## ATTACHMENT 2: REQUIRED ELEMENTS OF A PHER PROTOCOL

*Note: Text in italics is instructional.*

**TITLE**

**PRINCIPAL INVESTIGATOR**

**PRÉCIS**

*The purpose of the précis is to provide a short summary. For protocols with an NIH Lead PI, the précis is used to post this scientific summary on CT.gov. The précis is used by some institutes in the review of financial conflict of interest.*

### I. BACKGROUND INFORMATION, SCIENTIFIC RATIONALE AND SIGNIFICANCE

*This section should be no more than 10 pages in length. References should be included but do not count toward the page limit.*

**A. Historical background**

**B. Previous pre-clinical or clinical studies leading up to, and supporting the proposed research (for example, include description of experimental drug or device if any)**

**C. Rationale and scientific basis for the proposed research, and potential benefits to patients and/or society**

### II. SPECIFIC AIMS (Research Objectives)

**A. Objectives and/or hypotheses to be tested**
*State in bullet form the primary and secondary study objectives. Objectives should be tied to measurable endpoints described in subsequent sections of the protocol (e.g., statistical section, survival, response, surrogate markers) and all endpoints must be clearly defined.*

**1. Primary objective**
*The primary objective provides the major focus of the study and takes priority over other aspects of the study and drives statistical analyses.*

2. **Secondary objective(s) (if applicable)**
   *Secondary objectives allow for investigation of contributory questions that, while scientifically important, do not have the same significance as the primary objective.*

3. **Exploratory objective(s) (if applicable)**

## III. STUDY DESIGN

**A. Study design summary**
*Brief description of what study design has been selected*

**B. Study endpoints/outcome measures**
*Identify Primary and Secondary outcome measures*

- *Outcome measures should be prioritized*
- *Generally, there should just be one primary variable with evidence that it will provide a clinically relevant, valid and reliable measure of the primary objective (e. g. lab procedure, safety measure)*
- *Secondary outcome measures should be included whether or not they add information about the primary objective or address secondary objectives. Discuss their importance and role in the analysis and interpretation of study results.*

## IV. STUDY POPULATION

***A.*** **Description of study populations including any vulnerable subjects***.*
*(For more information about vulnerable subjects in research see NIH HRPP SOP "14A – Research Involving Human Subjects.")*

- *Provide brief description of type of subject groups*
- *State accrual number for each group*
- *State target number of completers if applicable*

*State if withdrawals/dropouts will be replaced*

**B. Rationale for subject selection**
*The protocol must include a rationale for research subject selection based on a review of gender/ethnic/race categories at risk for the disease/condition being studied; justify any exclusion based on considerations such as gender, race/ethnicity, age, pregnancy*

**C. Inclusion criteria**

- *Do not list the same criterion under inclusion and exclusion (e. g. include age 18 and over, exclude age under 18)*
- *Describe co-enrollment guidelines for concurrent participation in other protocols (if applicable)*

**D. Exclusion criteria**

## *V.* STUDY SCHEDULE AND METHODS

*Describe all phases of the study, in chronological order when possible, including:*

**A. Study Overview**

- *Summarize study design, number of visits, site location, and duration of visits and how long a person will be in the study*
- *State which visits are inpatient or outpatient*
- *Identify relationship of this study to other protocols (specify if subjects are required to participate in other protocol)*

**B. Screening**

- *Describe screening procedures (i.e. those procedures done to determine eligibility), including examinations and laboratory testing*
- *Specify time frame for completion of screening studies relative to time of enrollment*

*If applicable, identify screening protocol to be used for this study and briefly describe what evaluations will be done under the screening protocol*

**C. Study Visits and Procedures**

**1. Participant visits and procedures**

- *Describe all evaluations and timeframe for completion; include blood draw amounts*
- *Describe, in chronological order, when possible. May name visits (e.g. enrollment/baseline, study phase, follow-up)*
- *Clearly identify which procedures are solely for research purposes, which are clinical care done for evaluation or treatment of the subjects' condition, and which are both*
- *Clearly identify if radiation is used and if it is medically-indicated, for research only or both*

- *Include visits ("follow-up visits") done after completion of study interventions (if applicable)*
- *Identify relationship to other protocols*
- *Include questionnaires or other psychological instruments and estimate how long they will take to complete, and whether they address sensitive topics (Attach as appendix)*
- *Genetic counseling (If applicable, specify by whom; would counseling happen in person; will understanding be assessed?)*

**2. Laboratory evaluations, if not standard diagnostic tests**

***3.*** **Explain how the return of lab results will comply with CLIA** *(for example, and if applicable, laboratory tests will be performed at a CLIA-certified lab, if required by applicable law.)*

**D. End of Participation. You should address issues such as:**

**1. Planned procedure for ending protocol**

*a. Transfer of care to assure continuity of care, if applicable*
*b. Medical care offered at completion of study procedures, if applicable*
*c. State what information will be shared with subjects or their health care providers*

**2. Premature withdrawal**

*a. Provide criteria for removal of participants from study*

## VI. CONSIDERATIONS FOR STUDIES INVOLVING DRUGS, DEVICES OR BIOLOGICS

**A. Description of drug or device used to investigate the study hypothesis.** *If a commercially available drug is used, justify whether (or not) an IND is required. If an IND is required for commercially available or investigational agents, provide the number and identify the Sponsor. If a device is used, identify the device, justify whether an IDE is required or not, and identify the Sponsor if applicable. Provide the investigators' brochure and address Sponsor reporting in the appropriate sections. (For more information about INDs, see NIH HRPP SOP 15 "Research Regulated by the Food and Drug Administration (FDA): General Procedures for Both IND and IDE Applications", SOP 15A "Research Regulated by the Food and Drug Administration (FDA): Information and*

*Policies Specific to Research Involving Investigational New Drugs (Including Biological Products)"or NIH HRPP SOP 15B "Research Regulated by the Food and Drug Administration (FDA): Information and Policies for Investigational Device Exemption (IDE) Applications").*

**B. Describe the biologic/gene to be used.**

**C. Describe the drug/other agent. Provide information on toxicity, formulation, administration, dosages and their adjustment, incompatibilities, the investigator's brochure (for IND agents.)**

**D. Describe the device. Provide a summary of known effects, toxicities, method of administration.**

## VII. STATISTICAL CONSIDERATIONS

**A. Description of the statistical analyses** *(Describe analysis to be used for primary and secondary study endpoints and any exploratory analyses, including level of significance and handling of missing or spurious data, and any planned interim analysis)*

**B. Method and timing for analyzing outcome measures**

**C. Sample size justification** *(Include accrual number request, taking into account screening failures and withdrawals)*

**D. Final analysis plan**

## VIII. MONITORING OF PROBLEMS AND QUALITY ASSURANCE AND REPORTING

**A. Collection, monitoring, and analysis of changes from the protocol plan, adverse events and problems.** (*NIH HRPP SOP 16 provides detail about NIH requirements for monitoring and reporting of* adverse events (*AEs) and unanticipated problems (UPs.)*

**Anticipated AEs and problems**

- *This section should describe all potential AEs that can be anticipated and monitored for this protocol*
- *If this is either a natural history or limited encounter protocol, specify the occurrences that you wish to exclude from AE reporting. (E.g., 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 may monitor, but may not consider as reportable, occurrences that are purely a consequence of an underlying genetic or medical condition under study in a protocol.*

- *Furthermore, AEs may not be ascertained in limited encounter protocols such as linkage studies or tissue array studies, in which investigators are not providers of medical services*

**B. Plan to monitor and analyze events**

*Describe plan to monitor and report AEs for this protocol (anticipated and unanticipated, serious and non-serious) and UPs.*

**C. Type and duration of follow-up of subjects after UPs and/or serious adverse events (SAEs)**

**D. Reporting procedures**

- *In this section, describe the reporting of UPs, protocol deviations and (for FDA-regulated research) SAEs. The PI can request and the IRB can approve a written plan in the protocol for not immediately reporting specified expected SAEs (for example, expected death from the underlying illness.) In addition, UPs that are not AEs should be reported to the IRB. An unanticipated problems is an event that is:*
  - *unexpected in nature, frequency or severity, and*
  - *related or possibly related to the research and*
  - *suggests that the risk of harm to subjects or others is increased*
- *Some examples of possible UPs include: theft or loss of identifiable data, product instability, freezer thaws, etc.*

**E. Criteria for stopping the study or suspending enrollment or procedures**

- *State what review will be done to determine if research can resume*

**F. Data and Safety monitoring plan** *(For more information about data and safety monitoring see NIH HRPP* SOP 17 "Data and Safety Monitoring."*)*

- *State what parameters will be monitored for the study as a whole*
- *Frequency of monitoring (by time, cohort or study milestone)*
- *Identify who monitors the study*
- *Monitoring process should reflect study risk (e.g. monitoring can be conducted by multiple entities, including the PI, investigator, independent study monitor, independent monitoring committee, DSMB.)*

- *If a DSMB is used, describe the:*
  - *Proposed membership (or state name of existing DSMB)*
  - *Proposed charge to the DSMB*
  - *Proposed meeting frequency/schedule*

***G.*** **Quality assurance/site monitoring** *(For more information about quality assurance see NIH HRPP* SOP 23 "Quality Management System for the NIH HRPP"*) Identify who performs or is responsible for the monitoring e.g. external auditor*

## IX. HUMAN SUBJECTS PROTECTION ISSUES

### A. Study Population

**1. Justification for inclusion or exclusion of women, men, minorities, and children or other vulnerable subjects** *(Vulnerable subjects include those who lack consent capacity, the mentally ill, prisoners, cognitively impaired subjects, pregnant women, children, and employee volunteers. For more information about vulnerable subjects in research see "*SOP 14A - Research Involving Vulnerable Subjects (General Considerations)*",* SOP 14B "Research Involving Pregnant Women, Human Fetuses and Neonates"*,* SOP 14C "Research Involving Prisoners"*,* SOP 14D "Research Involving Children"*,* SOP 14E "Research Involving Adults Who Are or May Be Unable to Consent"*, or* SOP 14F "Research Involving NIH Staff as Subjects"*)*

***2.*** **Justification for sensitive procedures** (*Such procedures can include: use of placebo, medication withdrawal, provocative testing, deception)*

***3.*** **Safeguards for protecting vulnerable populations**

**4. Recruitment plans**

- *Description of recruitment strategy*
- *Source of subjects*
- *Recruitment venues*
- *How potential subjects will be identified and approached*
- *Anticipated accrual rate*
- *Types of advertisements planned (e.g. national newspaper, local flyers; specific names are not needed)Provide recruiting materials, including advertisements, list-serve notices, letters to participants or physicians, and recruitment website content, as attachments to protocol*

- *Provide pre-screening questions as attachment*

**B. Reimbursement, incentives, travel reimbursement and in kind benefits**

- *Describe whether participants will receive reimbursement/incentives and describe amount, form and timing of any such compensation in relation to study activities (include financial and non-financial incentives)*
- *Describe who will receive incentives (if not the subject). For example, if minors, state whether the minor or the parent/guardian will receive the incentive. If incapacitated adult, state if payment will be provided to the subject or to a guardian*
- *State if any items are provided in kind (e.g. vouchers, iPads)*

**C. Risks and discomforts** *(Summarize risks of the study. Describe steps taken to minimize risk).*

*Risks can include:*

- *Physical harms from therapeutic interventions (such as drugs/devices/gene transfer/radiation) or Diagnostic interventions (blood draws/imaging/biopsies)*
- *Psychological harms (misunderstanding, anxiety, self-esteem, depression)*
- *Risks to family relationships (related to determination of genetic/disease status, parentage, adoption)*
- *Discrimination (insurance, employment)*

**D. Potential benefits**

- *Describe whether the study has the potential for direct benefits to participants (include only those physical or psychosocial benefits that derive directly from an intervention being studied)*
- *Describe any collateral benefit to participants (for example, medical or genetic counseling care and other benefits associated with being a research subject that are not directly related to the specific study intervention. Do not include financial compensation as a direct or collateral benefit)*
- *Benefits to society (describe whether the study is likely to yield generalizable knowledge)*

**E. Classification of risk for the study as a whole**

- *For example, for research with Adults, classify as minimal risk OR more than minimal risk*

- *For Adults without consent capacity (if applicable)NIH HRPP* SOP 14E "Research Involving Adults Who Are or May Be Unable to Consent," *provides some suggestions for classifying risk.*
- *For Children, classify as one of the following:*
    - *45 CFR 46.404 Research that does not involve greater than minimal risk*
    - *45 CFR 46.405 Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual child*
    - *45 CFR 46.406 Research involving no greater than a minor increment over minimal risk and no prospect of direct benefit but likely to yield generalizable knowledge*
    - *45 CFR 46.407 Research not approvable under classifications above, but presenting a reasonable opportunity to further the understanding, prevention or alleviation of a serious problem affecting the health or welfare of children*
      *(NOTE: An IRB cannot approve research under 45 CFR 46.407, unless the Secretary of DHHS also provides approval. For more information see NIH HRPP SOP 14D "Research Involving Children")*

**F. Assessment of Risk/ Benefit ratio** (for more information about risk and benefit, see *SOP 4 "Human Research Protection Program (HRPP) Documentation and Records", Appendix B "NIH Protocol Review Standards".)*

- *Describe overall balance of risk and benefit considerations, state whether the risks are reasonable in relation to anticipated benefit*

**G. Alternatives to participation or alternative therapies**

- *Treatment/ therapeutic alternatives should be discussed. State if none..*

**H. Subject Confidentiality** *("For more information about confidentiality and privacy, see NIH HRPP SOP 18 "Privacy and Confidentiality.")*

- *Describe protections for maintaining confidentiality of subject data, forms, records and samples, etc.*

**1. For research data and medical records**

- *Describe whether identifiers will be attached to data, or whether data will be coded or unlinked*
- *If unlinked or coded, and additional information (age, ethnicity, sex, diagnosis) is available, discuss whether this might make specific individuals or families identifiable*

- *If research data will be coded, how will access to the "key" for the code be limited? Include description of security measures (password-protected database, locked drawer, other). List names or positions of persons with access to the key*
    - *Under what circumstances will data/samples be shared with other researchers?*
    - *Will pedigrees be published? Include description of measures to minimize the chance of identifying specific families*
    - *Will personally identifiable information be released to third parties?*
    - *State who has access to records, data, and samples. Consider if monitors or auditors outside of study investigators will need access*
    - *Discuss any additional features to protect confidentiality (such as use of a certificate of confidentiality, etc.)*

2. **For stored samples - including sharing samples and PII.** (*For more information about working with human specimens or data see SOP 5 "NIH Research Activities with Human Data/Specimens".)*

    - *Will participant identifiers be attached to samples, or will samples/data be coded or unlinked from identifiers?*
    - *Description of any clinical/demographic information that will be included (age, ethnicity, sex, diagnosis, stage, treatment)*
    - *How might this information make specific individuals or families identifiable?*
    - *Under what circumstances will data/samples be shared with other researchers?*

3. **Research use of stored human samples, specimens or data.** *Address each of the items listed below. (For more information about working with human specimens or data see SOP 5 "NIH Research Activities with Human Data/Specimens".)*
    - *Intended Use: Example language (may not be applicable to a particular study): Samples and data collected under this protocol may be used to study [XX]. [No] genetic testing will be performed.*
    - *Storage: State whether samples or data will be retained, list type of samples and location of storage. There are many acceptable approaches to data storage. An example of language for describing data storage is as follows: " Access to stored samples will be limited using [either a locked room or a locked freezer]. Samples and data will be stored using codes assigned by the investigators. Data will be kept in password-*

*protected computers. Only investigators will have access to the samples and data."*

- *Tracking: Describe method of tracking, such as the name of the software tracking program or other logging/tracking method*
  - *Disposition at the Completion of the Protocol: (Describe the disposition of the specimens, the protocol will remain open, they will be sent to a repository, etc… as applicable) There are multiple approaches for disposition of samples after research is conducted.*
  - *Approach for responding to requests from subjects for destruction of samples (if applicable)*

**I. Informed Consent Process** *(Consult with the IRB regarding enrollment of non-English speakers, and, if appropriate, use of long-form translated consent documents or a short-form consent document.)*

**1. Consent/assent documents and other informational items provided to subjects**

- *Confirm whether the consent form contains all required regulatory elements*
- *List all consent documents and materials submitted with this protocol*
  - *(Include consent and/or assent forms, printed or web-based materials, phone scripts and any other related material.)*
- *If needed, describe special documents or materials (Braille, another language, audiotape, etc.)*

**2. Designation of those obtaining consent/assent**

**3. Assent and/or consent procedures and documentation**

- *Describe how informed consent will be administered. Describe any proposed waivers or alterations to informed consent. Describe any special circumstances regarding obtaining consent. Describe plans for obtaining consent from speakers of languages other than English.*
- *One example of possible language in this section is as follows: "All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions regarding this study prior to signing."*

## X. ADDITIONAL NIH REQUIREMENTS

### A. Study Staff Roles and Qualifications

*For individuals at non-NIH sites, include the name of the site, FWA# and contact information. For more information about collaborations see NIH HRPP SOP 20 "NIH HRPP Requirements for Collaborative Research".*

- *Identify each investigator by name and include credentials*
- *Identify role in study*
- *State qualifications to perform the study role*
- *Investigators with similar roles and qualifications can be described as a group*

### B. Conflict of Interest (*For more information about conflict of interest requirements see NIH HRPP SOP 21 "Conflict of Interest Requirements for Researchers and Research Staff".)*

- *Confirm whether investigators will abide by their own institutional conflict-of-interest policies*
- *If applicable, describe the role of a commercial company or sponsor. If there is a commercial company or sponsor for the study, state what the company/ sponsor will provide to the institution and what the institution will provide to them. State if personal identifiers of participants will be shared with the sponsor*

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### *C.* Technology transfer

- *List any tech transfer, material transfer, or any confidential disclosure agreement/s and the parties involved*

## XI. REFERENCES

## XII. APPENDICES/ATTACHMENTS (as applicable)

**A.** Flow sheets
**B.** Eligibility checklist
**C.** Case report forms (CRFs)
**D.** Rating scales and questionnaires
**E.** Recruiting materials
**F.** Screening questionnaires for Patient Recruitment Office
**G.** Other