SECTION 3

STUDY POLICIES

INTRODUCTION

To ensure equitable consideration for all Women's Health Initiative (WHI) collaborating investigators and institutions, policies have been developed to govern certain aspects of the WHI research effort. These include policies for publication and presentation, and ancillary studies. These policies have been given very careful consideration and are intended to assist investigators in the various processes involved in these areas.

3.1 Study Documents

3.1.1 Protocol: Purpose

The WHI Protocol is the primary policy document which formally describes the background, design and organizational structure of the WHI. It provides the scientific, methodological, and organizational framework for WHI. It also represents a permanent record for interested members of the scientific and lay communities.

3.1.2 Changes to the Protocol

Changes to the Protocol may infrequently be required. Proposed changes that affect the conduct of WHI will need a 2/3 majority approval by the Council and a 2/3 majority approval by the Data and Safety Monitoring Board (DSMB). Recommendation is then made for Protocol change to the Director of the National Institutes of Health (NIH). When a change has been approved, the Clinical Coordinating Center (CCC) will notify the Clinical Center (CC) Principal Investigators (PIs) of the change and send revised sections of the Protocol to the Program Office and CCs. Once finalized, any Protocol amendments must be submitted to local IRBs for approval. Any amendments affecting the HRT Clinical Trial (CT) call for notifying the FDA by the IND sponsor. The CCC will file the obsolete sections for reference and keep a log of the changes.

3.1.3 WHI Manuals: Purpose

The Manuals detail the standardized procedures, policies and definitions used in the WHI CT and Observational Study (OS). They are used for training of staff and as the key reference for staff and investigators.

3.1.4 Changes to the WHI Manuals

Over time, revisions to the WHI Manuals will take place to reflect changes in procedures and guidelines or to clarify ambiguities. Proposed revisions should be submitted to the CCC, which will make the changes and forward the revisions to the Council for review and approval. Major revisions that affect the conduct of WHI will be brought to the attention of the PIs and staff by distribution of bulletins. Once approved, the CCC will notify the CCs of any changes and will send revised pages to all CCs. The PIs and the DSMB will be informed of any major changes.

The CCC will maintain a log of the changes, listing the date of change, the section number and name containing the change, and a brief description of the change with each Manual update. The CCC will file all obsolete pages for reference.

3.1.5 WHI Manual Structure

The WHI Manuals are contained in several volumes. The allocation of topics to volumes was based on the WHI staff members who would most use the various sections.

Volume 1 - Study Protocol and Policies: This manual contains the Protocol for the CT and OS, the committee structure and the policies governing the scientific conduct of the study. As this is a document written for and by WHI Investigators, procedural aspects of the study that are performed by Investigators (e.g., outcomes classification) are included in this manual.

Volume 2 - Procedures: This manual describes all Clinical Center (CC) procedures and guidelines for operations other than Nutrition Intervention. As the primary CC training and reference source, this manual serves as the standard by which CC operations are assessed.

Volume 3 - Forms: All standardized study forms (excluding outcomes and QA related forms) are displayed in the Forms Manual in numerical order. Accompanying each form is a detailed set of instructions describing

who completes the form, when and how each data item should be coded, and what should happen to the form when completed.

Volume 4 - Dietary Modification Intervention: The Dietary Modification (DM) Intervention Manual consists of two parts: the Group Nutritionist Manual and the Participant Manual. The Group Nutritionist Manual describes the procedures for carrying out the intervention sessions for the DM component. The Participant Manual contains information pertinent to each intervention session.

Volume 5 - Data System: This is a user's manual for the WHI computing system. Information is provided on the general hardware and software used as well as the specific WHI database, WHILMA.

Volume 6 - DXA Quality Assurance Manual for Hologic QDR-2000 Bone Densitometer: This is a user's manual for the WHI Bone Density CCs. This manual is intended as a supplement to the Hologic User's Manual.

Volume 7 - Quality Assurance Manual: This manual provides procedures and checklists for CC QA Activities.

Volume 8 - Outcomes: This manual contains a description of the WHI Outcomes documentation process and gives detailed procedures and forms for ascertaining and adjudicating WHI Outcomes.

See *Vol. 7 - Quality Assurance, Section 2 - Documentation* for more information.

3.2 Publications and Presentations

3.2.1 Policy Objectives

The objectives of the publications and presentations editorial policy are to assure and uphold:

- Expeditious and timely dissemination to the scientific community of all pertinent data resulting from WHI;
- Accurate and scientifically sound publications and presentations from WHI CT and OS and its collaborating investigators;
- Promotion of and encouragement for analysis and submission of manuscripts among the WHI investigators.
- A system for fair determination of authorship on WHI collaborative publications.
- Opportunities for investigators from all participating WHI centers to participate and be recognized in study-wide publications and presentations; and
- Procedures that allow the NIH to review in a timely fashion publications and presentations summarizing data collected during the course of the trial.

3.2.2 Definitions

- **Group-authored Publications and Presentations**

  Group-authored publications and presentations include the major WHI design paper and the baseline and primary outcome papers of the OS and CT. An appropriate list of participating investigators will be identified in an appendix to such publications, and members of the actual writing team will either remain anonymous or, as appropriate, be acknowledged in the publication.

- **Individually-authored Studywide Publications and Presentations**

  Individually-authored studywide publications and presentations are all others reporting baseline, design, and results of methodological studies based on the studywide common data set.

- **Other Publications and Presentations**

  Other publications and presentations are those not encompassed by the above two categories; they relate to work done in substudies or ancillary studies by a subset of CCs or in a single CC. This category also includes publications and presentations that use WHI data solely to illustrate new methodologies or procedures. Papers based solely on local data should not give the impression that they represent overall WHI findings, but should describe how the data was derived.

- **WHI Investigators**

  A WHI study investigator is defined as a research investigator with a current and active contract or consulting agreement with NHLBI or its contractors to work on the WHI study. Anyone else would be a colleague of a WHI investigator, or further out would be a non-WHI investigator.

3.2.3 Review of WHI Publications and Presentations

To minimize the possibility that published materials may be based on faulty data, it is the WHI policy that all definitions, criteria and data used in 1) group-authored, 2) individually-authored studywide and 3) other publications and presentations be submitted to the Publications and Presentations (P&P) Committee for review. The Chair will assign the paper proposals and final manuscripts to 2-3 members of the Committee for P&P review. They will review the papers for overlap with other WHI papers, scientific merit, analytic issues, interpretation and discussion issues, and policy issues. The paper proposals and final manuscripts will simultaneously be submitted to the NIH Project Office for review. Paper proposals approved by the P&P committee and the NIH Project Office will then go through the writing group process. When the final

manuscript has been approved by the P&P Committee and the NIH Program Office, final manuscripts may be submitted for publication. Once published, the P&P committee will send notification of publication to the WHI Investigators. The P&P Chair will monitor turn-around times for all reviews, to guard against undue delays. Publications and presentations shall be in compliance with the rules and procedures of disclosure set forth in the Privacy Act. Confidential or proprietary information shall not be disclosed without the prior written consent of the individual or institution. Privacy Act compliance and documentation of written disclosure consents are the responsibility of each institution involved in the paper/presentation.

3.2.4 Authorship for Group-Authored and Individually-Authored Studywide Publications and Presentations

1. Publications and presentations from these two categories (see *Section 3.2.2 - Definitions*) will be identified by the P&P Committee based on suggestions from WHI investigators. For each report identified, a writing committee of volunteers -- selected from investigators at all participating institutions -- is to be appointed by the P&P Committee and charged with the responsibility of preparing the report within stated time limits that conform to a production timeline that includes intermediate deadlines as well as a final deadline for journal submission. The P&P Committee is charged with the task of periodic, systematic review of the work of all writing committees; aiding and encouraging them as appropriate; revising their membership or reconstituting them when indicated (with written notification and right of appeal).
2. It is the intent that selection of writing committee members be equitable and fair to all groups and individuals participating in this collaborative program, especially with regard to junior faculty colleagues and junior investigators.
3. For individually-authored papers, the writing group chair determines the order of authorship. A major criterion for the order of authorship is the level of effort and contribution made by the members of the writing committee.
4. At the request of the writing committee chair, if members of a writing committee have shown little or no interest in participating in the work of the committee or have failed to contribute to the task of preparing the manuscript, their names may be left off the list of authors, pending review by the P&P Committee. The chairperson of the P&P Committee is to make the final decision upon receipt of a written request from the chairperson of the respective writing committee; the affected individuals are to be informed in writing that they have the right to appeal the decision to the P&P Committee as a whole.
5. For all group-authored and for most individually-authored papers and "other" publications, an acknowledgment of all WHI Centers with their PIs and a list with a reasonable number of key personnel are to appear in each publication, printed in an appendix per journal guidelines. NIH support and contract numbers are to be on the front page of the manuscript.
6. All publications are to include an acknowledgement that approximates the following:

   This study was funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, Department of Health and Human Services. The active study drug and placebo were supplied by Wyeth-Ayerst Research Laboratories, Philadelphia, Pennsylvania."

   For the CaD trial, the text would read *"... supplied by SmithKline Beecham Consumer Healthcare, Parsippany, New Jersey."*
7. All requests for reprints are to be directed to the lead author of the paper.

3.2.5 Authorship for Other Publications and Presentations

1. Proposals for publications and presentations based on special data sets collected on WHI participants by CCs involved in substudies, umbrella studies or ancillary studies are also to be submitted to the P&P Committee. In general, the writing committee preparing such a report is to consist of individuals designated by the participating study investigators, but it may include WHI PIs from other sites who wish to collaborate. Authorship for OS Blood Studies and Umbrella Studies is addressed in *Section 3.1.10*. All WHI PIs will be informed of such ancillary proposals through periodic circulation of P&P

progress reports (see *Section 3.3.1 - WHI Publications and Presentations Committee Progress Report*). The authorship of such a report is to be designated in the usual manner for a scientific report, with the order of names appearing after the title to be decided upon by the participating CCs. In addition to a statement of authorship, such a paper is to have a clear statement that this work was a substudy or ancillary study of WHI and the support from NIH is to be acknowledged.

2. Requests to use WHI data for purely illustrative purposes should be directed to the chair of the P&P Committee. The committee will act on the request with due attention to the requester's link to the WHI and to the potential impact on other WHI-related publications and presentations.

3. Where appropriate, a listing of participating study centers and investigators who are not authors are to be included. This decision is to be made by the P&P committee.

4. All substudy, ancillary study, and local manuscripts must be reviewed and approved by the P&P Committee before submission for publication, as noted in *Section 3.2.3 – Review of WHI Publications and Presentations*. WHI PIs are also to receive copies of these manuscripts prior to their submission for information purposes; manuscripts will be sent by the P&P Committee. The manuscripts should give a clear reference, on the front page of the article, to WHI and the collaborative nature of the program, including the contract number with the NIH. A reprint of every published paper should be sent to the NIH Program Office and the CCC for archival purposes.

5. All requests for reprints of these types of publications and presentations are to be directed to the appropriate individual, usually the primary author.

3.2.6 Clearance of Abstracts and Presentation of Reports

1. All such abstracts must be approved by the P&P Committee and the Program Office before they are submitted to any national and/or international organizations. Approved abstracts will be periodically circulated among the WHI PIs for information purposes. If the abstract is accepted for presentation, the P&P Committee is to be notified. It is permissible to submit previously cleared abstracts to other meetings; copies should be sent to the CCC for inclusion in the listings of publications and presentations.

2. In the case of papers scheduled for presentation before organizations issuing press releases, the presenter may submit the text of the presentation or other materials after they have been approved by the P&P Committee and the Program Office for release to the press. If the presentation is based on a manuscript not yet accepted for publication in a peer review journal, a sentence must be included on the front page indicating the preliminary nature of the results. The same principles of notification and acknowledgment apply to both abstracts/presentations and publications (see *Section 3.2.4 – Authorship for Group-Authored and Individually-Authored Studywide Publications and Presentations*).

3.2.7 Invitations to WHI for Presentation of Papers

The WHI investigators welcome opportunities to participate and present reports at national and international scientific meetings. When an invitation is received by a WHI investigator, WHI policies with regard to publications and presentations are as follows:

1. When an invitation is directed to the Chair of the Council or the Chair of the P&P Committee, the respective chairs will decide who is to represent WHI. Invitations directed to the NIH will be reviewed and approved by the NIH Program Office, which will, in turn, notify the P&P Committee.

2. When a WHI investigator receives a personal invitation to make a presentation, he/she should notify the P&P Committee to ensure listing of the presentation on behalf of the WHI Research Group.

3. All presentations in response to such invitations should be based on published WHI reports unless prior approval is granted by the P&P Committee and the Program Office.

4. Requests received by PIs or their staff to present or discuss at local meetings any previously published WHI data need no prior clearance by the P&P Committee and acceptance of such invitations is encouraged.

3.2.8 Procedures for Identifying Studywide Publications

1. At periodic intervals, the P&P Committee is to distribute to all participating WHI institutions an updated progress report of all approved WHI publications (e.g., approved, in preparation, submitted, in press, published). See *Section 3.3.1 – WHI Publications and Presentations Committee Progress Report*..
2. New proposals for publications can be identified by the P&P Committee or by a WHI investigator, committee investigator or WHI staff.
3. Requests for proposed publications should include a 2-5 page document, to be submitted to the P&P Chair, that includes:
   - tentative title;
   - name of convener (proposer);
   - introduction;
   - keywords;
   - objectives;
   - analysis plan (pertinent variables, analysis definitions, characteristics of population to be analyzed, table shells limited to a reasonable number);
   - tentative conclusions; and
   - pertinent references.
   - See *Section 3.3.2 – Example of Manuscript Proposal*.

3.2.9 Identification of Writing Committees, Selection of Writing Committee Chair, and Work of Writing Committees

1. Once a studywide publication has been identified and approved for preparation by the P&P Committee, the Chair of the committee is to communicate with all WHI investigators via the WHI email "All Investigators" list, requesting nominees qualified to participate as members of the writing committee[1] for that paper. The request for nominees is to include a specific date (deadline) for submission of nominations. Any investigators wishing to participate on the writing committee must have approval from their Principal Investigator. If the nomination or the approval of the nomination does not come directly from the Principal Investigator, this approval will be verified by the P&P committee. In general a writing committee should consist of up to 8 members. A proposal submitted to the P&P committee may list up to

[1] After some discussion among Robert (Bob) Hiatt, P&P Committee Chair, Jacques Rossouw, Lead Program Officer, and Ross Prentice, CCC PI, the P&P Committee has determined the following numbers of authors per WHI unit to be recognized on study wide papers.

"Short" list: each CC is allowed to submit 1 name; NIH - 3; CCC - 5; plus the following provision for the CCC Subcontractors: Bowman Gray - 2; University of California at San Francisco - 1; Medical Research Laboritory - 1; University of Washington - 1; University of Minnesota – 1.

"Long" list: each CC is allowed a maximum of 5 names; NIH - 3; CCC - 16; plus the following provision for the CCC Subcontractors: Bowman Gray - 4; University of California at San Francisco - 3; Medical Research Laboritory - 2; University of Washington - 2; University of Minnesota – 1; McKesson BioServices – 2.

3 authors, including the convener. These authors will not need to go through the nomination process and will be included in the final 8 authors.

2. The P&P Committee is to select, from the submitted list of nominees, the membership of the writing committee for that paper, after which it appoints a Chair of the Writing Group. In most circumstances, the investigator submitting the proposal for approval, i.e., the convener, will be appointed Chair of the Writing Group. Investigators are limited to convene no more than two writing groups at one time. Criteria for selection of writing group members will include level of expertise (related to the publication topic), balanced representation across WHI sites, and consideration of individual commitments to other WHI writing group endeavors (to ensure that no one person is "overloaded" with WHI writing responsibilities). On occasion, the convener may suggest names for consideration as writing group members. Such requests should include a statement indicating the rationale for these nominations. The P&P Committee shall make the final decision on a case-by-case basis concerning these special requests. There may be unusual situations in which a non-WHI investigator can be considered for a writing group, but approval by the chair of the P&P committee of such a request is likely to be rare given the very broad range of talents already extant in WHI. If additional expertise outside of WHI is desired, this could be obtained through asking a non-WHI person to review and comment on the paper rather than serve as a co-author. Writing Groups for all papers involving analyses of WHI data must include one CCC representative, usually with statistical expertise. Students are, in general, not eligible to participate on writing groups. The exception to this has been advanced graduate students at the CCC who will have a major involvement with development of a proposal as a part of their thesis work.

3. The P&P Committee will track individuals that are turned down for writing groups, and give previously rejected, but qualified individuals preference for future papers they wish to work on. Additionally, the memo sent to individuals who were not selected for writing group participation will include information as to why they were not chosen.

4. The Chair of the P&P Committee is to contact the newly appointed Chair of the Writing Group and to send him/her a list of the expected responsibilities of 1) the Writing Group Chair, 2) the Writing Group members and 3) the P&P Committee. See *Sections 3.3.3 – "Letter of Intent"* and *3.3.4 - WHI Responsibilities of Writing Group Chair and Writing Group Members.* Copies of these communications should also be sent to all Writing Group members.

5. As soon as the chair is identified, it is his/her responsibility to communicate with other committee members to identify data needed from the CCC, and to establish a plan for writing the manuscript. To expedite publication, one or more meetings of the writing committee may be necessary, but in view of cost considerations, it is recommended that such meetings be held to a minimum and, to the degree possible, be incorporated as part of other scheduled meetings, such as Annual General meetings or national scientific meetings or by means of conference calls. The following steps should be followed in the preparation of the manuscript. The chair of the writing committee should:

   a. Contact each writing committee member to identify tasks for members of the writing committee.

   b. If the CCC will be doing the statistical analyses, contact the Statistics Unit Manager at the CCC to be assigned a statistician for the paper. It is the lead authors responsibility to maintain contact with the assigned statistician.

   c. Coordinate additional data analyses requests (e.g., additional dummy tables) with the CCC representative who is on the writing committee.

   d. Convene the first meeting or conference call of the writing committee at a time when the CCC has completed the preliminary analyses or before if necessary to finalize the analysis plan.

   e. Keep the Chair of the P&P Committee informed of the paper's progress, notify the Chair of any delays or departures from the established production schedule and provide explanations for any delays that do occur.

6 If a problem of overlap emerges, the P&P Committee will confer with the involved writing committee chairs to resolve the situation.

7 Members of each WHI writing committee should participate actively in preparation of the publication assigned to that committee. The chair has the responsibility to obtain input from every member of his/her committee. The input from every member of the writing committee is essential. If any member of the writing committee does not respond to the chair's request or does not contribute to the writing of the paper, the chair must take immediate action, through the P&P Committee, to replace that individual, who has the right to receive written notice of this action and to appeal to the P&P Committee. It is the responsibility of the chair of the writing committee to approve the final version of the paper before its submission to the P&P Committee. All members of the writing committee should have seen the final draft before its submission to the P&P Committee. The chair of the writing committee should inform the P&P Committee of any substantial minority opinions or reports within the writing group so that serious concerns are not arbitrarily overruled by the writing committee chair without the knowledge of the P&P Committee.

8 The convener of each writing group is to update the P&P Committee on manuscript progress every six months after the writing group is formed. If the P&P Committee has not received a report from a convener within 12 months, or if satisfactory progress has not been made and delays are attributable to the operation of the writing group, the Committee will replace the convener with another member of the writing group. If no writing group members are interested in assuming the lead position in the writing group, the manuscript will be inactivated. If the convener or writing group members later decide to pursue this topic, a new proposal can be submitted to the P&P Committee for approval.

3.2.10 Reporting of Race and Ethnicity Data

1 Descriptive tables: WHI publications should describe the demographics of the study population included in the analysis, or refer to another publication that describes the demographics. The demographics should include a listing by race/ethnicity (numbers and/or percentages).

a. The race/ethnicity subgroups (alternative nomenclature in brackets) that should be listed in alphabetic order are those by which participants identified themselves at enrollment, with some minor modifications: American Indian/Alaskan Native (American Indian or Alaskan Native); Asian/Pacific Islander (Asian or Pacific Islander); Black (African-American); Hispanic (Latino); White not of Hispanic origin; Unknown (not one of above). Note that the Unknown category will therefore include those women who selected “Other” race/ethnicity as their response.

b. The unqualified use of the term “other” should be avoided.

c. “Combining” of these specific race-ethnic groups in the descriptive demographic tables is not allowable.

2 Analysis and interpretation of the data:

a. The design of the WHI trials does not recognize an a priori hypothesis supporting significant differences of clinical or public health importance, and therefore recruitment by race/ethnicity was not geared towards testing separate hypotheses for any particular group. When it is unknown whether there may be differences, the new NIH policy still includes that should be done by race/ethnicity in clinical trials. The NIH definition of “valid analyses” differs from analysis with the power to ascertain a “statistically significant” difference (see below). This definition applies to clinical trials, but for WHI purposes will alsothe observational studies by substituting “exposure” or “characteristic” for the “intervention effect”.

b. Valid analyses may be of a simple nature (e.g. a tabulation of the prevalence of a characteristic or outcome by race/ethnic group with or without statistical testing), or may be more complex (e.g. univariate or multivariate statistical testing for differences by race/ethnic group). All key results in

the full dataset should be reviewed to determine whether the results are similar in each race/ethnic group. If the results appear to differ by race/ethnicity, then the results should be reported separately for the group(s) that appear to differ, in addition to the results for the combined data. In multivariate modeling, it may be necessary to combine some subgroups (e.g. small subgroups, or subgroups that appear to have similar results), either for main effects or interactions, in order to preserve stability of the model. These may be identified as "other race/ethnic groups" in multivariate models but caution should be used in interpreting any effects associated with this subgroup.

c. All publications should indicate whether any race/ethnicity effects were hypothesized from previous literature and include an explanation of how the data by race/ethnicity were dealt with, whether or not there were sufficient data to do group-specific analyses, and whether or not there appeared to be differences by race/ethnicity. Investigators are encouraged to pursue hypothesis driven analyses in this area, wherever feasible. It is not the intent of these guidelines to promote simplistic, or unfocussed examinations of the data. If these analyses reveal no differences, a brief statement to that effect, indicating the groups and/or subgroups analyzed, will suffice.

If journal policy does not allow full publication of data by race/ethnicity in the main body of the article, the data by race/ethnicity should be made available to other researchers by means of an appendix to the article, or by publication on the NHLBI WHI website (contact Nancy Morris in the Project Office).

3.2.11 Umbrella Grant and OS Blood Ancillary Study Publication Policy

Investigators with funded umbrella grants or OS blood studies will submit separate proposals for all publications that they wish to produce between now and the end of the WHI project. After P&P approval, these analyses will proceed and may each have not more than four co-authors who are umbrella grant investigators. These proposals will be circulated throughout WHI to obtain additional authors by the usual WHI process. After a group of authors has been established for a manuscript, a proposal will be developed as for any other WHI paper and reviewed by the P&P Committee using the usual review process. After approval, data analyses will be performed in collaboration with the Coordinating Center. The funding for statistical analyses will generally be provided in the ancillary study or umbrella grant budget. Final manuscripts will be submitted to the P&P Committee and NHLBI Project Office for approval as for any WHI manuscript. Initially, manuscripts will be proposed by the Umbrella studies or OS blood studies investigators. However, two years after funding, data generated by Umbrella grant or OS blood studies funding will be available to Umbrella study, ancillary study and WHI investigators for additional paper proposals. These data are the property of the WHI study.

3.2.12 Preparations and Submission of Abstracts

1. All abstracts must be approved by the P&P Committee and the Program Office before they are submitted to any national and/or international organizations. In order for the CCC to meet the need for data requests for abstracts and allow sufficient time for writing the abstracts the writing committees should plan well in advance and be selective in their data requests. That is, only tables which relate to the major topics of the abstract should be requested.
2. Abstracts will be expeditiously reviewed by two P&P Committee members with simultaneous review by the Project Office. Abstracts will be reviewed when they are submitted, so that the review, approval, or a request for modifications will not be delayed until the Committee meets. Reviewers will be asked to respond expeditiously and to recommend approval, modifications, or disapproval of the abstract. Abstracts must be submitted to the committee for review at least three weeks before the due date.
3. All abstracts accepted for presentation or publication should be submitted to the CCC for archival purposes.

3.2.13 Preparation and Submission of Papers for Publication

1. Clearance and approval through the P&P Committee and through the NIH Program Office are required for all WHI publications prior to their submission for publication.
2. All publications are to include an acknowledgement that approximates the following:

   The research upon which this publication is based was performed pursuant to Contract No.__ with the National Institutes of Health, Department of Health and Human Services.
3. All review and clearance functions of the P&P Committee and of the NIH are to be done judiciously and expeditiously and solely to help fulfill the Policy Objectives set forth in *Section 3.2.1 - Policy Objectives* above, and are in no sense censorship functions.

3.2.14 Identification of Additional Papers

1. WHI investigators who identify additional studywide publications that draw on data collected by all CCs, should submit a written proposal to the Chair of the P&P Committee. Upon receipt of the proposal, the policies and procedures described in *Section 3.2.9 – Identification of Writing Committees, Selection of Writing Committee Chair, and Work of Writing Committees* are to apply.
2. If a specific writing committee decides that the topic or charge to that writing committee is too broad and should be divided into two or more papers rather than the one paper originally assigned, that writing committee (through its chair) is to communicate with the Chair of the P&P Committee indicating the writing committee's recommendation for the division of the paper into two or more components. The writing committee is to identify which of the components it feels are to be its responsibilities and is to suggest titles and outlines for the other components. The P&P Committee is to consider these recommendations and, when appropriate, redefine the charge to the existing writing committee. The additional papers are to be specified, following procedures as outlined in *Section 3.2.9 – Identification of Writing Committees, Selection of Writing Committee Chair, and Work of Writing Committees.*
3. If in its deliberation, any writing committee identifies other topics or titles, either directly or indirectly related to the charge of that specific writing committee, the Chair of the Writing Committee is to communicate these suggestions to the Chair of the P&P Committee.

3.2.15 Use of WHI Data for Theses by Graduate Students

1. All requests for use of WHI data by graduate students, medical students, residents and other trainees for theses or other projects are to be reviewed by the P&P Committee and the Program Office.
2. It is required that the student requesting use for WHI data is associated with the study through one of the WHI investigators who is acting as the student's "sponsor" with regard to the data.
3. WHI data may not be used by students if the data relate to major WHI papers in progress or if the P&P Committee deems that data to be necessary for a future major paper.
4. If the P&P Committee recommends approval for the use of the requested data, a writing committee is to be established and is to include the student as convener of the committee.
5. The writing committee is to take no action regarding the paper until the student has completed and defended the thesis provided this occurs in a reasonable length of time, to be determined on a case-by-case basis. The student's sponsor is to report the student's progress to the P&P Committee at least annually.
6. The student must include in the completed thesis:
   a. a statement acknowledging WHI for use of the data, and
   b. a statement indicating that opinions, ideas, and interpretations included in the thesis are those of the student alone and not those of the WHI investigators.

7. When the thesis has been completed, as determined by the sponsor, the entire writing committee is to proceed to prepare the paper(s) for publication. It is the responsibility of the WHI PI "sponsor" to ensure that the thesis accurately reflects the conduct and data from the WHI, as dissertations are technically available to the public without having gone through the P&P review process.
8. The standard WHI publication policy is to apply to any material published from the thesis.
9. WHI reserves the right to proceed with preparing a paper for publication on the thesis topic through the activation of a writing group if, in the view of the P&P Committee and the student's sponsor, the student has not made reasonable progress in completing the thesis.

3.2.16 Use of WHI Data for Grant Application or Contract Proposal

WHI data which have not been previously published but which are needed for grant applications or contract proposals must have prior approval for use by the WHI Council and Program Office.

3.2.17 Policy for the WHI Distributed Baseline Data Set

1. Purpose of the data set distribution:

   The WHI investigators have completed the collection of baseline data on participants of the Observational Study and Clinical Trials. The data set represents valuable scientific information on a large sample of postmenopausal women. The WHI baseline data set is made available, under specified conditions and terms, to qualified investigators. This is done in order to take full advantage of information available in the data set, to maximize the publication of findings from the WHI study. The WHI baseline data set will be released to the public in year 2004.

   All personal identifiers have been removed from observations in the WHI baseline data set to protect the privacy of participants. Both to protect the privacy of the participants and the integrity of the study, investigators who are granted access to these data must adhere to the requirements of the Data Distribution Agreement. Failure to comply with the Data Distribution Agreement could result in subsequent restrictions on use of the data set, and/or repudiation of a presentation or a published manuscript by the Steering Committee and the NHLBI.

2. Purposes for which the data set may be used include the following:

   a. Exploratory analyses for the purpose of developing manuscript proposals.
   b. Background information for use in grant proposals.
   c. Analyses for manuscript development.
   d. Analyses for ancillary study proposals.
   e. Analyses for classroom teaching purposes.
   f. Extracts of local data for use by graduate students in writing theses.

3. Format of the distributed data set and timing of data set distribution:

   All WHI Principal Investigators are to sign the “WHI Data Distribution Agreement.” Preparation of the data set, clear documentation of the format of the data set, and a code to access the data will be provided by the Coordinating Center. Preparation of the data set includes the masking of participant and clinical center identifiers, assurance of data quality, computation of derived variables and scales, and transfer of the data set onto a data medium. If local data are needed, the CC PI may send a request to the CCC (statinfo@whi.org) for a file containing the mapping of the masked participant ID and original WHI Member ID for their local data. This request should include a brief statement indicating why this information is needed.

Initially, there will be two types of data released. One is "Form Level" data, which will include all questions from the baseline forms. In addition, summary variables and constructs will be provided, including psychosocial variables, physical activity variables, summary nutrient data from the FFQ, cognitive function score computed from *Form 39*, and summary variables on hormone use from *Form 43*. Documentation will include identification and description of the original and calculated variables included in the data set. The data set was made available for Clinical Centers use in early 2001. Updates may be provided as needed and resources permit.

4. Conditions for release of baseline data sets:

   The data set will be released to principal investigators with the following understanding and under the following conditions:

   a. The principal investigator signs the "WHI Data Distribution Agreement." Any Co-Investigators, colleagues, or students requesting to use the data set must sign the "WHI Data Distribution Agreement for Use of Data by Co-Investigators, colleagues, and students."

   b. The Principal Investigator is responsible for the use and safe keeping of the data set. The data set is not transferable to other parties and can only be accessed through the PI. Baseline data may be made available to WHI Co-Investigators.

   c. Co-Investigators who use the data set must sign a document, which states that they have read the conditions for use of the data set and agree to abide by them.

   d. The Principal Investigator must provide assurances to the P&P Committee that an individual with appropriate competence in data analysis is available at the clinical center and will participate in data analyses. A biosketch of the statistician who is available for consultation on data analysis must be provided.

   e. Data may not be shared with outside commercial enterprises.

   f. Each Principal Investigator will provide a report annually to the P&P Committee on use of the data set during the previous 12 months. This report will also be incorporated into the Clinical Center's annual report to the Project Office.

5. Release of the distributed data set to other sites:

   A copy of the data set will be made available to the WHI Project Office on request. Ancillary study principal investigators who are not WHI investigators will not receive a copy of the data set, but will continue to receive appropriate data extracts from the Coordinating Center.

6. Use of data for the development of manuscript proposals and abstracts:

   a. Manuscript proposals using distributed data sets will follow the established WHI process for manuscript development. This process includes submitting a manuscript proposal to the P&P Committee and the Project Office for review. After P&P and Project Office approval of the proposal, interested individuals may be nominated to serve on the writing group. The P&P Committee monitors progress of writing groups. The final manuscript must be reviewed and approved by the P&P Committee and the Project Office prior to submission for publication.

   b. Abstract development and submission will continue to follow the abstract procedures that have been developed by the P&P Committee. These procedures include submission of the abstract to the P&P Committee for review and approval. Presenters of oral or poster session papers that use WHI data must provide a copy of the talk, slides, or poster materials to the P&P Committee and the Project Office.

   c. All WHI investigators are eligible to develop manuscripts and abstracts using the WHI data set. A WHI investigator is defined as any investigator who is actively involved in WHI and identified as such on the NHLBI contract with any one of the forty Clinical Centers or the Coordinating Center.

d. Individuals who do not meet the above criteria are defined as non-WHI investigators. These individuals may request use of the WHI dataset. However, for a non-WHI investigator to use the dataset, the site-specific PI must submit a written request to the P&P Committee with a justification for data access. The P&P Committee will review the request and submit a recommendation to the Steering Committee. The Steering Committee must approve the request for data access to be given.

e. As a general rule, manuscripts using the distributed data set may have up to four authors from a single institution. However, exceptions to this guideline will be entertained.

f. Statistical analyses: Competency in data analysis must be documented for data that are analyzed at the Clinical Center. A biosketch of the individual responsible for data analysis will provide the necessary documentation. Methods used for statistical analyses must be provided to the P&P Committee for all manuscripts that are developed for publication. Clinical sites may apply to the Coordinating Center for statistical assistance in analysis for manuscripts through the usual P&P process. The Coordinating Center Statistical Unit will not provide direct assistance when Clinical Centers undertake their own analyses but will respond to generic questions regarding data access, and data definition and coding that are addressed to the WHI email address: statinfo@whi.org.

g. To assure the protection of participant privacy, cells of fewer that 10 observations may not be published.

h. All publications that use WHI data must acknowledge the contributions of the WHI investigators and the support of the NIH/NHLBI.

7. Enforcement of policies governing the protection and use of distributed data sets:

The WHI Steering Committee approves these policies governing the protection and use of the distributed data set. Therefore, the policies will be enforced. Any violation of the policies governing the protection and use of the distributed data set may result in proscription of any further use of the data set. The WHI Steering Committee or the NHLBI may disavow publications resulting from analyses that were not performed in conformance with the P&P policy.

3.2.18 Accepting Outside Funding for WHI Statistical Analyses

The WHI P&P Committee will review proposals for outside funding of WHI statistical analyses. Preliminary approval shall be contingent on demonstration that the following principals are upheld:

- Outside funding can only be accepted to support P&P approved analyses of WHI data.
- WHI controls the analysis design, execution, interpretation, and publication.
- The contract associated with the outside funding must be consistent with all WHI policies and procedures.
- Conflicts of interest, whether real or apparent, must be disclosed. It is necessary to disclose both the funding organization and its mission so that the reader can judge whether it might bias the results. It is also necessary for the WHI investigator(s) involved to assure the P&P Committee in writing that their acceptance of outside funding will not impose on the design, execution, interpretation, or publication of the proposed WHI paper. (A form for this purpose will be developed by the CCC).
- A mechanism will be developed to ensure approval by all PI's (following preliminary approval by the P&P Committee).

Quality Control:

1. Quality control procedures will be further developed by the CCC. However, at a minimum, these procedures will include review of all statistical output relevant to manuscript tables and the final paper by a CCC biostatistician.

2. Activities related to biostatistical review of analyses performed with outside funding will not receive priority over analyses performed within the CCC.

3.2.19 End of Study Clinical Trial Priority Papers

Procedures for abstracts and presentations at national/international meetings:

1. Writing groups for unauthored and priority papers should present to the P&P Committee at the time of submission of the paper proposal or during the process of ms preparation a list of one or more abstracts, the meeting to which they will be submitted, and the name of the first author (presenter). It is suggested that the group chooses lead authors of abstracts that are different than the lead author of the paper. The P&P Committee will review these to encourage dissemination of results to a wide range of meetings, and to encourage fairness in abstract presentations.
2. In the case of abstracts for the 3 remaining unauthored papers, the lists of proposed abstracts and lead authors will be submitted to the SC for approval.
3. In the case of the unauthored E+P paper, it is assumed that future abstracts will be suggested by the existing writing groups following the above procedure. In the event of an unsolicited opportunity such as that of the AHA meeting, the presenter should be chosen by the appropriate E+P writing group, depending on the nature of the meeting (if it is a cardiovascular or cancer meeting, the writing groups will meet together to choose a presenter).
4. In the case of the other unauthored papers an unsolicited request for presentation of the major results should be considered by the unauthored writing group and the selection submitted to the SC for approval. The person selected for presentation does not need to be a member of the unauthored writing group.
5. If a WHI PI or other investigator is approached to present published WHI data at a specific national or international meeting as an invited speaker, the investigator should request approval from the P&P Committee. This will be accomplished in an expedited fashion and not held up for committee review unless it raises an unexpected complex issue. If approved, the investigator will be authorized to present on behalf of the WHI investigators. In the case of a request to a member of the Project Office, the PO must approve before submission to the P&P Committee.
6. If a WHI investigator is invited to write a review article that will contain discussion of WHI data, or if he/she is invited to write a commentary in response to a critique of WHI, permission must be obtained from the P&P Committee, and the manuscript must be submitted for expedited review prior to publication.

Procedure for finalizing the author list for the priority authored E+P papers, and for the end of study priority authored papers.

1. The list of end of study priority papers should be expanded to follow the suggestions made by the breakout groups at the SC meeting. Specifically that would separate the CVD papers into separate papers for CHD and stroke for diet, and to CHD, stroke and embolic events for the E trial, and add QOL papers for the E trial and for the DM trial.
2. According to the above expansion there will be 27 priority papers. With 8 authors per paper that will yield 216 slots. It is proposed that a specified number of slots (16 for the CCC/subcontractors and 5 for each CC) be allotted and that the PI name him/herself, a past PI, or a Co-I to fill the slots for each CC. This will provide each CC with the flexibility to include key investigators as appropriate for that CC. The POs should be invited to join writing groups by the lead of the group (following NHLBI guidelines as stated in 3.19-1).
3. Flexibility to allow expansion of a writing group to 12 in the case of popular topics. In certain cases, an additional author such as the statistician from the CCC or the head of a CORE lab may be added at the discretion of the writing group.
4. If only a small number of authors are named for a priority paper, the paper proposal will be circulated to allow for additional interested CC investigators to join.

Bylines for publications:

- Priority authored papers shall have a byline including, after the names on the writing group, 'for the WHI Investigators.' The 'long' shall be included as a footnote.
- Unauthored papers should have the byline 'The WHI Investigators'. The footnote should include the long list from each clinic. The study should pay for additional charges that this might incur. It is intended that a major journal be the venue for the 3 unauthored CT papers. If a journal, after negotiations, will not adhere to the above policy then the SC will be consulted before an alternative byline is used.

3.2.20 Writing Group Appeals

This policy would apply to Priority Papers and papers with the byline "for the WHI Investigators"; P&P appeal will also be available to all Writing Groups.

1. One or more writing group members disagree with a presentation of the data, including the analyses and authorship.
2. The member(s) should discuss the disagreement with the lead author, who makes a decision on how to resolve the dispute.
3. Either the member(s) disagree(s) with the decision, or the lead author does not respond to the request for changes. The writing group member(s) should ask for a polling or formal vote of the entire writing group relating to the issue(s) in dispute.
4. If this does not resolve the issue(s), and the writing group member(s) believe(s) that it is in the best interests of the WHI to not allow the paper to proceed, there should be available an appeal to the P&P Committee Chairperson, who will attempt to resolve the issues or appoint an appropriate P&P member to resolve the issues in a meeting or conference call with the lead author and the member(s) who are in disagreement.
5. If this is unsuccessful, and if the chairperson of the P&P with the approval of the committee cannot make a decision, then the P&P chairperson should solicit expert opinion from within WHI and if necessary from outside the study.
6. The decision of the advisory expert(s) in conjunction with the P&P Committee will be final.
7. If final arbitration is necessary, the P&P Committee through the chairperson will make the Executive Committee aware of the sequence of events and final decision.

3.3 Examples of Publication and Presentation Documents

3.3.1 WHI Publications and Presentations Committee Progress Report

Updated Stage of Approved Papers

#	Name of Manuscript	Writing Group	Data Focus	Type	Stage	Comments	P&P Approval Date	Next Stage	Publish Date	Publisher
1	Informed consent in the Women's Health Initiative Clinical Trial and Observational Study	**McTiernan**, Franzi, Johnson, Manson, Nevitt, Rossouw, Taylor, Carleton	Gen.	2	10	Published	9/30/94			Journal of Women's Health, Vol. 4, Num.5
2	Combined hormone replacement therapy and occurrence of disease in postmenopausal women	**Johnson**, McTiernan, Bachman, Beresford, Dunn, Grady, Judd, Hunninghake, Manson	Gen.	2	5			6/97		
3	Women's Health and the Women's Health Initiative	**Cochrane**, Hunter, Johnson, Matthews, Strickland, Wactawski-Wende and Woods	Gen.	2	3	Currently "on hold"				
4	Book chapter entitled "The Women's Health Initiative: Overview of the nutrition component"...for book titled "Nutrition and Women's Health"	**Tinker**, Burrows, Henry, Patterson, Van Horn, Rupp	Gen.	2	10	Published				Nutrition & Women's Health, Chapter 18, 510-542, 1996
5	Women Health Initiative: Why now? What is it? What's new?	**Matthews**, Shumaker, Hunt, Bowen, Klesges, Kaplan, Ritenbaugh, Langer, Weiss	Gen.	2	9	In Press			1997	American Psychologist

**On a regular basis, P&P Progress Reports will routinely be sent to the WHI PIs only. It is the responsibility of each PI to forward these reports to the WHI Co-PIs, Co-Investigators, and staff who are interested in WHI publications and presentations.

3.3.2 Example of Manuscript Proposal

Tentative title: "Relationships of Cerebral MRI Findings to Age, Cardiovascular Disease, and CVD Risk Factors"

Convener: Elwood Jones

3.3.2.1 Introduction

Magnetic resonance imaging (MRI) is currently the best technique available for detection and definition of ischemic and hemorrhagic stroke. In addition, MRI detects other abnormalities of unknown significance believed to be related to cerebrovascular disease or vascular dementia. Such abnormalities include gray matter changes (widening of sulci, narrowing of gyri, loss of gray matter depth, and ventricular enlargement), all of which appear to increase with age and with functional impairment [1-2]. White matter changes such as periventricular areas of increased signal intensity (corresponding to leukoaraiosis as detected by computed tomography) and widened perivascular spaces can also be detected and measured, and appear to increase in frequency with age, prior stroke, and hypertension [3-5]. Ventricular enlargement can also be measured and is known to increase with age [6-7].

The clinical and prognostic significance of gray matter, white matter, and ventricular changes have not been studied extensively, but these changes have been correlated with major cardiovascular disease risk factors in small clinical samples. The CHS feasibility study would permit assessment of the associations of these findings with cardiovascular disease, stroke, and their risk factors in a population-based sample of 300 men and women aged 65 and older. These preliminary findings will help to focus study of cerebral MRI abnormalities as related to cardiovascular disease, and may suggest possible etiologies and correlations of these abnormalities.

This manuscript has three objectives:

1. to describe prevalences of MRI-defined gray matter and white matter changes by age;
2. to identify associations between MRI-defined changes and cardiovascular disease and its risk factors; and
3. to determine independence of age-MRI change associations from known clinical and subclinical cardiovascular disease and cardiovascular disease risk factors.

Note that case-control status would be largely ignored in this analysis, as cases and controls are matched for age and gender. Strong caveats would be included in the manuscript that one-third of this sample had reported a prior stroke, and thus they are not directly comparable to a general population. We might also want to estimate general CHS prevalences by weighting the feasibility study prevalences by the sampling fractions used. I also assume some might quibble with calling ventricular enlargement a gray matter change, but it seems to fit better with the other atrophy measures than with white matter changes. Given the length of the tables, we might want to consider dealing with gray matter/ventricles separately from white matter changes, but sample size is so small that there may be very few findings at all.

Note also that this manuscript would not deal with MRI findings suggestive of stroke, nor would it examine the relationships between MRI findings and cognitive function. These are extensive topics in their own rights, and should have separate papers devoted to them.

3.3.2.2 Analysis Plan

A. Definitions:

1. Gray matter changes-- atrophy

a. Sulci, score 0-9 (SULCI49)

b. Bifrontal distance in cm (BIDIST49)

c. Inner table distance in cm (ITDIST49)

d. Focal atrophy, yes/no (FOCAL49)

e. Ventricular changes, score 0-9 (VENT49)

2. White matter changes

a. Grade, score 0-9 (WHGRD49)

b. Predominant location, periventricular vs. subcortical (WHPLOC49)

c. Perivascular spaces, normal vs. increased (PERISP49)

B. Suggested tables (only significant associations will be shown); perhaps initially stratified by case-control status to be sure associations are similar in all three groups.

Table 3.1
Prevalence of Gray Matter and Ventricular Changes by Age

		sulcal score mean (std)	ventricular size mean (std)	adjusted* bifrontal distance n (%)	focal atrophy mean (std)
Women					
age	65-69				
	70-79				
	80+				
Men					
age	65-69				
	70-79				
	80+				

* bifrontal distance adjusted for inner table distance

Table 3.2
Prevalence of White Matter Changes by Age

		white matter grade mean (std)	location: sub-cortical > peri ventricular n (%)	increased perivascular spaces n (%)
Women				
age	65-69			
	70-79			
	80+			
Men				
age	65-69			
	70-79			
	80+			

Table 3.3
Prevalence of Gray Matter and Ventricular Changes by Clinical Disease, Subclinical Disease and Risk Factors

	sulcal score mean (std)	ventricular size mean (std)	adjusted* bifrontal distance n (%)	focal atrophy mean (std)
confirmed CHD				
absent				
present				
confirmed CHF				
absent				
present				
confirmed stroke				
absent				
present				
confirmed PVD				
absent				
present				
diabetes by OGTT				
none				
impaired				
diabetes				
atrial fibrillation by ECG				
absent				
present				
carotid stenosis				
none				
1-49%				
$\geq$ 50%				
LVSWM abnormalities				
normal				
borderline/abnormal				
LV ejection fraction				
normal				
borderline/abnormal				
hypertension				
none				
140-159/90-94				
$\geq$ 160/95 or meds				
smoking				
never				
past				
current				

Table 3.4
Correlates (r) of Gray Matter and Ventricular Changes (Continuous Measures)

	sulcal score	ventricular size	adjusted* bifrontal distance	focal atrophy
total cholesterol				
fibrinogen				
factor VII				
albumin				
creatinine				
hemoglobin				
fasting glucose				
fasting insulin				
systolic BP				
diastolic BP				
weight				
BMI				
physical activity				
FEV1/height				
intimal-medial thickness				

Table 3.5
Independent Correlates of Gray Matter Changes Based on Significant Variables from Bivariate Analyses

Factors	sulcal score beta P	ventricular size beta P	adjusted* bifrontal distance beta P	focal atrophy beta P
age				
confirmed stroke				
etc.				

Table 3.6
Independent Correlates of White Matter Changes Based on Significant Variables from Bivariate Analyses

Factors	white matter grade beta P	location: sub-cortical > peri ventricular beta P	increased perivascular spaces beta P
age			
confirmed stroke			
etc.			

3.3.2.3 Conclusions

This is intended to be primarily a descriptive paper, to help guide us in interpreting MRI data from the full study. It may also help to identify factors associated with MRI findings which we may want to consider as confounders in analysis. To my knowledge, little is known of correlates of MRI abnormalities since CHS is among the first studies to use the technique on a population basis. For those who want hypotheses to test, I assume the major one will be that increased age is independently associated with these findings even in the upper age ranges contained in CHS.

3.3.2.4 References

1. Miller AKH, Ralston RL, Corsellis JAN. Variation with age in the volumes of gray and white matter in the cerebral hemispheres of man: Measurements with an image analyzer. Neuropathol Appl Neurobiol 1980; 6:119-132.

2. Brant-Zawadzki M, Fein G, Van Dyke C, Keirman R, Davenport L, De Groot J. MR imaging of the aging brain. AJNR 1985; 6:675-782.

3. Bradley WG, Wauch V, Brant-Zawadzki M, Yadley RA, Wycoff RR. Patchy, periventricular white matter lesions in the elderly; a common observation during NMR imaging. Noninvas Med Imag 1984; 1:35-41.

4. Gerard G, Weisberg LA. MRI periventricular lesions in adults. Neurology 1986; 36:998-1001.5. Zatz LM, Jernigan TL, Ahumada AJ Jr. White matter changes in cerebral computed tomography related to aging. J Comp Assist Tomogr 1982; 6:19-23.

5. Zatz LM, Jernigan TL, Ahumada AJ Jr. Changes on computed cranial tomography with aging: intracranial fluid volume. AJNR 1982; 3:1-11.

6. Gyldensted C. Measurements of the normal ventricular system and hemispheric sulci of 100 adults with computed tomography. Neuroradiology 1977; 14:183-192.

3.3.3 "Letter of Intent"

(Sent from P&P Chair to Writing Group Chair after P&P Committee approval of: 1) paper proposal, 2) Writing Group membership and 3) Writing Group Chair appointment)

Dear _____:

On behalf of the WHI Publications and Presentations Committee, I would like to congratulate you on your appointment to Chair of the Writing Group for WHI manuscript #___, tentatively entitled "_____."

Our mutual goal is the orderly and expeditious publication of this WHI manuscript. Towards this end, we look forward to working with you and members of your Writing Group to facilitate preparation of the first draft.

As Chair of a writing group, you assume responsibility for coordinating analysis and writing efforts and ensuring that the manuscript is completed according to the pre-determined production timeline. The P&P Committee will monitor your progress and will offer assistance, should you encounter any problems in adhering to the production schedule.

The enclosed attachment, entitled " WHI Responsibilities of Writing Group Chair and Writing Group Members," details the responsibilities involved in preparing the approved paper. Please review these guidelines carefully. A copy of this letter and the enclosed guidelines have been sent to members of your Writing Group so that they too will be aware of their responsibilities .

High quality and credible publications represent the ultimate goal of ambitious projects such as the WHI. As scientists and study investigators, we have a responsibility to disseminate relevant information to the scientific community in a timely manner. Your efforts support these goals.

Sincerely,

Chair, WHI P&P Committee

cc: Writing Group members (names listed alphabetically)

Encl: "WHI Responsibilities of Writing Group Chair and Writing Group Members"

3.3.4 WHI Responsibilities of Writing Group Chair and Writing Group Members

Responsibilities Writing Group Chair[2]

Overall responsibilities:

During all phases of manuscript development, coordinate writing group efforts and ensure timely preparation of the manuscript according to the production timeline.

Detailed charges:

- Communicate with the Writing Group members, the CCC, the P&P Committee, the NIH Program Office, and the target journal editors.
- Prepare outlines.
- Request data analyses from CCC.
- Assign tasks/set deadlines for Writing Group members.
- Conduct periodic Writing Group meetings or conference calls.
- Circulate manuscript drafts to Writing Group members.
- Establish consensus among Writing Group members concerning target journal, subject to final approval by P&P Committee.
- Prepare quarterly progress reports to P&P Committee.
- Establish authorship order based on level of effort/input.
- Submit final manuscript draft to P&P Committee and to Program Office.
- Submit approved manuscript to target journal following final approval by Program Office.
- Submit reprint of published article to CCC.

Responsibilities Writing Group Members[3]

Overall responsibilities:

- Actively participate in preparation of the manuscript.
- Fulfill assigned writing group tasks in a timely manner.
- Complete all appropriate responsibilities noted above.

[2]Failure of the Writing Group Chair to meet these responsibilities could result in dismissal as Chair and replacement with another Writing Group member or WHI Investigator committed to fulfilling these functions.

[3]Failure of a Writing Group member to meet these responsibilities could result in dismissal from the Writing Group and replacement with another WHI Investigator committed to fulfilling these functions.

3.4 Ancillary Studies

3.4.1 General Policy

Investigators are encouraged to propose and conduct ancillary studies. Such studies enhance the value of the WHI and ensure the continued interest of the diverse group of investigators who are critical to the success of the study. To protect the integrity of WHI, ancillary studies must be reviewed and recommended by the Design and Analysis (D&A) Committee and NIH Program Office. D&A may refer an ancillary study to the Council for a final decision. The Council or the Program Office may obtain assistance from the DSMB in reviewing a proposal for any ancillary study. All funded studies involving CT participants will be reported to the DSMB. By definition, ancillary studies will require outside (non-WHI) funding.

In reviewing a proposal for any ancillary study, the primary consideration will be the compatibility of the study with the overall goals and procedures of the CT component or OS component of the WHI. Maintaining the integrity of the WHI, with respect to the achievement and maintenance of high adherence and follow-up for the duration of the trial, must be of paramount importance in order to ensure the validity of the study findings reported at the termination of the trial. Any proposed ancillary study which would interfere with one or more procedures of the WHI, is judged to have a reasonable potential to result in a decrease in adherence or follow-up, or could lead to early termination, is unlikely to be approved. Review of the proposal will include the balancing of important considerations, such as the possible effects on the conduct of the WHI of early disclosures of any results relevant to the primary aims of the study, the safety of the WHI participants, scientific merit and the scientific benefit that such results could add to the interpretation of the results of the trial.

In accordance with these goals, in general, no randomization assignments will be made available to investigators for an ancillary study until the termination of the relevant randomized trial component of the WHI. However, any proposed ancillary study that would include analyses where the primary exposure is any of the randomized treatments (blinded or not) under evaluation in the WHI, regardless of whether the outcome is an intermediate marker of a primary endpoint of the study, an outcome related to a primary endpoint, or an outcome unrelated to any primary endpoint, will be considered on a case-to-case basis by the D&A Committee with regard to any possible impact that release of the results would have, and thus possible restrictions on the timing of their release. All analyses involving such exposure variables from such an ancillary study would be conducted by the CCC. In certain circumstances, the DSMB may require that results of an ancillary study be held until after the release of the relevant randomized trial findings. If an ancillary study does not involve, as a primary exposure, a randomized treatment of the WHI, but does need to control for a woman's randomized treatment assignment as a possible confounding variable, then such analyses would be conducted by the CCC, and the investigator would receive the results from the CCC without being unblinded to individual treatment assignments. Such results could be released prior to the termination of the randomized trial component of the WHI, if so approved.

3.4.2 Definition

An ancillary study is one based upon information from WHI CT or OS participants in an investigation which is not described in the WHI Protocol and involves additional data which are not collected as part of the routine WHI data set, or additional biologic specimens for analysis or storage. This does not apply to women who were screened by WHI but are not enrolled in any aspect of WHI. Separate informed consent must be obtained from all ancillary study participants, and should clearly identify the ancillary study as one being performed in addition to the main study. The informed consent should be explicit that participation or nonparticipation in the ancillary study has no effect on participation in the main study. An ancillary study may also use WHI data in the analysis (e.g. demographic information, medication use, etc.).

A WHI PI or co-investigator must be included as a co-investigator in every ancillary study proposal, to promote continuity with the WHI. An investigator from the WHI CCC must be included as an investigator in every ancillary study proposal involving the use of blinded data, to promote data quality control, unless the

CCC deems this unnecessary. Any ancillary study involving data coordination and other services from the CCC is encouraged to provide for involvement by the CCC.

When blood (or other tissue) is obtained from WHI participants that is not part of the protocol, and when this is possibly intended for use in scientific studies now or at a later date, this blood will be regarded as being part of an ancillary study. Such activity composes staff and participant burden as well. The CC must obtain formal approval from the Design and Analysis subcommittee and the Program Office before this practice is initiated. Without significant scientific justification, such extra blood draws will not be approved.

3.4.3 Approval Process

3.4.3.1 Approval to Submit an External Funding Request

Every ancillary study will initially be sent to the D&A Committee for review. The ancillary study principal investigator has the responsibility for selecting the CCs that will participate, if appropriate (i.e., not a single center study). All ancillary studies must be approved by the NIH Program Office before submission to the funding agency.

Before an ancillary study will be cleared for an external (to main WHI program) funding request, it must be demonstrated that the ancillary study will have scientific merit and will not unduly:

1. Interfere with the completion of the main objectives of the WHI or complicate interpretation of the WHI results, including lack of fiscal burden.
2. Result in unblinding the study interventions.
3. Adversely affect participant burden or cooperation in the WHI.
4. Jeopardize the public image of the WHI.

Investigators will provide an abstract and a 3-6 page summary of the proposed ancillary study to the D&A Committee, which will discuss the proposal in light of the above approval criteria (1-4). An investigator is encouraged only to submit an initial abstract for studies requiring randomization assignment or other restricted data. A worksheet that summarizes the study proposal has been provided by the CCC and should be used with all study applications.

The summary must contain:

A. Identifiers:

1. Proposal title
2. Initiating investigators, all collaborators, all CCs involved;
3. Planned starting date;
4. Funding source, plans, estimated cost, start date, and duration and methods for avoiding fiscal burden.

B. Design and Methods:

1. Brief background and scientific rationale;
2. Reason for using WHI cohort(s) and which cohort (CT, OS);
3. Use of WHI participants;
4. Use of WHI participant specimens;
5. Study questions or hypotheses (1-3 or so);
6. Sample size, justification;

7. Methods, data to be collected;
8. Involvement of other CCs and the CCC (documented);
9. Burden on participants and staff;
10. Impact on main study;
11. Procedures to ensure confidentiality and maintain blinding.

C. Data Handling

1. Data needed from main study for analysis of ancillary study;
2. Impact on the CCC (Indicate how the CCC will be reimbursed and whether a CCC investigator is needed and has agreed to participate).

D. Literature Cited

E. Budget

1. Estimated costs: coverage of staff effort by budget;
2. CCC budget and costs.

The D&A Committee will use this information to assess the scientific value overall and to WHI of the study, and to determine its potential impact on the main study (WHI) with respect to staff and participant burden and potential benefit to or conflict with main study goals. As a part of the review of a proposed ancillary study, the D&A Committee may obtain input from other committees as appropriate (i.e., OS, Behavior, Special Populations) and will report its approval or disapproval to submit an external funding request to the Council. The D&A will make every reasonable effort to expedite their review and recommendation. Following D&A approval, the approval of the NIH Program Office must be sought. The materials submitted to D&A must be submitted to the Program Office.

The Program Office may also request review by the DSMB as part of the process of clearance to submit an external funding request.

The Program Office will review the proposal to determine that it will not compromise, complicate, or jeopardize the conduct of the WHI. Priority will be given to studies which: **1)** do not interfere with main WHI objectives, **2)** have scientific merit, **3)** produce the least burden on WHI participants, particularly CT participants, **4)** have objectives closest to those of WHI, and 5) require the unique characteristics of the WHI cohort. Review of proposed ancillary studies for in-depth, NIH-style review is not the primary responsibility of this review process. The Committee, however, will give a general scientific appraisal of all ancillary studies, according to its qualifications and capabilities.

3.4.3.2 Use of Biological Specimens - Priorities for Blood Specimens

Use of blood drawn as part of the WHI study is prioritized in the following manner:

1. Core analytes : core WHI analytes have been specified as part of the original WHI RFP. Additional high priority analytes have been specified in the Biomarkers Task Force Report and the Dietary Biomarkers Committee Report.
2. Reserved for potential analyses related to study safety.
3. Reserved for future analyses of currently unknown issues.
4. Available for ancillary studies.

Access to Priority 4 bloods for ancillary studies will be postponed until 1997 and 2004 for the CT and 1998 and 2004 for the OS. The exception is for OS ancillary studies included in the proposal prepared by the

Biomarkers Task Force for which there is no moratorium. Ancillary studies requiring blood prior to then will need to include blood draw and analysis as a component of their proposal. A prioritization scheme for other ancillary studies will be developed and reviewed by Council and relevant committees as well as the NIH Program Office. This scheme will be used to select which ancillary studies can use remaining blood at the target dates. All ancillary studies must still be reviewed and approved by the D&A committee and other committees as relevant, without exception.

3.4.3.3 Recruitment and Consenting of WHI Participants to Ancillary Studies

Generally speaking, any WHI participant may be recruited for an approved ancillary study. Women who have been screened at any level in WHI and who did not enroll in WHI are not WHI participants. Studies involving such women do not need the approval of WHI. Studies involving women contacted by WHI but who have not yet entered the screening process for WHI also do not need WHI approval. All ancillary studies must have a separate, institutionally-approved consent.

Study protocol requires that women should not be enrolled in WHI if they are currently participating in another intervention study. The Informed Consent enjoins participants while they are enrolled in any component of WHI not to participate in any future intervention studies. While women who are enrolled in any component of WHI can be advised not to join another intervention study, they cannot be prevented from doing so. However, WHI investigators should not actively recruit WHI participants into any intervention study.

3.4.3.4 Funding

Financial support for ancillary studies must come from a non-WHI source. No WHI contract funds are to be used to plan, conduct or report ancillary studies. All recruitment and other materials for WHI ancillary studies should be mailed separately from WHI mailings and should be covered by non-WHI funds.

3.4.3.5 Approval to Initiate Ancillary Study

Following notification of funding for an ancillary study, regardless of (non-WHI) funding source, the investigators will submit the following ancillary study information for review and approval by the D&A Committee and the Program Office.

1. Description of Changes From Initial Proposal
2. Informed Consent Documents
3. Complete Study Protocol
4. Study Budget

Narrative description (1-2 pages) of methods for, and ability to, avoid fiscal burden on main WHI program; letter of support from WHI Investigator associated with the study (for those from non-WHI investigators); a courtesy copy of each annual, quarterly or other report(s) submitted to the primary funding agency and a description of the reporting schedule.

The funding should include realistic estimates of CCC costs for data handling, which should be confirmed by the CCC. These materials will be expeditiously and concurrently reviewed by the D&A Committee and the Program Office. Note that the clearance for a CC to begin participation in an ancillary study may be dependent on its currency and performance in meeting basic WHI program requirements. Upon receipt of approvals from these sources, the study may begin.

3.4.4 Analysis and Data Ownership

Data generated in ancillary studies are the responsibility of the primary investigator of the ancillary study. Ownership of data generated in ancillary studies resides with the investigators who have collected these data.

It is the intention of the WHI CCC to distribute a data file with selected needed information to the ancillary study primary investigator after the conclusion of the ancillary study. In cases where the analysis of an ancillary study includes randomization assignment, and occurs before release of the results of the WHI CT, the results of the analysis will be reviewed and approved by the DSMB prior to approval by the P&P Committee or the Council. These data are provided solely for the ancillary study analysis. The D&A Committee may require the analyses that include randomization assignment to be completed at the CCC to avoid individual unblinding, even if group results are considered suitable for release. Before any collaborative data will be released to ancillary study investigators, the primary investigator of the ancillary study must sign a statement noting that she or he:

- is responsible for the scientific integrity of the study;
- is willing to follow the conditions for review and approval of abstracts and manuscripts which result from the ancillary study;
- will return the original file to the WHI CCC, purge all containing data provided by the CCC, and destroy all hard copy listings of such data once the analysis for the ancillary study has been completed.

The D&A Committee will monitor the development of the ancillary studies, determine whether they have received funding, record their initiation dates, and monitor their progress with assistance from the CCC. A written progress report on each ancillary study will be made annually by its primary investigator to the D&A Committee. The Council will receive an annual progress report on all ancillary studies from the D&A Committee.

Publications resulting from ancillary studies will follow the same policies as described in the WHI Publication and Presentation Policy, except that the writing will be determined by the ancillary study investigators.

3.4.4.1 Ancillary Study Tracking

Every approved WHI ancillary study will be included in the WHI study database (WHILMA) list of studies. Each CC participating in the ancillary studies will document the enrollment of every WHI participant in each ancillary study in WHILMA. See *Vol. 5 - Data System* for details. Investigators will be required to report annually to the D&A committee and NIH Program Office with copies to the CCC the following information: (a) when funding is received; (b) number of study participants enrolled; (c) impact on main study conduct, if any; (d) total number of clinics participating.

3.4.4.2 Approval of Publications and Presentations

All publications and presentation which use the WHI main study data will be submitted to the WHI P&P Committee and the NIH Program Office for approval prior to submission to the target journal. Consult the P&P Policy for further details about publications policy.

~~3.4.2~~3.4.5 Umbrella Studies Publication Policy

The following policy was approved by the Steering Committee in June 2000. Investigators with funded umbrella grants will submit separate proposals for all publications that they wish to produce between now and the end of the WHI project. After Publications and Presentation Committee (P&P) approval, these analyses will proceed and may each have not more than four co-authors who are umbrella grant investigators. These proposals will be circulated throughout WHI to obtain additional authors by the usual WHI process. After a group of authors has been established for a manuscript, a proposal will be developed as for any other WHI paper and reviewed by the P&P Committee using the usual review process. After approval, data analyses will be performed in collaboration with the Clinical Coordinating Center. The funding for statistical analyses will generally be provided in the umbrella grant budget. Final manuscripts will be submitted to the P&P Committee and NHLBI Project Office for approval as for any WHI manuscript. Initially, manuscripts will be proposed by the Umbrella studies investigators. However, two years after funding, data generated by Umbrella grant funding will be available to Umbrella study and WHI investigators for additional paper proposals. These data are the property of the WHI study.

3.5 Quality Assurance Site Visits

During the course of the study, the CCC will hold site visits approximately annually at each CC to ensure that study procedures are understood and carried out correctly. Reports from QA site visits will be given to CCs with any required or recommended action items. Clinical Centers will have 30 days to submit a response to the CCC. The CCC will then submit the QA site visit report and response, if any, to the Program Office. See further details in *Vol. 7 - Quality Assurance.*

3.6 Clinical Center Access to Local WHI Data

Clinical Center investigators and staff shall have the right and ability to extract from the database all participant data generated at their own site for the purposes of clinic management and scientific pursuits. This access will apply to all questionnaire data and local laboratory values. Data generated centrally (e.g., central lab values and randomizations) will not be routinely accessible to CC personnel. The CCC will work toward efficient methods for extracting data that can then be manipulated by CC personnel to meet local needs.

3.7 Policy for CC Modifications to the Local WHI Computing System

The WHI computing system, including all hardware, software, and networking, was designed, tested and implemented by the CCC to achieve study-wide goals for data management and communications. The CCC has assumed responsibility for the maintenance of this system through either direct CCC support or by arranging maintenance agreements with appropriate outside vendors. The CCC is able to support this system with minimal staff only when there is sufficient uniformity across sites to guarantee transfer of knowledge and applications. Notwithstanding these considerations, many CCs have features in their facilities, staffing, and pre-existing computer environments that imply a need for tailoring of the WHI system to improve efficiency. Examples of this tailoring include: adding more workstations, installing site-specific software, adding other peripheral devices (e.g., printers, modems), and interfacing with pre-existing systems. To balance the competing needs for uniformity and tailoring, the following approach will be used.

1. The CCC will publish a list of standards for all components of the computing system. In the absence of any other list, the spreadsheet attached to each CC's contract showing the computer budget will serve as the standard. In addition, the CCC will specify any modifications that are specifically banned.

2. The CCC computing staff will support all CC equipment meeting these standards. CCC staff will support other components only when time and expertise are available.

3. Clinical Centers must notify the CCC computing staff in writing or by electronic mail of any intent to change hardware, software, or networking in any way prior to implementing these changes. Examples of the type of information required will include: purpose of modification, model numbers and optional features of hardware, physical location, version of software, CC staff to implement change, and CCC support required. The CC will not implement any such changes to their system until either 30 days have passed from their submission or they have been notified that the CCC has no objections. If objections are raised, the CCC will work with the CC to establish a reasonable alternative or compromise. If this cannot be done to both parties' satisfaction, the Data Management Working Group will be asked to provide additional guidance. The exact procedure for prior notification will be specified in *Vol. 5 - Data System*.

   This prior notification does not constitute prior approval. The purpose of this notification is to allow the CCC to track changes that may affect the functioning of the primary system and to prevent any known problems. To the extent that the CCC is already aware of any problems that this may create, the CCC will inform the CC involved. Lack of such notification does not imply that this change will be successful or that any testing or evaluation has been done. The CCC is not prepared to test modifications of the WHI system outside the intended path of development for the entire study. Clinical Centers should be informed that further development of the system will proceed under the assumption of the published standards. Equipment not meeting those standards (e.g., lower quality workstations such as 386 models) may work with the current system but may not work with planned upgrades.

   In tracking the changes proposed by CCs, the CCC will develop a database of equipment and software configurations that are successfully implemented. This database will be used to guide later requests for similar changes and to expedite the review process.

4. The CC staff will not be given supervisory authority on the network or database administrator authority on the WHI Oracle application. This authority is restricted to the CCC to assure the integrity of blinded study operations as well as the CCC's ability to support the system. Thus modifications that require access to these more fundamental aspects of the computing system will require coordination with the CCC.

5. The CC is responsible for implementing and maintaining all CC-related changes including compliance with all software licensing agreements.

6. The CCC and the Data Management Working Group will jointly review notices and requests for modifications to the computing system on a regular basis. When multiple CCs request similar enhancements to the system and the Data Management Working Group determines that these changes would be of study-wide benefit and sufficiently high priority, the CCC will work toward developing new

standards that address these particular needs (e.g., selecting a modem to be used at all sites). Implementation of these new standards may depend upon identification of additional resources.

3.8 Participant Materials

3.8.1 Reviewing and Archiving CC Materials

The purpose of centrally reviewing and archiving materials generated by CCs is 1) to review these documents before dissemination for accuracy and consistency with overall study protocol and procedures, and 2) to maintain a file of participant documents.

3.8.1.1 CC Submission of Materials

Clinical Centers will send a copy of all locally-developed written participant materials to the CCC for review before using them for recruitment, retention, intervention, and health-related activities. Materials used at the CCs to assist with internal flow such as scheduling may be archived at the CCC, but will not be reviewed unless review is requested. The CCC may share these internal flow materials with other CCs. See *Figure 3.1* for list of sample materials and actions needed.

The CCs send a draft copy of the materials for review or archiving to the CCC via FAX, e-mail (CC Participant Material mailbox in DaVinci), express mail, or US mail. Clinical Centers also include information on how and when the material will be used.

3.8.1.2 IRB Approval

Each CC is responsible for its own IRB approval of CC-generated WHI materials.

3.8.1.3 CCC Review for Accuracy and Readability

The CCC will review all participant materials used in the WHI for accuracy and readability, depending on their content and purpose. This will also include review for consistency with overall study protocol and procedures. The CCC will send required and suggested revisions of these materials to the CC Program Office and the within one week after receipt of the materials. The CC may assume their documents are approved if they have not received an initial response from the CCC within one week after receipt at the CCC. WHI committees or WHI staff groups may also be asked to review certain CC materials, depending on content.

Clinical Centers will incorporate the required revisions for accuracy and send a copy of the finalized material to the CCC for archiving. The CCC encourages open communication whenever differences of opinion exist.

Clinical Centers may incorporate CCC feedback on readability into the materials at CC discretion. Guidelines for readability are in *Vol. 2 - Procedures, Section 3.1.5.- Guidelines for Developing Recruitment Materials.*

3.8.1.4 Approval of Study-Wide Materials

Participant materials and press releases developed by CCs may be adopted for study-wide use. Study-wide materials undergo review by the Council and the Program Office. The Council may refer materials to other committees for additional review. The following are considered when reviewing study-wide materials: study protocol and procedures, participant burden, and quality assurance. Materials will be implemented study-wide only after approval by the Council and the Program Office.

3.8.1.5 Archiving at the CCC

The CCC will archive written participant materials used in the WHI. Participant materials include those distributed to women randomized into the CT or enrolled in the OS, as well as those distributed to potential participants during recruitment. The purpose of this archive is to provide a permanent record of all participant materials used in the trial and reference materials for other CCs.

3.8.1.6 Summary

The following table provides a sample of the types of clinic materials submitted for archiving and reviewing. This is not meant to be an exhaustive list, but to provide a general guideline for the review process.

Figure 3.1
Types of Clinic Materials

Materials	Require CCC Review for Accuracy	Require Archive at CCC	Require Approval by Council and Program Office
Recruitment materials	Yes	Yes	Study-wide use only
OS participant materials	Yes	Yes	Study-wide use only
CT Intervention materials	Yes	Yes	Study-wide use only
Retention materials	Yes	Yes	Study-wide use only
Health-related materials	Yes	Yes	Study-wide use only
CC materials for internal flow	No	No	No

3.9 Access to Samples in WHI Blood Repository

3.9.1 Introduction

In the Fall of 1998 the study governance was restructured and committees were reconstituted. This has led to a loss of some measure of institutional memory in regard to certain study policies and procedures. In particular, there have been uncertainties in connection with the conduct of the OS Blood Competition, and the governance of OS Umbrella Studies. Furthermore, the existing policies and procedures are scattered among a number of sources, including protocol policy and procedures documentation, committee minutes, and memoranda.

The Steering Committee approved the following policies and procedures dated 9-27-99. Some minor changes and additions were made to remove ambiguities or streamline procedures. These updated policies include subsequent approval of the D&A policy on the Blood Competition and adds a section on confidentially as proposed by the Blood Biomarkers and Genetics Task Force and approved by the Executive Committee.

Blood Repository

The Blood Repository is maintained at –70 degrees centigrade at McKesson BioServices in Rockville, MD. McKesson is a subcontractor to the Clinical Coordinating Center. Each sample is in a sealed and bar-coded vial, which occupies a unique position in the repository for retrieval after identification in the study database. After a study has used a vial, unused remaining specimens will be returned to the central repository. A central laboratory will be selected to perform DNA extractions from the buffy coats. The first study to request DNA from a particular sample will be billed for the cost of extraction.

3.9.2 Observational Study

3.9.2.1 Sampling Frame, Volumes, and Objectives of Blood

Every OS participant has a fasting blood draw at baseline and at 3 years.

(a) The baseline blood samples are intended for future nested case-control studies.

(b) A 1% subsample of OS participants (oversampled for minority groups) provided a second blood sample within weeks of the baseline sample for repeatability studies; this subsample is also being used to describe the distribution of blood variables at baseline. The subsample includes approximately 1000 women (500 white, 200 black, 200 Hispanic, 100 Asian/Pacific Islander/Native American).

(c) The 3 year samples are intended to be used in conjunction with the baseline samples in one or both of the following ways: (1) to obtain an average value for a blood variable, or to correct for regression-dilution bias, and (2) to study the relationship of change in a blood variable over 3 years to future events in nested case-control studies.

The blood draws at baseline and at 3 years are identical, excluding RBC obtained only at baseline. The blood volume taken is 45 ml, and after processing the following aliquots are stored for each participant:

- 4 x 1.8 ml vials of serum
- 3 x 1.8 ml vials of citrated plasma
- 3 x 1.8 ml of EDTA plasma
- 1 x 1.8 ml RBC (from EDTA tube)
- 2 x buffy coats (EDTA and citrate tubes)

Note that all OS participants also have a WBC, hematocrit, and platelet count performed at baseline and a WBC at Year 3, and these data are entered into the database.

Maximum volumes are: 7.2 ml serum, 10.8 ml plasma (citrate or EDTA), 2 buffy coats, 1 RBC at baseline, plus similar amounts at 3 years (note: some samples are incomplete).

1. ***Core Analytes:*** Core analytes are blood variables that will be performed in nested case-control studies as part of the main study because they are expected to have a relationship to the main study outcomes. The core ***analytes*** will be repeated at Year 3. The major core analytes were defined in the RFP and subsequently modified according to the recommendations of the Biomarkers Task Force (1994). The core analytes are:

   - Lipids: serum cholesterol, triglycerides, LDL-C, HDL-C, HDL-2, HDL-3, Lp(a)
   - Coagulation: fibrinogen, factor VII
   - Antioxidants: tocopherol, carotenoids
   - Carbohydrate metabolism: glucose, insulin

2. ***Additional Analytes:*** The Biomarkers Task Force (1994) also recommended that certain additional analytes be measured in smaller subsamples of 300 OS participants at baseline and 3 years. The additional analytes are:

   - Folate, B6, B12, homocysteine
   - 25-OH vitamin D
   - Ferritin
   - Fatty acid profile

   The WHI Central Laboratory (Medical Research Laboratories, a subcontractor the Clinical Coordinating Center) has assayed the designated *core analytes* in the 1% OS repeatability subsample at baseline, and the core analytes could potentially be assayed in subsets of other OS participants earlier than study termination for use in ancillary case-control studies, especially those that focus on main study outcomes (e.g. umbrella studies). In either circumstance the core analyte results would be made available to ancillary study investigators. In return, ancillary study investigators would be asked to make their results available to the main study upon at the time of the completion of the grant cycle, or at the time of the initial publication. Publications resulting from ancillary studies using core analyte data will acknowledge the provenance of the data. The main WHI study may incorporate ancillary study data in publications after obtaining the permission of the ancillary study investigators, and will acknowledge the provenance of the data.

   As of fall 2000, the WHI Central Laboratory has not begun work on *additional analytes*. The additional analytes could be made available to ancillary study investigators if they would enhance the ancillary study. This would avoid duplication of analytes on the same samples. The conditions would be similar to those pertaining to core analytes, except that the approval of the P&P Committee and EC/SC would need to be obtained prior to publication in order to ensure that the main study results are not pre-empted by the ancillary study.

3. ***Volume of blood reserved for core analytes and additional analytes:*** Based on the Biomarkers Task Force (1994) estimates, the following types and volumes of blood are reserved for current and future main study purposes (note: similar amounts are reserved for baseline and Year 3 bloods):

   - Serum: 3 x 1.8 ml
   - Citrate: 2 x 1.8 ml
   - EDTA: 2 x 1.8 ml
   - Buffy coat: 1 vial

4. ***Volume of blood potentially available for ancillary studies:*** By difference, the maximum types of blood and ***volumes*** available from each of the baseline and Year 3 sampling periods are:

   - Serum: 1 x 1.8 ml
   - Citrate: 1 x 1.8 ml
   - EDTA: 1 x 1.8 ml
   - Buffy coat:

- 1 vial
- RBC: 1 vial

3.9.2.2 Ancillary Studies

1. ***Volume available for ancillary studies:*** Current D&A Policy as approved by Council does not specify the volume of blood available for ancillary studies, or whether the policy applies to baseline bloods only. The policy does state that bloods for ancillary studies have a lower priority than bloods reserved for main study purposes. Core analytes and the additional analytes recommended by the Biomarkers Task Force (1994)(which overlap with the Umbrella Studies) have the highest priority.

2. ***OS Blood Competition:*** The "Plan for Conducting the Competition for Use of Blood Resources by OS Ancillary Studies" was approved (with modifications in respect of timing) at the Fall 1998 Steering Committee meeting. It states that "Current policy requires that no more than 2 ml of sera or plasma are available for Ancillary Studies (not including Umbrella Studies). Studies which plan to use analytes that are already included in the planned core analytes can use the results (when available) from those analytes if they coincide with the (ancillary) study plans. If it is judged to be in the interest of the main study, core analytes may be performed and be made available to ancillary study investigators as well.'' This policy was amended by the approval at the Spring, 2000 SC meeting of the D&A Committee's proposal for the Year 2000 OS Blood Competition (see separate document for details).

   The policy will be applied as follows (note that the previously mentioned 2 ml limit has been altered to 1.8 ml to coincide with the aliquot sizes as stored):

   (a) For the first two rounds of the competition (in 1998 and 2000) no more than 1.8 ml of each of serum and plasma from the baseline and/or Year 3 blood draw will be made available to each Umbrella Study, however exceptions may be determined on a case by case basis. Other ancillary studies will be limited to no more than 1.8 ml total of serum and/or plasma from the baseline and/or Year 3 blood draw, with no exceptions. In addition, one buffy coat and the RBC sample from each of the baseline and Year 3 bloods will be made available to Umbrella/ancillary studies.

   A further guideline is needed to protect a particular participant's sample from being called on by multiple studies, each of which may be within the guidelines in the preceding paragraph. This further guideline states that the bloods dispensed from the repository for an individual participant's blood draw from a particular examination cycle is limited to 1.8 ml of each of serum and plasma (with the possible exceptions for Umbrella Studies as above) e.g. if an Umbrella/ancillary study accesses these volumes from a particular participant's blood draw, then another or subsequent Umbrella/ancillary study cannot call on that participant's bloods concurrently or on a future occasion.

   (b) Any further volumes of blood available for Umbrella/ancillary studies will be reviewed annually prior to each round of the Blood Competition.

   (c) A policy for dealing with the bloods remaining in the repository at the end of clinical center funding (in 2005) but before the end of Clinical Coordinating Center funding (in 2007) will be formulated at a later date. The policy will take into account whether the needs of the main study have been satisfied, whether the main study or part of it will be extended, and any relevant NIH/NHLBI-wide policies.

3. ***Timeline:*** The first OS Blood Competition was initiated in Fall, 1998. The next round of competition is being held in 2000, and further rounds will be held annually thereafter. It is possible that a final round will be held in the period 2005-2007 prior to the planned end of the Clinical Coordinating Center funding. Umbrella Studies can apply for bloods at any time, which may or may not coincide with the timeline for the Blood Competition.

4. ***Procedures:*** A process for the OS Blood Competition was first approved by Steering Committee in the Fall of ***1998***. According to this process, the D&A Committee would solicit proposals for the use of bloods at the time interval specified for the Blood Competition. Proposals first had to be approved as an ancillary

study by D&A and separately by NHLBI, then by an expanded D&A Task Force that added the Chair of the OS Committee, NHLBI, and investigators with expertise that may not exist in the D&A alone.

Following approval of the D&A proposal for the Year 2000 OS Blood Competition proposal, the process has been simplified. Proposals will undergo simultaneous review by D&A Committee (expanded to include the Chair of the OS), the CCC, and NHLBI. NHLBI will submit initially approved proposals to EC and SC for final approval. Note that under the simplified process, the ancillary study investigator would send a single proposal to the CCC D&A Coordinator, and would receive notification of the outcome from the Project Office on behalf of the EC/SC.

The current policy contains a number of other elements.

- It comments on various types and sources of samples. Urine samples from the BMB centers will be prioritized for studies on osteoporosis and fractures. Use of genetic material will be governed by the IRB from which the proposal emanates. The competition will focus on nested case-control studies. Use of common controls for multiple studies will be highly desirable. Use of bloods from specific racial groups will be reviewed carefully since the blood resources for these are considerably smaller.

- The policy states that applicants must specify the use of the blood including types and amounts of bloods, numbers of study participants, analyses to be done, which years requested, and for which kinds of study participants.

- A detailed justification for the need for using the WHI blood resource needs to be provided. A completed WHI Ancillary studies application form must accompany the proposal.

5. ***Criteria for ranking proposals***: The criteria will be provided to investigators preparing a proposal. The review will be similar to a NIH Study Section review with the following priorities:

(a) Innovation - new information unique to WHI (10 points)

(b) Relevant to the mission of WHI (10 points).

(c) Parsimonious use of blood (size of individual blood sample aliquot required, number of blood samples, potential for sharing blood)(10 points).

(d) Adequacies of proposed methods and sample size to meet the specific aims of the study (10 points).

(e) Prior use of blood samples by specific center requesting blood (PI of previous submission). Centers that have never previously requested blood, should have priority (5 points).

(f) Willingness to share data with main study (5 points).

Note: ancillary studies that place a burden on the main study, or that request blood that is not available (i.e. reserved for the main study), will not be approved. The maximum score is 50. Proposals with scores below 35 will generally not be approved.

The D&A Committee and the CCC will resolve any “housekeeping” issues such as whether individual studies should be consolidated into one, common controls could be used, or whether a reduced amount of blood could be used, and if necessary obtain revised proposals from the affected studies, before providing the NHLBI and EC/SC with a list of studies recommended for approval. The studies should be ordered by priority score, and will identify the PI of the ancillary study, the WHI PI sponsoring the study, title of study, a one-sentence description of study (if not evident from the title), a list of analytes to be measured, the numbers, volumes and types of blood requested, whether core or additional analytes are requested, and any pertinent comments.

Bloods held for approved but unfunded studies would be re-evaluated by the D&A Committee after three NIH funding cycles or 9 months, whichever is longer.

3.9.2.3 Umbrella Studies

Umbrella Studies are ancillary studies in the OS with some unique features. They had their genesis in the Blood Biomarkers Task Force Report (1994), where it was recognized that certain studies are so closely allied to the main study goals that they

(a) would have been funded out the main study if funds permitted,

(b) needed to be closely integrated into the main study (including adding their data to the main study, and the main study in turn making available questionnaire and core laboratory data to the Umbrella Study investigators), and

(c) (needed to be reasonably comprehensive in respect of each of the main study outcomes.

With this in mind the Task Force initially proposed four nested case control ancillary studies in the areas of Coronary Heart Disease, Breast Cancer, Colorectal Cancer, and Osteoporosis/Fractures. Because of their comprehensive nature these studies subsequently became known as Umbrella Studies. The D&A Committee recognized that Umbrella Studies would have priority access to bloods. The OS Committee subsequently expanded the list of Umbrella Studies (with approval of Council) to add Stroke and Diabetes to the original four. The OS Committee coordinated the identification of Working Groups for the purpose of generating ROI proposals. All investigators were polled for their interest in participating in the Umbrella Studies in three rounds between 1995 and 1996.

The OS Committee recognized that members of the Working Groups were acting on behalf of the entire WHI investigator group, but that Working Group members nonetheless needed to have some priority in the use of these data. The OS Committee proposed a complicated system of dual oversight between OS and P&P to ensure that Working Group members have appropriate representation on writing groups for the eventual publications.

The governance of Umbrella Studies will be simplified to be more consistent with that of other ancillary studies:

(a) The OS Committee will coordinate the formation of Working Groups for the preparation of ROI proposals, will obtain the concurrence EC/SC for the membership of Working Groups, and will advise Working Groups during the preparation of proposals. The OS Committee will monitor the progress of Working Groups, and if necessary recommend to EC/SC the reconstitution of Working Groups if satisfactory progress is not being made in the initial preparation, resubmission, or funding of the ROI. For the purpose of eventual publications arising out of the Umbrella Study, at the appropriate time, the OS Committee will recommend the Chair and members of the Writing Group to the P&P Committee. The proposed members of Writing Group will include investigators who made substantial contributions to the planning, conduct, or analysis of the data.

(b) The “Expanded” D&A Committee will evaluate the Umbrella Study according to the process and criteria noted above. Studies recommended for approval will be forwarded for approval to NHLBI and finally to the EC/SC.

(c) The P&P Committee will constitute the writing groups for publications according to the usual process for any writing group, except that the recommendation of the OS Committee will be taken into account (see P&P policy of authorship on Umbrella Studies for details, as approved at Spring 2000 SC meeting). Essentially, the P&P policy for Umbrella Studies states that there will be up to 8 authors, with the lead investigators nominate up to 4 authors, and the remaining 4 authors will be nominated through the usual P&P process from among WHI investigators.

3.9.2.4 Confidentiality

All blood samples, including buffy coat aliquots used for DNA extractions and genetic studies, are labeled with a blood sample number that contains no personal identifiers. McKesson BioServices, who stores the blood samples, and laboratories performing analyses and/or genetic testing on the blood specimens have access to only the blood sample number. Laboratories report the results by the blood sample number.

CCC and CC data containing personal identifiers are stored in password-protected databases on separately password-protected networks. *Form 100-Blood Collection and Processing* provides the only link between the blood sample number and any participant information. At the CCC, the blood sample results are stored separately from the *Form 100* data. CCs responsible for an ancillary study may receive laboratory data directly from a laboratory, and these CCs store the laboratory data separately from the personal identifiers in WHILMA (WHILMA does not provide a mechanism for Clinical Centers to store the laboratory data in WHILMA).

3.9.2.5 Informed Consent

NHLBI has reviewed all current IRB-approved Clinical Center and Clinical Coordinating Center informed consent documents for adequacy in regard to use of stored blood samples including buffy coat specimens for WHI study purposes. All the informed consents allow for the use of bloods for WHI study purposes, and the confidentiality of data from laboratory analyses are the same as for other WHI data (see above). None of the informed consents make specific provision for the sharing of data with entities or persons not connected with WHI. With one exception, all the informed consents allow for DNA analyses without the need for reconsenting. The one exception has been asked to raise the issue with its IRB to bring the informed consent in line with other clinical centers.

3.9.3 Clinical Trial

The DSMB has indicated that it would be unlikely to approve the release of intermediate outcome data (including blood biomarkers by treatment assignment) prior to the end of the main study (however, exceptions may be made for safety analyses). Therefore, timing of ancillary studies using blood biomarkers would have to coincide with planned release of main study data in the period of 2005-2007. In practical terms, this means that proposals for blood biomarkers could be considered from 2001 onwards, with the proviso that publication of results would need to be coordinated with the main study results. Note that while the SC has approved the Summary of Policy and Procedures for Access to Samples in the WHI Blood Repository, it has not made a specific decision about access to Clinical Trial bloods. The FY2000 Blood Competition is restricted to OS samples. The sections below assumes the feasibility of expanding the blood to the CT starting in 2001.

3.9.3.1 Sampling Frame, Volumes, and Objectives of Blood

Every CT participant has a fasting blood draw at baseline and at 1 year. In addition, a 6% cohort (identified at baseline) has fasting blood draws at years 3, 6, and 9.

(a) The baseline blood samples are intended for analysis of study outcomes in subgroups, and future explanatory nested case-control studies within treatment groups.

(b) The Year 1 bloods are intended for future explanatory nested case-control studies relating short-term treatment effects (between baseline and Year 1) to subsequent clinical outcomes.

(c) The 6% subsample of CT participants is intended to describe the baseline characteristics of the study population, and to describe the group treatment effects and/or secular trends in the subsample cohort over the duration of the trial. The subsample is stratified by HRT/DM study component and is oversampled for minority groups. It is anticipated that the subsample will comprise the following: DM participants: 965 white (only 500 initially analyzed), 501 black, 328 Hispanic, 214 Asian/Pacific Islander, 90 Native American; HRT participants: 1067 white (only 500 initially analyzed), 533 black, 353 Hispanic, 198 Asian/Pacific Islander, 55 Native American. The 6% subsample also completes the 4-Day Food Record, allowing correlation of nutrient intake by self report with blood biomarkers.

The CT bloods at baseline and at 1 year are identical to those for the OS baseline. The CT bloods in the 6% subsample at years 3, 6, and 9 omit RBCs and buffy coats. The blood volume taken is 45 ml, and after processing the following aliquots are stored for each participant:

- 4 x 1.8 ml vial of serum
- 3 x 1.8 ml vials of citrated plasma
- 3 x 1.8 ml of EDTA plasma
- 1 x 1.8 ml RBC (from EDTA tube)
- 2 x buffy coats (EDTA and citrate tubes)

Note that all CT participants also have a WBC, hematocrit, and platelet count performed at baseline, and these data are entered into the database.

Maximum volumes are: 7.2 ml serum, 10.8 ml plasma (citrate or EDTA), 2 buffy coats, 1 RBC at baseline, plus similar amounts at 1 year in all CT participants. The 6% subsample in years 3, 6, and 9 are of similar amounts of serum/plasma, no buffy coats or RBCs. Note that some samples are incomplete.

1. ***Core Analytes:*** Core analytes are blood variables that will be performed in the 6% subsample, and in nested case-***control*** studies, as part of the main study because they are expected to have a relationship to the main study outcomes and to the study treatments. The core analytes will be repeated at Year 1, and will be run concurrently with the baseline samples. The major core analytes were defined in the RFP and subsequently modified according to the recommendations of the Biomarkers Task Force (1994). The core analytes are:

   - Lipids: serum cholesterol, triglycerides, LDL-C, HDL-C, HDL-2, HDL-3, Lp(a)
   - Coagulation: fibrinogen, factor VII
   - Antioxidants: tocopherol, carotenoids
   - Carbohydrate metabolism: glucose, insulin

2. ***Additional Analytes:*** The Biomarkers Task Force and later the D&A Dietary Biomarkers Subcommittee recommended that certain additional analytes be measured in smaller subsamples of approximately 300 CT participants, preferably drawn from within the 6% subsample. These recommendations were accepted by Council with a number of minor modifications. The additional analytes are:

   - DM at baseline, years 1, 3:
     Folate, B6, B12, homocysteine, serum/plasma fatty acids, selenium.
   - DM at baseline, years 1, 3, 6, 9:
     Estrone, estradiol, %free estradiol, % bioavailable estradiol, estrone sulfate, sex hormone binding globulin, DHEA-S, free testosterone, androstenedione, prolactin.
   - HRT at baseline, year1:
     PAI-1.
   - DM and HRT at baseline, year 1:
     LDL oxidation status (if feasible).
   - DM and HRT at baseline, year 6:
     ferritin

- DM and HRT at baseline, years 1,3:
  Apo A-1, apo A-IV, apo B, apo C-II, LDL subfractions, HDL-triglycerides, cholesteryl esters and triglycerides in VLDL and LDL, C-II in HDL fraction, and ratio of HDL C-III to total CIII.
- DM, HRT, Ca/D at baseline, years 1, 3:
  25-OH vitamin D

It is anticipated that the core analytes and certain additional analytes will be measured as explanatory variables in intervention-outcome analyses when sufficient cases have accumulated, or for safety reasons.

The WHI Central Laboratory (Medical Research Laboratories, a subcontractor the Clinical Coordinating Center) has assayed the designated core analytes at baseline and year 1 in the 6% subsample. It has not been determined that measurement of all additional analytes falls within the workscope of the Central Laboratory; however a laboratory has been identified and subcontracted for the sex hormone analyses. Thus, it is possible that some additional analytes may be measured as part of the funding of an ancillary study, or alternatively as part of the funding of the Central Laboratory. Measurement of certain additional safety analytes recommended by DSMB and by the Blood Biomarkers and Genetics Working Group (CVD Biomarker Study) has been approved by the Steering Committee.

As in the OS studies the core analytes and additional analytes could potentially be made available to ancillary study investigators. In return, ancillary study investigators would be asked to make their results available to the main study. Conditions would be similar to those pertaining to OS studies, however in addition the DSMB will make a recommendation on the timing of the release of data by treatment assignment.

3. ***Volume of blood reserved for core analytes and additional analytes:*** Based on the 1994 Biomarkers Task Force estimates, the following types and volumes of blood are reserved for current and future main study purposes (note: similar amounts are reserved for baseline and year 1 bloods):

   - Serum: 3 x 1.8 ml
   - Citrate: 2 x 1.8 ml
   - EDTA: 2 x 1.8 ml
   - Buffy coat: 1 vial

4. ***Volume of blood potentially available for ancillary studies:*** By difference, the maximum types of blood and volumes available from each of the baseline and Year 3 sampling periods are:

   - Serum: 1 x 1 8 ml
   - Citrate: 1 x 1.8 ml
   - EDTA: 1 x 1 8 ml
   - Buffy coat: 1 vial
   - RBC: 1 vial

3.9.3.2 Ancillary Studies

1. ***Volume available for ancillary studies:*** Current D&A Policy as approved by Council does not specify the volume of blood available for ancillary studies, or whether the policy applies to baseline bloods only. The policy does state that bloods for ancillary studies have a lower priority than bloods reserved for main study purposes. Core analytes, safety analytes, and the additional analytes have the highest priority.

2. ***CT Blood Competition:*** The policy for access to CT bloods needs to be more restrictive than that for OS bloods, since the main study must be assured of access to case samples for core analytes and other explanatory or safety analytes. Note that the 6% sample bloods have been set aside for specific core and additional analytes.

(a) For the first two rounds of the competition for CT bloods (in 2001 and 2002) no more than 1.8 ml total of serum and/or plasma from the baseline and/or Year 1 blood draw will be made available to an ancillary study, with the exception being ancillary studies that undertake to measure (and make available) the designated additional analytes. In addition, one buffy coat and the RBC sample from each of the baseline and Year 1 bloods would be made available.

A further guideline is needed to protect a particular participant's sample from being called on by multiple studies, each of which may be within the guidelines in the preceding paragraph. This further guideline states that the bloods dispensed from the repository for an individual participant would be limited to 1.8 ml total of serum and/or plasma (with the exception noted above) e.g. if an ancillary study accesses these volumes from a particular participant, then another or subsequent ancillary study could not call on that participant's bloods concurrently or on a future occasion.

(b) Any further volumes of blood available for ancillary studies would be reviewed again in 2003 prior to the third round and before each subsequent round of the competition for CT bloods.

(c) A policy for dealing with the bloods remaining in the repository at the end of clinical center funding (in 2005) but before the end of Clinical Coordinating Center funding (in 2007) will be formulated at a later date. The policy will take into account whether the needs of the main study have been satisfied, whether the main study or part of it will be extended, and any relevant NIH/NHLBI-wide policies.

3. ***Timeline:*** CT Blood Competition will ***be*** held in 2001, and annually thereafter. It is possible that a final round will be held in the period 2005-2007 prior to the planned end of the Clinical Coordinating Center funding.

4. ***Procedures:*** The process for the CT Blood Competition is similar to that of the OS competition, except that a final layer of DSMB review will be added, and in almost all cases publication will be delayed to the end of the main study. D&A Committee would solicit proposals for the use of bloods at the time interval specified for the ***Blood*** Competition. Proposals will undergo simultaneous review by D&A Committee, the CCC, and NHLBI. NHLBI will submit initially approved proposals to the DSMB, EC and SC for final approval. Note that under the simplified process, the ancillary study investigator would send a single proposal to the CCC D&A Coordinator, and would receive notification of the outcome from the Project Office on behalf of the EC/SC.

The current policy contains a number of other elements.

- Urine samples from the BMD centers will be prioritized for studies on osteoporosis and fractures. Use of genetic material will be governed by the IRB from which the proposal emanates. The competition will focus on nested case-control studies. Use of common controls for multiple studies will be highly desirable. Use of bloods from specific racial groups will be reviewed carefully since the blood resources for these are considerably smaller.

- Applicants must specify the use of the blood including types and amounts of bloods, numbers of study participants, analyses to be done, which years requested, and for which kinds of study participants.

- A detailed justification for the need for using the WHI blood resource needs to be provided. A completed WHI Ancillary studies application form must accompany the proposal to D&A Committee.

5. ***Criteria for ranking proposals:*** The criteria will be provided to investigators preparing a proposal. The review will be similar to a NIH Study Section review with the following priorities:

(a) Innovation - new information unique to WHI (10 points).

(b) Relevant to the mission of WHI (10 points).

(c) Parsimonious use of blood (size of individual blood sample aliquot required, number of blood samples, potential for sharing blood)(10 points).

(d) Adequacies of proposed methods and sample size to meet the specific aims of the study (10 points).

(e) Prior use of blood samples by specific center requesting blood (PI of previous submission). Centers that have never previously requested blood, should have priority (5 points).

(f) Willingness to share data with main study (5 points).

Note: ancillary studies that place a burden on the main study, or that request blood that is not available (i.e. reserved for the main study), will not be approved. The maximum score is 50. Proposals with scores below 35 will generally not be approved.

The D&A Committee and CCC will resolve any "housekeeping" issues such as whether individual studies should be consolidated into one, common controls could be used, or whether a reduced amount of blood could be used, and if necessary obtain revised proposals from the affected studies, before providing the EC/SC with a list of studies recommended for approval. The studies should be ordered by priority score, and will identify the PI of the ancillary study, the WHI PI sponsoring the study, title of study, a one-sentence description of study (if not evident from the title), a list of analytes to be measured, the numbers, volumes and types of blood requested, whether core analytes are requested, and any pertinent comments.

Bloods for approved but unfunded studies would be re-evaluated by the D&A Committee after three NIH funding cycles or 9 months, whichever is longer.

Following D&A and CCC review and recommendation, the NHLBI and the DSMB will review the ancillary study for compliance with the main study goals, in particular whether the applicant agrees to conditions safeguarding the integrity of the main study. Unblinding of investigators and publication of unblinded results will generally not be permissible prior to the publication of the main study results. Once a proposal has passed these hurdles, final approval rests with the EC/SC.

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Section 3
Study Policies

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