Folic Acid for Vascular Outcome Reduction in Transplantation (FAVORIT) Trial

Ancillary Studies Policy

I. General Policy

To enhance the value of FAVORIT and to ensure the continued interest of the investigators, the Executive Committee welcomes proposals from individual investigators to carry out ancillary studies. Nevertheless, to protect the integrity of FAVORIT, such ancillary studies must be reviewed and approved by the Executive Committee and the Ancillary Studies Committee before their inception. In general, ancillary studies require outside (non-FAVORIT) funding to support clinical centers and/or the core laboratory and/or the core data center.

II. Definition of an Ancillary Study

An ancillary study is a proposal from FAVORIT investigators (i.e., as principal or co-investigators or one of their colleagues) for an investigation involving FAVORIT participants (or specimens) that is not in the original FAVORIT protocol and requires data (or assay of specimens) that are not collected (or in the case of samples, not assayed) as part of the routine FAVORIT data set. Furthermore, each clinic investigator in the ancillary study must agree to participate and receive IRB approval, as appropriate.

III. Requirements for Approval of an Ancillary Study

The proposal must be in writing using standard scientific investigation format. Before an ancillary study can be approved, it must be shown that it has scientific merit and that it will not do any of the following:

- Interfere with the completion of the main objectives of FAVORIT
- Adversely affect participant cooperation or compliance in FAVORIT
- Create a diversion of study resources (personnel, equipment, or study samples), either locally or centrally
- Jeopardize the public image of FAVORIT
- Not require outcome information until the trial is completed

IV. Preparation of Request for Approval of an Ancillary Study

FAVORIT utilizes a two-step process for reviewing ancillary study proposals:

- Step 1 involves the submission of a brief description of the ancillary study for "concept approval."

- Step 2 requires the submission of a more complete technical proposal. Submission materials must be in an electronic format (PC-compatible).

Step 1: Letter of Intent
Submit a request for concept approval to the FAVORIT Executive Committee (Andrew Bostom, M.D., Chair). Include a brief (2-4 page) description of the proposed ancillary study that specifies the following:

1. Identification of principal investigator of the ancillary study
2. Names of definite or possible co-investigators/collaborators
3. Description of objectives/specific aims
4. Scientific merit of the study
5. Study design, sample size, and timeline
6. Methodology for new data collection and indication of what existing data will be needed
7. Who will conduct data analysis?
8. If existing specimen aliquots are to be used, specify which aliquots, volume necessary for the planned analyses, and location (laboratory) where analyses will be performed
9. Proposed funding sources
10. Discussion of impact on FAVORIT study personnel
11. Discussion of impact on FAVORIT study participants
12. Agreement that all ancillary data (clinical information, laboratory assay results) will be shared with the FAVORIT Data Coordinating Center (core data center).

Step 2: Ancillary Study Proposal

If concept approval is granted, a complete proposal must be submitted to the FAVORIT Executive Committee (Andrew Bostom, M.D., Chair). Approval of the technical proposal is required prior to submission to the funding agency or study initiation.

The proposal should approximate the material to be submitted to the proposed funding agency. It should include (but not be limited to) the following:

1. Description of objectives/specific aims
2. Scientific merit of the study
3. Study design and hypotheses
4. Methodology for data collection
5. If existing specimen aliquots are to be used, specify which aliquots, volume necessary for the planned analyses, and location (laboratory) where analyses will be performed
6. Power calculations, proposed statistical analyses
7. Prototype for an informed consent document, if applicable
8. Identification of principal investigator of the ancillary study
9. Names of definite or possible co-investigators/collaborators
10. Proposed funding sources
11. Budget for core data center
12. Budget for core laboratory, if applicable
13. Budget for clinical centers
14. Agreement that all ancillary data (clinical information, laboratory assay results) will be shared with the FAVORIT Data Coordinating Center (core data center)
15. Plans for monitoring of safety of study participants.

IV. FAVORIT Review of Ancillary Study Proposals

Investigators of ancillary studies are required to first submit a letter of intent of their proposed project to the FAVORIT Executive Committee. If the Committee approves the feasibility of the project (concept approval), it will then request a fully developed proposal for review. Concurrently, the letter of intent will be shared with the FAVORIT Data and Safety Monitoring Board for their approval.

Upon receipt of the fully-developed proposal, it will be distributed to the FAVORIT Ancillary Studies Committee for review, using appropriate consultants if necessary. The Ancillary Studies Committee will either make a recommendation to the Executive Committee (for approval or rejection) or request modification of the ancillary study proposal. The key criteria for approval of proposals are scientific merit and impact on the main FAVORIT study.

If the ancillary study has concept approval from the FAVORIT Data and Safety Monitoring Board (DSMB) and approval of the full proposal by the Executive Committee, the FAVORIT Study Chair (Bostom) will write a letter to the principal investigator of the ancillary study indicating approval and support of FAVORIT Executive Committee. This letter can be used to document approval and support for use in submission of grant applications for funding and for local IRB approval. If either the FAVORIT DSMB, the Executive Committee, or the Ancillary Studies Committee fail to provide approval, the proposal will be rejected.

V. Selection of Investigators in Ancillary Studies

If concept approval is indicated by the Executive Committee, the Ancillary Studies Committee will circulate a notice to the clinical centers and central units, with a request for FAVORIT investigators, in addition to those submitting the proposal, to become collaborators. Investigators must volunteer in writing (electronically) to the Ancillary Studies Committee. The Ancillary Studies Committee will compile the list of volunteering investigators and make recommendations to the Executive Committee.

If there are more volunteers than necessary, approval for collaboration will favor those investigators with prior work or publications in the field. The Executive Committee shall have final authority on the composition of the ancillary study investigators. The Ancillary Studies Committee will keep track of volunteering investigators and those investigators submitting proposals for all ancillary studies. Consideration of collaborating with the existing core data center and core laboratory is strongly urged.

VI. Progress Reports

The Principal Investigator shall provide a written annual report on the progress of the ancillary study.

VII. Analysis and Publication of Results of Ancillary Studies

The investigator of the ancillary study, and if necessary the Executive Committee, will consult with the Data Coordinating Center during data analysis to ensure that all study data used in analysis of ancillary study results are consistent with data in the main study database. Outcome analyses will need to be done through the core data center. Data from ancillary studies will be sent to the core data center at the conclusion of the ancillary study.

Writing of manuscripts from ancillary studies data shall include members of the FAVORIT writing group (i.e. investigators, relevant individuals). Manuscripts resulting from ancillary studies shall be submitted for review and require approval by the Executive Committee before submission for publication or presentation. Before submission to the FAVORIT Executive Committee, all manuscripts using data collected in an ancillary study must be approved by the investigator (or his/her designee) who assumes lead responsibility for the ancillary study. The phrase "FAVORIT Study" should be included in the title and listed as a key word whenever possible. Manuscripts will also contain an appendix listing all participating FAVORIT principal investigators as well as other individuals deemed appropriate.

IMPORTANT NOTE: No ancillary study analyses involving FAVORIT follow-up data, including outcomes, can be completed until the FAVORIT final results are released.

VIII. Release of Results of Ancillary Studies to Participants

Results of ancillary studies shall be reported to patients and/or to their physicians if medically useful. Such reporting should follow standard FAVORIT protocol for notification of participants.