

June 2005

Guidelines for use of the Health Professionals Follow-Up Study: External collaborators.

A. Submitting a Proposal to the Advisory Committee.

1. Any investigator wishing to develop a collaboration with the Health Professionals Follow-Up Study (HPFS) Research Group to use the HPFS data should first send a two-page description of the proposed analyses ("letter of intent") to Dr. Walter Willett, Principal Investigator. If a project is judged feasible (given HPFS database resources), of substantial scientific interest, and is not currently under consideration by an HPFS Investigator (typically listed as a specific aim of a submitted or funded grant), the investigator will be invited to submit a detailed proposal to the HPFS Advisory Committee. The format of the letter of intent and full proposal are described in detail below.

2. Letter of intent. The letter of intent should briefly outline the hypothesis being proposed, its significance, the reason for proposing use of HPFS data, and required covariate data. Letters of intent can be submitted at any time throughout the year. Within approximately 14 days, the applicant will be notified whether submission of a more detailed proposal would be appropriate.

The reasons for proposing use of the Health Professionals Follow-Up Study (HPFS), rather than another data source, must be clearly described. Although the HPFS is a unique resource, it is heavily used and added demands on investigator time must be clearly justified. Therefore, the HPFS data will be used for analyses where other studies, cannot provide adequate or similar information. In addition, proposals to evaluate highly speculative hypotheses are not considered appropriate and will not be approved by the Advisory Committee. Finally, analyses which are either already funded or have been proposed by HPFS investigators will not be considered for approval by the Advisory Committee, which provides ongoing input to the development of specific aims for HPFS studies.

3. Study proposal. Full study proposals will be reviewed by the Advisory Committee three times per year. Submission deadlines are February 15, June 15, and October 15. The proposal's format should be similar to an NIH grant (i.e., specific aims, background and significance, preliminary studies and methods) but should be no longer than 10 pages in length.

4. It is anticipated that Advisory Committee decisions will be made four to eight weeks of proposal submission. The Advisory Committee will decide to accept, accept pending revisions, or reject a proposal. For either of the latter two outcomes, a summary of the reasons for the Advisory Committee decision will be provided. An "accept pending revisions" will be given if the proposal has considerable scientific merit, yet one or more issues need to be addressed before the project can proceed. Arrangements will be made to provide an expedited review of a revised proposal, which addresses the concerns of the Advisory Committee.

For proposals that will require the development of funding outside the proposing organization, the approval process described above must be factored into the timing of any grant application. The Advisory Committee and HPFS Investigators cannot take responsibility for missed deadlines.

B. Conducting Studies Using the HPFS Archive.

1. The exact nature and scope of the project must be described in a written collaborative agreement and signed by the external collaborator, the primary HPFS investigator, and a representative from each investigators institution. Use of data (or other covariate data) from the HPFS cohort is limited to the defined, specific project for which the Advisory Committee approval was obtained. If further research or analytic activities develop from the original project, the external collaborator must obtain appropriate approval for such activities. In signing the collaborative agreement, external collaborators also will be confirming that they have read these guidelines ("Guidelines for use of the Health Professionals Follow-Up Study data") and both understand and agree to comply with them.

2. Since no funds have been allocated to manage the development of these outside collaborative arrangements, other than those associated with the Advisory Committee, all costs must be borne by the collaborating outside investigators institution. Unless the initial development and review of the proposal requires substantial data exploration to determine feasibility, it is not anticipated that this cost would exceed \$5000/proposal. The actual cost will be based on the time required of an HPFS Investigator and programmer to determine approximate case numbers that might be considered appropriate for the proposed analyses and related exposure distributions.

3. Outside collaborators must provide a draft of any grant proposal (e.g., NIH grant) to the collaborating HPFS investigator at least two months prior to the application due date. This will allow the HPFS investigator an opportunity to provide feedback, and will provide time to obtain any additional data (e.g., other exposure distributions) that will maximize the probability of funding for the proposal. In keeping with the policies of the Harvard School of Public Health, the final grant proposal must be reviewed by Dr. Walter Willett, Chair of the Department of Nutrition and Dr. Eric Rimm, Director of the Health Professionals Follow-Up Study, at least 10 business days before submission. Failure to meet this deadline will result in delay of submission. This institutional policy also is followed by all HPFS investigators and cannot be circumvented. The primary HPFS investigator will provide a letter of support to the external investigator to be included in the application indicating Health Professionals Follow-Up Study interest in collaborating on the proposed study.

4. Study costs

(a) External collaborators must provide funds to cover the cost of initial programming needed to identify cases and exposure distributions.

(b) The cost of all pilot studies required to determine the feasibility and validity of the proposed project must be assumed by the potential external collaborator.

(c) At least one Health Professionals Follow-Up Study investigator must be included as a co-investigator (with appropriate time commitment) on any grant proposal where use of HPFS data is proposed. Any nonacademic outside user (e.g., from a private company) similarly must be able to provide salary support for an investigator. The level of effort will vary according to the size and complexity of the project but will be expected to range from 5% to 10% FTE per year.

(d) To insure integrity of the Health Professionals Follow-Up Study data, it is the policy of the HPFS that no data leave the Harvard School of Public Health. Secondly, because of the

complexity of the database and the HPFS Investigators' knowledge of the strengths as well as the limitations of these data, substantial input is required of HPFS Investigators to insure both valid and maximal use of the available data. For these reasons, a data analysis center is being created to provide data analyses for all outside collaborators. Analysis plans will be drawn up by the outside collaborator in conjunction with the primary HPFS investigator; these plans will be given to the statistician who will oversee all analyses. To cover the costs of needed complex programming and data management, each study must include 5% FTE statistician time and 20% FTE programmer time.

(e) The arrangement for payments will be through formal subcontracts with the Harvard School of Public Health in which full overhead as approved by NIH will be considered a direct cost to the proposing institution cost base.

5. Human Subjects considerations

(a) All projects must receive approval from the Harvard School of Public Health Human Subjects Committee prior to implementation.

(b) As analyses of genetic susceptibility to disease are associated with complex ethical considerations, a full discussion of the ethical implications of these analyses must be part of the initial proposal. The HPFS investigators and/or the Advisory Board would normally consult prior to seeking approval from the Harvard School of Public Health Human Subjects Committee. Investigators should be aware that analyses, which identify participants at very high risk of disease, are particularly problematic in this regard.

6. The programs used for analysis must be carefully reviewed and approved by an HPFS epidemiologist and statistician in addition to the study programmer and the external collaborating investigator. Importantly, the sign off must be by a HPFS investigator who understands how the cases and population for analysis are being defined, is familiar with HPFS variable definitions, and can understand the code generated by the programmer.

7. A proposed timeline for completion of projects should be discussed prior to submission of any grant. All projects need to be completed within the constraints of the current HPFS system. Although additional staff may be hired if they are needed consistently, it is not possible to substantially increase (and then decrease) staffing levels for any single project. HPFS facilities do not allow for such staffing changes and it is not possible to adequately train new technicians in a sufficiently short period of time to allow such changes. At the beginning of a project, external collaborators should review with the HPFS a proposed schedule for project completion and may contact the Project Director to discuss study progress.

8. The external collaborator must agree to keep the HPFS investigators updated on the progress of the study by providing either a written or verbal report at least every 6 months. Failure to adhere to a reasonable progress schedule (as assessed by the Advisory Committee) could lead to termination of the collaborative relationship with no further data tables or additional analyses provided.

C. Data Analysis and Publication Issues.

1. The external collaborating investigator should forward all analysis results to the Health

Professionals Follow-Up Study. All primary data sets of laboratory results will be maintained on the Channing SUN computer system.

2. All data analyses will be conducted on the HPFS computer system. The most efficient way for these analyses to be accomplished will be for the outside investigator and the collaborating HPFS investigator to agree on the analysis plan in advance (to whatever extent possible). The external collaborating investigator will provide to the statistician a set of data analysis requests and a series of empty tables that indicate how the results are to be presented. The HPFS data analysis center will proceed to complete the analyses and return the completed tables to the collaborating investigator. In completing the analysis plan, the HPFS investigator also will work as needed with the statistician in supervising the HPFS programmer assigned to the project.

3. At least one member of the HPFS Investigative team will be a coauthor on any manuscript resulting from this collaboration and, as such, will need to sign-off on any manuscript prior to its submission for publication. This will take the form of a brief note indicating review and approval of the final manuscript by the HPFS Investigator; this note will be attached to the manuscript when sent for Channing Review. All manuscripts must be submitted for review to the Channing Laboratory and the Department of Medicine at the Brigham and Women's Hospital ("Channing Review"). This additional review also is required of all HPFS investigators. External investigators should plan on the entire process taking at least 4 weeks (and longer if there are issues to be resolved concerning analysis or interpretation of the data). Any initial presentation of these data at meetings also must receive sign-off from the designated HPFS collaborating investigator(s).

4. Any dispute regarding data interpretation may be brought to the Advisory Committee for consideration. Where appropriate, the Advisory Committee will seek additional consultation from independent experts. Since the Advisory Committee meets as a group only once per year, considerable delay in coming to a resolution could occur. Therefore, it behooves all collaborating investigators to work closely with the designated HPFS investigator in resolving any dispute. Final decisions rest with Dr. Willett, the HPFS Principal Investigator, in consultation with the Advisory Committee.