Ancillary Studies Policies and Procedures

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I. Ancillary Studies Policies

Scope: This policy applies to SPIROMICS and SOURCE cohort ancillary studies, defined by studies that increase participant burden or add new data.

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). An ancillary study to the SPIROMICS and/or SOURCE cohorts is one that uses study participants but derives funding other than from those awards. 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 and instead should be submitted through the Publications Committee through the manuscript proposal process. Ancillary studies are distinct from substudies, which are components of the parent study protocols, performed on subsamples of participants, and funded by the parent studies. Funds to expand the main study protocols that are provided to the Contract Office and Steering Committee from the COPD Foundation will be considered part of the respective protocols and will not be considered ancillary studies.

Philosophy: SPIROMICS and SOURCE investigators are encouraged to consider ancillary studies and to involve other investigators, within and outside of SPIROMICS and SOURCE, in this process. However, any proposal that solicits funding from an industry source should be discussed with the Industry Advisory Committee very early in the process to assure that there are no duplications or conflicts with efforts to fund the parent studies.

Necessary approvals: Ancillary study proposals must be reviewed and approved by the Ancillary Studies Committee and by the Steering Committee before submission for funding. Before implementation of funded ancillary studies at sites, their protocols and informed consents must also be approved by the Observational Safety Monitoring Board (OSMB) and NHLBI if participant burden is present or if deemed appropriate for other reasons by the committee. In both these review processes, the Ancillary Studies Committee provides initial review and makes recommendations to the Steering Committee. Generally, the Ancillary Studies Committee will request review at the various working groups (e.g., physiology, imaging, biomarkers/genetics/genomics) before considering approval. Investigators should work with the Genomics and Informatics Center (GIC) to schedule discussions with these working groups once the ancillary study is submitted for consideration. Because this process can take time, investigators wishing to obtain approval of an ancillary study should begin the process well in advance of any pending deadlines.

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

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

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

1. Do not make use of samples from participants with the fewest samples.
2. Use previously thawed samples whenever possible.
3. Can perform the desired assays on more than one sample type (e.g., serum or EDTA plasma) to allow selection of the most abundant type available.
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 and/or SOURCE 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. The determination that 50% of samples remain will be based on the total number of expected samples for that sample type at the study visit in question. Approval for the selection of samples from participants with <50% of a given sample type for a given study visit will be made by the Ancillary Studies Committee and the Steering Committee 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 and/or SOURCE entailed by

an ancillary study (such as costs to the GIC 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 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 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 participants:* Confidentiality of individually identifiable data about 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 and/or SOURCE 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 GIC 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 ancillary studies:* A new ancillary study that involves participants, staff, or biological samples of an existing ancillary study of the SPIROMICS and/or SOURCE cohorts, but not those of the respective main cohort study, will be 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 Ancillary Study and Steering Committees for informational purposes. If a new ancillary study involves participants, staff, or biological samples of an existing ancillary study as well as those of the main study, review and approval process by both the parent ancillary study and main study will be required. Please contact the PI of the parent ancillary study for information regarding the appropriate administrative contact.

6. *Inclusion of investigator(s):* A SPIROMICS or SOURCE 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/or SOURCE, and serving as a liaison to the Steering Committee. In addition, each manuscript and abstract are generally expected to include a SPIROMICS or SOURCE investigator.

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

8. *Early communication with SPIROMICS and/or SOURCE Centers:* The proposing investigator and/or their liaison should consult with PIs of pertinent Clinical Centers, Reading Centers, Laboratories, and the GIC, 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 GIC for subsequent circulation and review. Studies submitted for review less than 8 weeks before a funding application deadline may not receive timely approval. Additional time may be required if involvement by other committees is high.

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

11. *Industry participation:* Proposals for industry sponsorship or collaboration are welcomed to maximize the scientific productivity of the SPIROMICS and/or SOURCE network, but they also raise unique legal and ethical considerations. Such proposals will be evaluated in accordance with the procedures described above. In addition, it will be the responsibility of the ancillary study PI to obtain agreement through an appropriate contractual mechanism that all data produced by the ancillary study will be shared with the GIC.

    As an initial step in study planning, the PI should contact the 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 GIC or Project Office upon request. Further, all new industry-sponsored ancillary studies should first be vetted through the Industry Partnership Committee. The purpose of this review is to identify potential issues/overlap with the established industry engagement processes in place or ongoing via the COPD Foundation.

12. *Status reports:* The ancillary study PI should keep the GIC 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 GIC 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 OSMB 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, they must communicate this to the GIC. 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 and 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 Publications Committee. All the publications, presentations, and abstracts from an ancillary study must be reviewed and approved by the Publications Committee and the Steering Committee.

15. *Conflicts of Interest:* As an integral part of the submission process, the PIs of ancillary studies must declare any relationships related to the ancillary study that could be perceived as a conflict of interest. For this purpose, the Ancillary Studies Committee prior to submission or presentation, in accordance with the general rules for publications and presentations will develop a form, which will be reviewed by the Committee co-chairs and if appropriate, the NIH Program Officer. The completed conflict of interest form will be available for review upon request by members of the Ancillary Studies Committee, Steering Committee, or Executive Committees of the SPIROMICS and/or SOURCE cohorts.

16. *Incorporation of ancillary study data into SPIROMICS and/or SOURCE database(s):* The data collected by the ancillary study are first to be provided to the GIC for integration into the main database, after which the ancillary study 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 investigators in collaboration with the ancillary study 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 Studies Review Procedures

1. Investigators wishing to propose studies that either involve industry-sponsorship or which pose potential burdens on participants, clinical sites, the GIC, or study samples must discuss their studies with the Executive Committees of the SPIROMICS and/or SOURCE studies, respectively, before submitting a proposal to the Ancillary Studies Committee.

2. No existing biospecimens or data will be released to an ancillary study by the GIC or Reading Centers until the study receives full approval, including negotiation of any necessary contracts, data use agreements, and material transfer agreements. Investigators are not to negotiate unilaterally with industry sponsors for use of SPIROMICS or SOURCE resources without involving the NHLBI Program Office and the GIC.

3. The process of applying for approval of an ancillary study begins by the Principal Investigator submitting to the GIC:
    - a completed ancillary study proposal and COI statement.
    - at least 8 weeks before funding application deadline.

4. The Ancillary Studies Committee co-chairs will review proposals for administrative compliance to assure that all questions have been answered and to determine involvement of other labs and/or Reading Centers. If the proposal is incomplete, it will be returned by email to the investigator for revision and resubmission to the GIC.

5. The Ancillary Studies Committee co-chairs will assign 1-3 committee members as reviewers, to whom the GIC will email the proposal and the reviewer template document. The co-chairs will also forward the proposal to the chairs of Working Groups for awareness; the Working Groups will notify the ancillary study PI of meeting times so that their proposal can be vetted appropriately, and feedback provided to the Ancillary Studies Committee before that meeting.

    The co-chairs will decide whether to utilize one of the two monthly committee calls, which generally occur the second Monday and fourth Thursday of each month, or to handle the review entirely by email. In general, email reviews are highly discouraged, hence all investigators should submit their proposals within the recommended timeframe to assure adequate time for review through the regular channels.

    Chairs of all relevant Working Groups will 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 specific reviewer comments and the comments of relevant Working Groups.

The Ancillary Studies Committee is encouraged to invite the PI (and/or the PI's sponsor) to present the proposal and answer questions. To permit frank discussion, the PI and/or sponsor will be absent during discussion and voting.

6. To approve or reject proposals, a quorum will be defined as the presence of at least one co-chair and six members.

7. For a proposal that poses burden, after it is reviewed and approved by the Ancillary Studies Committee, the Project Office will weigh the burden on participants or clinical sites/Reading Centers/GIC against the scientific enthusiasm and participant appeal. Studies without a favorable balance will not be approved, and the study will not be forwarded to the Steering Committee and the OSMB.

8. Proposals will be discussed by the Steering Committee, generally during their regular monthly conference calls. The co-chairs of the Ancillary Studies Committee will be 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, but this is highly discouraged. The Steering Committee may also invite the PI (and/or the PI's sponsor) to present the proposal. To permit frank discussion, the PI and/or sponsor may be asked to be absent during discussion and voting.

9. Based on the closed session discussion and voting, the Ancillary Studies Committee may choose the following options:
    - Approval without revision.
    - Contingent approval with revision, in which case there should be an additional explicit determination of whether the revision needs to come back to full committee or can be reviewed and approved by the co-chairs, potentially in consultation with the reviewers.
    - Recommendation for revision with full committee re-review.
    - Rejection.

    If the proposal requires revisions, the comments of the Ancillary Studies Committee (and Steering Committee, if applicable) will be 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).

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

Conversely, proposals that are approved by the Steering Committee that do involve participant burden will be 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 will be sent to the Ancillary Studies Committee co-chairs, Steering Committee chair, and GIC Project Director. The GIC will also notify the PI of the progress in the review process.

11. The Executive Secretary of the OSMB will forward the final proposal, any relevant review materials, and the modified Burden Table to the OSMB for review (allow three weeks).

12. The results of the OSMB review will be communicated by formal letter to the GIC Project Director. The results are also communicated by email to the chairs of the Steering Committee, Ancillary Studies Committee, and the PI.

13. 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 Studies Committee Members

Co-Chairs:

- Wanda O' Neal, PhD
- Jeffrey Curtis, MD

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
- 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
- Prescott Woodruff, MD, MPH