HALT-C Policies and Procedures

I. Policies

Trial Organization

The following are key components in this multi-site trial:

- Project Officer (NIDDK);
- The funded components: Clinical Centers (CC), Data Coordinating Center (DCC), Virology Lab (VLAB), and Central Repository;
- Steering Committee (SC) (and subcommittees); and
- Data and Safety Monitoring Board (DSMB).

Each of these components is discussed below. Figure 1 summarizes the main lines of communication between these components.

A. NIDDK:

The Project Officer for the HALT-C Trial will be responsible for the close coordination of all aspects of the trial. All technical direction for the trial resides with the Project Officer who will serve as executive secretary of the Data and Safety Monitoring Board (DSMB) and will serve as a liaison between the DCC and the DSMB. The Project Officer will assist in quality control, interim data and safety monitoring, final data analysis and interpretation, preparation of publications, and coordination and performance monitoring. A representative of NIDDK will serve on each committee.

B. Clinical Centers:

Each clinical center will need to recruit up to 180 patients and randomize and follow approximately 90 patients. Clinical Centers will be responsible for collecting trial data, recording information on the trial forms, sending these data to the DCC, and collecting and shipping specimens to the Repository.

Key Clinical Center responsibilities include:

- Recruiting adequate numbers of women and designated minority patients
- Providing bilingual interviews as needed
- Assisting with Phase 1 protocol development by serving on subcommittees, pre-testing sections of the protocol as required and taking appropriate leadership roles for protocol segments
- Completing recruitment on time
- Working proactively to retain patients and keep high adherence to therapy
- Completing all trial protocols according to the MOO and collaborating with the DCC to ensure high quality data
- Participating in manuscripts and presentations.

C. Data Coordinating Center (DCC):

The DCC shall have primary responsibility for the following tasks:

- Preparation of the trial protocol, forms, data management system, and a management plan
- Monitoring and support of enrollment and follow-up
- Compilation and preparation of the data, assuring data quality, and data analysis
- Administrative support of the work of the Project Officer and the trial subcommittees
- Participation in manuscripts and presentations
- Developing and monitoring all Quality Assurance/Quality Control procedures

D. Virology Laboratory (VL):

This central laboratory will perform key assays for the trial. Key responsibilities include:

- Participation in protocol development
- Leadership in development of the specimen processing and analysis protocols and production of the laboratory
- Completion of all assays in a timely manner
- Implementation of adequate quality assurance in assay performance
- Participation in manuscripts and presentations

E. Central Repository (CR):

BBI Biotech, located in Gaithersburg, MD will serve as the Central Repository for the trial. This repository will be responsible for receipt, storage and distribution of serum, plasma, peripheral blood mononuclear cells(PBMC) and frozen liver tissue.

F. Steering Committee (SC):

The SC is the primary decision making body for the trial, subject to NIDDK final approval.

1. Membership includes:

   NIDDK: Project Officer (1 Vote)
   CCs: Principal Investigator of each of the ten CCs (1 Vote each)
   VLAB: Principal Investigator of VLAB (1 Vote)
   DCC: Principal Investigator of DCC (1 Vote)

2. Chair:

   A chair of the SC is appointed on a rotating basis from CC Principal Investigators.

G. Executive Committee:

The SC chair, Project Officer, Scientific Advisor, DCC Principal Investigator, and DCC Project Director form a small Executive Committee that convenes monthly or as needed with the following non-decision-making functions:

- Development of SC agendas
- Calling ad hoc SC meetings or calls as needed
- Follow-up on all SC decisions to ensure implementation
- Monitoring activities of SC Subcommittees
- Monitoring of recruitment and retention

H. Subcommittees of the Steering Committee:

In Phase 1, Subcommittees are focused on protocol development. In Phases 2 and 3, the focus is on standard implementation, quality control, analysis and manuscripts.

Phase I Subcommittees include:

- Protocol Committee
- Clinical Assessment Committee
- Ancillary Studies Committee
- Forms Committee
- Pathology Committee

Phase 2 & 3 Subcommittees include:

- Recruitment and Retention Committee
- Protocol Committee
- Ancillary Studies Committee

  - Genetics/Genomics/Proteomics Sub-committee
- Publications Committee
- Pathology Committee
- Laboratory/Repository Committee
- Clinical Outcomes (including Adverse Events)
- Study Coordinator Committee
- Data Management Committee
- Exemption Committee
- Forms Committee

I. Data and Safety Monitoring Board:

The primary purpose of this Board will be to monitor and provide independent ethical oversight for the trial. The DSMB will provide advice to NIDDK, as needed. This board will review the protocol developed during Phase 1, plans for recruitment and follow-up, and any other questions pertinent to the ethical conduct of the trial. It will review protocol changes and might suggest changes as needed. During Phase 2, it will monitor the data at regular intervals to determine whether significant benefit or harm has been demonstrated in either treatment group or whether there is other compelling need to stop the trial. Please see Addendum #1 of this section of the Manual of Operations for the complete DSMB charter.

The Principal Investigator of the DCC, the Project Officer, and at least one scientific advisor from NIDDK may participate as ex-officio, not-voting members of this board.

J. Outcome Review Board (ORB):

An Outcome Review Board will be appointed to review all clinical outcome events. Members of the Board will include Principal Investigators from the Clinical Centers and the NIDDK Scientific Officer. The schedule for ORB membership is included in Section I.2 of this manual.

Clinical Centers will submit the appropriate forms and source documents to the DCC. The DCC will send copies of these documents to two members of the ORB, and to a third if there is not consensus. Outcomes will be evaluated by the ORB based on pre-determined criteria for each outcome variable. ORB members will not know the treatment status of patients.

K. Publication Policies:

The Publications Committee will review all publications. No trial data may be presented or published without prior approval of the Publications Committee. Detailed publication policies and guidelines are included in Addendum #2 of this section of the Manual of Operations.

L. Ancillary Study Policies and Procedures:

The Ancillary Studies Committee has developed policies and procedures for modification of existing studies and for the development of new studies. These detailed policies and procedures are located in Addendum #3 of this section of the Manual of Operations.

M. Genetics/Genomics/Proteomics Sub-committee:

Formation of the Genetics/Genomics/Proteomics Sub-committee was approved on 10/09/2002. This group will review new proposals with a genetic focus, whether from HALT-C clinical centers or outside the study. The group will determine whether the proposal is appropriate to the main study goals of HALT-C, what genetic resources are required, whether the request is allowed by the HALT-C genetic consent forms, and whether the technology being proposed and the study design are appropriate. A critical function will be to determine whether the proposal complements or conflicts with other genetic studies currently approved or likely to be considered at a later date. Because this is a complex,

multifaceted area with rapidly developing technologies, the group may need to call on expertise beyond that contained within HALT-C. The group will identify a HALT-C investigator to work with any external proposer. Any potential for developing a contractual relationship with industry need to be referred to the NIDDK. Recommendations will be brought to the Ancillary Studies Committee. As with all new testing and proposals, approval will be required by the Steering Committee.

II. Procedures

A. Changes to the Protocol

All changes to the HALT-C protocol must be approved by the Steering Committee, clinical center IRBs, DCC IRB, NIDDK, and the DSMB.

B. Communications

- Numbered Memos:

The DCC will distribute memos, numbered in sequential order, detailing all protocol and procedural changes made during the course of HALT-C. These memos will be distributed to all Principal Investigators, Clinical Center staff, NIDDK staff, DCC staff, Virology lab Principal Investigator and Project Manager, and Repository Project Manager. Each HALT-C institution should maintain a central notebook for these memos, which will be reviewed during site visits.

- Numbered Communications:

The DCC will distribute communications, numbered in sequential order, detailing other updates and information about data management. These memos will be distributed to all Clinical Center Study Coordinators, Clinical Center Data Managers, and DCC staff. Each HALT-C institution should maintain a central notebook for these communications, which will be reviewed during site visits.

- Trial Directory:

The DCC maintains a directory containing contact information of all HALT-C Trial staff. This directory is available on the website maintained for the trial:

https://paws.neri.org/sitelogin.asp

This is a password-protected site. The password will be changed periodically and new password information will be distributed in a Numbered Memo, as described above.

Please forward all changes in contact information and names and contact information for all new HALT-C Trial staff to the DCC for incorporation into the directory.

C. Transfer of patients between HALT-C centers:

In the event of transfer of patients between HALT-C centers patients will keep their initial HALT-C Patient ID number. The DCC will change a variable in the DMS so that the new HALT-C center will be able to data enter forms and have access to this patient's data. The patient's previous HALT-C center will no longer be able to access this information. This patient will show up on reports for the new center only. Additional information on transferring patients is included in Section D.3 of this manual.

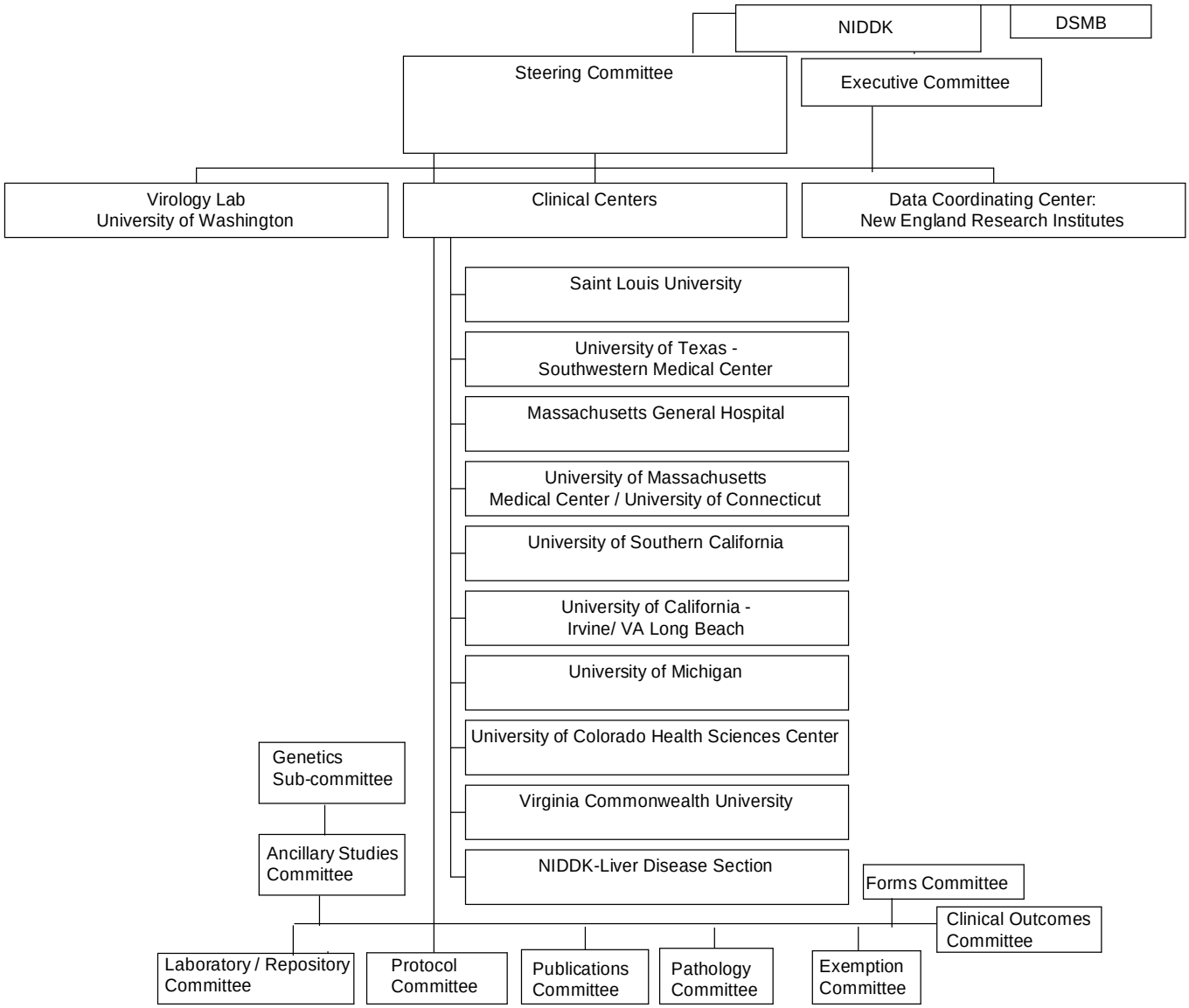
Prior to transfer of patients between HALT-C centers the following procedures are recommended:

1.) Patient notifies current center of interest in transferring HALT-C follow-up to another HALT-C clinical center.
2.) The HALT-C centers develop a timeline for this transfer and for the completion of the following items:

- All un-entered data forms must be data entered and all pending edits resolved before the transfer of the patient can occur.
- All specimens stored locally must be shipped to BBI.

3.) Notify the DCC of the transfer date. Please let the DCC know if the patient will be dropping out of any ancillary studies.
4.) The new HALT-C center must consent the patient with their main trial consent form.
5.) If distributed vials and used trial medications are not returned or accounted for at the current center this must be documented in the patients record and at the pharmacy. The new center must also have a note in the patients record and pharmacy noting that trial medications distributed at another HALT-C center were returned or accounted for at their center.

Figure 1: Trial Organization



Addendum #1: Data and Safety Monitoring Board Charter:

I. OVERVIEW

The Data and Safety Monitoring Board (DSMB) advises the National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK) regarding patient safety and the efficacy of therapy in the HALT-C Trial. Nine clinical centers, a data coordinating center (DCC), and a virology center are conducting the clinical trial through contracts with NIDDK. The NIDDK intramural Liver Diseases Section is also participating as a tenth clinical center. The trial is governed by the Steering Committee, composed of the principal investigators of each center and the NIDDK project officer. An Executive Committee, consisting of the chair of the Steering Committee, the principal investigator and project director of the DCC, and NIDDK staff monitors the day-to-day progress of the trial and plans Steering Committee meetings.

II. DSMB RESPONSIBILITIES

The initial responsibility of the DSMB was approval of the initiation of this clinical trial. After this approval, and at periodic intervals during the course of the trial, the DSMB responsibilities are the following:

- Review the research protocol, informed consent documents and plans for data safety and monitoring, including all proposed revisions;
- Evaluate the progress of the trial, including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, performance of the trial site, and other factors that can affect study outcome;
- Consider factors external to the study such as scientific or therapeutic developments that may affect the safety of the participants or the ethics of the trial;
- Protect the safety of the study participants;
- Report on the safety and progress of the trial;
- Make recommendations to NIDDK, the Steering Committee, and, if required, to the FDA and IRB concerning continuation, termination or other modifications of the trial based on the observed beneficial or adverse effects of the treatment under study;
- If appropriate, conduct interim analysis of efficacy in accordance with stopping rules which are clearly defined in advance of data analysis and have the approval of the DSMB;
- Ensure the confidentiality of the trial data and the results of monitoring;
- Assist NIDDK by commenting on any problems with study conduct, enrollment, sample size and data collection.

III. MEMBERSHIP

The Data Safety Monitoring Board consists of at least 5 members appointed by NIDDK. Three members will constitute a quorum. Members shall have no financial, scientific, or other conflict of interest with the trial. Collaborators or associates of the investigators in this trial are not eligible to serve on the DSMB. Written documentation attesting to absence of conflict of interest is required.

Dr. Gary Davis has been selected by NIDDK to serve as the DSMB Chairperson. He is responsible for overseeing the meetings and developing the agenda in consultation with the NIDDK Project Officer. The Chair is the contact person for the DSMB. An NIDDK Representative will serve as the DSMB

Executive Secretary (ES). Other NIDDK officials may serve as ex-officio members of the DSMB. The DCC shall provide the logistical management and support of the DSMB.

A safety officer will be the contact person for severe adverse event reporting. Procedures for notifying the Chair of the DSMB and the NIDDK Project Officer will be discussed.

IV. BOARD PROCESS

Meetings of the DSMB will be held 2 times a year at the call of the Chair, with advance approval of the NIDDK Project Officer. An NIDDK representative will be present at every meeting.

Meetings shall be closed to the public because discussions may address confidential patient data. Meetings are attended, when appropriate, by members of the Steering Committee. Meetings may be convened as conference calls as well as in person. An emergency meeting of the DSMB may be called at any time by the Chair of the DSMB or by NIDDK should questions of patient safety arise.

V. MEETING FORMAT

DSMB meetings consists of an open, closed, and executive sessions. This format can be modified as needed.

A. Open Session:
The open session will be attended by voting DSMB members, the Executive Committee, the NIDDK ES, and members of the Steering Committee as needed.

Issues discussed will include conduct and progress of the study, including participant recruitment, data quality, general adherence and toxicity issues, and any other logistical matter that may affect either the conduct or the outcome of the trial. Patient-specific data and treatment group data shall not be presented in the open session.

B. Closed Session:
The closed session will be attended by voting DSMB members, representatives from NIDDK, the study biostatistician (principal investigator of the DCC), and the NIDDK ES.

Analyses of blinded outcome data are reviewed by masked intervention groups, including baseline characteristics, primary and secondary outcomes, adverse events, adherence and dropouts, and examination of any relevant subgroups.

C. Executive Session:
The executive session will be attended by voting DSMB members and the NIDDK ES.

The DSMB will discuss information presented to it and decide whether to recommend continuation or termination, protocol modifications or other changes to the conduct of the study.

For treatment comparisons, the DSMB can become unblinded if trends develop either for benefit or harm to the participants.

Reasons for Early Termination:

1. Serious adverse effects in entire intervention group or in a dominating subgroup;
2. Greater-than expected beneficial effects;
3. A statistically significant difference by the end of the study is improbable; or
4. Logistical or data quality problems so severe that correction is not feasible.

Should the DSMB decide to issue a termination recommendation, full vote of the DSMB will be required. In the event of a split vote, majority vote will rule and a minority report should be appended.

D. Open Session:
The final session will be attended by voting DSMB members, the Executive Committee, and NIDDK ES.

The chair of the DSMB shall report its recommendation regarding study continuation and concerns regarding the conduct of the study. Requests regarding data presentation for subsequent meetings will be made. Subsequent DSMB meetings will be scheduled.

VI. REPORTS

A. Interim Reports:
Interim reports are generally prepared by the study statistician(s) and distributed to the DSMB and the NIDDK Project Officer at least 10 days prior to a scheduled meeting. These interim reports are numbered and provided in sealed envelopes within an express mailing package or by email if the DSMB prefers. The contents of the report are determined by the DSMB. Additions and other modifications to these reports may be directed by the DSMB on a one-time or continuing basis. Interim data reports generally consist of two parts. Part 1 (Open Session Report) provides information on study aspects such as accrual, baseline characteristics, and other general information on study status. Part 2 (Closed Session Report) may contain data on study outcomes, including safety data and depending on the study, and efficacy data. The Closed Session Report is considered confidential and should be destroyed at the conclusion of the meeting. Data files to be used for interim analyses should have undergone established editing procedures to the extent possible. Interim analyses of efficacy data are performed only if they are specified and approved in advance and criteria for possible stopping are clearly defined.

B. Reports from the DSMB:
A formal report prepared by the ES in consultation with the Chair will be sent to the full DSMB within 4 weeks of the meeting. Once approved by the DSMB, the NIDDK will forward the DSMB report to the Steering Committee. It is the responsibility of the Steering Committee members to distribute the DSMB report to all co-investigators and to assure that copies are submitted to their respective IRBs as appropriate.

Each report should conclude with a recommendation to NIDDK to continue or to terminate the study. This recommendation should be made by formal majority vote. A termination recommendation may be made by the DSMB at any time by majority vote. In the event of a split vote in favor of continuation, a minority report should be contained within the regular DSMB report. The report should not include unblinded data, discussion of the unblinded data, etc.

C. Mailings to the DSMB:
On a scheduled basis (as agreed upon by the DSMB) blinded safety data should be communicated to all DSMB members. Severe adverse events will be provided to the DSMB chair as they occur. Any concerns should be brought to the attention of the NIDDK Project Officer.

D. Access to Interim Data:
Access to the accumulating endpoint data should be limited to as small a group as possible. Limiting the access to interim data to the DSMB members relieves the investigators of the burden of deciding whether it is ethical to continue to randomize patients and helps protect the study from bias in patient entry and evaluation.

VII. CONFIDENTIALITY

All materials, discussions and proceedings of the DSMB are completely confidential. Members and other participants in DSMB meetings are expected to maintain confidentiality.

Addendum #2: HALT-C Trial Publication and Presentation Guidelines

(Version 3.3.1, Approved 06/04/2004)

A. GOALS

1. Promote timely and high-quality presentation and publication of findings.

2. Support broad and equitable participation by HALT-C investigators in presentations and publications

3. Define prospectively a set of equitable rules and guidelines that can be used to determine authorship and the order in which authors are listed

4. Select topics for publication and presentation, assign authors to Writing Groups, and set priorities for publications and presentations

5. Provide editorial support and timely review for presentations and publications

6. Defend the academic freedom of HALT-C investigators collectively to publish results emanating from the Trial while providing limitations on publication of results from any one Center that could threaten the integrity of collective data

B. SCOPE OF GUIDELINES

1. These guidelines will apply to original manuscripts (including methodology, validation, laboratory approaches, etc.), abstracts, oral and poster presentations, letters to the editor, meeting proceedings, extended abstracts that include data collected as part of the HALT-C Trial, and reviews that include original HALT-C Trial data not previously published in a primary source. In addition, these policies apply to both the results of the Clinical Trial and to the results of Ancillary Studies related to the Trial.

2. These policies remain in effect even after formal conduct and funding of the Trial are complete.

3. For purposes of publications and presentations, all data derived from the HALT-C Trial or from specimens collected during the Trial are the collective intellectual property of the study investigators, not those of any individual investigator, collaborating investigator, or the study sponsors from government and industry. (Legally, the data and specimens collected are the property of the US Government.)

4. These guidelines will become part of the Policy Manual for the Trial.

C. PUBLICATIONS COMMITTEE

1. The Publications Committee of the HALT-C Trial will consist of the Principal Investigator — or his/her designee — from each of the 10 Clinical Centers, the Data Coordinating Center, the Virology Center, and the NIDDK.

2. The Chairperson of the Publications Committee will be elected for a term of one year by members of the Publications Committee. During the month of April, and no later than May 1 of each year of the Trial, the election will be coordinated by the Data Coordinating Center. The number of consecutive or interrupted terms that a chairperson may serve will not be limited.

3. The Publications Committee will mediate and settle all disputes and conflicts over publications issues, priorities, and authorship, etc., among study investigators. Investigators who perceive inequities in authorship or other problems relating to authorship should discuss these concerns with the Publications Committee chairperson; if the difficulty cannot be settled in this informal manner, the concerned investigator should submit a letter to the Publications Committee chairperson outlining the problem. The document will be reviewed and discussed by the Publications Committee, and a formal written reply will be made to the investigator. If the chairperson of the Publications Committee has a perceived or real personal stake in the outcome of the conflict and cannot preside in an unbiased way, he or she should be recused, and another member of the Publications Committee should assume the chairperson's role in resolution of the dispute. If Publications Committee deliberations fail to resolve such a dispute, the dispute will be submitted for resolution to the Steering Committee.

4. The Publications Committee reserves the right to amend Publications Committee Guidelines as necessary, in order to clarify their intent.

D. TYPES OF PUBLICATIONS

1. Study-Wide, Main Papers that represent reports of the main outcomes of the Trial, based on analysis of study-wide data

2. Secondary Manuscripts that address issues more peripheral to the main study outcome but that are based on data collected as part of the main study. This would include ancillary studies that are study-site-wide.

3. Local Papers that represent reports of data collected from locally initiated and separately conducted ancillary studies unique to one or several sites

4. Methodology/Validation Papers

5. Abstracts, meeting proceedings, extended abstracts, oral and poster presentations

6. Letters to the Editor

7. Press Releases

E. AUTHORSHIP

1. Authors should participate in the writing of the paper according to guidelines of the International Committee of Medical Journal Editors (N Engl. J Ed 1991; 324:424-8). Those who participated in conception and design, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript relating to important intellectual content, and final approval of the manuscript should be included as authors. Statistical expertise and virology expertise that relate directly to the conduct of the study are additional criteria for authorship. Provision of study material or patients; collection and assembly of data; provision of administrative, technical, or logistic support; and obtaining funding do not necessarily merit authorship but should be considered on a case-by-case basis, especially when other contributions are included. Honorary authorship will not be considered.

2. For each Study-Wide Main Paper, the writing of the manuscript will be assigned to a Writing Group, to consist of three to four Trial Investigators, one of whom will be designated the Chairperson or Responsible author, plus a representative of the Data Coordinating Center.

The Publications Committee will nominate the Writing Group and Chairperson and send the selection to the Steering Committee for final approval. The Writing Group, plus any ad hoc contributors who fulfill criteria for authorship, will be included as authors. The Writing Group for each publication will be listed in an Acknowledgments section of the manuscript.

3. Selection of first authors: Unless he/she delegates otherwise, the Chairperson of the Writing Group will be the first author.

4. For Study-Wide Main Papers, the list of authors should be limited to one investigator per Clinical Center, Virology Center, and Data Coordinating Center, as well as the NIDDK. Because so many personnel from each Center are participating in the Trial, including all personnel is impractical and contrary to journal guidelines and limitations. The selected list of masthead authors will end in "and the HALT-C Trial Group." All study participants should be listed in an appendix or footnote that identifies study centers and the roles of participants per center. For journals that limit the number of masthead authors, the task of designating a smaller number of masthead authors will fall to the Publications Committee. In case this contingency arises, the following order of authorship will apply until the journal's limit is reached:

    a. The Writing Group

    b. Investigators felt by the Writing Group to have made special contributions to the concept, design, or analysis of the study (often these will already be included in the Writing Group)

    c. Investigators felt by the Writing Group to have contributed special effort to the execution of the study (often these will already be included in the Writing Group)

    d. Investigators ranked by number of study subjects enrolled.

5. Order of Authorship: For some manuscripts, the contribution of primary investigators may be equivalent among study Centers. For others, especially secondary manuscripts, manuscripts describing ancillary studies, or manuscripts suggested by a subset of study investigators, level of input will be considered in order of authorship. For all manuscripts, factors to be included in decisions about order of authorship are contribution to concept, design, and analysis; role in drafting of the article and/or revising it critically for important intellectual content; number of study patients enrolled; completeness/integrity of the data and specimens from the investigator's site; and leadership role. The Publications Committee may amend the order of authorship to recognize an exceptional contribution to the study or the manuscript by an individual Investigator. The Writing Group for each Main Paper will suggest an order of authorship that will be approved first by the Publications Committee and then the Steering Committee.

6. The Publications Committee will oversee the writing and authorship of manuscripts and insure that the tasks of writing and the recognition of authorship are distributed fairly among study investigators and not dominated by any one investigator or study center.

7. Failure to complete assignment:

    a. If a Writing Group does not complete its work on a manuscript or fails to meet timeline milestones, the Chairperson of the Publications Committee may reassign the roles of first author and/or select new Writing Group members. This exigency will be exercised if no draft is produced within 4 months of the availability of a clean data set for the manuscript.

8. Investigators who have left HALT-C Trial

    a. Over the multi-year course of the HALT-C Trial, one or more Investigators or Co-Investigators are likely to leave their institutions, change primary interest, or terminate their roles in the HALT-C Trial for a variety of professional and personal reasons. Because such Investigators will have to be replaced, the new Investigator will assume the masthead authorship role for the Trial site. Ordinarily, the role of such Investigators can be acknowledged in an appendix. For some studies, for example ancillary studies in which the former Investigator may have played a primary or very strategic role, the Publications Committee may elect to recognize the important contribution of the former Investigator by including him/her as an author (even to appoint him/her to a Writing Group). Similarly, the Publications Committee would be the entity that would entertain a petition from the former Investigator to be included as an author. If the former Investigator meets the criteria for authorship, as defined above, the Publications Committee will have the discretion to include him/her as an author. If the former Investigator's petition is denied by the Publications Committee, the Investigator will have recourse to a final decision by the Steering Committee. Similarly, if Publications Committee deliberations fail to resolve a dispute over authorship of a former Investigator, the dispute will be submitted for resolution to the Steering Committee.

9. Non-HALT-C Trial Investigators

    a. For some ancillary studies, HALT-C Trial investigators may wish to invite outside experts to participate as scientific collaborators. Such addition of investigators should be presented for approval to the Ancillary Studies Committee, and this approval should be ratified by the Steering Committee. Ordinarily, manuscript authorship would be limited to HALT-C Trial investigators. If, however, such an outside expert has played a primary or very strategic role in the study, the Publications Committee may elect to recognize the important contribution of the outside Investigator by including 5him/her as an author (even to appoint him/her to a Writing Group). Such a request should be presented by a HALT-C Trial member of that ancillary study. If the outside investigator meets the criteria for authorship, as defined above, the Publications Committee will have the discretion to include him/her as an author. If the petition from the HALT-C Investigator to include the outside Investigator as an author is denied by the Publications Committee, the HALT-C Investigator making the proposal will have recourse to a final decision by the Steering Committee. Similarly, if Publications Committee deliberations fail to resolve a dispute over authorship of an “outside” investigator, the dispute will be submitted for resolution to the Steering Committee.

10. Ancillary Study Investigators Who Are Not Members of the Steering Committee

    a. Several ancillary studies involve internal collaborators who are not part of the Steering Committee. Such investigator groups will follow the HALT-C Publication and Presentation Guidelines. Within the ancillary study group, however, more specific guidelines may need to be developed. The object of such ancillary-study-group-specific guidelines will be to define the conduct of Writing Groups, determine Order of Authorship within the group, and establish timelines for receipt by the Publications Committee of documents and slide material to meet publication, abstract submission, and presentation deadlines.

F. SELECTION OF TOPICS

1. The main outcome report shall address the impact of long-term antiviral therapy on precirrhotic and cirrhotic chronic hepatitis C, i.e., the primary objective of the HALT-C Trial.

2. Another obvious outcome to be addressed in a published report will be the response of previous interferon nonresponders to “lead-in” therapy with pegylated interferon plus ribavirin.

3. The Publications Committee may suggest topics to be covered in manuscripts, and these will be discussed during Publications Committee meetings and conference calls.

4. Record of topics for other manuscripts will be kept by the Publications Committee and expanded as the study progresses.

5. Any member of the Steering Committee can propose a topic for an abstract or manuscript (other investigators should channel their requests through the Steering Committee member of their study site). Proposals should be submitted in writing to the Publications Committee; a summary of up to one page should include (on a form to be designed by the Data Coordinating Center)

    a. a brief description of the background/hypothesis/purpose
    b. a definition of the subjects to be included
    c. a list of variables of interest
    d. a list of possible collaborators
    e. for abstracts, the date of submission and date of the meeting

6. Criteria for judging proposals to the Publications Committee:

    a. scientific merit of the hypothesis or aim of the proposal
    b. availability of appropriate data to address the hypothesis or aim

7. Overlap between proposals: If overlap in content exists between two proposals, the chairperson of the Publications Committee will arrange a conference call among the two investigators, the chairperson of the Publications Committee, and the chairperson of the Steering Committee to review the two proposals and either eliminate overlap or consolidate the two proposals. Alternatively, the Publications Committee will make these determinations, based upon principles outlined in section C.3, above.

8. For approved proposals, the Publications Committee will ask the Data Coordinating Center to distribute a copy to all Principal Investigators (members of the Steering Committee). Within three weeks of receiving the proposal, each participating institution will forward to the Chair of the Publications Committee a list of investigators who would like to participate in the Writing Group. The Publications Committee will then select at least four to five investigators from among the proposed participants (a larger number at the discretion of the Publications Committee) to constitute the Writing Group and appoint a member of the Writing Group to chair the group; this person will usually be the person who proposed the project. As is the case for Main Papers, the selection of Writing Groups and their chairpersons will be submitted to the Steering Committee for final approval.

G. RESPONSIBILITIES OF THE WRITING GROUPS

1. The Writing Groups are responsible for development of the full proposal for final approval by the Publications Committee. The full proposal should be submitted to the Publications Committee and should include the following:

    a. the basic analytic approach (preliminary, univariate, multivariate analyses)
    b. mock tables to include which variables are involved at each stage and in what combination

c. for multivariable analysis, the description of the model, including dependent and independent variables
d. the graphic needs of the final manuscript
e. target audience and potential journal
f. proposed timeline for each stage of the analysis and writing
g. plans for meeting with the statisticians at the Data Coordinating Center
h. proposed first author and list of co-authors

2. All data analysis will be done through the Data Coordinating Center, which will evaluate requests for the items listed above (G.1. a-d, g). Based upon their review of these requests, the DCC should provide an estimate of the time and resources required. A preliminary time-and-resource estimate should be included in the proposal of the Writing Group after consultation with the DCC.

3. The Chairperson of the Writing Group will be responsible for assigning tasks to other members of the Writing Group and for overseeing the completion of these tasks on schedule. Writing Group members should participate actively in the writing and review of the manuscript assigned to the Group.

4. If, during the course of work on a manuscript, the analysis is found to be too broad for a single manuscript, the Writing Group may suggest that the data would be more suitable for more than a single manuscript. The Writing Group should notify the Publications Committee that they plan to narrow the scope of the manuscript, and/or they can resubmit a new written plan to the Publications Committee for other potential manuscripts. An amended analysis plan should be submitted to the Publications Committee, if the analysis evolves or deviates substantially from that in the original plan filed with the Publications Committee.

5. Manuscripts should be prepared at the center of the Writing Group Chairperson, with assistance from the Data Coordinating Center. The completed manuscript should be submitted for review to members of the Publications Committee and NIDDK for final review.

H. ADMINISTRATIVE DETAILS

1. All manuscripts and abstracts should include “the HALT-C Trial Group” in the list of authors.

2. Each manuscript emanating from the HALT-C Trial will be numbered, and the number should be included in a footnote or acknowledgment on the title page of the manuscript as follows: “This is publication 1 of the HALT-C Trial.” Such numbering will apply to full manuscripts, not to abstracts.

3. All HALT-C Trial manuscripts should include an acknowledgment of NIDDK funding, with specific contract numbers (all the 11 contract numbers are needed), as well as NIH funding numbers of participating General Clinical Research Centers. Acknowledgment of partial funding by Hoffmann-La Roche should be included as well. When appropriate, other-institute support should be acknowledged, for example, NIAID support for publications emanating from the Virology/Immunology Ancillary Study; other support to be cited would include the National Cancer Institute, National Center for Minority Health and Health Disparities, etc., as appropriate for an individual manuscript. For abstracts, acknowledgments can be limited to NIDDK funding without fund numbers, which would be too numerous to list.

4. Requests for reprints of Main Papers, other study-wide manuscripts, and local papers can be addressed to, and distributed by, either the DCC or the First Author, at the First Author’s discretion.

5. For each HALT-C Trial manuscript, a paragraph that contains financial disclosures for all authors should be submitted. The financial disclosure should be incorporated into the text of the manuscript or into the letter of submission, according to the convention of the specific journal. This financial disclosure will be based on the information that the DCC has collected from the authors.

I. EDITORIAL FUNCTIONS

1. The Publications Committee will serve as the editorial review committee for all manuscripts.

2. For each manuscript prepared, two Publications Committee members who have not written the paper will be designated to provide a timely review (within three weeks) of the manuscript for editorial clarity and data integrity before the manuscript is submitted for publication.

3. The Publications Committee may suggest modifications before final approval or may suggest alternative journals.

4. Manuscripts, abstracts, or other publications that involve study-drug treatment or that focus on virologic or other test results obtained with commercial assays should be submitted to the industrial sponsor for comment at the same time as submission to NIDDK; however, the industrial sponsor will have no authority to prevent or delay publication.

5. If a dispute occurs between the authors and the Publications Committee, resolution of the dispute should be the responsibility of the Steering Committee.

J. ABSTRACTS AND PRESENTATIONS

1. Proposals for submission of abstracts should be submitted to the Publications Committee at least 6 weeks prior to the submission deadline. Priority for data analysis will be given to abstracts by the Publications Committee in consultation with the Data Coordinating Center. Assignments may be made to already existing Writing Groups, or a new Writing Group may be formed according to guidelines listed above. The complete proposal for an abstract may be briefer than one for a manuscript, but accepted abstracts require a complete proposal submission to the Publications Committee.

2. Abstracts should be submitted to the Publications Committee at least 7 days prior to submission to the organization sponsoring the meeting. The Data Coordinating Center will distribute the abstract to all Steering Committee members for review, and two members of the Publications Committee will be selected by the Chair of the Publications Committee for expedited review.

3. Abstracts will also be submitted to the NIDDK at least 7 days prior to submission.

4. Slide material (including tables and graphs) to be presented for accepted abstracts and posters should be reviewed by the Publications Committee at least 7 days prior to presentation.

5. Unpublished HALT-C Trial data presented at national and international meetings must be approved in the same way as abstracts. This may entail review of slides and printed material by the same mechanism as that used to review abstracts. When previously approved slides are to be presented at a national or international meeting, the Publications Committee should

be notified at least 7 days in advance, the slides should contain an acknowledgment of the original source, but formal re-approval will not be required. Requests for permission by meeting organizers, industrial sponsors, or non-HALT-C investigators to reproduce slides, to videotape or audiotape presentations, and/or to publish written summaries of these presentations must be submitted to the Publications Committee, which will review the material to ensure that previously unpublished data are protected. Publications Committee approval is not required for local presentations and accompanying syllabus material (medical school lectures, continuing education courses, grand rounds lectures, research seminars, etc.). Investigators are encouraged to consult the Publications Committee chairperson when questions about the propriety of a local presentation arise. If the chairperson cannot address such questions readily, the issue should be considered by the entire Publications Committee (via conference call or written communication).

6. Abstract citation of support and HALT-C Trial label:

   a. With the first mention of HALT-C in an abstract, the name should be spelled out [Hepatitis C Antiviral Long-Term Treatment against Cirrhosis (HALT-C) Trial]. This should be in the title or in the body of the abstract. Also, as indicated in H.1., above, all manuscripts and abstracts should include "…and the HALT-C Trial Group" in the list of authors in the authorship line.

   b. Suggested abstract funding acknowledgment: "Funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK for brevity, if needed), with additional support from others as appropriate for an individual abstract, such as NIAID for immunology studies.

7. Letters to the Editor should be approved according to the same process as that used for abstracts.

K. NIDDK APPROVAL

1. Final manuscripts prepared by members of the Writing Groups and Publications Committee should be approved by the NIDDK before submission for publication. The NIDDK should complete its review within 30 days, after which, if no objections are raised, the manuscript can be submitted. (For abstracts, submission to the NIDDK will be required 7 days prior to submission.) (Although approval by the industrial source of study medications is not required, as a courtesy, manuscripts that include drug treatment or that focus on virologic or other test results obtained with commercial assays will be submitted to the industrial sponsor at the same time as the NIDDK. As noted above, the industrial sponsor will not have authority to prevent or delay publication.)

L. PUBLICATION PRIORITIES AND ACCESS

1. No investigator should jeopardize the publication of HALT-C Trial data in a peer-reviewed journal by releasing or presenting data prematurely. Press releases should be timed to coincide with publication of manuscripts and should respect any applicable publication embargoes.

2. No individual site will be permitted to publish site-specific results that compete and interfere with the integrity of study-wide reports of the results of the HALT-C Trial.

3. Press Releases should be approved by the Publications Committee and the Steering Committee.

4. All manuscripts and abstracts will be stored electronically on the HALT-C Trial secure website, to which all study personnel have access. Slide material prepared for presentations should be made available to other HALT-C investigators in electronic format, to be distributed as an e-mail attachment by the Data Coordinating Center.

Acknowledgments

In drafting these publications guidelines for the HALT-C Trial, we had the benefit of referring to publications guidelines from the following sources: authorship guidelines of the Annals of Internal Medicine and publications guidelines of the Hepatitis Interventional Therapy Group; the NIAID-sponsored NCICAS (ACTIVE Study); the NHLBI-sponsored SHOCK Trial and Registry; the NIA-sponsored Health, Aging, and Body Composition Study (HEALTH ABC); and the NHLBI-sponsored Natural History of Transfusion-Associated Non-A, Non-B Hepatitis Study.

Addendum #3: HALT-C Ancillary Studies Procedures and Policies:

Procedures for Ancillary Study (AS) Approval in HALT-C
Approved by HALT-C Steering Committee: April 15, 2005

I. General Considerations

Ancillary studies (AS) are investigations that are not part of the HALT-C main study, but that propose questions and test hypotheses that are relevant to the goals and purposes of the HALT-C clinical trial. Ancillary studies may involve all HALT-C participants and clinical sites, or subsets of either, depending on the eligibility criteria of the study, sample size needed, and interest of HALT-C investigators in participating. 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.

Investigators not part of the HALT-C clinical trial must have at least one HALT-C investigator as a sponsor and collaborator.

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

All analyses of data must be confirmed by the HALT-C Data Coordinating Center (New England Research Institutes [NERI]) and resources provided to NERI for these efforts. The data from the ancillary study 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.

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). Ancillary studies requiring identification of outcomes by study group may not have access to such information until the end of the randomized phase of the trial in August 2007.

II. Procedures for Submitting a New Ancillary Study Proposal

1. PI 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
   Fax: 617-926-0144
   e-mail: ksnow@neri.org

2. NERI reviews Proposal for completeness, potential competition with other ancillary studies, and HALT-C sample utilization. NERI consults with Chairs of HALT-C AS Committee to determine

whether the Protocol will be adequately reviewed for scientific merit by Outside Funding Agency (1 week).

3. 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 7 votes.

      1) If there are no dissenting votes, the proposal is provided to the SC at least 2 weeks prior to the next meeting or call.

      2) A member of the AS who disapproves of the proposal should state his or her reasons. At the discretion of the AS committee chairperson(s), disapprovals by a minority of those voting can be discussed and resolved first or forwarded to the SC with the proposal.

      3) If the majority of those voting disapprove, the applicant has one opportunity to resubmit.

   c. Steering Committee (SC) reviews the Proposal at the next SC Conference Call/Meeting. The SC primarily considers the appropriateness of the study for HALT-C (Appendix B) and secondarily considers the scientific quality of the study.

   d. The PI of the Proposal will be notified of the decision of the HALT-C SC within 8 weeks of submission. A letter from the chairperson of the HALT-C SC or designee will constitute official approval (Appendix D).

   e. The PI is required to submit the Proposal to the outside funding agency within 4 months of SC 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 SC approval must be withdrawn or resubmitted for AS and SC approval.

4. 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 Scientific Reviewers need to be assigned to the Proposal or whether the general knowledge of the HALT-C PI's 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. 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. 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 7 votes.

      1) If there are no dissenting votes, the proposal is provided to the SC at least 2 weeks prior to the next meeting or call.

2) A member of the AS who disapproves of the proposal should state his or her reasons. At the discretion of the AS committee chairperson(s), disapprovals by a minority of those voting can be discussed and resolved first or forwarded to the SC with the proposal.

3) If the majority of those voting disapprove, the applicant has one opportunity to resubmit.

d. Steering Committee reviews the Proposal at the next SC Conference Call/Meeting. The SC considers the appropriateness of the study for HALT-C (Appendix B) and the scientific merit of the study (Appendix C).

e. The PI of the Proposal will be notified of the decision of the HALT-C Steering Committee within 8 weeks of submission. A letter from the chairperson of the SC or designee will constitute official approval (Appendix D).

5. General Comments

a. Proposals that have received scientific review and approval by the HALT-C Ancillary Studies Subcommittee and by the HALT-C Steering 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 Subcommittee 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.

III. Minor Modifications to Approved Ancillary Study

1. Definition: a minor modification is a minor change in the studies to be performed in an approved ancillary study. Minor modifications meet the following criteria:

a. Essentially the same hypothesis and/or aims of the approved AS,

b. No new specimens needed from HALT-C Repository (BBI or AFIP)

c. No additional budget requested from HALT-C

d. Minimal effort from NERI (to obtain sample, perform analyses, etc)

e. 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.

2. The PI requesting the minor 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. The PI submits the minor modification request to NERI.

3. Approval process for Minor Modifications

a. Minor modification requests should be sent 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 Subcommittee.

c. Members of the appropriate AS Group (or the AS Subcommittee) 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/Subcommittee. 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.

   2) PI can proceed with the proposed work

   3) The approval of the minor modification is noted in the minutes of the next AS Group/AS Subcommittee Conference call and the minor modification is attached to the minutes of the conference call.

   4) 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.

   5) The HALT-C Steering Committee is notified of the minor modification at the next HALT-C Steering Committee Meeting or Conference Call.

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 Steering 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 Steering 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.

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 mm^2 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 Steering 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,

Adrian Di Bisceglie, MD
Chairman, HALT-C Steering Committee

Cc: Kristin Snow, James Everhart, Greg Everson, Tim Morgan

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