A2ALL Collaborative and Ancillary Studies Policy

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1. Background and General Considerations

1.1. Resource

The Adult to Adult Living Donor Liver Transplantation Cohort (A2ALL) studies comprise a large and well-characterized cohort of candidates for and recipients of liver transplantation and their potential or actual living donors. To make the best possible use of this extraordinary resource, the A2ALL Consortium encourages both internal and external investigators to submit proposals for Ancillary Studies (AS).

1.2. Definition

AS propose questions and test hypotheses that are relevant to the goals and purposes of the A2ALL Study. New AS require additional tests, data or data analyses that are not currently obtained or performed in A2ALL. AS may involve data and samples from all A2ALL participants or subsets of either. These studies may include the use of stored specimens (DNA, serum or liver tissue) from A2ALL participants.

1.3. Funding

AS must be independently funded by the investigator or by resources obtained by the investigator. AS proposed by investigators who are not part of the A2ALL Study must include at least one A2ALL investigator as a collaborator or co-investigator.

Ancillary studies are usually supported by sources outside A2ALL. Examples of these outside sources include NIH research grants or awards, program announcements, institutional grants, and private sources such as industry.

1.4. Industry Sponsorship

If the proposed AS involves industry support, contact A2ALL's NIDDK Project Officers (averell.sherker@nih.gov and jill.smith@nih.gov) before discussing in detail with the company.

1.5. Analysis

All analyses of data performed by the investigator as part of the AS must be confirmed by the A2ALL Data Coordinating Center (DCC) (at the University of Michigan) prior to submission of an abstract or a final manuscript. The final budget of the funding source for the AS should include financial compensation to the DCC for these efforts. The data from all AS will become part of the A2ALL database and will be available to other investigators. Raw and "processed" data from AS will be archived and will become part of the A2ALL study. If the AS proposes analyses of existing A2ALL data the PI of the AS, must complete and submit a Data Use Agreement before the DCC will provide the data.

2. Ancillary Studies Committee

2.1. Membership and Voting

The AS Committee consists of one member from each of the nine sites, the Data Coordinating Center (DCC), and NIDDK, each of whom has one vote. Each Member may designate an Alternate to participate should the Member not be available. The A2ALL Steering Committee will appoint a Chair for the AS Committee.

2.1.1. Quorum

A quorum consists of the NIDDK and Data Coordinating Center (DCC) representatives, plus a majority of the clinical sites' representative members/alternates. Decisions are based on a majority vote of a quorum of the Members.

2.1.2. Meetings

Committee conference calls will be scheduled monthly.

2.2. Duties

- Review of all proposals for AS and make recommendations for approval or disapproval to the A2ALL Steering Committee
- Maintain list of the status of all AS – dates of submission, review, decision for approval or rejection, date of initiation of the study, enrollment, samples used, and progress reports.
- Work with DCC to maintain a list of samples, tissues, slides and other A2ALL materials available and utilized for ancillary studies

3. Definitions

The Committee will recognize and review two types of proposals, EXPEDITED and FULL REVIEW.

3.1. Expedited Proposals

Expedited proposals do not require full scientific review by A2ALL. These are studies that have already had or will have extensive external scientific review by another funding agency or body. One example of this type of study would be a grant that has been reviewed and funded by NIH but is requesting access to samples or data from A2ALL to complete a component of the funded project. This type of study may also be viewed as "collaborative". In general, it will be assumed that funding agencies outside the home University that solicit proposals from the entire US will conduct adequate scientific review of these proposals. Examples of these funding agencies are NIH, NCI, or national or international professional societies or foundations. For AS Expedited Study review, A2ALL has the goal of providing a decision within 4 to 6 weeks of submission of the proposal.

3.2. Full-Review Proposals

Full review is required for Ancillary Studies that have not undergone external scientific review. One example would be a study of a new treatment or intervention with funding source but lack of independent scientific review of design, methods, and proposed analysis of results. Scientific review by Members of A2ALL or designees of A2ALL would be required for approval. Because of the need for a full scientific review, the time from submission to notification may be longer than 4 to 6 weeks, but should be completed within 10 weeks.

4. Procedures for Submitting a New Ancillary Study Proposal

The investigator submits a Proposal of four pages or less to the DCC. The template for new AS Proposals is found in Appendix B. It is recommended that the PI talks with the DCC prior to and during protocol development to ensure that A2ALL samples are available, that the protocol is statistically sound and that financial and data analysis issues are adequately addressed. Send proposals to:

Peg Hill-Callahan
Project Manager
peg.hill-callahan@arborresearch.org

5. Review Process for Proposed Studies

5.1. Review Process for Expedited Review Studies

- Proposals submitted by the first Friday of the month will be considered by the AS Committee by the time of its next conference call, usually held on the last Friday of the month. The investigator should plan to participate in that call to address questions posed by the AS Committee members.
- The DCC reviews Proposal for completeness, potential competition with other AS, and A2ALL sample utilization.
- The DCC consults with the Chair of A2ALL AS Committee to determine whether the Protocol will be adequately reviewed for scientific merit by Outside Funding Agency (1 week).
- The DCC will contact the investigator concerning the need to be available for the next AS Committee call.
- The DCC forwards the Proposal to the AS Committee (along with comments regarding sample utilization, competition with other studies, scientific review body, and a copy of the Review Sheet (Appendix C)).
- AS committee members review the appropriateness of the proposal for the A2ALL Study (as outlined in Appendix C).
- Members have two weeks to vote via email to approve or disapprove the proposal or abstain from voting. A full quorum is as described in Section 2.1.1.
- If no AS committee member votes to disapprove or raises substantive concerns about the proposal, then it will be considered approved. The Chair (or designee in case of conflict

of interest) will provide a letter to the investigator to that effect (see Appendix D for an example of proposed letter).

- A member of the AS Committee who disapproves of the proposal should state his or her reasons. If any member votes to disapprove or raises substantive concerns, then the proposal will be discussed at the next AS committee call. The submitting investigator should be available for that call.
- The outcome of AS proposals that are discussed at the AS call will be any one of the following:
    - Approval or rejection by voice vote (by a majority of at least 7 members).
    - Suitable clarification on the call to allow e-mail re-vote by the AS committee within the following two weeks. Majority of 7 members on the re-vote would be needed for approval.
    - Request a more substantial revision, which would require resubmission to the AS committee. The effect of this would be similar to a vote to reject, but would provide specific guidance for re-submission.
- The Steering Committee is notified of the AS Committee's decision at its next meeting or conference call.
- The Principal Investigator of the Proposal will be notified of the decision of the A2ALL Ancillary Studies Committee within 5 working days of the Committee decision. A letter from the chairperson of the A2ALL AS Committee or designee will constitute official notice (Appendix D).
- The Principal Investigator is required to submit the Proposal to the outside funding agency within 4 months of AS Committee approval. Proposals that would deplete the A2ALL repository (e.g., serum, DNA, liver tissue, or liver biopsy slides) and are unsuccessful in obtaining funding or resources within a year of AS Committee approval must be withdrawn or resubmitted for AS Committee approval.

5.2. Review Process for Fully Reviewed Studies

In general, the A2ALL AS Committee will evaluate the scientific merit of Proposals supported or funded by non-national sponsors, funding agencies, or funding sources within the home University.

- The Chair of AS Committee will decide whether additional Scientific Reviewers need to be assigned to the Proposal or whether the general knowledge of the A2ALL investigators is sufficient to judge the scientific merit of the proposal (1 week). The NIH Project Officer consults with the AS Committee to select suitable external Scientific Reviewers, should they be needed (several weeks).
- For Proposals in which the general knowledge of the A2ALL investigators is sufficient to judge the scientific merit of the Proposal, the DCC forwards the Proposal to the AS Committee (along with comments regarding sample utilization, competition with other studies, scientific review body, and Appendices B and C).
- For studies in which additional scientific reviews are needed, the DCC forwards the Proposal to the reviewers with a request to provide a written review of the Proposal within two weeks.
- Upon receipt of the scientific reviews, AS Committee reviews appropriateness and scientific merit of the Proposal for the A2ALL study (Appendices B and C). AS

Committee members have two weeks to vote by e-mail to Approve or Disapprove the Proposal, or Abstain from voting. A quorum is as described in Section 2.1.1.

- If no AS Committee member votes to disapprove or raises substantive concerns about the proposal, then it will be considered approved. The Chair (or designee in case of conflict of interest) will provide a letter to the investigator to that effect (see appendix D).
- A member of the AS Committee who disapproves of the proposal should state his or her reasons. If any member votes to disapprove or raises substantive concerns, then the proposal will be discussed at the next AS committee call. The submitting investigator should be available for that call.
- The outcome of AS proposals that are discussed at the AS call will be any one of the following:
    - Approval or rejection by voice vote (by a majority of at least 7 members).
    - Suitable clarification on the call to allow e-mail re-vote by the committee within the following two weeks. Majority of 7 members on the re-vote would be needed for approval.
    - Request a more substantial revision, which would require resubmission to the AS committee. The effect of this would be similar to a vote to reject, but would provide specific guidance for re-submission.
- The Steering Committee is notified of the AS Committee's decision at its next meeting or conference call.
- Because of the need for a scientific review, the time from submission to notification may be longer than 4 to 6 weeks, but should be completed within 10 weeks. A letter from the chairperson of the AS Committee or designee will constitute official approval (Appendix D).

5.3. Appealing the AS Committee's Decision

An investigator who disagrees with the final decision of the AS Committee may request a discussion and vote of the A2ALL Steering Committee by sending a brief memo outlining the investigator's concerns to the NIDDK Project Officer and to the Chair of the A2ALL Steering Committee. The Project Officer and Chair have two weeks to decide whether the concerns of the PI are sufficient to merit review of the Protocol by the A2ALL Steering Committee.

5.4. Ongoing Review of Approved Ancillary Studies

The AS Committee reviews approved AS annually. The Principal Investigator must submit a summary of the study to the AS Committee on an annual basis. Annual summaries should include the number of samples/patients analyzed, preliminary results, any problems encountered, published abstracts and manuscripts, etc. At the annual review, the AS Committee will approve, terminate, or request modifications/clarifications to the AS.

6. Modifications to an Approved Ancillary Study

6.1. Definitions

Requests for changes to approved ancillary studies are categorized as Minor or Major Modifications.

6.1.1. Minor Modification

A minor modification is a minimal change in the hypotheses, specimens needed or analyses to be performed in an approved ancillary study. Minor modifications meet the following criteria:

- Essentially the same hypothesis and/or aims of the approved AS,
- No new specimens needed from A2ALL
- No additional budget requested from A2ALL
- Minimal effort from DCC (to obtain data, samples, perform analyses, etc.)
- Exploratory studies using a small number of A2ALL specimens (e.g., 1-3) may qualify as minor modifications if they meet criteria 2-4.
    - A major modification is a change in the hypotheses, a request for additional specimens needed or a request for additional analyses to be performed. Examples of major modifications include:
        - Additional serum, plasma, DNA, liver tissue specimens
        - Significant change in the hypotheses or aims of the AS
        - Additional data analysis by the DCC

6.1.1.1.Approval process for Minor Modifications

- The investigator requesting the modification will write a short summary of the requested modification, including a brief reason for performing the study, methods, samples to be evaluated (number, amount, location of the samples), DCC resources needed, etc.
- The investigator submits the minor modification request to the DCC. The Chair of the AS Committee review the minor modification request to ensure it meets the definition of a Minor Modification. (2 weeks).
- The DCC circulates the Proposal to the members of the appropriate AS Group and the NIDDK Project Officer. In instances where there is no study group associated with the approved AS, the minor modification request will be sent to all members of the A2ALL Ancillary Studies Committee.
- Members of the AS Committee and the NIDDK Project Officer vote Approval/Disapproval. The vote should be conducted by e-mail but may be conducted during a conference call of the AS Committee. This vote shall be performed within 1 month of the determination that requested change is a minor modification.
- If the Minor Modification is approved, then:
    - The DCC notifies the Investigator in writing that the modification was approved. The investigator can then proceed with the proposed work
    - The approval of the minor modification is noted in the minutes of the next AS Group/AS Committee Conference call and the minor modification is attached to the minutes of the conference call.
    - For minor modifications to studies associated with Study Groups (e.g. Immunology, HCV, HCC) the DCC sends the minor modification proposal and the Approval Memo to the Co-Chairs of the AS Committee. The minor modification is noted at the next conference call of the AS Committee (AS Committee does not vote on the approval) and in the minutes of the AS

Committee Conference call. The minor modification is attached to the minutes of the AS Conference call.

- The A2ALL Steering Committee is notified of the minor modification at the next A2ALL Steering Committee Meeting or Conference Call.

6.1.2. Major Modification

A major modification is a change in the hypotheses, a request for additional specimens needed or a request for additional analyses to be performed. Examples of major modifications include:

- Additional serum, plasma, DNA, liver tissue specimens
- Significant change in the hypotheses or aims of the AS
- Additional data analysis by the DCC

6.1.2.1.Approval process for Major Modifications

The investigator requesting the modification will write a short summary of the requested modification, including a brief reason for performing the study, methods, samples to be evaluated (number, amount, location of the samples), DCC resources needed, etc. Requests for Major Modifications need to be evaluated and approved using the procedures described above for approval of "STUDIES REQUIRING FULL SCIENTIFIC REVIEW BY A2ALL" (Section 5.2).

7. Publications, Abstracts and Presentations Arising from an Ancillary Study

Abstracts and manuscripts are to be sent to the A2ALL Publication Committee (attn: Peg Hill-Callahan) for review and approval 7 days and 30 days, respectively, prior to submission. A2ALL Publications Committee needs to be informed when abstracts and manuscript are accepted.

8. Miscellaneous issues

8.1. Consent and IRB issues

Each AS must have its own consent form and every site participating in the AS must have approval from their IRB to participate in the AS. Each site must provide the AS Committee of A2ALL with a copy of their IRB-approved consent prior to the initiation of any activities related to the AS at that site. Copies of notices of renewals of IRB approval must also be provided to the AS Committee on an annual basis. The DCC will maintain records of all IRB approvals and IRB-approved consents.

8.2. Confidentiality

Confidentiality of a study participant's identifiable health data 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 Study ends.

8.3. 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.

8.4. 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 Biosample 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/)

8.5. Discussions with Industry

- Contact the NIDDK project office before beginning substantive discussions with any potential industry sponsor.
- Explain to the company the process for approval of Ancillary Studies in A2ALL.
- Involvement with industry may require a CRADA (Cooperative Research and Development Agreement) or clinical trial agreement with NIH.
- In general, industry funding for a project will pass from the sponsor to NIDDK and then distributed to the participating centers via adjustments to existing contracts or new contracts.
- Business negotiations with a potential sponsor should be conducted through NIDDK. Individual investigators should not make any promises to a company regarding its involvement in A2ALL. The A2ALL investigators will work closely with NIDDK on the negotiations with the sponsor.

9. Appendix A: Ancillary Study Proposal Form

Part I (1 page)
Proposal Name:

Proposal PI:

Co-Investigators:

A2ALL PI:

Funding Agency and Review Body (e.g., NIDDK; my university/other):

I agree to follow A2ALL Policies and Procedures when conducting this study. I acknowledge that the data obtained from this study will belong to the NIH and will be placed in the A2ALL database for use by other investigators. I understand that I cannot begin experiments using A2ALL specimens/data until I receive approval from the A2ALL Ancillary Studies Committee and funding from the Scientific Review Body for my proposal. I also understand that the data analysis for this proposal will be performed by the DCC (unless otherwise approved by the A2ALL study) and that Protocols approved by the A2ALL Ancillary Studies Committee will be placed on the A2ALL Restricted Website.

_____ _____
Proposal Principal Investigator Date

_____ _____
A2ALL Principal Investigator Date

Part II: Protocol (4 page limit, single space)

1. Aims/hypotheses
2. Background/rationale
3. Relations to aims of A2ALL study
4. Study design, experimental groups
5. Methods, data usage
6. Anticipated results
7. Statistical support
8. A2ALL samples to be used in the study (complete Part III: Sample Requirements)
9. Financial issues (e.g., cost for data analysis and obtaining samples from Repository)
10. References

Part III: Sample Requirements. (link to web site with actual sample availability)

Visit – per A2ALL protocol	Liver # patients, mm*	Blood # patients, ml	DNA # patients, ug	Liver Biopsy Slides # patients, slides/patient	Other (describe) # pts, amount
Visit 1					
Visit N					

* Assume 1 mm tissue weighs about 0.75 mg (= 0.5 mm^2 X Π X density of tissue)

Data needed (please specify):
Comments (if any):

10. Appendix B: Ancillary Study Proposal Review Sheet

Please review the Proposal Form submitted by the investigator and evaluate the proposed study as it relates to the goals and purposes of the A2ALL Study:

1. Is this proposal appropriate for the A2ALL study?
2. Does this proposal address the aims of the A2ALL study?
3. Does the proposal conflict with another A2ALL ancillary study?
4. Does the proposal place undue burden on the A2ALL personnel or study samples?
5. Should the A2ALL study defer scientific review of the proposal to the outside funding agency?

Vote: Approval or Disapproval

Comments to the A2ALL AS Committee Chair or the DCC:

Comments to the PI:

11. Appendix C: Scientific Review of New Proposals

General questions:

1. Do you feel qualified to judge the scientific merit of this proposal?
2. If not, is there adequate expertise within the A2ALL Study to review this proposal?
3. Who would you suggest as a Reviewer for this Proposal?

Specific criteria for Scientific Review are based on NIH grant review guidelines (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-05-002.html).

Each criterion will be addressed and considered in deciding the overall score, weighing them as appropriate for each application. Note that an application does not need to be strong in all categories to be judged likely to have major scientific impact and thus deserve a high priority score.

1. Significance: does the Proposal address an important problem? If the aims of the Proposal are achieved, how will scientific knowledge or clinical practice be advanced? What will be the effect of these studies on the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field?
2. Approach: Are the conceptual or clinical framework, design, methods and analysis adequately developed, well integrated, well reasoned, and appropriate to the aims of the Project? Does the applicant acknowledge potential problem areas and consider alternative tactics?
3. Innovation: Is the project original and innovative? For example: Does the project challenge existing paradigms or clinical practice; address an innovative hypothesis or critical barrier to progress in the field? Does the project develop or employ novel concepts, approaches, methodologies, tools or technologies for this area?
4. Investigators: Are the investigators appropriately trained and well suited to carry out this work? Is the work proposed appropriate to the experience level of the principal investigator and other researchers? Does the investigative team bring complementary and integrate expertise to the project?
5. Environment. Does the scientific environment in which the work will be done contribute to the probability of success? Do the proposed studies benefit from unique features of the scientific environment, or subject populations, or employ useful collaborative arrangement? Is there evidence of institutional support?

Vote: Approval or Disapproval

Comments to the A2ALL AS Committee Chair or the DCC:

Comments to the PI:

12. Appendix D: Sample Approval Letter by theA2ALL Ancillary Studies Committee

October 13, 2004

Mary Smith, PhD
New Research Building
Very Famous Medical Center
447 High Ave
Springfield, XX 92215

RE: Your New Proposal

Dear Dr. Smith:

The A2ALL Ancillary Studies Committee APPROVED of your proposal entitled "Name of Proposal" on October 8, 2004.

Please note the following stipulations:

1. You must provide funding to compensate the DCC for data analysis and to obtain the samples from the A2ALL biorepository
2. The A2ALL study is deferring judgment of the scientific value of your proposal to the NIH. If you do not receive NIH funding but would like to use the A2ALL specimens, or if you plan to submit your proposal to another funding agency, you will need to re-submit your proposal to the A2ALL study for evaluation and approval.
3. You must provide the DCC with the NIH reviews of your proposal.
4. If you receive funding from your funding source, then your approval to use A2ALL specimens requested in your proposal expires at the end of your NIH funding for the proposal Approval for your proposal expires on DATE (1 year from approval) if you do not receive funding for the project.
5. You must submit an annual report on the results of your proposal to the A2ALL Ancillary Studies Committee.
6. You must notify the DCC prior to submission of abstracts and manuscripts, and when abstracts/manuscripts are accepted.
7. Other specific stipulations:

Please contact me if you have questions.

Sincerely,

Dr. Who, MD
Chair, A2ALL Ancillary Studies Committee

Cc: Chair SC of A2ALL, DCC representative, (NIH) Averell Sherker, Jill Smith