Study of Osteoporotic Fractures
Principles and Procedures for Ancillary Studies and Proposals for Additional Funding
June 2006

I. Introduction

These principles and procedures have been adopted by the SOF Steering Committee to address the approval of proposals for ancillary studies and proposals for additional funding. The proposals for additional funding apply both to situations where new data is being collected or analyzed, such as ancillary studies, and to situations where no new data is to be collected or analyzed but additional funding is required.

II. Ancillary Studies

A. Definition of an Ancillary Study

An ancillary study is defined as one that involves participants in the Study of Osteoporotic Fractures and requires procedures or measurements that are not included in the protocol for the main study. There are slightly different guidelines for the approval of ancillary study proposals that will only be conducted at the investigator's own clinical center, and some additional requirements for the approval of ancillary study proposals that involve the use of biochemical samples, such as serum, urine, or DNA.

Studies that generate new data from existing measurements (such as the reading of x-rays or CT scans) are not ancillary studies for the purposes of these guidelines.

B. Criteria for Ancillary Studies

SOF investigators and investigators without an affiliation with SOF may propose ancillary studies. There must be at least one SOF principal investigator and at least one member of the Coordinating Center included among the investigators of any ancillary study.

Investigators are encouraged to propose and conduct an ancillary study either at their own site or in cooperation with other sites, as long as it meets the following criteria:

- it would not interfere with the recruitment of participants for the main study
- it would not interfere with the collection of data planned for the main study
- it would not impose substantial burden on participants in the study or staff of the clinics or Coordinating Center (substantial amounts of new data will generally require funding for more staff and additional visits)
- the research question is worthwhile
- the methods of the study are scientifically rigorous.

C. Guidelines for Ancillary Study Proposals

An investigator who wishes to conduct an ancillary study must submit a formal proposal to the SOF Steering Committee. The proposal, generally 3-5 pages in length for studies not involving biochemical samples, and 5-7 pages in length for studies involving biochemical samples, should include the following elements:

- the research question(s) with clearly stated hypothesis
- a list of investigators who will be actively involved in the ancillary study
- the background and rationale for the study, including references
- the methods and procedures to be employed
- if data would be collected, a plan for data collection and analysis (including who will be responsible for collecting and analyzing the data)
- the sample size required to answer the research question (including the assumptions underlying these estimates)
- an estimate of the impact of the study on the main trial (e.g. staff and participant time, etc.)
- a proposal for how to approach any IRB/consent issues
- for studies involving biochemical samples: impact of the study on existing biochemical samples, aliquoting, etc. Note: There are limitations on requests for blood for hip fracture and breast cancer cases. If you are requesting use of these specimens, please add a note addressing this point.
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E. Use of SOF Breast Cancer and Hip Fracture Blood Specimens

The following guidelines apply to ancillary study proposals requesting the use of SOF Breast Cancer or Hip Fracture Blood Specimens:

- a SOF PI must serve as a co-sponsor
- proposal must be supported by preliminary results; proposals for preliminary data will not be approved.
- proposals that only confirm what is already established will not be approved.
- proposals that require ≥ 1 ml will not be approved, unless the study is exceptional and compelling.
- proposals should specify that the technology proposed requires the minimum amount of biospecimens necessary
- proposed studies should have adequate power, but may not use serum from more than half the available breast cancer cases after that collection
  - Proposals should use 2 or 3 non-cases per case to increase power.
- proposals must explain why the cases must include cases with joint outcomes (eg, breast cancer and hip fractures or breast cancer and strokes)
  - The SOF Steering Committee will analyze the characteristics of those who had just one outcome and those who had joint outcomes to help determine whether exclusion of cases with 2 outcomes would importantly bias the results.
  - Proposals should consider a design that does not include breast cancer or hip fracture cases within the non-cases.

The SOF Steering Committee will reserve 2 ml (from existing 12 ml) from all breast cancer and hip fracture cases for studies after 2010.

F. Review Process for Ancillary Study Proposals

All ancillary study proposals will be reviewed by the SOF Steering Committee, through electronic balloting, during monthly SOF Principal Investigator calls or during annual Steering Committee meetings. Additional external reviewers with related expertise may be asked to review proposals at the discretion of the Steering Committee. Approval from four out of the five Steering Committee members is required fro the approval of an ancillary study.

There are two slightly different review procedures for ancillary study proposals, depending on where the study is going to be conducted:

1. **Studies to be conducted only at the principal investigator's clinical center**
    a. Ancillary study proposals that will be conducted only at the principal investigator's clinical center will not require the approval of the SOF Steering Committee. However, proposals for these studies should be sent to the Coordinating Center so that they can distributed to the Steering Committee.
    b. Ancillary study proposals conducted only at the principal investigator's clinical center that involve locally stored biospecimens will require approval by the SOF Steering Committee.

2. **Studies to be conducted at more than one clinical center**
    a. Ancillary study proposals that will be conducted at more than one clinical center will require the approval of the SOF Steering Committee.

The SOF Steering Committee may request additional information, or the refining or redefinition of the research question. The committee will also address whether the proposal overlaps with the main study or any approved ancillary studies. If there are strong concerns expressed by members of the committee, the proposal will be discussed further on a monthly SOF Principal Investigator call or during the annual Steering Committee Meeting.

After an ancillary study has been approved, it will be assigned a tracking number, and will be circulated to all SOF investigators.

G. Changes after Approval

If substantial changes in the design of the protocol or in the potential impact of the protocol on the main study occur after approval, then the investigators must submit a revised protocol to the SOF Steering Committee for review.

The committee may, by majority vote, terminate an ancillary study if it judges that a study has become too burdensome or its scientific value has diminished, or it has failed to make substantial progress toward the completion of its goals.

H. IRB Approval
The appropriate institutional review boards must eventually approve all ancillary studies before they are performed, but IRB approval is not required to submit a proposal.

I. Financial Support
Approval by the SOF Steering Committee does not imply that financial supporter time for data analysis will be provided. All ancillary studies must be approved by the SOF Steering Committee before any proposal for funding is prepared. Proposals for funding must include coverage of all relevant costs, including:

- costs of realiqoting specimens
- increased costs of storing the new aliquots
- plan for returning unused specimens and covering the costs of it's storage.
- clinical center investigators
- coordinators and staff for data collection
- procedure-related costs
- equipment and supplies needed at the clinic
- Coordinating Center and data management costs

Proposers should allow at least 8 weeks between submission of the ancillary study proposal to the Ancillary Study Committee and the funding application deadline.

J. Data Disposition
All data collected in ancillary studies will be included in the SOF database. The database will be made available to all SOF investigators. A timeline for sending the data to the Coordinating Center should be included in the ancillary study proposal. The main SOF investigator named in the proposal will arrange for analysis of the data by one of the SOF analysts.

K. Analysis Plans and Publications Resulting from Approved Ancillary Studies
At least one analysis plans related to the approved ancillary study must be submitted for review by the SOF Publications Committee once funding has been received. Analysis plan proposals as well as any resulting abstracts or publications must proceed through the normal SOF analysis plan and publications approval procedures. Results of the ancillary study must be published regardless of whether they are positive or negative. Please see the SOF Publications Guidelines for more information on these procedures.

L. Periodic Review of Approved Ancillary Study Status
Every six months, the primary investigator on each approved ancillary study will be asked to provide a one-page summary of the status of the study. The status of the studies will be reviewed and discussed at each Steering Committee Meeting. If there is no progress on a plan for a year, or if serious conflicts with the specific aims or daily

conduct of the study arise, the SOF Ancillary Studies Committee may vote to withdraw approval of the plan.

III. Proposals for Additional Funding (Including Ancillary Studies, NIH Grants, and Other Grants)

These guidelines apply to all proposals for funding, even if no additional data are to be collected. Proposals for additional funding will be handled similarly to ancillary study proposals as described above, with the following modifications. A brief protocol, as described above, should be submitted to the Steering Committee before any proposal for funding is developed. This brief protocol should be approved by the Steering Committee before a proposal for funding is prepared.

After a proposal for funding has been prepared, it should be reviewed and given final approval by the Steering Committee before being submitted for funding. To avoid delay in the preparation and submission of proposals, this final approval should generally be given to a relatively mature, but not necessarily final, draft of the proposal. All members of the Steering Committee should receive a copy of the final submission. The Coordinating Center and Steering Committee should be regularly updated on the status of any funding applications or proposals.