SPIROMICS
SubPopulations and InteRmediate Outcome Measures In COPD Study

SOURCE
SPIROMICS Study of Early COPD Progression

SPIROMICS and SOURCE

Ancillary Studies Policy

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I. Policy

A. Scope and Philosophy

i. The Ancillary Studies Policy applies to ancillary study proposals and applications to the SPIROMICS and/or SOURCE cohort studies. Proposals and applications involving multiple cohorts that originate outside of SPIROMICS and/or SOURCE still require Ancillary Studies Committee review and approval. Proposals and applications originating from SPIROMICS and/or SOURCE that include or involve additional outside cohorts will receive the norm and standard review from the Ancillary Studies Committee.

ii. Ancillary studies, as defined in detail below, are those that meet any of the following criteria: increased participant burden; generation of novel data elements: requiring full access to raw image HRCT or MRI files; requiring access to biospecimens; or requesting a letter of support for funding or funding applications.

iii. Review and approval by the Steering Committee are also required to safeguard participants, to assure efficient use of biospecimens, to manage potential conflicts or duplication of efforts, and to fulfill the requirement for return of novel data elements to the Genomics and Informatics Center (GIC) and to the National Heart, Lung, and Blood Institute (NHLBI).

iv. SPIROMICS and/or SOURCE investigators are encouraged to consider ancillary studies and to involve other investigators, within and outside of SPIROMICS and/or SOURCE, throughout the ancillary study process.

v. Proposals that solicit funding from an industry or for-profit source should first be proposed and discussed with the Industry Advisory Committee to assure that there are no duplications or conflicts with efforts to fund the parent studies and aims before submitting to the Ancillary Studies Committee for review.

B. Ancillary Study Defined

i. An ancillary study involves the generation of novel data elements, either by collection directly from participants or from a new analysis of previously collected samples, images, or other sources (e.g., medical records, linkage to publicly available data).
   a. Data elements produced from existing SPIROMICS and/or SOURCE data solely by a mathematical transformation (e.g., by dividing one variable by another) are not considered generation of new data. As a guideline, if the GIC cannot easily generate the data, such as a case for identification of new classifications of SPIROMICS and/or SOURCE participants by machine learning that would require specific expertise and complex modeling, it would be considered an ancillary study. If there is uncertainty, the investigator should contact one of the Ancillary Studies Committee chairs for clarification and a decision.

ii. Submission of an ancillary study proposal is the preferred means of requesting access to SPIROMICS and/or SOURCE biospecimens, raw DICOM imaging files, MRI images, or any combination thereof, both for internal and external investigators.

iii. Studies that use data or biospecimens from one or more studies that are themselves ancillary to SPIROMICS and/or SOURCE also require review and approval by the Ancillary Studies Committee.

iv. An ancillary study to SPIROMICS and/or SOURCE is also one that uses study participants but derives funding elsewhere.
   a. Examples include studies funded by investigator-initiated NIH research awards (R01s), grants from academic institutions, private sources (e.g., pharmaceutical

companies), or those performed at no cost (generally because of the special interest of a researcher).

v. Grant and funding applications that request a letter of support (LOS) must be submitted as an ancillary study, even if only involving secondary analysis of existing datasets.
vi. Ancillary studies are distinct from sub-studies, which are components of the parent study protocols, performed on a subset of participants, and funded by the parent study.

C. Approval Requirements

i. Ancillary study proposals must be reviewed and approved by the Ancillary Studies Committee and by the Steering Committee before submission for funding or before any data/biospecimens are requested.
    a. If participant burden is present or if deemed appropriate for other reasons by the Ancillary Studies Committee, before implementation of funded ancillary studies at sites, protocols and informed consents must also be submitted to the GIC for approval by the Observational Study Monitoring Board (OSMB) and NHLBI.
    b. In both review processes, the Ancillary Studies Committee provides initial review and makes recommendations to the Steering Committee.
ii. The Ancillary Studies Committee will request review and support by the various Working Groups (e.g., Genetics, Genomics, and Biomarkers, Physiology, Imaging, Environmental and Social Determinants of Health (SDOH), Bronchoscopy, Exacerbations, etc.) before considering ancillary study approval.
    a. Investigators should work with the GIC or the Ancillary Studies Committee chairs to schedule discussions with the relevant Working Groups. These discussions should occur before the ancillary study is submitted for committee review.
    b. This process can take time, therefore investigators wishing to obtain approval of an ancillary study should begin the process well in advance of any pending deadlines. A recommended timeframe is provided below.

D. 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 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, studies requesting biological samples will be given highest priority 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 sample 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.

Furthermore, to conserve biospecimens 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 enough of the sample type remain. Approval for the selection of samples from participants with lower than the optimal number of aliquots 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. Ancillary study investigators should consult with the GIC to understand the current state of biospecimen inventories.

E. Ancillary Study Investigator Responsibilities

i. Costs*:* The investigator proposing an ancillary study must provide or cover all additional funds required to conduct the study.
   a. 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 the GIC and biorepository for pulling and shipping biospecimens, etc.).
   b. It is important to note that the GIC 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, ancillary study progress tracking, data submission to repositories, and other functions. These services can be of critical value to an ancillary study. Therefore, investigators proposing an ancillary study with the intention of seeking grant funding should consult with the Project Director and GIC to determine what level of involvement will be required of the GIC and the associated costs/budget. In general, the GIC should be budgeted via a subcontract on the grant application. If necessary, or in cases for smaller dollar amounts, the GIC will agree to invoice the investigator for work done.

ii. Confidentiality and identification of participants: Confidentiality of individually identifiable data about participants must be assured. As a rule, no personal identification of participants will be provided to ancillary study investigators. There are no assurances that participants will be able to be identified nor contacted in the future for the purposes of an ancillary study, particularly after SPIROMICS and/or SOURCE ends.

iii. 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 managed, 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 ancillary study.

iv. Genetic studies*:* Genetic studies can only include participants who provided appropriate informed consent. Investigators should consult the GIC to determine the number of participants with genetic samples eligible for analysis based on responses from informed consent. Medical and other (ethical, legal, and social) implications of the findings and reporting of results must be addressed in the proposal being reviewed.

v. Ancillary studies to existing ancillary studies*:* A new ancillary study that involves participants, staff, or biological samples of an existing ancillary study of SPIROMICS

and/or SOURCE, but not those of the respective main cohort study, will be considered an ancillary study only to the existing ancillary study. Such proposals are to be submitted to the parent ancillary study for review and approval and circulated through the Ancillary Studies and Steering Committees for informational purposes only. 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 existing ancillary study and the main study will be required. Please contact the investigator of the existing ancillary study for information regarding the appropriate administrative contact.

vi. Inclusion of investigator(s): Ideally, an investigator from SPIROMICS and/or SOURCE would be included as a co-investigator on an ancillary study. The SPIROMICS and/or SOURCE investigator can serve as a liaison to the Ancillary Studies and Steering Committees, can help assure that the study remains compatible with the parent studies, and that phenotypes and datasets are interpreted in a manner consistent with the parent study.

vii. Inclusion of sites: A major strength of SPIROMICS and SOURCE are the multicenter designs and large cohort sample sizes, which increases precision and reduces false-negative findings.
   a. Especially for ancillary studies that will involve any interactions with SPIROMICS and/or SOURCE study participants, the proposing investigator is strongly encouraged to involve all study clinical 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.
   b. This consideration is similar for ancillary studies that will involve data elements derived by SPIROMICS and/or SOURCE core repositories or from ancillary studies to SPIROMICS and/or SOURCE (e.g., X01 proposals, sub-studies such as the Bronchoscopy sub-study), and should similarly involve leaders of those groups.

viii. Early communication with SPIROMICS and/or SOURCE clinical centers: The proposing investigator and/or their liaison should consult with Principal Investigators of pertinent Clinical Centers, Reading Centers, Biospecimen Repositories, 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.

ix. Timeline: All ancillary study proposals must be submitted to the GIC via the Carolina Data Acquisition and Reporting Tool (CDART) Manuscript and Ancillary Study Tracking (MAST) Data Management System (DMS) for management, circulation, and review. Submissions to CDART MAST received less than 8 weeks before a funding application deadline may not receive timely approval. Additional time, greater than 8 weeks, may be required if involvement by other committees is high and warranted.

x. 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.

xi. Industry participation: Ancillary study proposals for industry sponsorship or collaboration are welcomed to maximize the scientific productivity of the SPIROMICS and 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 investigator to obtain agreement through an appropriate contractual mechanism that all data produced by the ancillary study will be returned to the study via submission to the GIC.
As an initial step in study planning, the investigator should contact the NHLBI 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 upon request. Further, all new industry-sponsored ancillary studies should first be vetted through the SPIROMICS and SOURCE Industry Advisory Committee. The purpose of this review is to identify potential issues/overlap with the established industry engagement processes via the COPD Foundation.

xii. Status reports: The ancillary study investigator is required to update the GIC (primarily through the CDART MAST entry) of major developments throughout the life cycle of the application or proposal, including success of funding, funding amount and duration, start date, changes in protocol, as well as any resulting publications or presentations. The GIC will query investigators 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. Ancillary study investigators are expected to update CDART MAST and respond expeditiously to inquiries.

xiii. Revising and resubmitting proposals: Ancillary studies that are not approved or approved but not funded become inactive by default after three years. If the investigator wishes for the study proposal to remain active beyond three years of approval, a request for extension can be made. If the investigator wishes to resubmit the proposal for funding, they must communicate this to the GIC and update the proposal entry in CDART MAST. A summary of the main points of the critique, plus a summary of the investigator's response to the critique should be provided and communicated to the Ancillary Studies Committee. A statement about any changes to participants' burden must be included, if applicable. If either the science, scope, or burden has changed, the revised proposal must be submitted via CDART MAST and re-reviewed by the Ancillary Studies and Steering Committees, or in the case of relatively minor or administrative changes, the Executive Committee.

xiv. Review of publications and presentations: Manuscript proposals based on ancillary study data require review and approval from the SPIROMICS and SOURCE Publications Committee. All publications, presentations, and abstracts from an ancillary study must be linked by association when entered in CDART MAST and reviewed and approved by the Publications Committee.

xv. Conflicts of Interest: As an integral part of the submission process, the investigators 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 chairs and if appropriate, the NHLBI Project 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 SOURCE cohorts.

xvi. Incorporation of ancillary study data into SPIROMICS and/or SOURCE database(s): The new data collected or generated by the ancillary study should be submitted to the GIC for integration and release. The ancillary study investigator will be given the exclusive opportunity to analyze, present, and publish data collected under the auspices of the ancillary study however, the ancillary study data, once submitted, will be made available for additional use by other investigators in collaboration with the ancillary study investigators under the NIH and NHLBI data sharing policies referenced below. It is the responsibility of the ancillary study investigator to state in writing to the Steering Committee any special circumstances that would militate against following these guidelines for data sharing.

NIH and NHLBI data sharing policy references:

- NIH Data Sharing Policy (Jan 2023): https://sharing.nih.gov/data-management-and-sharing-policy
- NHLBI Supplement to the NIH Data Sharing Policy (Oct 2023): https://www.nhlbi.nih.gov/grants-and-training/policies-and-guidelines/nhlbi-policy-for-data-sharing
    - NHLBI 3rd Party Policy (May 2023): https://www.nhlbi.nih.gov/grants-and-training/policies-and-guidelines/third-party-involvement-in-nhlbi-supported-clinical-trials-and-other-population-based-studies-awardee-contractor-third-party-related-issues

II. Review Procedures

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

B. Neither existing biospecimens nor 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 and material distribution and use agreements (DMDA) and material transfer agreements (MTA). Investigators are not to negotiate unilaterally with industry sponsors for use of SPIROMICS and/or SOURCE resources without involving the NHLBI Project Office and the GIC. Primary data will be transferred for analyses and integration into the project only through the GIC.

C. The process of proposing an ancillary study begins by the Principal Investigator submitting to the GIC via CDART MAST, specifically the Ancillary Study Tracking (AST) form including:
    i. a completed ancillary study proposal form, attached proposal document, and COI statement.
    ii. at least 8 weeks before funding application deadline; 9 weeks required if there is a genetic component.
        a. Information regarding the submission process to CDART MAST is available on the SPIROMICS website via this link. The GIC will manage all submissions and notify the Ancillary Studies Committee of reviews during their meetings twice monthly. Investigators should contact the GIC at spiromics@unc.edu with any questions or issues regarding ancillary study submissions or review status and outcome.

D. The Ancillary Studies Committee chairs will review proposals for administrative compliance to assure that all questions have been answered and to determine involvement of other labs, cores, biorepositories, and/or reading centers. If the proposal is incomplete, it will be returned by email to the investigator for revision in CDART MAST and resubmission to the GIC.

E. The Ancillary Studies Committee chairs will select and assign one to three Ancillary Studies Committee members as reviewers, to whom the GIC will email the proposal and the reviewer template document to complete. The committee chairs will also forward the proposal to the chairs of Working Groups for awareness; the Working Groups will notify the ancillary study investigator of meeting times so that their proposal can be presented, discussed, and vetted appropriately, and feedback provided to the Ancillary Studies Committee before meeting to review.

The chairs will decide whether to utilize one of the two monthly committee meetings, or to manage 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 during scheduled conference calls). The Ancillary Studies Committee review and recommendation for approval are communicated to all Steering Committee members on the bimonthly call (i.e., twice a month), including specific reviewer comments and the comments of relevant Working Groups.

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

i. To approve or reject a proposal, a quorum must be present. A quorum is defined as the presence of at least one Ancillary Committee chair, a representative from the GIC, and six entities (e.g., includes committee members, clinical sites, and cores). If a quorum is not present, the meeting will be recorded for reference of discussion and a provisional decision will be made and sent for email review by the full Ancillary Studies Committee.

ii. For a proposal that poses participant burden, after it is reviewed and approved by the Ancillary Studies Committee, the NHLBI Project Officer will weigh the burden on participants or clinical sites, reading centers, GIC, etc. 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 nor the OSMB.

iii. The Ancillary Studies Committee chairs will present to the Steering Committee and the Steering Committee will discuss proposals during the regularly scheduled conference calls which occur twice monthly. In some cases, as determined by the Steering Committee chair, email reviews will be conducted, but this is highly discouraged. The Steering Committee may also invite the investigator (and/or the investigator's sponsor) to present the proposal. To permit frank discussion, the investigator and/or sponsor may be asked to be absent during discussion and voting by the Steering Committee.

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

    If the proposal requires revisions, the comments of the Ancillary Studies Committee (and Steering Committee, if applicable) will be sent to the investigator by the GIC (with cc to Ancillary Studies Committee and Steering Committee chairs, Project Director, and GIC). The investigator must address these comments in a separate letter that accompanies the revised proposal and submit these to the GIC via CDART MAST. The GIC will manage the revision as described above.

x. Proposals approved by the Steering Committee that <u>do not</u> involve participant burden will receive a formal letter of approval via email from the GIC. The GIC will copy the Ancillary Studies Committee chairs, Steering Committee chairs, and the Project Director on these email communications.

xi. Conversely, proposals approved by the Steering Committee that <u>do</u> involve participant burden will undergo an additional level of review.
    a. The GIC will send the proposal to the NHLBI Executive Secretary for the OSMB and the NHLBI Project Officer with all review materials including informed consent, updated study proposal, and participant burden tables.
    b. Copies will be sent to the Ancillary Studies Committee chairs, Steering Committee chair, and Project Director. The GIC will also notify the investigator of OSMB review progress.
    c. The NHLBI Executive Secretary for the OSMB will forward the final proposal, any relevant review materials, and the modified burden table to the OSMB for review. Up to three weeks should be allowed.
    d. The OSMB review outcome will be communicated by formal letter to the Project Director and the GIC. The outcome is also communicated by email to the chairs of the Steering Committee, Ancillary Studies Committee, and the proposing ancillary study investigator.
    e. In addition to the NHLBI letter of approval and if the investigator of the ancillary study requests it, the Steering Committee chair will write a letter of support that may be included in the investigator's grant application.

III. Committee Members

Chairs:

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

Members:

- Wayne Anderson, PhD
- Igor Barjaktarevic, MD, PhD

- R. Graham Barr, MD, PhD
- Lori A. Bateman, MS
- Surya Bhatt, MD
- Eugene Bleecker, MD
- Jessica Bon, MD
- Russell Buhr, MD, PhD
- Alejandro Comellas, MD
- Christopher Cooper, MD, PhD
- David Couper, PhD
- Claire Doerschuk, MD
- Brad Drummond, MD
- MeiLan Han, MD
- Nadia Hansel, MD, MPH
- Annette Hastie, PhD
- Eric Hoffman, PhD
- Victor Kim, MD
- Wassim Labaki, MD
- Fernando Martinez, MD
- Deborah Meyers, PhD
- Jill Ohar, MD
- Victor Ortega, MD, PhD
- Robert Paine III, MD
- Stephen Peters, MD, PhD
- Jessica Sieren, PhD
- Lisa Postow, PhD
- Benjamin Smith, MD, MSc
- Vickram Tejwani, MD
- Prescott Woodruff, MD, MPH

GIC Committee Liaison:

- Bryant Lesnoski, MS