**NHGRI IRB**

**Human Subjects Research Protocol Template**

Project title:

Draft/version number (day, month, year)

NHGRI Protocol Number (when assigned)

Principal Investigator:

Title/Section/Branch/Institute:

IND/IDE reference number: (if applicable)

**Collaborating Institutions:** (*if applicable*)

*List the name of the Site and FWA# for each institution; see* <http://ohrp.cit.nih.gov/search/asearch.asp#ASUR> *for assurance #s*

# Protocol Summary

Full Title: *Enter the full title*

**Principal Investigator:**

**Sample Size:** N= *If there are separate sample sizes for multiple subgroups, indicate those as well.*

**Accrual Ceiling:** *Include sample size plus an estimate for persons found to be ineligible during screening, after signing a screening consent.*

**Study Population:** *Include a brief description such as health status (e.g., healthy volunteers or HIV-positive), gender, age, etc.*

**Accrual Period:** *Length of time to completely enroll the study; may include a projected start date.*

**Study Design:** *Provide an overview of the study design, including description of study type (e.g., natural history, data collection, and training), include details such as sample size, purpose, duration, selection and schedule of interventions (e.g., blood draw, apheresis, endoscopy, etc…), if applicable*

**Study Duration:** Start Date: End Date: *Provide the total length of time required to open and complete the study including completion of all subject activities (intervention + follow-up) and include a projected end date*

**Primary Objective:** *Include primary study question(s) and method(s) by which outcomes will be determined.*

**Secondary Objectives:** *Include secondary study question(s) and method(s) by which outcomes will be determined.*

**Exploratory Objectives:** *Include exploratory study objective(s) that may address separate research questions from the parent protocol. (if applicable)*

**Endpoints:** *Include the specific observation (or subject-level summary to be used to address the primary study objective, for example AUC, survival, etc…).*

Update table to accurately reflect page numbering

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# List of Abbreviations (add or remove abbreviations as applicable to this protocol)

AE Adverse Event/Adverse Experience

CFR Code of Federal Regulations

CLIA Clinical Laboratory Improvement Amendment of 1988

COI Conflict of Interest

CRADA Cooperative Research and Development Agreement

DAC Data Access Committee

dbGaP Database of Genotypes and Phenotypes

DUC Data Use Certificate

DHHS Department of Health and Human Services

DSMB Data Safety and Monitoring Board

FWA Federal Wide Assurance

GCP Good Clinical Practice

GINA Genetic Information Nondiscrimination Act

GWAS Genome-Wide Association Study

HIPAA Health Insurance Portability and Accountability Act

ICF Informed Consent Form

iPSC Induced Pluripotent Stem Cells

IRB Institutional Review Board

MTA Material Transfer Agreement

N Number (typically refers to number of subjects/sample size)

NHGRI National Human Genome Research Institute, NIH

NGS Next Generation Sequencing

NIH National Institutes of Health

OHRP Office for Human Research Protections

OHSRP Office of Human Subjects Research Program

PHI Protected Health Information

PII Personally Identifiable Information

PI Principal Investigator

PK Pharmacokinetics

QA Quality Assurance

QC Quality Control

SAE Serious Adverse Event/Serious Adverse Experience

SOP Standard Operating Procedure

UP Unanticipated Problem

UPnonAE Unanticipated Problem that is not an Adverse Event

WES Whole Exome Sequencing

WGS Whole Genome Sequencing

* Instructions:
  + Insert your responses for each section. Address each point in all sections that are relevant. Indicate “not applicable” as necessary.
  + Use a readable font, like Times New Roman 11-point type, to facilitate legibility. Please endeavor to keep the protocol to the minimum necessary length.
  + Update the Table of Contents page when the document is complete.
  + Update version control and the Table of Contents with any updates or modifications made after the initial review.
  + Delete the italicized bulleted instruction after the instruction has been addressed.
  + All highlighted sections must be updated or removed as applicable. Remove highlighting when updated.

# Precis

* (In 400 words or fewer, describe the study objectives, population, design, and outcome measures)

# Objectives and specific aims.

* (List the objectives concisely; whenever possible, state objectives as hypotheses.)

# Brief rationale and background

* *(Write a* ***brief*** *[****no more than 5 pages in length****] summary of the clinical background, limits of current knowledge, and significance of this protocol. For background on drugs and devices, cite animal studies, prior experience in humans, and discuss potential toxicities. Include* ***up to 20*** *key references.)*

# Description of study design

* (Brief description of what study design has been selected.)

# Description of procedures:

* *(what will be done, when will it be done, where will it be done, duration of participant involvement. Specify which procedures are being done for research only, and which are being done both for research + clinical care. If a procedure will have both clinical and research indications, please specify exactly what standard clinical care requires and what is being done additionally for research (e.g., clinically indicated lumbar puncture with collection of additional CSF for research).* ***Please include a flow-sheet or chart that depicts the subject's participation in the protocol from recruitment and consent to completion of the study procedures).***
  1. Medical information *(what information will be collected, any sensitive information, how long will it be stored, are there future anticipated uses?)*
     1. Research only medical information
     2. Clinically indicated medical information
  2. Diagnostic studies *(include use of radiation or sedation.)*
     1. Research only diagnostic studies
     2. Clinically indicated diagnostic studies
  3. Biological Specimens *(How much will be collected, what disease categories will be studied, will cell lines be created, how will samples be stored, how long will samples be stored, are there future anticipated uses?)*
     1. Research only collection of biological specimens
     2. Clinically indicated collection of biological specimens
  4. Approved Drugs Being Used for Research *(Include dosage in study and range approved for clinical use.)*
  5. Unapproved Drugs/Devices *(indicate if approved for other use, include dosages in study, and IND or IDE number, if applicable. For devices, include a rationale for a Non-Significant Risk or Significant Risk determination.)*
  6. Describe questionnaires or other psychological instruments and estimate how long they will take to complete, and whether they address sensitive topics (Submit copies.)

# Description of study population

* 1. Estimated number of participants, enrollment ceiling, and anticipated enrollment by year.
  2. Description and justification of clinical inclusion/exclusion criteria. *(affected individuals, family members, controls? Define clinical criteria: Will this determination be made by review of prior records or will a screening evaluation be performed? Justify population choice in regards to age, gender, ethnicity, primary language spoken, prisoners, pregnant women, fetuses, people with impaired decision-making ability, healthy volunteers, lab personnel. Refer to SOP 14 for requirements when using vulnerable populations)*
  3. Location of study *(specify NIH Clinical Center facilities and/or other off-site locations).*
  4. Description of recruitment strategies *(How participants will be identified; note efforts to include under-represented minorities; submit copies of recruitment advertisements and letters.)*
  5. For existing sample/data sets, note whether samples were originally collected for research or clinical practice. If obtained for research, include a description of the original purpose of study and prior plans for sample storage. Was consent obtained that would be applicable to this study? (*Include copy of original consent forms.*)
  6. Description of criteria for withdrawal from study.

# Description of study statistical considerations and/or analytic plan:

* (Write a **brief [no more than 3 pages in length]** description of how data will be used to answer hypotheses, sample size and power calculations, methods of analysis, criteria for significance, as applies to this protocol.)

# Description of potential benefits of study:

* 1. Direct benefits to participants *(Include only those physical or psychosocial benefits that derive directly from an intervention being studied)*
     1. Specific results that will be given to participants or their health care providers (Is laboratory CLIA certified? What are the plans to return DNA sequencing results? Will genetic counseling be provided?)
  2. Collateral benefit to participants *(medical or genetic counseling care and other benefits associated with being a research subject at the NIH that are not directly related to the specific study intervention. Do not include financial compensation as a direct or collateral benefit.)*
  3. Benefits to society

# Description of likelihood and seriousness of harms and how safety will be maximized:

* *(Include potential physical and psychosocial harm from both research-related and medically-indicated procedures, alternative interventions that might be advantageous to participants, and provisions for medical or other professional interventions in the event of adverse events.)*
  1. Therapeutic interventions *(drugs/devices/gene transfer)*
  2. Diagnostic interventions *(blood draws/imaging/biopsies)*
  3. Radiation *(Provide documentation of approval from Radiation Safety Committee.)*
  4. Sedation
  5. Risks to family relationships and other psychosocial or economic harms *(e.g., discovery of misattributed parentage, anxiety, depression, stigma, discrimination)*

# Description of how privacy and confidentiality of medical information/biological specimens will be maximized

* *(Reference SOP 18, “Privacy and Confidentiality” and SOP 5, NIH Research Activities with Human Data/Specimens.* Will participant identifiers be attached to data, or will samples/data be coded or unlinked? (Even if names are removed, how likely is potential identification?)
  1. Description of any clinical/demographic information that will be included. (age, ethnicity, sex, diagnosis, stage, treatment)
  2. How might this information make specific individuals or families identifiable?
  3. If research data will be coded, how will access to the “key” for the code be limited? Include description of security measures (e.g., password-protected database, other). List names or positions of persons with access to the "key" for the code.
  4. Will pedigrees be published? Include description of measures to minimize the chance of identifying specific families.
  5. Will personally identifiable information be released to third parties?
  6. Under what circumstances will data/samples be shared with other researchers or deposited in various repositories, biobanks, and/or databases voluntarily or as mandated by NIH policies (e.g. genomic data sharing policy, available at <http://gds.nih.gov>)? As applicable, include discussion of specific data sharing plans and secondary data use limitations (e.g. general use, health-only use, disease-specific use).
  7. Describe any additional features to protect confidentiality.
  8. What circumstances would prompt the PI to report to the IRB loss or destruction of samples. For additional information, see SOP 5, “NIH Research Activities with Human Data/Specimens” or contact OHSRP at 301-402-3444.

# Assessment of risk/benefit ratio

* *(Reasonableness of risks to participants in relation to the potential benefits of the study and in relation to the importance of the knowledge that may reasonably be expected to result.)*

# Unanticipated Problems: Collection, monitoring, analysis and reporting of adverse events and protocol deviations

* 1. Describe all potential adverse events that can be anticipated and monitored for this protocol. If this is either a natural history or limited encounter protocol, explain this to the IRB and specify the occurrences that will be excluded from adverse event reporting.
     1. For natural history protocols, describe range of medical events independent of any protocol encounter that are known to occur in subjects who qualify for study enrollment. Natural history protocols will monitor, but not consider as reportable, occurrences that are purely a consequence of an underlying genetic or medical condition under study in a protocol. Furthermore, adverse events need not be ascertained in limited encounter protocols such as linkage studies or tissue array studies, in which NHGRI investigators are not providers of medical services.)
        1. Possible language for a natural history study: Because the disorder under investigation is rare, anticipated adverse events associated with those disorders -- and the rates of those events – cannot be pre-specified. Adverse events that are clearly related to the natural history of the participant's disorder, based on what is currently known about the disorder, will not be reported to the IRB.  If an event occurs more frequently or is otherwise not consistent with what is known about the natural history of the disorder, it will be reported as an Unanticipated Problem (see Section 12.2. below).
     2. For higher risk studies where AEs are anticipated, please indicate the mechanism that will be used to evaluate AE severity.
        1. Possible language for a high-risk study: All AEs occurring from the time the informed consent is signed through the specified study follow-up period of [X] years will be documented, recorded, and reported. A laboratory abnormality should be reported as an adverse event if it requires an intervention. Interventions include, but are not limited to, discontinuation of treatment, dose reduction/delay, additional assessments, or concomitant treatment. In addition, any medically important laboratory abnormality may be reported as an adverse event at the discretion of the investigator. This could include a laboratory result for which there is no intervention, but the abnormal value suggests a disease or organ toxicity. For the purposes of this protocol all SAEs, and any Adverse Events that are of grade [threshold], will be reported to the trial safety office and will be further reported (i.e. in expedited fashion for qualifying events, to FDA, the IRB, and the DSMB) as may be appropriate and required.
  2. Describe plan to monitor and report adverse events and protocol deviations, as outlined in SOP 16 (available at <https://federation.nih.gov/ohsr/nih/index.php>).
* ***All protocols should include the following standard language, at a minimum:***

Adverse events, protocol deviations, unanticipated problems (UP), Unanticipated Adverse Device Effects (UADEs), serious adverse events, sponsor and serious, are defined as described in NIH HRPP SOP 16 ("Reporting Requirements for Unanticipated Problems, Adverse Events and Protocol Deviations"). All adverse events occurring during the study, including those observed by or reported to the research team, will be recorded. Serious unanticipated problems, Unanticipated Adverse Device Effects and serious protocol deviations, will be reported to the IRB and CD (Clinical Director) as soon as possible but not more than 7 days after the PI first learns of the event. Not serious unanticipated problems will be reported to the IRB and CD as soon as possible but not more than 14 days after the PI first learns of the event. Not serious protocol deviations will be reported to the IRB as soon as possible but not more than 14 days after the PI first learns of the event.

Deaths will be reported to the Clinical Director within 7 days after the PI first learns of the event.

* 1. Describe whether a Data Safety and Monitoring Board (DSMB) and/or any other additional monitoring measures will be used.

# Description of alternatives to participation

* *(Other clinical or research interventions, if any, participants should consider.)*

# Description of consent process

* 1. Who will obtain consent *(PI, AIs)?*
  2. Setting where consent will be obtained *(location of in-person discussion, phone, mail).*
  3. What information will be provided to participants? *(Include consent and/or assent forms, printed or web-based materials, phone scripts and any other related material.).*
  4. Protections for participants who may be vulnerable to coercion or undue influences *(pregnant women, fetuses, children, people with impaired decision-making ability).*
* Adults who lack capacity *[if applicable]*

The condition(s) under study *[SPECIFY]* are characterized by cognitive impairment, and the research questions cannot be answered by only enrolling adults who can consent. The risks of this research for adults who lack capacity to provide consent are *[describe unique risks to this population, or state that the risks are equivalent to those faced by subjects that can provide consent]*. There [is a *or* is no] prospect of direct benefit for adults unable to provide consent.

The PI or a designee will determine whether adult subjects are able to provide consent using both formal assessments of intellectual capacity (such as neuropsychological testing results) and/or determinations made based on conversations with the impaired adult at and before the time of consent. If there are any questions about the subject's ability to provide consent, a consult with the Bioethics Ability to Consent Assessment Team will be called.

In accordance with OHSRP SOP 14E, if the subject does not have capacity to provide consent, it is possible to have the participant's legally authorized representative (LAR) provide consent on his or her behalf. For this study, a court appointed guardian, DPA, or LAR identified from the next-of-kin hierarchy can enroll adults who are not able to provide consent.[[1]](#footnote-2) In cases when a decisionally-impaired subject has not already assigned a DPA and doesn't have a guardian appointed on his/her behalf, the ACAT (Ability to Consent Assessment Team) will be asked to evaluate his/her ability to assign a surrogate.

Once the LAR has been identified, *[specify the PI or designee, if minimal risk or prospect of direct benefit; or the ACAT team if greater than minimal risk with no prospect of direct benefit]* will assess the appropriateness of the participant's LAR to provide consent. An appropriate LAR is one who at least: 1) understands that the protocol involves research; 2) understands the risks, potential benefits (if any), and alternatives to the study; and 3) has sufficient reason to believe participation in the study is consistent with the subject's preferences and values. When subjects are judged to have mental competence above that of a 7-year-old, the team will use the assent process (when possible and appropriate) in addition to obtaining informed consent via a LAR.

* Obtaining reconsent from children at age of majority (waiver request when minor subjects will not be followed as adults) *[if applicable]*

This protocol does not include on-going follow-up with minor subjects after they become adults. However, it may include ongoing analysis of samples and data collected from minor subjects. We request a waiver of the requirement to obtain new consent from minors when they reach the age of majority for such analysis. This protocol meets the conditions set forth in 45 CFR 46.116(d):

--Our research involves no more than minimal risk.

--The waiver will not adversely affect the rights and welfare of subjects.

--The research could not practicably be carried out without the waiver (many of our participants are overseas and will difficult to re-consent and most of our participants have cognitive impairment as a result of their genetic syndrome).

--Whenever appropriate, the subjects will be provided with additional pertinent information.

* Obtaining reconsent from children at age of majority (non-waiver) *[if applicable]*

Minors will be asked to complete an adult research consent form when they reach 18 years of age. If they do not complete the adult research consent form, they will be classified as a partial withdrawal. In the case of partial withdrawal, their specimens and data will be kept for future analyses, but they will not be recontacted to request additional data or samples, or to recruit them into additional studies.

* Statement regarding divorced parents with joint custody *[if applicable]*

In cases where parents share joint legal custody for medical decision-making of a child (e.g., by a custody agreement or court order), it is NIH policy (OHSRP SOP 14D) that both parents must give their permission regardless of the risk level of the research. There are limited exceptions when one parent has since died, become incompetent, or is not reasonably available (e.g., in prison). Consent from the second parent can be obtained by telephone per NIH SOP 12.

* 1. Are there special circumstances regarding obtaining *consent? (Waived consent, opt-out, verbal consent, consent with speakers of other languages and translation of materials into other languages.)*
  2. If this study involves collaborating sites, indicate if there is a single IRB review or if each site’s IRB will review their site’s participation in the study. Describe plans for ensuring appropriate IRB review and approval of consent forms at each site.

# Description of any financial compensation

* 1. Describe the rationale for and amount of any proposed compensation, consistent with SOP 13.
  2. Describe whether compensation will be modified if participant withdraws early.

# References

Bibliography of cited literature

1. Note that a court appointed guardian or DPA can provide authorization for research in all risk categories, but a LAR identified from the next-of-kin hierarchy can only enroll subjects in minimal risk or prospect of direct benefit research. The language in the protocol should be tailored according to the risk level of the research for adults. [↑](#footnote-ref-2)