Ancillary Study Policies and Procedures

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I. Ancillary Study Policies

Definition of an ancillary study: An ancillary study involves the collection of new data, either directly from participants or from previously collected samples, images, or other sources (e.g., medical records). A SPIROMICS ancillary study is one that derives funding from other than SPIROMICS contract funds. Examples include studies funded by investigator-initiated NIH research awards (R01s), grants from academic institutions, private sources (e.g., drug companies), or those performed at no cost (generally because of the special interest of a researcher). Grant applications that involve only secondary analysis of existing datasets are not ancillary studies. It is anticipated that funds to expand the main study protocol provided to the Contract Office and Steering Committee from the NIH Foundation determined by will be considered part of the SPIROMICS protocol and will not be considered ancillary studies. An ancillary study is distinct from a substudy, which is a component of the SPIROMICS protocol performed on subsample of SPIROMICS and which is funded by the SPIROMICS contract.

Philosophy: SPIROMICS investigators are encouraged to consider ancillary studies and to involve other investigators, within and outside of SPIROMICS, in this process.

Necessary approvals: The SPIROMICS Ancillary Studies Committee and Steering Committee must approve ancillary study proposals prior to submission for funding and prior to implementation at the SPIROMICS sites. The Observational Safety Monitoring Board (OSMB) and NHLBI proposal and informed consent review may also be required prior to approval, if participant burden is present, or if deemed appropriate for other reasons by the committee. The SPIROMICS Ancillary Studies Committee provides initial review and makes recommendations to the Steering Committee in this process.

Review criteria: At each level of review, highest priority will be given to studies that:

1. Do not interfere with the main SPIROMICS objectives
2. Have the highest scientific merit
3. Yield minimal burden to SPIROMICS participants and very little demand on SPIROMICS resources, such as biospecimens
4. Require the unique characteristics of the SPIROMICS cohort
5. Are consistent with and can further the overall goals of SPIROMICS

In addition, priority for studies requesting biological samples will be highest if they:

1. Do not make use of samples from those participants with the fewest samples
2. Use thawed samples whenever possible
3. Assays desired can be done on more than one sample type to allow selection of the most abundant type available (e.g. serum or EDTA plasma)
4. Use the smallest sample volume or sample size possible; evidence of attempts to minimize volumes will be examined by relevant subcommittees (e.g., Sputum)
5. Can be integrated with other studies to conserve samples or limit freeze-thaw cycles

Further, to conserve specimens for use by SPIROMICS Investigators for analyses related to the primary study aims, biospecimens for ancillary studies will only be taken from participant/visit combinations where >50% of the sample type is remaining. 50% of samples remaining is based on the total number of expected samples for that sample type at the study visit in question.

The Ancillary Studies Committee and Steering Committee may approve selection of samples from participants with <50% of a given sample type for a given study visit on a case by case basis.

Responsibilities of Ancillary Study Investigators:

1. Costs: The investigator applying for an ancillary study must supply all additional funds required to conduct the study. The Steering Committee will be concerned with both the obvious and the hidden costs to SPIROMICS entailed by an ancillary study (such as costs to the Genomics and Informatics Center for coordinating the additional data collection, costs to Clinical Centers for notification of alert values, costs to laboratory for retrieving samples, etc).

   It is important to note that the SPIROMICS Genomics and Informatics Center (GIC) at the University of North Carolina nearly always incurs expenses on behalf of ancillary studies by providing support in data collection, data management, quality control, data analysis, study coordination and communications, events ascertainment, and other functions. These services can be of critical value to an ancillary study. PIs who plan to propose an ancillary study with the intention of seeking grant funding should first consult with the SPIROMICS GIC Project Director to determine what level of involvement will be required of the GIC and the associated costs. In general, this will result in a subcontract proposal from the GIC to be included in the PI's grant application.

2. Confidentiality and identification of SPIROMICS participants: Confidentiality of

individually identifiable data about SPIROMICS participants must be assured. As a general rule, no personal identification of participants will be provided to ancillary studies staff. There are no assurances that participants will be able to be identified and contacted in the future for the purposes of an ancillary study, particularly after SPIROMICS ends.

3. Clinical implications of findings: The proposing investigator must clearly delineate any findings of clinical significance that may result from the study, including genetic findings, and propose how these will be handled, including reporting to participants and their physicians and providing recommendations for follow up. This includes incidental findings, such as pathology identified from an imaging study that is not the focus of the study.

4. Genetic studies: Genetics studies may include only participants who provided appropriate informed consent. Investigators should consult the Genomics and Informatics Center to determine the number of participant samples eligible for analysis based on responses from the appropriate informed consent. Medical and other (ethical, legal and social) implications of the findings and reporting of results must be addressed in the proposal.

5. Ancillary studies to existing SPIROMICS ancillary studies: A new ancillary study that involves participants, staff, or biological samples of an existing SPIROMICS ancillary study but not those of the main SPIROMICS study is considered an ancillary study only to the parent (existing) ancillary study. Such proposals are to be submitted to the parent ancillary study for review and approval, and will also be circulated to the main SPIROMICS Ancillary Study and Steering Committees for informational purposes. If a new ancillary study involves participants, staff, or biological samples of an existing SPIROMICS ancillary study as well as those of the main SPIROMICS study, review and approval process by both the parent ancillary study and main SPIROMICS study will be required. Please contact the PI of the parent ancillary study for information regarding the appropriate administrative contact.

6. Inclusion of SPIROMICS investigator(s): A SPIROMICS investigator must be included as a co-investigator on an ancillary study. This individual is responsible for presenting the study to the Ancillary Studies Committee, monitoring the study to assure continuing compatibility with SPIROMICS and serving as a liaison to the SPIROMICS Steering Committee. In addition, each manuscript and abstract is generally expected to include a SPIROMICS investigator.

7. Inclusion of SPIROMICS sites: A major strength of SPIROMICS is its multicenter design and its large sample size of the cohort, which increases precision and reduces false negative findings. The proposing investigator is strongly encouraged to involve all SPIROMICS sites and should contact all relevant sites to assess interest before submitting the Ancillary Study proposal, or justify for scientific or feasibility reasons why all sites are not involved.

8. Early communication with SPIROMICS Centers: The proposing investigator and/or his/her liaison should consult with PIs of pertinent Clinical Centers, Reading

Centers, Laboratories, and/or the Genomics and Informatics Center, depending on the anticipated involvement of Clinical Center staff and oversight, sample analysis, and data management and analysis. Such discussions should focus on feasibility and provision of necessary resources and do not constitute formal approval of the study.

9. Timeline: All proposed ancillary studies must be submitted to the SPIROMICS Genomics and Informatics Center for subsequent circulation and review. Studies submitted for review less than 8 weeks prior to a funding application deadline may not receive timely approval. Additional time may be required if other committee involvement is high.

10. Final application or proposal: A copy of the final proposal as submitted for funding should be submitted to the Genomics and Informatics Center and to the NHLBI Project Officer.

11. Industry participation: Proposals for industry sponsorship or collaboration will be evaluated in accordance with the procedures described above. In addition, it will be the responsibility of the PI to obtain agreement through an appropriate contractual mechanism that all data produced by the SPIROMICS ancillary study will be shared with the Genomics and Informatics Center. As an initial step in study planning, the PI should contact the SPIROMICS Project Officer to determine if an agreement between NHLBI and industry should be developed and implemented or to approve the agreement between industry and the investigator's institution. Industry-sponsored ancillary studies should comply with current NHLBI guidelines, which are available from the Genomics and Informatics Center or Project Office upon request.

12. Status reports: The ancillary study PI should keep the SPIROMICS Genomics and Informatics Center apprised of major developments in the life of the application or proposal, including success of funding, start date, changes in protocol, and any resulting publications or presentations. The SPIROMICS Genomics and Informatics Center will query PIs twice per year, or as needed, for a status update of their ancillary studies, the results of which will be included in the Steering Committee and Monitoring Board reports.

13. Revising and resubmitting proposals: Ancillary Studies that are not approved or not funded become inactive. If the PI wishes to resubmit the proposal for funding, s/he must communicate this to the Genomics and Informatics Center. A summary of the main points of the critique, plus a summary of the PI's response to the critique should be provided. A statement about changes to participant burden must be included. If either the science, scope, or burden has changed, the revised proposal must be approved by the Ancillary Studies/Steering Committees, or, in the case of relatively minor or administrative changes, the Executive Committee.

14. Review of publications and presentations: Manuscript proposals based on ancillary study data require approval of the SPIROMICS Publications Committee. All the publications, presentations and abstracts from an ancillary study must be reviewed and approved by the SPIROMICS Publications Committee and the Steering

Committee prior to submission or presentation, in accordance with the general rules for publications and presentations.

Incorporation of ancillary study data into SPIROMICS database: The data collected by the ancillary study are first to be provided to the SPIROMICS Genomics and Informatics Center (GIC) for integration into the main database, after which the ancillary investigators will receive the integrated file containing necessary data from the main study. The ancillary study PI will be given the exclusive opportunity to analyze, present, and publish data collected under the auspices of the ancillary study. After a reasonable time (in general, 12 months after data collection and cleaning are complete) the ancillary study data will be made available for additional uses by other SPIROMICS investigators in collaboration with the ancillary investigators. It is the responsibility of the ancillary study PI to state in writing to the Steering Committee any special circumstances that would militate against these guidelines for data sharing.

II. Ancillary Study Review Procedures

1. Investigators wishing to propose studies that pose participant, clinic, or sample burden are encouraged to discuss their studies with the NHLBI Project Office for SPIROMICS before submitting a proposal to the Ancillary Studies Committee.

2. Principal Investigator submits ancillary study proposal (at least 8 weeks prior to funding application deadline) as an email attachment (MS Word preferred) to the SPIROMICS Genomics and Informatics Center (GIC) (see Appendix 1).

3. Ancillary Studies Committee chair reviews proposal for administrative compliance (assures that all questions have been answered) and to determine involvement of other SPIROMICS labs and/or reading centers. If the proposal is not complete, it will be returned by email to the investigator for revision and resubmission.

4. Ancillary Studies Committee chair will assign 1-3 reviewers in which the SPIROMICS GIC sends the proposal and reviewer document by email. The chair will decide whether to utilize the monthly committee call, generally one week prior to the monthly Steering Committee call, or handle the review by email. Chairs of all relevant subcommittees communicate their reviews to all members of the Ancillary Studies Committee and Steering Committee by email (or in conference call). The Ancillary Studies Committee review and recommendation for approval are communicated to all Steering Committee members on the monthly call, including the comments and the comments of relevant subcommittees.

5. For a proposal that poses burden, after it is reviewed and approved by Ancillary Studies Committee, the Project Office will weigh the participant/clinic burden against the scientific enthusiasm and participant appeal. Studies without a favorable balance will not be approved, and the studies will not be forwarded to the Steering Committee and the OSMB.

6. Proposals will be discussed by the Steering Committee, generally during their regular monthly conference calls. The chair of the Ancillary Studies Committee is invited to be present for that portion of the Steering Committee conference call. In some cases, as determined by the chair of the Steering Committee, email reviews will be conducted. The Steering Committee may also invite the PI (and/or the PI's SPIROMICS sponsor) to present the proposal and answer questions and absent him/herself during discussion and voting.

7. If the proposal requires revisions, the comments of the Ancillary Studies Committee (and Steering Committee, if applicable) are sent to the PI by the GIC (with cc to Ancillary Studies Committee and Steering Committee chairs and GIC Project Director). The PI must address these comments in a separate letter that accompanies the revised proposal and send these to the GIC who forwards them to the appropriate committee(s).

8. Proposals that are approved by the Steering Committee but involve no participant burden (though they may use scans or repository samples), and minimal clinical implications are sent a formal letter of approval to the PI from the GIC. (Copies of these communications are sent to the Ancillary Studies Committee and Steering Committee chairs and GIC Project Director.)

9. Proposals that are approved by the Steering Committee and involve participant burden are sent by the GIC to the NHLBI Executive Secretary and the NHLBI Project Officer, together with all review materials including informed consent, updated study proposal, and participant burden tables. Copies are sent to the Ancillary Studies Committee chair, Steering Committee chair, and GIC Project Director. The GIC also notifies the PI of the progress in the review process.

10. The Executive Secretary of the SPIROMICS Monitoring Board forwards the final proposal, any relevant review materials, and the modified Burden Table to the Observational Safety Monitoring Board for review (allow three weeks).

11. The results of the Observational Safety Monitoring Board review are communicated by formal letter to the GIC Project Director. The results are also communicated by email to the chairs of the Steering Committee and Ancillary Studies Committee, and the PI.

12. In addition to the NHLBI letter of approval, and if the PI of the ancillary study requests it, the Steering Committee Chair will write a letter of support that may be included in the PI's grant application.

III. Ancillary Study Committee Members

Chair:

- Wanda O' Neal, PhD

Members:

- Wayne Anderson, PhD
- Igor Barjaktarevic, MD, PhD
- R. Graham Barr, MD, PhD
- Patricia Basta, PhD
- Lori A. Bateman, MSc
- Surya Bhatt, MD
- Eugene Bleecker, MD
- Russell Bowler, MD, PhD
- Alejandro Comellas, MD
- Christopher Cooper, MD
- David Couper, PhD
- Jeffery Curtis, MD
- Claire Doerschuk, MD
- Brad Drummond, MD
- MeiLan Han, MD
- Nadia Hansel, MD, MPH
- Annette Hastie, PhD
- Gregory Hawkins, PhD
- Eric Hoffman, PhD
- Richard Kanner, MD
- Victor Kim, MD
- Fernando Martinez, MD
- Deborah Meyers, PhD
- Robert Paine III, MD
- Stephen Peters, MD, PhD
- Lisa Postow, PhD
- Lisa Viviano, MSc
- Nicole Wilson, MSc
- Prescott Woodruff, MD, MPH