A useful model considers the potential harm that may occur with genomic research. These harms may be physical, psychological, legal, social, economic, or concern privacy. Although there is overlap among these categories, they may nevertheless be used to consider all aspects of risk.

A. Physical Risks

In genomic research, physical risks generally include risks associated with the collection of blood, saliva, or other tissues for the acquisition of DNA from which to construct a genomic. These risks may be minor because they are related to routine clinical procedures, such as venipuncture, or major because they are related highly invasive sample, such as obtaining a brain biopsy.

B. Psychological Risks

Genomic research may detect previously unrecognized disease, which can lead to psychological distress. For example, a research study sequencing a section of DNA for prediction of drug side effects might uncover a genetic predisposition to a serious and untreatable disease such as Huntington Chorea.

Genomic research can uncover information about familial risks of disease. This can result in distress among family members of the subject. For example, a research study sequencing a section of DNA for prediction of drug side effects that uncovers a genetic predisposition to Huntington Chorea would have implications for family members who may have a high likelihood of carrying this same genetic predisposition. While the discovery of a genetic predisposition could be seen as a risk to some, others might consider such a discovery to be beneficial in that it can aid family members to develop preventative medicine strategies for themselves or others.

C. Privacy Risks

When genomic and phenotypic data are broadly shared in a database or repository, privacy risks may arise. Coded data can be released to the public, health insurance providers, employers, or others. Data may be susceptible to computer or physical security breach. Data without identifiers may be susceptible to re-identification through linkage to other publicly available databases.

One additional privacy risk in genomic research is the risk that an employer or health insurance company could be used to discriminate against a subject based on information it receives through a data breach by the investigators or others.

D. Legal Risks

Genomic data may result in legal harms due to disputed claims of paternity. In some countries, genomic data may demonstrate familial or social relationships that raise citizenship questions or complicate access to goods or services.

E. Social Risks

Genomic research may cause stigmatization or discrimination against an individual, family, or group of people with a particular genetic trait. Genomic data can raise issues that a person’s biological father is not the person considered to be their father. Genomic data can uncover unexpected issues of family heritage. Families who believe that their ancestors came from a particular part of the world may find through

genomic testing that their origin was, in fact, from another part. Genomic testing can demonstrate that a particular genetic defect may be prevalent in one's family. These types of discoveries may lead to social stigmatization by others.

F. Economic Risks

The results of genomic research could cause a discontinued or reduced health insurance benefit resulting in an economic hardship. In some cases, genomic data may demonstrate an underlying condition that might be used to prevent or terminate employment in a particular field. The legal and social risks noted above may secondarily cause economic hardship.

Because of the evolving nature of genomics and the fact the genomics research may take place over decades, it is important to recognize that the above risks are only examples and that unforeseen risks are likely to occur.

Mitigation of the Risks of Genomic Research

When genomic research involves risks, there are a number of ways to mitigate those risks.

A. Information Security

One important mitigation strategy is the securing of research information. Many of the above risks involve a breach of confidential information. Therefore, decreasing the risk of a breach of confidentiality reduces the risk of subsequent psychological, privacy, legal, and social harms.

There are three main approaches to securing information: Administrative procedures, physical procedures, and technical procedures.

Physical procedures relate to the tangible location of data, such as keeping data and computers under lock and key, controlling access to offices using research records, and using security guards. Physical safeguards prevent unauthorized access, tampering, and theft. Investigators conducting research should establish procedures to limit physical access to print and electronic research records that are identifiable. These limitations might include locked cabinets, locked offices, and housing of database servers in rooms with tightly controlled access. Procedures should define who has access to keys and combination locks and how these access privileges are granted and withdrawn. Investigators should have procedures defining when and how print and electronic media can enter and leave a secure location. Investigators should also have procedures for safe disposal of written and electronic records, including procedures for shredding or securing erasing computer media.

Technical procedures involve the use of technology, such as password protection, encryption, and firewalls. These procedures limit access to confidential information to those individuals or computer programs that have been granted access rights. Investigators should have procedures so that all individuals with access rights have unique usernames and passwords. For particularly sensitive information, consideration may be given to two-factor authentication whereby a user has to provide two means of identification, one of which is a password and the other is typically a physical token, such as a card or cell phone that is unique to the user. Computer systems should be designed to log off automatically after a period of inactivity. Networked computers should be protected by firewalls that limit network access to the minimum required for research operations. Confidential information should be routinely encrypted in a manner that is automatic and does not require user intervention, such as whole disk encryption. Computer systems should be monitored for malicious software (viruses, spy ware, key loggers) and audit trails performed to detect proactively unauthorized intrusion.

Administrative procedures relate to the conduct of people, such as having policies and procedures, procedures for training research staff, confidentiality agreements, and certificates of confidentiality. In some countries, legal protections exist (genetic non-discrimination laws or certificates of confidentiality) that should be implemented as a research procedure to prevent the harmful sharing of data. Investigators conducting genomic research should establish policies that require research staff to maintain confidentiality. Newly hired staff should undergo training before being permitted to access confidential information. All research staff should sign non-disclosure agreements affirming the requirements of maintaining confidentiality. The research team must know what information is confidential, with whom information may be shared, and with whom information may not be shared. Periodic training and reminders should be implemented to reinforce initial training. The hiring process

should evaluate whether individuals being considered are likely to comply with the required administrative procedures and detect red flags (e.g., criminal record or previous terminations) that indicate a high risk. Staff should also be trained on proper behaviors, such as keeping passwords secret, maintaining physical custody of laptops and other mobile devices, and following procedures to keep doors and file cabinets locked. Procedures should be in place to manage inadvertent breaches, to implement corrective action plans to minimize future recurrence, and when appropriate, implement employee action, sanction, or termination. Investigators should establish procedures so that terminated employees lose all access privileges.

Other important administrative procedures in genomic research to limit access to data involve limiting the probability of disclosure. Investigators can strip identifiers from genomic and phenotypic information. Information useful to identification, such as dates and ages, can be randomly perturbed. Data can be aggregated into intervals, such as grouping all ages into decade ranges. Information can be coded, and the key stored separately from the coded data.

Finally, data transfer agreements that outline the roles and responsibilities of institutions sharing data are an important administrative procedure to maintain data security. If an inadvertent identification is discovered, it must be reported and handled with extreme care by all parties involved, including by contacting the original subject(s) from whom the data was obtained.

Although many discussions of information security focus on technical procedures, breakdowns in administrative procedures are the greatest risk and the most common cause of breach. Often, the behavior that leads to breaches is inadvertent, but serious breaches can also occur with malevolent intent. Most importantly, mitigation of information risk must be balanced across technical, physical, and administrative approaches.

Secure data storage and access are paramount. While those operating databases and registries should promote sharing, appropriate confidentiality measures should be in place to ensure the secure transfer and use of shared data.

B. Controls on Sharing of Information with Subjects

Some genomic research protocols include sharing genomic information with subjects. This sharing of information can lead to social, psychological, or economic harms. When conducting genomic research where the meaning of genomic findings is uncertain or exploratory, subjects can be informed that the results of their genomic testing will not be shared with them. When knowledge of genomic findings can have an important benefit, the withholding of information becomes less tenable. However, situations arise where the benefits of sharing of data are outweighed by the social, psychological, or economic harm associated with a subject knowing the information.

C. Anticipation of Incidental Findings

Incidental findings refer to unexpected genomic results that are not the intended goal of the research. For example, screening of genes responsible for variations in the metabolism of drugs discovers a pattern that can only be explained by the fact that the subject's father is, in fact, not the biological father. Sharing of information related to incidental findings is similar to the sharing of information expected to result from research, but differs in important ways.

Because genetic testing utilizes a series of technologies that could provide subjects or their families with findings of potential medical significance, whether related or

unrelated to the primary purpose of the test, there is debate about when and whether incidental findings of medical significance should or should not be reported to the subject or their family.

In the clinical setting, where incidental findings are discovered from such tests, laboratories and clinicians are required to act in the best interests of the patient, which, absent a compelling and specific reason to do otherwise, may require reporting incidental findings to the patient. In many cases, there is a requirement for patient counseling prior to testing in order to provide clear expectations for what results will and will not be returned to the patient.

In many cases, genomic testing in research relates to the development of a particular assay or product to see whether the results return is accurate, in which case the reporting of incidental findings to subjects could be erroneous or unreliable.

The risks posed by incidental findings can be reduced by offering subjects the choice of being informed of such findings. Subjects can be provided the opportunity to consider the risks and benefits of learning about incidental findings. The investigator and subject can decide to withhold from subjects information related to paternity, sanguinity, or ethnic origin that may be traumatic or stigmatizing and provide information related to other testing results. Some would argue that investigators are obligated to inform subjects of all incidental findings and MOPH encourages investigators and institutions to provide incidental findings to subjects in research, and, where possible, affected known family members with similar genetic mutations. However, this is not a requirement when conducting genomic research. In addition, there may be a legal or medical obligation to inform subjects of certain incidental findings. If there are limitations on non-disclosure of incidental findings, the subject should be informed as part of the consent process.

Investigators and subjects may agree that incidental findings will be provided to the subject after the genomic testing is complete. The risks posed by incidental findings can be mitigated by offering pre-test and post-test counseling and care to subjects in whom a condition is identified. When such information cannot be withheld, counseling and behavioral therapy may be offered.

Institutions should establish a policy on the management of incidental findings. The policy should be informed by local legal requirements. The policy should define the obligation of investigators. The policy should also define the degree to which subjects will be allowed to decline to be informed, and the obligations of investigators to provide counseling or treatment to investigators. Investigators should follow this policy when conducting research.

D. Physical Safety

The issues of physical safety with genomic research primarily involve the procedures for access to tissue. Use of proper technique by personnel trained to obtain specimens is an important step to mitigate risk. Physical risks can be mitigated by obtaining tissue and blood from existing sources rather than performing additional procedures. Physical risks can be reduced by combining tissue collecting with a procedure already being performed for medical care. For example, extra samples might be obtained with a medically indicated screening colonoscopy rather than performing a second colonoscopy. When invasive procedures must be informed, fewer lower risk procedures should be substituted whenever scientifically feasible.

E. Compensation and Care

When economic burdens include the need for medical or psychological services, or the loss of medical benefits, the research sponsor can mitigate those risks through compensation for inconveniences, psychological care and replacement of lost medical and psychological benefits.

F. Preventing the Re-identification of De-identified Data

A recently recognized problem is that data sets without traditional identifiers (name, social security number, date of birth, address) can be linked to databases that do contain identifiers. Investigators have been able to take published genome sequences, identify markers on the Y chromosome (which are highly correlated with one's last name), and using a publicly-available genealogy database, determine the last name of the person associated with the DNA sequence. In some countries, using only state or providence of residence, age, and last name, investigators have been able to re-identify a substantial fraction of published DNA sequences.

Other Ethical issues of Genomic Research

A. Informed Consent

When subject samples are collected for genomic research, several issues should be addressed. First, the description of the genetic test (including potential limitations and the possibility of incorrect results) should be disclosed as well as possible outcomes and methods for communicating and maintaining the confidentiality of any test results. Second, investigators should disclose whether samples will be used only for this research study and whether they will be destroyed upon completion of the study. Third, if there are planned future uses for the sample, these future uses should be specified. Investigators may have a duty to re-contact a subject if a future use is explicitly precluded from the consent form in the original study. Subjects should be told whether investigators or others will communicate results from subsequent testing on their samples. Permission to use de-identified samples must be obtained during the consent process, and the scope of potential future research should be explicitly stated. Fourth, if the samples are stored, investigators should disclose whether samples will be withdrawn or destroyed at any time. Fifth, subjects should receive assurance that their personal information will be held in confidence with controls and that identifiable information about them will not be available to downstream investigators without consent.

B. Re-use of Samples and Data from Prior Research

Conducting research with samples and data obtained from previously conducted research raises issues of valid consent. When subjects donate biologic specimens in one research study, what type of consent is required for uses of those specimens in other research studies ("secondary uses")?

Informed consent disclosures for the original research typically fall into one of three cases:

- Samples and data collected as part of clinical research may be used without limitation for future research.

- Samples and data collected as part of clinical research may be used for specific types of research, but do not explicitly limit other forms of research. ("We will use your biologic specimens and data to study diabetes.")

- Samples and data collected as part of clinical research may be used for specific types of research and limit other forms of research. ("We will use your biologic specimens and data to study diabetes. We will not use your biologic specimens and data to study anything other than diabetes.")

The degree of informed consent required for future genomic research on existing specimens collected as part of previously conducted research represents an area of controversy due to conflict between the ethical principles of respect for persons and beneficence. A reasonable compromise to resolve this conflict is to require an independent review of the original informed consent language to determine whether data may be shared for secondary research. For studies initiated after the implementation date of this policy, investigators should obtain consent for genetic and phenotypic data to be used for future research purposes and to be shared broadly. The consent should include an explanation about whether subjects' individual-level data will be shared through unrestricted- or controlled-access repositories. For past studies, the independent review should ensure that future

research not be inconsistent with the original informed consent. In the above three examples, genomic research in an area other than diabetes would not be inconsistent in the first two, but would be inconsistent with the third.

C. Development of Commercial Products

In genomic research, tissue specimens provided by subjects could be provided to collaborators, stored in a repository or bio bank, or used by the investigator for research or development of commercial products. Because genomic research may lead to the development of a commercial product either by the investigator or a secondary downstream user, investigators should disclose to subjects whether there are plans for the subject to receive payments or profits generated from these products. Language such as the following might be used to inform subjects of this issue: “Some of the research conducted using your samples or information, either by this research team or other future investigators, may lead to the development of new diagnostic tests, drug treatments or other commercial products. If this happens, there is no plan to provide you with any payment or profits generated from these products.”

D. Data and Sample Sharing Among Institutions

Data sharing between institutions has the potential to contribute to the advancement of knowledge and novel therapeutic solutions for public health and individual patients. To this end, MOPH promotes greater access to data in a responsible, equitable, ethical and efficient manner. In the practice of data sharing, there is a need to balance the needs of all parties involved, including investigators who could discover potential solutions to health problems and research subjects who have a reasonable expectation of privacy concerning the research use of their personal information.

MOPH recognizes the importance of making data available to investigators engaged in public interest health care research. Additionally, MOPH affirms the principle that scientists involved in data sharing should be bona fide investigators, and institutions sharing data should obtain proof of academic or other peer reviewed standing of investigators applying to receive data.

When engaging in data sharing, MOPH requires institutions to follow regulation, policy, and guidance published by MOPH, including, but not limited to the “Guidance for the Use of Stored Data and Biological Specimens in Human Research” and the “Policies, Regulations and Guidelines For Research Involving Human Subjects.”

Ethical Design and Conduct of Genomic Research

This section of this Policy provides guidance to investigators on the design and conduct of genomic research.

When designing and conducting genomic research, investigators should be guided primarily by the MOPH policy "Policies, Regulations and Guidelines for Research Involving Human Subjects" and the section titled Criteria for Institutional Review Board (IRB) approval of research.

A. Criterion 1

Criterion 1 requires that risks to subjects be minimized by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

Investigators should first evaluate the risks of their research in terms of physical, psychological, privacy, legal, social, and economic harm, as described above. The investigator should consider the previous discussion of the risks of genomics research. Each risk should be characterized in terms of probability (the likelihood that the harm will occur) and magnitude (the severity of harm). Minimizing risks by using procedures that are consistent with sound research design and that do not unnecessarily expose subjects to risk means considering alternative ways to conduct research that reduce either the probability and magnitude of harm, provided those alternatives do not affect the ability of the research to answer the scientific question or result in unintended consequences. For example, informational risks can commonly be reduced by the use of encryption, which does not typically affect the ability of research to answer the scientific question. The investigator should consider the previous discussion regarding steps that might be taken to mitigate the risks of genomic research.

B. Criterion 2

Criterion 2 requires that the risks to subjects must be balanced against the sum of two benefits: the anticipated benefit to individual subjects and the anticipated benefit to society (importance of knowledge expected to result). Often in genomic research, there is no benefit to individual subjects, in which case this criterion requires risks to subjects to be reasonable in relation to the importance of the knowledge that may be expected to result.

In considering the previous criterion, investigators should have reduced the risk to the lowest extent possible, while allowing the research to be completed. Therefore, in assessing this criterion, investigators should try to design research that maximizes benefit to subjects, if any, and also maximizes the importance of the knowledge expected to result.

Again, most genomic research does not involve direct benefit to subjects. However, investigators should consider opportunities to find benefit. Among other benefits, genomic results in some cases may be able to provide early identification of a treatable disease or condition, predict the best therapy. Depending on the specifics of the research, these benefits may be unattainable, or the genomic procedures too investigational to anticipate any benefit. Investigators should consider whether modifying the research can result in anticipated benefits to subjects, and if so, design those into the research when possible to maximize the relationship between risks and potential benefits.

To maximize the importance of the knowledge expected to result, investigators should scrutinize scientific design. Procedures should be feasible and results attainable. Procedures should be in place to ensure that protocol mandated procedures are followed as prescribed and to ensure that the resultant data are reliable. Protocols should include appropriate statistical analyses that have been vetted by statisticians. Lastly, investigators should consider whether alternative scientific designs might result in a greater likelihood of success or improved knowledge. In this regard, investigators should request that peers conduct a scientific review of their research plans to maximize the importance of the knowledge expected to result.

Maximizing the importance of the knowledge also requires operational control over research. Investigators should ensure that they have appropriate resources to carry out the research. These resources include sufficient and qualified people, time, and money. Investigators should ensure that they have access to the subject population required, and an appropriate recruitment plan to attract and retain the necessary subjects.

C. Criterion 3

Criterion 3 requires the selection of subjects to be equitable, taking into account the purposes of the research and the setting in which the research will be conducted. In designing genomic research, investigators should be particularly cognizant of the special problems of research involving populations that are vulnerable to coercion or undue influence.

To ensure that subject selection is equitable, investigators should be careful not to unfairly include or exclude a population. Inclusion is unfair when one population is exposed to the risks of research while another reaps the benefits of research. Inclusion is also unfair when subjects are targeted in a manner that exploits their vulnerability. Exclusion, similarly is unfair where one population is offered benefits only available within the research context, while another is excluded from such benefits. To ensure that the selection of subjects is equitable, investigators should examine their inclusion criteria as well as the process for recruitment. Inclusion of vulnerable populations should be based on scientific grounds rather than convenience.

D. Criterion 4

Criterion 4 requires informed consent to be sought and appropriately documented from each prospective subject or the subject's legally authorized representative.

To ensure that informed consent is appropriately sought and documented, investigators should have a written procedure by which they plan to carry out consent processes. This procedure should have the person obtaining consent take steps to verify that:

- The person providing consent has been given sufficient information.
- The person providing consent understands the information.
- The person providing consent does not feel coerced or unduly influenced.
- The person providing consent has sufficient time to make a decision.
- The individual providing consent understands the consequences of a decision.

- The individual providing consent can communicate a choice.
- The investigator stops the consent process if the person providing consent indicates that he or she does not want to consent.

To provide sufficient information, investigators should inform subjects of all required and appropriate additional elements of consent disclosure listed in “Policies, Regulations and Guidelines for Research Involving Human Subjects” in the sections titled “Basic elements of informed consent” and “Additional elements of informed consent.”

There are several special issues in obtaining informed consent for genomic research. Genomic procedures and their implications are complicated, but they must be described to the subject in a manner such that the subject understands the research procedures. When genomics research is combined with clinical care, the subject must be informed of the distinction between procedures conducted for clinical care and those performed for research purposes. Based on the risk analysis conducted by the investigators, subjects need to be informed of the reasonably foreseeable risks and their implications. Any potential benefits identified by the investigator should be disclosed, without any being explicitly promised. When there are no benefits, subjects should be so informed. Subjects should be told to whom the investigator plans to disclose and withhold information. Subjects should be informed that, despite reasonable efforts to maintain confidentiality, absolute secrecy cannot be promised, and there is always a possibility that the information obtained during research may be inadvertently disclosed to others with whom the investigator did not plan to share such information.

Investigators should also have a process to document consent in writing in accordance with legal requirements. Individuals obtaining consent should understand that the consent process is distinct from getting a signed consent document.

In some cases, the research cannot be conducted if consent is a requirement. When such research involves more than minimal risk and meets other criteria, the IRB may waive the requirement to obtain and document informed consent. In general, whenever there is personal contact or interaction with a subject, informed consent must be obtained and cannot be waived.

E. Criterion 5

Criterion 5 requires, when appropriate, the research plan must include adequate provisions for monitoring collected data to ensure subject safety.

When genomic research involves greater than minimal risk to subjects, investigators should monitor the harms and benefits accruing to subjects. Because of our limited experience with genomic research and the long periods of time over which genomics research occurs, genomic research is particularly susceptible to unanticipated problems. The purpose of monitoring is the early detection of unforeseen changes in the relationship of risks and potential benefits. Investigators should design this monitoring process to detect whether harms are occurring at an unexpectedly high rate or severity. Investigators should also design this process to detect whether benefits are occurring at an unexpectedly low rate or intensity. Such monitoring is often referred to as a “data and safety monitoring plan.”

When designing a data and safety monitoring plan, investigators should decide who will monitor the relevant data. Investigators may monitor the data themselves, but only to the extent that they have the requisite time or expertise. In some cases,

investigators should involve multiple individuals with genomic, statistical, and information security expertise.

When genomic research involves greater than minimal risk to subjects, investigators should also be explicit about what data are monitored. In most genomic research cases, subjects should be periodically evaluated for physical, psychological, privacy, legal, social, and economic harm, and such harm should be evaluated in terms of frequency and severity. In those cases of genomics research that hold out a prospect of benefit to subjects where that benefit is required to justify the risks of research, investigators should monitor the degree of benefit that subjects experience.

Investigators should ensure that data and safety monitoring plans also describe the frequency and length of monitoring. In some cases, an annual evaluation may be appropriate. When the risk of harm is moderate to high, more frequent monitoring might be appropriate. The higher the degree of uncertainty about risks and potential benefits, the more frequent the research should conduct monitoring.

Lastly, the data and safety monitoring plan should describe the actions to be taken when unexpected information is discovered. At a minimum, the actions should include notification to the IRB. However, the investigator should consider other actions to mitigate the change in the relationship of risks and potential benefits. These might include consideration of changes to the protocol, interventions with subjects that have been harmed, stopping the protocol on a temporary basis until changes are implemented, and in some cases, terminating the protocol.

F. Criterion 6

Criterion 6 requires, when appropriate, that there be adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

Privacy is about how subjects control access to themselves in terms of interaction, intervention, or access to information. Investigators should consider whether subjects will be comfortable taking part in the research procedures or having their data accessed. If not, research procedures should be changed to ensure that individuals do not feel that their privacy has been inappropriately invaded.

Confidentiality is about promises made to the subject about the control of data and the procedures in place to ensure that control. Investigators should examine promises being made to subjects about to whom data will be provided and from whom data will be withheld.

Investigators should consider the privacy and confidentiality ramifications associated with who will or will not receive genomic research results, how and whether data will be retained after the study is completed for future studies, where and how data or specimens will be stored, who will have access to the data or specimens, and how long the data or specimens will be retained. Where these plans exist in a genomic research protocol, the investigator should ensure appropriate safeguards are in place to protect privacy and maintain confidentiality using the mitigation strategies described above for information risks.

G. Criterion 7

Criterion 7 requires that, when some or all subjects are likely to be vulnerable to coercion or undue influence, additional safeguards are included in the study to protect the rights and welfare of these subjects.

Investigators should consider whether subjects will be enrolled who are vulnerable to coercion or undue influence. Such subjects include individuals for whom there is a power differential with the person obtaining consent (e.g., physician-patient, employer-employee, professor-student), language issues (e.g., the person obtaining consent and the subject do not speak the same language), decisional issues (e.g., children or adults with dementia), or excessive motivation (e.g., dying patients unrealistically considering genomic research to be a cure).

When subjects are vulnerable to coercion or undue influence, investigators should include procedures that minimize the possibility of coercion or undue influence. This might include assessment of the capacity to consent, use of witnesses to the consent process, obtaining permission from a parent or relative, or obtaining the assent of a subject incapable of consent. When enrolling vulnerable populations, investigators should ensure that the research question could not be answered by a non-vulnerable population and whether risks acceptable for a non-vulnerable population are acceptable for a vulnerable population.

Ethical Review of Genomic Research

These Guidelines addresses ethical issues that arise in genomic research in terms of the criteria for the approval of such research located in the MOPH policy entitled “Policies, Regulations and Guidelines for Research Involving Human Subjects.”

Most ethical issues encountered in genomic research affect whether a particular criterion for approval can be satisfied. This Policy addresses the interplay between each criterion with the ethical issue(s) to consider.

A. Criterion 1

Criterion 1 requires the IRB to determine that risks to subjects are minimized by using procedures that are consistent with sound research design, that do not unnecessarily expose subjects to risk, and, whenever appropriate, are already being performed on the subjects for diagnostic or treatment purposes. The ethical principle underpinning the concept of equitable selection is beneficence.

Although risks may be inevitable in research, individuals conducting research should nevertheless ensure that, when appropriate, measures are taken to minimize risk within the constraints defined by regulation. In doing so, research studies can protect the safety, rights, and welfare of subjects. There are four steps IRBs should follow to apply this criterion:

1. **Enumerate the risks of the research.**

   IRBs should consider the physical, psychological, privacy, legal, social, and economic harms that may arise from the conduct of the research. If the IRB is uncertain of the risks, the IRB should consult with scientific experts to obtain as much certainty as possible. In some cases, risks may be unforeseeable or unknown.

2. **Determine the probability and magnitude of each risk.**

   There are two factors that combine to make up a risk: *probability* and *magnitude*. Probability is the likelihood or chance of injury or loss occurring as the result of a study. Magnitude is the size or extent of injury or loss occurring as the result of a study. Knowing the probability and magnitude of injury or loss is important to assess whether incumbent risk is minimal. Knowing the probability and magnitude of injury also helps in minimizing risk, since risk can be minimized by reducing probability, magnitude, or both.

   The probability of a risk may range from occurring 100% of the time to occurring less than 1 in 1,000,000 cases. IRBs should assess the probability of a risk by objective data rather than a subjective manner. Understanding the probability of an injury or loss requires scientific expertise. Therefore, IRBs should rely on data when assessing the probability of risk rather than perception of risk. If the IRB does not know the probability of an injury or loss, the IRB should consult with scientific experts.

   IRBs can evaluate the magnitude of a risk by considering the effect, duration, and reversibility of the injury or loss. The effect might range from a minor inconvenience to permanent disability or death. The duration may range from a few seconds to life-long. The reversibility may range from easy and rapid

reversibility with a low-risk intervention, to a difficult and slow reversibility with a high-risk intervention.

3. Determine whether the research involves no more than minimal risk.

Compare the probability of the aggregate harms anticipated in the research to the probability and magnitude of harm or discomfort ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. That is, determine whether the research involves no greater than minimal risk. If so, risks to subjects are minimized and IRBs should determine that this criterion is met.

The following provides guidance on the probability of harms in daily life by magnitude:[1]

Magnitude	Example	Probability
Negligible	Bruise	1 in 1
Small	common cold	1 in 10
Moderate	bone fracture	1 in 1000
Significant	ligament tear	1 in 10,000
Major	loss of finger	1 in 10,000,000
Severe	Paraplegia	1 in 1,000,000
Catastrophic	Death	1 in 100,000

4. Consider an alternative way of performing the research that reduces the risks, yet allows the research to achieve its scientific aims.

When research involves greater than minimal risk to subjects, IRBs should determine whether the risks can be reduced in a way that does not affect the scientific aims of the research. Importantly, the requirement "by using procedures consistent with sound research design" is a restriction on the ways that the IRB can minimize risk, rather than a requirement for sound research design.

The first strategy to minimize risk is to consider the mitigation strategies noted above, such as minimizing informational risk. The second strategy is to consider whether any research procedures involving greater than minimal risk will be performed for non-research reasons, and if so, not repeat these procedures solely for the research.

B. Criterion 2

Criterion 2 requires the IRB to determine that risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects and the importance of the

[1] Annette Rid; Ezekiel J. Emanuel; David Wendler: Evaluating the Risks of Clinical Research. JAMA. 2010;304(13):1472-1479

knowledge that may reasonably be expected to result. The ethical principle behind the idea of equitable selection is beneficence.

Obtaining information and benefiting subjects should be the key outcomes of genomic research. However, as noted earlier, genomic research also poses risks to subjects. In developing genomic research, it is therefore, important to know how to weigh the risks against anticipated benefits. Anticipated benefits are events having a probability of occurring, but they may or may not occur. What is commonly called a "risk-benefit analysis" is an analysis of risk weighed against anticipated benefits. There are two specific anticipated benefits of research that should be analyzed in the "risk-benefit analysis": (1) the anticipated benefits to subjects, if any, and (2) the importance of the knowledge that may reasonably be expected to result.

After taking the steps above to analyze criterion 1, IRBs should take the following additional steps to apply this criterion:

1. **Enumerate the anticipated benefits to subjects.**

   The first step to applying this criterion to genomic research is to enumerate the specific anticipated benefits of the research to the individual subjects. During this step, IRBs should focus exclusively on anticipated benefits to individual subjects rather than anticipated benefits to subjects in aggregate or to others. Benefits in research cannot be guaranteed. As such, the IRB must analyze potential benefits. Potential benefit is defined as the likely chance of a positive outcome. Like risk, the possible positive outcomes may be physical, social, psychological, economic, or legal. Commonly, there are no anticipated benefits to subjects in genomic research other than the psychological benefit that comes from altruism.

   Though not a requirement, subjects may be compensated for taking part in research. Although this is an economic incentive to participate in research, this incentive should not be included in the analysis of risks and potential benefits. In some cases, participation in research may result in other economic benefits, such as the ability to get the results of an expensive test (e.g., whole genome sequencing) for free, or being able to gather information that will result in reduced medical costs in the future. These economic benefits can be considered as anticipated benefits to subjects for the purpose of an analysis of risks and potential benefits.

2. **Determine the probability and magnitude of each benefit.**

   Like risk, there are two factors that combine to make up an anticipated benefit: *probability* and *magnitude*. Probability is the likelihood or chance of a positive outcome occurring because of a study. Magnitude is the degree of positive outcome occurring because of a study.

   The probability of a benefit may range from occurring 100% of the time to occurring less than 1 in 1,000,000 cases. IRBs should assess probability by objective data rather than subjective impression. Like risks, humans are very poor at estimating the probability of benefit. IRBs should rely on data when assessing the probability of benefit rather than perception. If the IRB does not know the probability of a benefit, the IRB should consult with scientific experts.

Like risks, IRBs can evaluate the magnitude of a risk by considering the effect and duration. The effect might range from a minor improvement to prevention of a life-threatening situation. The duration may range from a few seconds to life-long.

3. Define the knowledge reasonably expected to result.

IRBs should then evaluate the aims of the research and what knowledge will result. Although IRBs often state they consider benefit to society, the only societal benefit that IRBs should consider is the importance of the knowledge reasonably expected to result. Knowing this requires the ability to evaluate the procedures in a protocol, the data collected, the methods of analysis, and the likelihood of success. Therefore, such an evaluation requires scientific expertise. If the IRB does not know what knowledge will result from the research, the IRB should consult with scientific experts.

4. Assess the importance of that knowledge.

Once it is clear what knowledge is likely to result from the research, the IRB should then assess the importance of that knowledge. Assessing the importance of knowledge does not require scientific expertise. It is a judgment call based on each IRB member's experience and background.

5. Determine whether the risks are justified by benefits

IRBs should then determine whether the risks of the research are justified relative to the sum of these two benefits:

- The anticipated benefits to subjects, if any.
- The importance of knowledge reasonably expected to result.

Research does not need to have both benefits. When research has no important knowledge reasonably expected to result, the risks can be justified solely by the potential benefits to subjects. When research has no potential benefits to subjects, the risks may be justified solely by the importance of knowledge reasonably expected to result.

The greater the risk of the research, the greater the demand for benefit in terms of the benefits to subjects, if any, and the importance of the knowledge that may reasonably be expected to result, or both. The demand for benefit lessens as the risk of the research lessens. When research involves minimal risk, the risks can be justified by minimal benefit.

In genomic research, there is usually no expectation of benefit for the subject. Such research can be approved if risks to the subject are reasonable compared to the importance of the knowledge that may reasonably be expected to result. Therefore, if the risks in the genomic research are minimized, the research could be approved even with no benefit to subjects and minimal importance of the knowledge expected to result.

In situations where risks in a genomic research study make the research greater than minimal risk, those developing the research must ask what anticipated benefits there are to subjects as well as whether the importance of the knowledge expected to result is balanced with the risks of the research. If

the risk to potential benefit ratio is acceptable, the research meets this criterion.

C. Criterion 3

Criterion 3 requires the IRB to determine that selection of subjects is equitable, taking into account the purposes of the research and the setting in which the research will be conducted and the special problems of research involving populations vulnerable to coercion or undue influence. The ethical principle behind the idea of equitable selection is justice.

This criterion requires there to be a fair sharing of the burdens and benefits of research. This criterion does not require equality, rather it requires equitability. Equality implies that two things are identical. Equitable implies that justice and fairness are present. While ensuring the safety of subjects during research, it is also important to share the burdens and benefits of research equitably. When fairness is not present in research, an injustice arises. An injustice occurs when a benefit to a subject, which is otherwise entitled, is denied without good reason. An injustice also occurs when a burden is unduly imposed on the subject.

The *burdens* of research are the risks that subjects face when participating in research. If research involves no more than minimal risk to subjects, there cannot be an unfair burdening of subjects. For research involving more than minimal risk, the requirement to equitably share burdens becomes more important. Similarly, when research involves populations vulnerable to coercion and undue influence, the requirement to ensure fairness in inclusion of these populations becomes more important.

The *benefits* of research can be divided into individual and social classifications. The individual benefits are the anticipated benefits to the subjects taking part in research. The social benefit is the knowledge expected to result. For genomic research involving no benefit to subjects, subjects excluded from research involving no benefit cannot be considered deprived of research benefits. The requirement to equitably share benefits becomes more important when the benefits of research increase compared to benefits available outside of the research. In terms of social benefit, it is important not to unfairly exclude populations who could benefit from the research. For example, genomic research limited to adults may unfairly deprive children from the knowledge expected to result from the research. Genomic research limited to men may unfairly deprive women from the knowledge expected to result from the research.

In assessing whether the selection of subjects is equitable, the IRB should take into account the purposes of the research. When research is seeking answers to questions about Qatari citizens, non-citizen Qatari residents can be equitably excluded. If research involves a question that only affects women, men can be equitably excluded.

When the IRB assesses whether selection of subjects is inequitable, the IRB should take into account the setting in which the research is conducted. When an investigator conducts research in one city, the research can be expected not to include subjects from far away, and this situation is commonly accepted as equitable selection. Subjects speaking an uncommon language for the setting of the research might be equitably excluded due to the resources that would need to be put in place relative to the benefit to subjects. Research conducted in a women's university could equitably exclude men.

The regulations state that when the IRB assesses whether selection of subjects is inequitable, the IRB should be particularly cognizant of the special problems of research involving populations vulnerable to coercion or undue influence. Individuals who are vulnerable to coercion or undue influence might be burdened because they can be manipulated to take part in research, and might be used repeatedly solely for convenience. IRBs should consider whether any populations are being unfairly taken advantage of by convenience or accessibility.

There is a built-in tension with regard to including or excluding vulnerable populations. Such populations might be excluded to provide protection. For example, high-risk research may start with adult subjects before proceeding to using children as subjects. On the other hand, research results from adults may not apply to children, and the exclusion of children deprives them of the benefit of the research.

D. Criterion 4

Criterion 4 requires the IRB to determine that informed consent will be sought and appropriately documented from each prospective subject or the subject's legally authorized representative. The ethical principle behind the idea of equitable selection is respect for persons.

IRBs should take the following steps to apply this criterion:

1. **Determine whether the consent process can be waived.**

   The MOPH policy allows the consent process to be waived under certain limited circumstances. See, for example, *"Policies, Regulations and Guidelines for Research Involving Human Subjects"* at page 9. If the IRB determines that the protocol qualifies for a waiver of consent, this criterion is met.

   With genomic research, waiver of consent is generally not available when there is interaction between the investigator and the research subject. Waiver of consent may be appropriate when genomic research is conducted on archived specimens. For example, specimens may be provided to an investigator with no individual identifiers or links to identifiers such that research on the specimens would not qualify as research involving "human subjects" as defined in MOPH Policy. For additional information regarding this issue, consult the MOPH Policy entitled "Guidance for the Use of Stored Data and Biological Specimens in Human Research."

2. **Evaluate the process the investigator will use to obtain consent.**

   The consent process starts when a potential subject is first approached and continues throughout the entire research process. Investigators must describe in their research protocol a process of consent (beyond the signing of a consent document). Without a description of the consent process, the IRB cannot determine whether this criterion is met.

   MOPH requires that in the consent process, subjects must have an opportunity to consider whether to participate, the possibility of coercion or undue influence must be minimized, the information that is given to the subject or the representative must be in language understandable to the subject or the representative, and there may not be exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the

investigator, the sponsor, the institution or its agents from liability for negligence.

3. Determine whether the consent process is legally acceptable.

The IRB must determine whether the investigator will obtain the legally effective informed consent of the subject or representative. Legally effective consent means:

- The subject (or representative?) has been provided with sufficient information to make a decision.
- The subject (or representative?) understands the consequence of a decision.
- The subject (and/or representative?) can make a decision.
- The subject (and/or representative?) can communicate a decision.

The IRB must first determine whether subjects will be provided with sufficient information. What constitutes sufficient information to make a decision is covered by determinations regarding the elements of consent disclosure.

Whether consent is legally effective depends, in part, on the subject. We refer to subjects who can provide legally effective consent as being “capable” or having “capacity.” Subjects unable to give legally effective consent are said to be “incapable” or to “lack capacity.” These subjects may be unable to understand the information provided, may not realize the consequences of a decision, or may be unable to make or communicate a decision.

Capacity to consent also depends on the type of research being conducted. An individual may lack capacity to consent to a complicated research study yet have the capacity to consent to a simple research study. Moreover, the capacity of an individual may vary over time. An individual might be ordinarily capable of consent, but lack capacity due to intoxication, medication, extreme pain, or severe illness. In most cases, genomic research is conducted with subjects who are fully capable to consent for themselves. However, MOPH understands that there could be a scenario where someone incapable of informed consent would participate in genomic research. For example, genomic studies might be conducted on subjects with end-stage dementia or severe psychiatric illness.

If an adult subject does not have the capacity to consent, the IRB may determine that a legally authorized representative (LAR), defined as someone authorized under Qatari law to consent on behalf of a prospective subject to the subject’s participation in the procedures involved in the research, may consent on behalf of the prospective subject. The IRB may require that the subject provide verbal assent to participate despite the subject lacking capacity to consent. If the prospective subject who lacks legal capacity is present during the consent discussion, his or her objection to participate in the study should be considered.

Capacity is not the same as legal competency. Legally competent individuals may lack capacity to consent to a particular research study. Likewise, legally incompetent individuals may have the capacity to consent to a particular

research study. IRB members need to know the expected capacity of potential subjects to determine whether consent is legally effective.

4. **Determine whether the consent process provides sufficient opportunity for the subject or representative to make a decision.**

   The IRB must determine whether the conditions of consent provide the subject with a sufficient opportunity to consider whether to participate. Time cannot be used to pressure or interfere with a decision. What constitutes a sufficient opportunity varies between research protocols.

   In genomic research, entire families may be affected by the decision of a family member to participate. Therefore, investigators should give subjects sufficient time to consider the effect of this research on both themselves and, possibly, their family. Time cannot be used to pressure or interfere with a decision. What constitutes a sufficient opportunity will vary depending on the nature of the genomic research.

5. **Determine whether the consent process minimizes the possibility of coercion or undue influence.**

   The IRB must determine whether the circumstances of consent minimize the possibility of coercion or undue influence.

   Coercion is the use of express or implied threats of violence, reprisal, or other intimidating behavior to compel a person to act against his or her will. A person who is coerced is deprived of the power to choose. As an example, when a subject says, “I must join this research study, or else I will die,” the subject is being coerced.

   Influence that is not undue is acceptable while undue influence must be minimized. For example, investigators can use advertisements and payments to influence subjects to take part in research provided they do not represent undue influence. An example of undue influence would be if a physician threatens to withhold certain treatments from a subject if the subject does not participate in the study. In this example, the physician is using his or her position of influence in a way that most people would deem “undue.” IRB members should use their judgment to decide whether influence is acceptable or undue, and expect that reasonable people may disagree.

6. **Determine whether the information provided during the consent process will be in language understandable to the subject or representative.**

   The IRB must determine whether the information given to the subject will be understandable. This refers to all information provided to the subject, whether it is oral or written. Since consent is an ongoing process, this also refers to the level of understanding when the subject agrees to take part and continued understanding during the research, not just the understandability of a single portion of the information provided, such as the consent document.

   Clear and concise language depends on the receptive ability of the subject, and the processes used by the investigator. The requirement is that during the consent process, the subject will have understood the information necessary to make a decision. This requirement applies both to written documents and oral communication. This is not a requirement that the subject

has to understand every word or phrase upon initial presentation in the absence of follow-up explanation.

In any reasonably complicated research study, some subjects will not understand everything on initial presentation. This is acceptable provided the investigator spends time restating information in different terms until it is understandable to the subject. It is unnecessary for the IRB to rewrite every document to be understandable to everyone. It is also insufficient for an IRB to assume that every document (even if rewritten by the IRB) will be understandable to everyone.

IRB members should assess understandability in the context of the entire consent process. Common strategies for understandability include the use of translators when subjects speak a foreign language, or the use of simplified explanations where subjects' language abilities are decreased. Other effective strategies to ensure understandability are for the investigator to ask the subject questions to assess understanding or to ask the subject to explain the research to the investigator.

Although many IRBs focus on and have standards for readability, readability is neither necessary nor sufficient to ensure understandable language during the entire consent process.

While the physical procedures in genomic research are often simple (e.g. blood draw, collection of tissue or saliva), what is done with the data or sample in the research is often complex and challenging for subjects to understand. Thus, investigators must make the consent process sufficiently understandable for subjects to be aware of the nature of the research, the consequences of their decision, and the extent to which their information or sample may be shared, either in this research or in future research. Clear and concise language should be used during the process and language must be readable.

7. Determine that the information provided during the consent document will not be exculpatory.

The IRB must determine that the informed consent process will not include exculpatory language. Exculpatory language waives or appears to waive a subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence.

Not all waiver statements are exculpatory. A good definition of exculpatory language is: "Language that has the general effect of freeing or appearing to free an individual or an entity from malpractice, negligence, blame, fault, or guilt."

If a subject is asked to waive his or her right to be compensated for injuries arising from research participation, such language is exculpatory because it has the general effect of freeing or appearing to free the investigator, sponsor, and/or the research institution from malpractice, negligence, blame, fault, or guilt.

If a subject is asked to waive his or her rights with respect to the tissue obtained by investigators for research purposes, such language may not be exculpatory provided no laws or policies provide such legal rights. If there are

no applicable laws or policies, such language does not free or appear to free the investigator, sponsor, and/or the research institution from malpractice, negligence, blame, fault, or guilt.

Exculpatory language issues often arise with disclosures about compensation available in the event of research-related injury. Statements such as, “The sponsor or institution will provide no compensation in the event of research-related injury” are considered exculpatory. Statements such as, “This sponsor or institution makes no commitment to provide free medical care or payment for any unfavorable outcomes resulting from participation in this research” are not considered exculpatory.

8. Determine whether the required elements of consent will be disclosed.

The IRB must determine that subjects are provided sufficient information to make a decision. The information that must be disclosed to subjects is contained in the “elements of consent.” One way to organize the elements of consent disclosure is to consider the following two categories:

- Disclosures required for all research
- Disclosures required whenever applicable

The IRB must determine that following disclosures are provided for all research:

- A statement that the study involves research
- An explanation of the purposes of the research
- An explanation of the expected duration of the subject’s participation
- A description of the procedures to be followed
- Identification of any procedures which are experimental
- A description of any reasonably foreseeable risks or discomforts to the subject
- A description of any benefits to the subject or to others which may reasonably be expected from the research
- A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject
- A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained
- An explanation of whom to contact for answers to pertinent questions about the research and research subjects’ rights
- An explanation of whom to contact in the event of a research-related injury to the subject
- A statement that participation is voluntary

- A statement that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled

- A statement that and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled

- An explanation as to whether any compensation is available for inconveniences and if injury occurs, if so, what it consists of, or where further information may be obtained.

- An explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained

While the required elements of consent disclosure are applicable to genomic research, there are unique considerations in genomic research that should be captured in the consent document, where applicable.

For example, in the section explaining the purpose of the research, subjects should be informed of the reason they are being asked to participate, including the reason why genetic information is being requested (e.g. “Your genetic information could help us in better understanding the causes of diabetes”).

In the section describing the research procedures, the procedures associated with the research should be clearly explained using lay language and simple terms. Procedures in genomic research could include the data or sample collection procedures, how samples and data will be coded or stored, the duration of sample or data storage, whether there will be access to the subject’s medical records and, if so, any processes for accessing them, whether samples or data will be shared with future investigators for research use, a description of investigators who might be provided access to the samples or data, and whether (and how) future re-contact is planned. Below are several examples of procedures that might be explained in a consent form for genomic research:

- “We will collect a sample from you by drawing 25 mL of blood from a vein in your arm. If you do not want blood drawn, we can instead collect tissue by swabbing cells from the inside of your cheeks.”

- “We will collect information from your medical records, such as your age and other background information, disease history, and medical treatments. We will access this information only once a few weeks after you give us permission to access your medical record.”

- “We may wish to obtain additional samples or follow-up information about your health or medical care in the future. In this case, a person from ABC Institution will contact you to ask whether you would be willing to participate in this additional research.”

- “Genotype and phenotype data will be shared for research purposes through the XYZ data repository.”

- “Anonymous information from the analyses will be put in a public database that will be available to anyone on the Internet.”

- “Your coded medical information and information from more detailed analyses of your coded samples may be put into a national database that will only be available to investigators who have received approval from the Ministry of Public Health or designee, such as the Qatar Biobank. Any information put into the database are considered de-identified (e.g. no names, addresses or telephone numbers)]”

- “We will not give you any individual results from the analysis of the samples you give us because it will likely take a long time for this project to produce health-related information that we will be able to correctly interpret. We will also share important general findings from this project and how they are contributing to our understanding of health and disease in our newsletter or website.”

As with all research, anticipated risks must be disclosed to subjects in the consent form and should be explained in terms of probability and magnitude. Potential risks vary depending on the protocol, but, as noted earlier in this Policy, special attention should be paid to explain psychological and social risks to the research subject and, where applicable, their family. Below are several examples of risks that might be explained in a consent form for genomic research if applicable:

- “You may discover information about yourself or your family that you do not want to know.”

- “You may feel emotional pain if you discover you have a genetic mutation.”

- “There is a risk that unauthorized disclosure of your health or genetic information may affect your employability, insurability, social reputation, or some other aspect of your life.”

- “There may be physical or computer security breaches arising from keeping information in an electronic format. These breaches could result in your employer or health insurance company receiving private genetic information about you, which could result in genetic discrimination.”

- “People may develop ways in the future to allow someone to link your genetic or medical information in our databases back to you.”

- “A genetic test result may affect your ability to obtain health, life, disability or some other insurance policy. Certain genetic variations may also be used by law enforcement agencies to identify a person or their relatives, meaning that your genetic information could be used in ways that could cause you distress, such as by revealing that you or a relative carry a certain genetic disease or condition.”

Potential benefits in genomic research vary among protocols. Such benefits must be disclosed to subjects in the consent form. For example, if the genetic test results will be shared with the subject, the subject should be told that knowledge resulting from the test may empower the person or family

members to plan for or make specific health decisions. Payment and monetary reimbursement for participation is not considered a benefit.

For genomic research, the consent element related to confidentiality of subject information should describe who will or will not receive genetic information obtained from the subject, or if the protocol allows it, the consent document should provide the subject with the choice to indicate who will receive the results (e.g. subject's family physician or family members). If data or specimens will be retained after the study for future research, the consent document should explain where the data or specimens will be stored, who will have access to the data or specimens, and how long they will be retained.

The consent element relating to voluntary subject withdrawal should indicate whether the research team can destroy the link between a subject's genetic and medical information and whether samples and data generated from a subject's sample have already been provided to other investigators or research centers or were placed in a formal research database such that the samples or data cannot be withdrawn from those institutions or databases.

Because genomic research may lead to the development of a commercial product either by the investigator or a secondary downstream user, where applicable, the consent document should indicate that there are no plans for the subject to receive payments or profits generated from these products.

Finally, depending on the specific nature of the genomic research, consent form language may require additional modifications. Investigators are encouraged to reference MOPH Regulations and Guidance whenever drafting a consent document.

9. Determine which of the additional elements of consent should be disclosed, and whether those elements of consent will be disclosed.

The IRB must determine whether certain of the following additional elements of disclosure are appropriate, and if so, determine that they are disclosed.

- A statement that the particular procedure may involve risks to the subject which are currently unforeseeable

  Example: The research involves an intervention whose risk profile is not well known, such as an unapproved drug.

- A statement that the particular treatment or procedure may involve risks to the embryo or fetus, if the subject is or may become pregnant, which are currently unforeseeable

  Example: The research involves pregnant women or women of child-bearing potential and involves an intervention whose risk profile to a fetus is not well known, such as an approved drug not approved for use during pregnancy.

- Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent

Example: The research protocol enumerates situations where subjects must be removed from the research, such as failure of the subject to follow protocol requirements.

- Any additional costs to the subject that may result from participation in the research

  Example: The subject may experience personal expense because of the research.

- The consequences of a subject's decision to withdraw from the research

  Example: If the subjects stops taking part in the study, there may be adverse consequences. For example, stopping use of a drug may cause withdrawal symptoms or may require substitution of another treatment.

- Procedures must be followed for orderly termination of participation by the subject

  Example: The research protocol specifies procedures that should be followed when withdrawing subjects.

- A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject (IRBs should consider whether more information could be learned about a gene that would affect individuals and consider whether to require such disclosures when considering criterion 1)

  Example One: The research protocol involves a drug in the early phases of investigation, so not a lot is known about the side effects or effectiveness of the drug. New information arising during the study involving new or increased study drug risks must be communicated to subjects.

  Example Two: In genomic research, if a study involves a series of visits over a long period of time and there is the discovery of a genetic finding during the course of the subject's participation, a statement of new findings would be appropriate. However, in many instances, a genomic study will only involve one subject visit/procedure (e.g. initial blood draw and data collection).

- A statement providing the approximate number of subjects involved in the study

  Example: The research protocol involves a very small number of subjects.

Commonly, none or only few of the additional elements of consent disclosure are applicable to genomics research.

10. Determine whether written documentation of the consent process can be waived

The MOPH policy allows the written documentation of the consent process to be waived under certain limited circumstances. If the IRB determines that the protocol qualifies for waiver of written documentation consent, the determination below about documentation is not required.

Written documentation may be waived if the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research. If documentation of consent is waived, it means that a consent process is followed, and the subject agrees to participate. However, in this situation, the subject does not sign a paper agreement.

In genomic research, waiver of the written documentation of consent may be an option when the research involves no more than minimal risk to the subjects and involves no procedures for which written consent is normally required outside of the research context. Waiver of the written documentation of consent may be appropriate when the written documentation of consent presents a confidentiality risk, when written document is not practical, or when alternative effective forms of documentation will be used such as audio or video recording.

11. **Determine whether the consent process will be appropriately documented in writing.**

    The IRB must evaluate the investigator's proposed process for written documentation of consent and can waive the requirement. Written documentation of consent requires the use of a written form approved by the IRB, the subject or subject's legally authorized representative to sign the form, and the person signing the form to receive a copy.

E. Criterion 5

Criterion 5 requires the IRB to determine that, when appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects. The ethical principle behind the idea of monitoring the data collected to ensure safety of subjects is beneficence.

In research, monitoring has three distinct meanings: monitoring individual subjects for harm, monitoring the progress of research, and monitoring data collected to ensure the safety of subjects. This criterion relates to the third form of monitoring: monitoring data collected to ensure the safety of subjects.

Before applying this criterion, IRBs should determine whether the research involves no more than minimal risk to subjects, and if so, the analysis is complete as monitoring the data to ensure the safety of subjects is not appropriate for minimal risk research.

If the research involves greater than minimal risk to subjects, the risks of genomic research are often uncertain and may change over the long period of time over which the research is conducted. Therefore, the research protocol should have a process to have one or more individuals examine the data gathered for all subjects to make sure that the overall risks and potential benefits are not different than those expected at the beginning of the research. The IRB should be satisfied that, in the event the safety profile of the research changes, the sponsor or research team's plans to monitor the data will detect this and take actions before subjects are at undue risk. Such monitoring is often referred to as a data and safety monitoring plan.

IRBs should take the following steps to evaluate a data and safety monitoring plan:

1. **Evaluate who will monitor the data.**

   Genomic research should be monitored by an individual or individuals who have genomic, statistical, and information security expertise and can be objective about the analysis. For some studies, investigators can monitor the data themselves. For other studies, multiple individuals are required who are independent of the investigator.

2. **Evaluate what data will be monitored.**

   In most cases of genomic research studies, there should be monitoring of physical, psychological, privacy, legal, social, and economic harm for an assessment of the observed versus expected frequency and severity. When genomics research holds out a prospect of benefit to subjects and where that benefit is required to justify the risks of the research, the research plan should include monitoring the degree of actual subject benefit.

3. **Evaluate how often data will be monitored.**

   Data and safety monitoring plans should describe the frequency and length of monitoring. With genomic research, annual monitoring is often implemented. When the risk of harm is moderate to high, more frequent monitoring might be appropriate. Monitoring should be conducted more frequently as the degree of uncertainty about risks and potential benefits increases.

4. **Evaluate what actions will be taken if new or changed risks are discovered.**

   When unexpected information is discovered, the data and safety monitoring plan should always notify the IRB. The IRB might also require that the protocol take other actions such as stopping enrollment or terminating the protocol.

   If the probability or magnitude of harm experienced by subjects as a group is greater than expected, the sponsor, investigators, and the IRB should reconsider whether the study should continue, change, or stop.

F. Criterion 6

Criterion 6 requires the IRB to determine that, when appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data. The ethical principle behind privacy and confidentiality is respect for persons.

This regulatory criterion refers to two distinct but overlapping concepts: privacy and confidentiality. Privacy is about *people*. Privacy is an attribute of subjects and not an attribute of data. Privacy is protected, which in turn renders privacy a right. Confidentiality is about *data*. Confidentiality is an attribute of data and not of subjects. Confidentiality is maintained; therefore, confidentiality has to be created. In order for this criterion to be satisfied, the genomic research protocol must, when appropriate, contain adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

IRBs should take the following steps to apply this criterion:

1. **Evaluate whether subjects have an expectation of privacy.**

   Privacy protections are required by this criterion only when subjects have an expectation of privacy. In most genomics research, subjects have such an expectation.

2. **Determine whether the protocol includes adequate provisions to protect the privacy of subjects.**

   When reviewing provisions to protect the privacy of subjects, IRBs should consider whether subjects will feel comfortable with any access to themselves in terms of interaction, intervention, and private identifiable information. Each individual sets his or her boundaries about what is private, and how a subject reacts to privacy issues depends on the situation and the subject's background, such as culture, age, and ethnicity. Boundaries also vary by individual. IRBs should try to understand how the subject will feel about genomic research rather than projecting how the IRB feels about genomic research onto the subjects.

3. **Determine whether the protocol includes adequate provisions to maintain the confidentiality of data consistent with the promises made and any legal requirements.**

   Confidentiality, on the other hand, is created when an investigator commits to limit sharing of subject data or there is a legal requirement to limit sharing of data. Here, the IRB should consider whether the provisions to limit disclosure of the data match the commitment made by the investigators and any legal requirements for confidentiality. The promised level of confidentiality may still pose a risk to subjects and be contrary to the ethical principle of beneficence. Therefore, the IRB should evaluate confidentiality risk under the first and second regulatory criteria: (1) risks to subjects are minimized by using procedures that are consistent with sound research design and that do not unnecessarily expose subjects to risk; and (2) risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects and the importance of the knowledge that may reasonably be expected to result.

   In genomic research, an IRB may determine that stricter confidentiality is required than the provisions in the protocol promise. If the IRB determines that stricter confidentiality will reduce risks to subjects without affecting the soundness of the research design, the IRB should require that change under criterion 1. If the IRB determines that confidentiality risks to subjects are unreasonable in relation to anticipated benefits, the IRB should require stricter confidentiality under criterion 2.

G. Criterion 7

Criterion 7 requires the IRB to determine that when some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects. The ethical principle for providing additional protections to vulnerable populations is respect for persons. The Belmont Report's principle of respect for persons implies that when subjects have limited autonomy, these subjects may require additional protections. Vulnerable populations refer to classes of individuals who are more susceptible to coercion or undue influence. Vulnerable

populations have historically been classes of individuals exploited for their ease of manipulation or convenience.

IRBs should take the following steps to apply this criterion:

1. **Determine whether any subjects are vulnerable to coercion or undue influence.**

   The following lists classes of individuals commonly considered to be vulnerable to coercion or undue influence.

   - Fetuses
   - Prisoners
   - Children
   - Mentally disabled persons
   - Economically disadvantaged
   - Educationally disadvantaged
   - Students
   - Employees
   - Persons with a life threatening disease

   Inclusion on this list does not automatically imply vulnerability. In research involving the review of existing records, autonomy may not be an issue because the research involves no interaction with subjects.

   Autonomy is ongoing and varies for each individual. Vulnerability may also be situational. For example, teenagers do not entirely lack autonomy on the day before their 18th birthday and then fully gain autonomy on the following day. Teenagers may also be excessively influenced by a role model but minimally influenced by parents or teachers. IRB members should evaluate each protocol to determine whether it involves populations that are vulnerable to coercion or undue influence.

   There are several factors that can be examined to decide whether research involves populations that are vulnerable to coercion or undue influence.

   - **Power Differential:** Vulnerable populations are influenced by individuals who have the power in the relationship. Examples include:
     - Children and parents.
     - Prisoners and guards.
     - Students and teachers or professors.
     - Employees and employers.

    - Patients and healthcare providers.

- **Communication Issues:** Vulnerable populations often have difficulty communicating. Examples include:

    - Children who are unable to communicate their wants and fears.

    - Individuals unable to speak the language of the investigators.

    - Illiterate individuals who are embarrassed to reveal their inability to read.

- **Excessive Motivating Factors:** Classes of individuals may be excessively motivated in a way that interferes with the ability to make a decision. Examples include:

    - Individuals focused on a perceived cure for a severe disease.

    - Prisoners focused on improving their sentence.

    - Economically disadvantaged persons focused on financial rewards.

    - Individuals in severe pain focused on relief.

- **Decisional Issues:** Certain classes of individuals lack the ability to make an informed decision, either because they cannot understand the information provided or they cannot understand the implications of a decision. These individuals may also lack the ability to decide between options or lack the ability to communicate a decision. Examples include:

    - Educationally disadvantaged individuals who may not understand the procedures.

    - Children who do not understand the implications of a decision.

    - Adults with cognitive impairments who are unable to decide between options.

    - Individuals with brain damage who are unable to communicate a decision.

    - Individuals given a sedative who are unable to think clearly.

MOPH Policy prescribes explicit additional protections for these specific classes of vulnerable populations:

- Children

- Prisoners

2. **When the research involves populations that are vulnerable to coercion or influence determine whether the research plan includes additional safeguards to protect the rights and welfare of these subjects.**

   Such additional safeguards fall into two groups:

   - Safeguards that provide additional protections not directly related to protecting autonomy.

   - Safeguards directly related to protecting autonomy, such as permission of a representative or assent.

   Safeguards that provide additional protections not directly related to protecting autonomy bear on whether to include vulnerable populations at all, especially where enrollment of vulnerable populations involves ceding consent to someone other than the subject.

   Other safeguards follow the general rule that there are certain research studies where non-vulnerable subjects may participate, but not vulnerable subjects. This may be acceptable regardless of any direct protections for autonomy. These safeguards include:

   - **Research Question:** Generally, the research question should be important to the vulnerable population being studied. For example, it would be appropriate to enroll adults with dementia in a study looking at an intervention to slow cognitive decline. However, it would be inappropriate to enroll such individuals in a study of an acne medication.

   - **Non-Vulnerable Population:** Generally, the research question should be one that cannot be answered unless a vulnerable population is involved. For example, it would be appropriate to enroll prisoners in a study looking at factors influencing multiple offenses. However, it would be inappropriate to enroll to them in a study of arthritis in the general population.

   - **Risk-Benefit:** Generally, IRBs require a more compelling relationship of risks and potential benefits when there is a vulnerable population. For example, consider a study that involves more than minimal risk but no prospect of direct benefit to the subjects. We might allow adults to take part in such research given the importance of knowledge expected to result. However, for children, regulations require vitally important knowledge or require risks to be a minor increase over minimal risk.

   Safeguards directly related to protecting autonomy, include, but are not limited to:

   - Assessing a subject's mental capacity.

   - Obtaining permission of one or more representatives.

   - Obtaining the subject's affirmative agreement (assent).

- Having an impartial witness observe the consent process to determine that consent was freely given.

- Using translators to communicate information.

- Requiring waiting periods between provision of information and making a decision.

Where a genomic research study is no greater than minimal risk, a standard safeguard for subjects who cannot consent for themselves is obtaining permission from a parent (when the subject is a minor) or other legally authorized representative (for adults who lack capacity to consent).

If sensitive genetic information will be shared with subjects, and some of the subjects may be vulnerable, an appropriate safeguard could be a program for pre-participation counseling. Though the specific safeguards will vary for each study, investigators should consider how the enrollment of vulnerable populations could create the need for additional safeguards to protect the rights and welfare of these subjects.

Education and Training Policy Statement

A. Institutional Review Board Members

Thorough ethical review of genomic research requires that IRB members be trained on issues involving genomic research. Specifically, IRB members should refer to this Policy document to understand how the criteria for approval of research should be applied to genomic research. Because genomic research is evolving over time, MOPH recommends continuing education for IRB members on this topic.

B. Investigators

In order to design and conduct research in accordance with MOPH requirements and guidance, investigators must be trained on ethical issues in genomic research. Investigators should pay specific attention to the issues of confidentiality, consent, data security, sensitivity to cultural norms about genetic abnormalities, and important disclosures to subjects during the consent process. Because genomic research evolves over time, MOPH recommends continuing education for investigators on ethical issues in genomic research.

C. Public Awareness

MOPH encourages institutions and organizations to increase public awareness of the purpose and potential benefits of genomic research. As the public becomes more comfortable with the ethical, cultural, and scientific issues in genomic research, the public may be more willing to participate in genomic research.

D. Healthcare Providers and Insurance Providers

MOPH expects healthcare providers and insurance providers to be aware of the ethical issues associated with genomic research and to create policies and procedures that protect the rights and welfare of human subjects who participate in genomic research. For example, health insurance providers should create non-discrimination policies so that subjects participating in genomic research are not treated unfairly based on the results of genetic tests in the research. Healthcare providers should create policies to properly handle information related to genomics research. Healthcare providers and insurance providers should also promote and conduct organizational training on privacy and information security to help ensure that information shared with these organizations about research subjects remains secure.