

HALT-C Policies and Procedures

Ancillary Studies Procedures and Policies (Addendum #3)

Procedures for Ancillary Study (AS) Approval in HALT-C
 Approved by HALT-C Steering Committee: January 18, 2008

I. General Considerations

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

Ancillary studies must be independently funded by the investigator or by resources obtained by the investigator. Ancillary studies proposed by investigators who are not part of the HALT-C clinical trial must include at least one HALT-C investigator as a collaborator or co-investigator ([link to website list](#)).

If the study involves industry support, contact the NIDDK project office before discussing in detail with the company ([Appendix E](#)).

All analyses of data performed by the investigator as part of the ancillary study must be confirmed by the HALT-C Data Coordinating Center (DCC) (at New England Research Institutes (NERI)) prior to submission of an abstract or a final manuscript. The PI must provide financial support to NERI for these efforts. The data from all ancillary studies will become part of the HALT-C database and will be available to other investigators. Raw and "processed" data from ancillary studies will be archived and will become part of the HALT-C study. If the investigator will be performing analyses of existing HALT-C data he or she must complete and submit a Data Use Agreement before the DCC can provide the data.[[put link here](#)]

Investigators not familiar with the HALT-C clinical trial should read the detailed description of the study design (Lee WM et al. Evolution of the HALT-C trial. *Controlled Clinical Trials* 2004;25:472-492). For a brief summary of the study, [click here](#) ([link to Overview of HALT-C Trial](#)). Additional citations of HALT-C publications are also found at that site.

II. The Ancillary Studies Committee

1. The Ancillary Studies Committee consists of one Member from each site (10 clinical sites, virology lab, NIDDK, and NERI), each of whom has one vote. Each Member may designate an Alternate to participate should the Member not be available.
 - a. A quorum consists of 8 Members/Alternates (or 8 votes by Members/Alternates). Decisions are based on a majority vote of a quorum of the Members.
 - b. AS Conference calls will be scheduled monthly.

III. Procedures for Submitting a New Ancillary Study Proposal

1. For AS that do not require extensive internal scientific review, HALT-C has the goal of providing a decision within 6-8 weeks of submission of the proposal. 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 investigator submits a 3-5 page Proposal to NERI. The template for new Ancillary Studies Proposals is found in Appendix A. It is recommended that the PI talks with NERI prior to and during Protocol development to ensure that HALT-C samples are available, that the Protocol is statistically sound and that financial and data analysis issues are adequately addressed. Send proposals to:

Kristin Snow, ScD
 New England Research Institutes
 9 Galen Street
 Watertown, MA 02472
 Phone: 617-923-7747 extension 292
 Fax: 617-926-0144
 e-mail: ksnow@neriscience.com

2. NERI reviews Proposal for completeness, potential competition with other ancillary studies, and HALT-C sample utilization. NERI consults with Chairs of HALT-C Ancillary Studies (AS) Committee to determine whether the Protocol will be adequately reviewed for scientific merit by Outside Funding Agency (1 week). NERI will contact the investigator concerning the need to be available for the next AS Committee call.

1. Proposals to be sent to Outside Funding Agency for scientific review: 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 new HALT-C Proposals.

- a. NERI forwards the Proposal to the AS Committee (along with comments regarding sample utilization, competition with other studies, scientific review body, and Appendix B).
- b. AS Committee reviews appropriateness of the Proposal for the HALT-C study (Appendix B). AS Committee members have two weeks to vote by e-mail to Approve or Disapprove the Proposal, or Abstain from voting. A quorum consists of at least 8 votes.
 - 1) If no AS committee member votes to disapprove or raises substantive concerns about the proposal, then it will be considered approved. The chairman (or designee in case of conflict of interest) will provide a letter to the investigator to that effect (see appendix D).
 - 2) 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.
 - 3) The outcome of AS proposals that are discussed at the AS call will be any one of the following:
 - (1) Approval or rejection by voice vote (by a majority of at least eight members).
 - (2) Suitable clarification on the call to allow e-mail re-vote by the AS committee within the following two weeks. Majority of 8 members on the re-vote would be needed for approval.
 - (3) 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.

- 4) The Steering Committee is notified of the AS Committee's decision at its next meeting or conference call.
 - c. The Principal Investigator of the Proposal will be notified of the decision of the HALT-C Ancillary Studies Committee within 6-8 weeks of submission. A letter from the chairperson of the HALT-C AS Committee or designee will constitute official approval (Appendix D).
 - 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 HALT-C repository (e.g., use 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.
 - e. Appealing the decision of the AS Committee: An Investigator who disagrees with the final decision of the AS Committee may request a discussion and vote of the HALT-C Steering Committee by sending a brief memo outlining the investigator's concerns to the NIDDK Project Officer and to the Chair of the HALT-C 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 HALT-C Steering Committee.
2. Proposals reviewed by HALT-C AS Committee for Scientific Merit. In general, HALT-C AS Committee will evaluate scientific merit of Proposals sent to non-national funding agencies and funding sources within the home University.
- a. Chairs of AS Committee decide whether additional Scientific Reviewers need to be assigned to the Proposal or whether the general knowledge of the HALT-C 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 Scientific Reviewers, should they be needed (several weeks).
 - b. For Proposals in which the general knowledge of the HALT-C investigators is sufficient to judge the scientific merit of the Proposal, NERI forwards the Proposal to the AS Committee (along with comments regarding sample utilization, competition with other studies, scientific review body, and Appendix B and C).
 - c. For studies in which additional scientific reviews are needed, NERI forwards the Proposal to the reviewers with a request to provide a written review of the Proposal within two weeks.
 - d. Upon receipt of the scientific reviews, AS Committee reviews appropriateness and scientific merit of the Proposal for the HALT-C study (Appendix 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 consists of at least 8 votes.
 - 1) If no AS Committee member votes to disapprove or raises substantive concerns about the proposal, then it will be considered approved. The chairman (or designee in case of conflict of interest) will provide a letter to the investigator to that effect (see appendix D).
 - 2) 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.
 - 3) The outcome of AS proposals that are discussed at the AS call will be any one of the following:
 - (1) Approval or rejection by voice vote (by a majority of at least eight members).

- (2) Suitable clarification on the call to allow e-mail re-vote by the committee within the following two weeks. Majority of 8 members on the re-vote would be needed for approval.
- (3) 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.
- 4) The Steering Committee is notified of the AS Committee's decision at its next meeting or conference call.
- e. Because of the need for a scientific review, the time from submission to notification may be longer than 6-8 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).
- f. Appealing the decision of the AS Committee: An Investigator who disagrees with the final decision of the AS Committee may request a discussion and vote of the HALT-C Steering Committee by sending a brief memo outlining the investigator's concerns to the NIDDK Project Officer and to the Chair of the HALT-C 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 HALT-C Steering Committee.

3. General Comments

- a. Proposals that have received scientific review and approval by the HALT-C Ancillary Studies Committee will be placed on the HALT-C restricted website and will be available for viewing by all persons having access to this website. Proposals in which the HALT-C AS Committee deferred scientific review to the NIH (or other qualifying scientific review body) will not be placed on the HALT-C restricted website until the protocol is funded by the NIH (or other funding agency).
- b. The AS Committee reviews ancillary studies 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 ancillary study.
- c. Abstracts and manuscripts need to be sent to the HALT-C Publication Committee (attn: Kristin Snow, ScD) for review and approval 7 days and 30 days, respectively, prior to submission. HALT-C Publications Committee needs to be informed when abstracts and manuscript are accepted.

IV. Modifications to Approved Ancillary Study

- 1. Requests for changes to approved Ancillary Studies are categorized as Minor or Major modifications. The definition and approval process for Minor and Major modifications are provided below
- 2. Definitions:
 - a. 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:
 - 1) Essentially the same hypothesis and/or aims of the approved AS,
 - 2) No new specimens needed from HALT-C Repository (BBI or AFIP)
 - 3) No additional budget requested from HALT-C

- 4) Minimal effort from NERI (to obtain sample, perform analyses, etc)
 - 5) Exploratory studies using a small number of HALT-C specimens (e.g., 1-3) may qualify as minor modifications if they meet criteria b, c and d.
- b. 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:
- 1) Additional serum, plasma, DNA, liver tissue specimens
 - 2) Significant change in the hypotheses or aims of the ancillary study
 - 3) Additional data analysis by NERI
3. The investigator requesting the modification should 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), NERI resources needed, etc.
4. Approval process for Minor Modifications
- a. The investigator submits the minor modification request to NERI. Chairs of the AS Committee review the minor modification request to ensure it meets the definition of a Minor Modification. (2 weeks).
 - b. NERI 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 Ancillary Study, the minor modification request will be sent to all members of the HALT-C Ancillary Studies Committee.
 - c. Members of the appropriate AS Group (or 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 Group/Committee. This vote shall be performed within 1 month of the determination that requested change is a minor modification.
 - d. If the Minor Modification is approved, then:
 - 1) NERI notifies the Investigator in writing that the modification was approved. The investigator can then proceed with the proposed work
 - 2) 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.
 - 3) For minor modifications to studies associated with Study Groups (e.g. Immunology/Virology) NERI 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.
 - 4) The HALT-C Steering Committee is notified of the minor modification at the next HALT-C Steering Committee Meeting or Conference Call.
5. Approval process for Major Modifications
- a. Requests for Major Modifications need to be evaluated and approved using the procedures for described above for approval of "Proposals which are reviewed by HALT-C AS Committee for Scientific Merit" (section III.2)

APPENDIX A: HALT-C Ancillary Study PROPOSAL

Part I (1 page)

Proposal Name:

Proposal PI:

Co-Investigators:

HALT-C PI:

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

I agree to follow HALT-C 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 HALT-C database for use by other investigators. I understand that I cannot begin experiments using HALT-C specimens/data until I receive approval from the HALT-C 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 NERI (unless otherwise approved by the HALT-C study) and that Protocols approved by the HALT-C Ancillary Studies Committee will be placed on the HALT-C Restricted Website.

Proposal Principal Investigator

Date

HALT-C Principal Investigator

Date

Protocol Part II (4 page limit, single space)

1. Aims/hypotheses
2. Background/rationale
3. Relations to aims of HALT-C study
4. Study design, experimental groups
5. Methods, data usage
6. Anticipated results
7. Statistical support
8. HALT-C 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

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

Visit	Liver # patients, mm*	Blood # patients, ml	DNA # patients, ug	Liver Biopsy Slides # patients, slides/patient	Other (describe) # pts, amount
Screen 1					
Screen 2					
Baseline					
Lead in Week 4					
Week 8					
Week 12					
W16					
Week 20					
Week 24					
Randomized Month 9					
Month 12					
Month 15					
Month 18					
Month 21					
Month 24					
Month 27					
Month 30					
Month 33					
Month 36					
Month 39					
Month 42					
Month 45					
Month 48					
Post- treatment					
Responders W30					
W36					
W42					
W48					
W60					
W72					

* Assume 1 mm tissue weighs about 0.75 mg (= 0.5 mm² X π X density of tissue)

Data needed (please specify):

Comments (if any):

APPENDIX B: Proposal Review Sheet for Appropriateness for Halt-C Clinical Trial

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

Vote: Approval or Disapproval

Comments to the HALT-C AS Committee Chair or NERI:

Comments to the PI:

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 HALT-C 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 HALT-C AS Committee Chair or NERI:

Comments to the PI:

APPENDIX D: Sample Approval Letter by the HALT-C Ancillary Studies Subcommittee

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 HALT-C 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 NERI for data analysis and to obtain the samples from the HALT-C biorepository
2. The HALT-C 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 HALT-C specimens, or if you plan to submit your proposal to another funding agency, you will need to re-submit your proposal to the HALT-C study for evaluation and approval.
3. You must provide NERI with the NIH reviews of your proposal.
4. If you receive funding from your funding source, then your approval to use HALT-C 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 HALT-C Ancillary Studies Committee.
6. You must notify NERI 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,

Timothy Morgan, MD
Co-Chair, HALT-C Ancillary Studies Committee

Cc: Adrian Di Bisceglie, Kristin Snow, James Everhart, Greg Everson

Appendix E: AS proposal discussions with industry

1. Contact the NIDDK project office before beginning substantive discussions with any potential industry sponsor.
2. Explain to the company the process for approval of Ancillary Studies in HALT-C.
3. Involvement with industry may require a CRADA (Cooperative Research and Development Agreement) or clinical trial agreement with NIH.
4. In general, industry funding for a project will come from the sponsor to NIDDK and will be added to the contracts of the participating centers.
5. Business negotiations with a potential sponsor should be through NIDDK. Individual investigators should not make any promises to a company regarding its involvement in HALT-C. The investigators will work closely with NIDDK on the negotiations with the sponsor