A2ALL Collaborative and Ancillary Studies Policy

Table of Contents

1. Background

The A2ALL studies comprise a large and well-characterized cohort of individuals listed for liver transplantation and their potential or actual living donors. To make the best possible use of this extraordinary resource, the A2ALL encourages external investigators, as well as A2ALL investigators, to develop ancillary studies.

2. Collaborative study and ancillary study definitions

A collaborative study is a study conducted by A2ALL in conjunction with one or more non-A2ALL investigators. The study may address scientific issues outside the scope of the Retrospective and Cohort studies. Data and/or specimens collected during the main A2ALL studies may be utilized in addition to incremental data and/or specimens if required.

A collaborative study may use the central resources of A2ALL (e.g., central repository, Data Coordinating Center). The collaborative study must make arrangements for whatever repository, data collection, management, and analysis support are needed.

An ancillary study is a study that is conducted outside A2ALL by one or more non-A2ALL investigators. A2ALL investigators may take part in an ancillary study. An ancillary study may use A2ALL patients or related materials including data sets, tissue samples and genetics samples, but is not a part of A2ALL activities. Ancillary studies are characterized as requiring new data or sample collection (i.e., above what is required by the A2ALL studies). An ancillary study may involve all A2ALL patients or A2ALL patients at one or several A2ALL sites. An ancillary study is not a statistical analysis of previously collected data.

An ancillary study may use the central resources of A2ALL (e.g., central repository, Data Coordinating Center) for ancillary study purposes providing such use is approved in advance and is supported by funding from the ancillary study. The ancillary study must make arrangements for whatever repository, data collection, management, and analysis support are needed.

3. Implementation of a collaborative or ancillary study – overview

Investigators wishing to conduct a collaborative or ancillary study must complete an application. The A2ALL Collaborative and Ancillary Studies Committee will review the application based on the following criteria, using the expertise represented by the Committee. (If the Committee feels it lacks the expertise to adequately evaluate the merits of an application, they may seek input from external experts):

- Relevance to the A2ALL Study Goals.
- Scientific merit: Does the study represent sound science? Is it likely that this question will still be of interest at the end of the study and its results of importance to liver transplantation and hepatology?
- Qualifications and interest of the investigator(s): Is the investigator capable of carrying out the study and maintaining responsibility throughout its duration?

- Study Design: Is the hypothesis well formed? Can valid conclusions be drawn? Is the analysis plan reasonable?

- Burden to the study: Are the patient and coordinator time and the amount of liver and blood acceptable?

- Uniqueness: Can the goals of the proposed study be met in settings other than A2ALL?

The Collaborative and will make a recommendation to the A2ALL Steering Committee as to whether the study should be approved. The A2ALL Steering Committee must approve the study for it to proceed. Investigators who are responding to a program announcement or applying for funding should gain A2ALL approval for the study before submitting their application to a funding organization. A study may be proposed by investigators outside of A2ALL. However, in that case, an A2ALL principal investigator or co-principal investigator must agree to serve as the liaison between the A2ALL and the study.

4. Procedure for proposing a collaborative or ancillary study details

Submission of a completed A2ALL Collaborative and Ancillary Study Proposal (SP) form to the Collaborative and Ancillary Studies Committee is required. . This form is available on the closed part of the A2ALL website (www.nih-a2all.org) and completed forms should be forwarded to the Data Coordinating Center (mhillca@umich.edu). If an external investigator is proposing a study, he/she can obtain the form through the A2ALL Steering Committee member who will be the liaison for the study. Completion of this form will require specification of the following information:

- The principal investigator for the study and his/her institutional affiliation.
- Names of other key investigators for the study and their institutional affiliations.
- Name of the A2ALL Steering Committee member who will act as study liaison.
- The study title, objectives, and estimated start and end dates.
- A concept sheet describing the research design and methods for achieving the study objectives (2 page maximum length; this is to be a concise, well organized description).
- The A2ALL resources which the study wishes to use:
    - New data or measurements that are to be collected on A2ALL patients or specimens
    - Existing A2ALL data that the study requires
    - Number of patients involved
    - Quantity of specimens to be collected from patients and the conditions of specimen collection
    - If access to previously collected specimens is needed for new measurements, the quantity and amount of specimens required
    - Frequency of visits or patient contacts or specimen collection
    - Types of interview questions or physical measures or data to be collected from patients
    - If access to previously collected A2ALL data is requested (e.g., measures on specimens or patients, treatment information), the nature of the requested data should be described
- The primary outcome variable and sample size, with justification.

- The funding source and status of funding for the study; any un-reimbursed work or personnel time expected of A2ALL must be specified so that the Collaborative and Ancillary Studies Committee can evaluate whether A2ALL is in a position to assume that un-reimbursed work or personnel time.
- The status of IRB approval and plans/procedures to protect patient confidentiality.
- Acknowledgment of the A2ALL Collaborative and Ancillary Studies Policy and the A2ALL Publication and Presentation Guidelines.

Each study must have the approval of the Principal Investigator at each A2ALL site that will participate in the study.

5. Review process for proposed studies

The Data Coordinating Center will circulate the study application to the members of the Collaborative and Ancillary Studies Committee with instructions to send their comments (see below for criteria) to the chair of the Collaborative and Ancillary Studies Committee. The committee chairperson will collate the comments and prepare a written memo to the Steering Committee specifying the Collaborative and Ancillary Studies Committee's recommendation. The Steering Committee will review that recommendation at their next meeting or conference call and make a decision for approval or disapproval. The principal investigator of the study and the A2ALL liaison will receive written feedback from the Steering Committee.

Collaborative and Ancillary Studies Committee members will be asked to assess proposals according to:

- Relevance to the A2ALL Study Goals
- Scientific merit
- Qualifications and interest of the investigator
- Study Design
- Burden to the study and interference with other A2ALL activities
- Uniqueness

6. Publications, abstracts and presentation arising from an ancillary study

Proposed publications arising from approved studies must be reviewed by the A2ALL Publications and Presentations Committee prior to journal submission. The primary purpose of the review is to ensure that any statements about the A2ALL protocol are accurate and that the A2ALL resources used in the ancillary study are appropriately acknowledged. The acknowledgement will indicate that the results and interpretations are those of the author(s) and do not necessarily represent the opinions of the A2ALL Study Group. A scientific review will also be conducted. The process for review will be:

- The draft manuscript should target a specific journal and be sent to the Publications and Presentations Committee via the Data Coordinating Center.

- The paper will be circulated to the A2ALL Steering Committee for voluntary comments directed to the corresponding author.
- The chair of the Publications and Presentations Committee will identify an internal reviewer for the paper and forward the paper to that individual.
- The reviewer will review the paper for accuracy of statements about the A2ALL resources used in the study and for appropriate acknowledgment of A2ALL.
- The reviewer will send comments to the chair of the Publications and Presentations Committee.
- The chair of the Publications and Presentations Committee will send a written review to the author.

If a manuscript is not accepted upon initial submission to a journal, the manuscript does not need to be re-reviewed by the A2ALL after revision and prior to resubmission to a journal, unless there have been substantive changes to the statements that relate to A2ALL resources or the acknowledgment of the A2ALL. The Collaborative and Ancillary Studies Committee Chairperson will decide if re-review by the A2ALL is needed.

Abstracts and presentations arising from these studies will not require approval from the A2ALL. However, A2ALL must be informed about such presentations and will provide review of materials if requested. It is expected that any presentation from a study will include appropriate acknowledgment of the A2ALL resources used by the study.

Authorship for publications and presentations from these studies is at the discretion of the Collaborative and Ancillary Studies Committee. It is expected that conventional authorship will be used, with an acknowledgment of A2ALL.

7. Collaborative and Ancillary Studies Committee charge

The Collaborative and Ancillary Studies Committee does the following:

- Reviews applications for collaborative and ancillary studies submitted to A2ALL and makes recommendations for approval or disapproval to the Steering Committee.
- Maintains a list of all proposed studies indicating approval status and the A2ALL liaison. For approved studies, the list will indicate initiation date and the A2ALL centers participating in the study.
- Maintains a list of allocations or commitments of existing or future A2ALL samples to central A2ALL and to other studies.
- The list of all proposed studies and the list of allocations and commitments of existing or future A2ALL samples will be available on the public portion of the A2ALL website.

8. Collaborative and Ancillary Studies Committee membership, election, and voting

The Collaborative and Ancillary Studies Committee has six members: a chairperson (elected by the Steering Committee), 3 clinical center principal investigators or co-principal investigators (elected by the Steering Committee), one investigator from the Data Coordinating Center, and an NIDDK representative. The chairperson and 3 members from the clinical centers serve for 2-year terms. Terms for the initially elected chair and members will run for 2 years from the date of the initial study review conducted by the committee. The members from the Data Coordinating

Center and NIDDK serve for the duration of the A2ALL study. Members and chairs may serve unlimited terms if elected.

The Data Coordinating Center will coordinate the election process. Investigators will be queried for their interest in being on the committee. A ballot with their names will be circulated for a vote by Steering committee members. Selection of the winner will be by highest number of votes. There will be separate elections for chairperson and for committee members. In the case of tie votes, the Project Executive Committee will decide the issue.

With respect to votes on matters decided by the Collaborative and Ancillary Studies Committee, each committee member has one vote. In case of a tie vote, the Steering Committee will decide by ballot if a meeting or conference call is not imminent.

If an Collaborative and Ancillary Studies Committee member proposes a study, collaborates on a study, or is affiliated with the institution of an investigator who proposes a study, he/she will be excused from reviewing and voting on that study proposal, similar to NIH peer review policies for avoidance of actual or perceived conflicts of interest.

9. Collaborative and Ancillary Studies Committee operation

The Collaborative and Ancillary Studies Committee is a subcommittee of the A2ALL Steering Committee. The A2ALL Data Coordinating Center supports the operations of the Collaborative and Ancillary Studies Committee by arranging Committee conference calls, receiving submitted applications for studies, administering the process for review of submitted applications, writing correspondence for the Committee, and maintaining the lists of studies and allocated/committed samples and the document and correspondence files relating the Committee's activities. The Data Coordinating Center relies on the named liaison for each study and the Collaborative and Ancillary Studies Committee members in completion of these activities.

10. Miscellaneous issues

10.1.1. Access to A2ALL data

Access by studies to A2ALL data collected on participants in the study will be governed by the A2ALL Steering Committee and administered by the Data Coordinating Center. When data will be available for analysis is at the Steering Committee's discretion. Much of the outcome data will not be available until the currently planned end of the study in 2009. Ancillary study investigators should therefore be aware that it might possibly be years before A2ALL data are released.

A2ALL datasets use the A2ALL Patient ID number to link patient records. Study investigators should request data on the A2ALL participants in their study by providing the A2ALL ID numbers of the patients whose data are requested. The DCC will accept SAS, Excel, Access, ASCII, and other data files of records of A2ALL ID numbers (word processing files are not acceptable, other identifiers are not acceptable).

The A2ALL data, which have been approved for provision to the study, will be provided in SAS data sets using whatever SAS version is in use at the DCC. Ancillary study investigators should be prepared to deal with SAS datasets.

10.1.2. Consent and IRB issues

Consent for the study cannot be part of any A2ALL consent –these studies are separate from the A2ALL by definition. Therefore, each study must have its own consent form. Each site participating in a collaborative or ancillary study must have approval from their IRB for participation in the study. Each site must provide a copy of their initial notice of IRB approval of the study and a copy of their IRB-approved consent to the Collaborative and Ancillary Studies Committee prior to initiation of ancillary study activities at the A2ALL site (IRB approval is not required for review of a study application). Copies of notices of renewal of IRB approval must also be provided to the Collaborative and Ancillary Studies Committee annually. The DCC will maintain a file of study IRB approvals and IRB-approved consents.

10.1.3. Funding issues

Collaborative and ancillary studies are supported by non-A2ALL resources. Investigators proposing studies must seek funding from outside sources to conduct their research. Examples include funding obtained through investigator-initiated NIH research grant awards (R01s), program announcements, grants from academic institutions, or private sources (e.g., drug companies, nonprofit health organizations). The A2ALL Steering Committee can provide letters of support for applications for funding for studies approved by the A2ALL. Conduct of studies must comply with all existing A2ALL and NIH policies and guidelines.

A study that wishes to use the services of the Data Coordinating Center or any other A2ALL central resource may contact the principal investigator of that resource regarding participation in the study. Such participation has to be funded with non-A2ALL resources.

10.1.4. Expiration of A2ALL approval

In general, approved studies must be initiated within one year of being approved, or the approval will be withdrawn; this will allow recycling of resources allocated to a study that does not go forward, e.g., due to failure to obtain funding. The principal investigator of the study and the A2ALL liaison will each receive written notice 2 months before a study's approval is due to expire. The study investigator may appeal this expiration of A2ALL approval, e.g., if a funding decision is pending or if an application for funding is being revised and resubmitted. The study investigator should send a letter requesting an extension of approval to the chair of the Collaborative and Ancillary Studies Committee. The letter should indicate the expected timeline for initiation of the study and describe the actions that are being taken to meet that timeline.

10.1.5. A2ALL liaison

A study that is proposed by an investigator outside of the A2ALL must have an A2ALL liaison. This person must be a principal investigator or co-investigator. The liaison serves as the communications link between the Steering Committee and the study. For example, the liaison would provide status reports on the study as needed at Steering Committee meetings and would assist the Data Coordinating Center as needed in communicating with the study. The liaison may participate in the study but participation is not required.

10.1.6. Changes to an approved study's protocol

If a major change occurs to an study's protocol after it has been approved by the A2ALL (e.g., addition of a visit, addition of a specimen, or addition of a measurement on a A2ALL specimen – something that affects the impact on the A2ALL participant or resource used), the Collaborative and Ancillary Studies Committee must approve the change before it is implemented. The Steering Committee will be asked to approve the alterations, based on the recommendation of the Collaborative and Ancillary Studies Committee.

10.1.7. Confidentiality

Confidentiality of individually identifiable data about A2ALLparticipants must be assured. A2ALL provides no assurances that studies will be able to identify and contact A2ALL participants in the future, particularly after the A2ALL ends.

10.1.8. Disposition of data and samples

Data for all aspects of A2ALL will be integrated into the database maintained by the DCC, where it will reside through the end of the study. All samples are to be returned to the NIDDK tissue or genetics repository. Exceptions to this policy can be considered on a case-by-case basis by the steering committee. Further access to samples and data will be in accordance to the ancillary study policies of A2ALL and the NIDDK repository (http://www.niddk.nih.gov/researchprograms/repositories/)