**Ancillary Studies Policies and Procedures**

# Ancillary Studies Policies

Scope: This policy applies to A1BC 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 is one that uses study participants but derives funding from awards beyond current A1BC funding. 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).

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. Similarly, abstract and manuscript proposals 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.

Philosophy: A1BC investigator are encouraged to consider ancillary studies and to involve other investigators, within and outside of A1BC, in this process.

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, the protocols and informed consents must also be approved by the Observational Safety Monitoring Board (OSMB) and NHLBI if participant burden is present and/or if deemed necessary for other reasons by the committee.

In the review processes, the Ancillary Studies Committee provides initial review and makes recommendations to the Steering Committee. Generally, the Ancillary Studies Committee may request review by specific investigators before considering approval. 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 A1BC cohorts.
5. Are consistent with and can further the overall goals of A1BC.

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 the review committee.
5. Can be integrated with other studies to conserve samples or limit freeze-thaw cycles.

Further, to conserve specimens for use by A1BC 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 A1BC entailed by an ancillary study (such as costs to coordinate 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 Columbia Data Center 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 A1BC Columbia PI to determine what level of involvement will be required of the coordinating center and the associated costs. In general, this will result in a subcontract proposal from the coordinating center to be included in the PI’s grant application.

1. *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 A1BC ends.

1. *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.

1. *Genetic studies:* Genetics studies may include only participants who provided appropriate informed consent (which is a component of the initial enrollment). Investigators should consult the steering committee 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.

1. *Inclusion of investigator(s):* An A1BC 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 A1BC, and serving as a liaison to the Steering Committee. In addition, each manuscript and abstract are generally expected to include an A1BC investigator.

1. *Inclusion of sites:* A major strength of A1BC is the multicenter design. The proposing investigator is strongly encouraged to involve all A1BC 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.

1. *Early communication with A1BC Centers:* The proposing investigator and/or their liaison should consult with PIs of pertinent Clinical Centers 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.

1. *Timeline:* All proposed ancillary studies must be submitted to the Ancillary Studies Committee for subsequent circulation and review. Studies submitted for review less than 8 weeks before a funding application deadline may not receive timely approval.
2. *Final application or proposal*: A copy of the final proposal as submitted for funding should be submitted to the Ancillary Study leadership.

1. *Industry participation:* Proposals for industry sponsorship or collaboration are welcomed to maximize the scientific productivity of A1BC, 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 (i.e., Alpha-1 Foundation, NIH-NHLBI) that addresses plans for data sharing.

As an initial step in study planning, the PI should contact the Alpha-1 Foundation to determine if an agreement between Alpha-1 Foundation and industry should be developed and implemented or to approve the agreement between industry and the A1BC. Industry-sponsored ancillary studies should comply with current NHLBI guidelines, which are available from the Project Office upon request.

1. *Status reports:* The ancillary study PI should keep the committee 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 committee 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 OSMB reports.

1. *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 ancillary study committee. 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 Ancillary Committee only.

1. *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.

1. *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. This declaration will occur through completion of a COI form provided by A1BC. The completed conflict of interest form will be included with the Ancillary Study proposal.

1. *Incorporation of ancillary study data into A1BC database(s):* The data collected by the ancillary study are first to be provided to the data coordinating center 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 Ancillary Committee any special circumstances that would militate against these guidelines for data sharing.

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# Ancillary Studies Review Procedures

1. No existing biospecimens or data will be released to an ancillary study by the data center 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 A1BC resources without involving the A1BC Ancillary Committee.

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

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

1. The Ancillary Studies Committee chair will assign 1-3 committee members as reviewers, and will email the proposal and the reviewer template document. Reviewer responses are requested within 10 business days. The Ancillary Studies Committee Chair will then schedule a conference call of the Steering Committee members to review the application.

The Ancillary Studies Committee will 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.

1. 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

ancillary committee chair. The PI must address these comments in a separate letter that accompanies the revised proposal and send these to the ancillary committee chair.

1. For a proposal that poses burden, after it is reviewed and approved by the Ancillary Studies Committee, the A1BC Steering Committee will weigh the burden on participants or clinical sites/data coordinating center against the scientific enthusiasm and participant appeal. Studies without a favorable balance will not be approved.

1. Proposals will be discussed by the Steering Committee, generally during their regular monthly conference calls. The chair of the Ancillary Studies Committee will present the summary of the review. In some cases, as determined by the chair of the Steering Committee, email reviews will be conducted. The ancillary committee proposal will be circulated to all PIs for review at the Steering Committee meeting.
2. Proposals that are approved by the 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 committee to the PI. Copies of these communications are also sent to the Steering Committee chairs.