Guidelines for External Collaborators: Use of the Nurses' Health Studies Archived Data

A. Submitting a Proposal

A.1. Letter of intent: Investigators wishing to develop a collaboration with the Nurses' Health Studies Research Group to use the data archive are asked to initially submit a brief (2-page) description of the proposed project ("letter of intent") to Dr. Francine Grodstein, NHS Director (fgrodstein@partners.org) and/or Dr. Healther Eliassen, NHSII Director (nhahe@channing.harvard.edu) as applicable. The letter of intent should briefly outline the following:

- Hypothesis being proposed
- Scientific significance of the project
- Cohort participant data variables required for analysis
- Reasons for proposing use of NHS/NHSII data, rather than another source

Although the NHS data are a unique resource, it is heavily used and added demands on staff and investigator time must be clearly justified. Therefore, these data will only 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.

A letter of intent may be submitted at any time throughout the year. It will be reviewed by Dr. Grodstein and/or Dr. Eliassen and the NHS team of investigators at a regular bi-weekly study meeting. If a project is judged feasible (given database resources), of substantial scientific interest, is not currently being pursued by another investigator, and is not currently under consideration (typically listed as a specific aim of a submitted or funded grant), the letter of intent for collaboration will be approved. It is also possible that the applicant will be asked to submit additional information if it is unclear from the letter whether the research fulfills requirements. The applicant will be notified of the decision within approximately 14 days after the letter of intent was submitted.

A.2. Study proposal and appeals: If the proposed investigation outlined in the letter of intent is rejected and the applicant does not agree with the reason for this decision, the applicant can appeal the decision by submitting a proposal to the NHS External Advisory Committee (submit through Dr. Grodstein or Dr. Eliassen). Submission deadlines are February 15, June 15, and October 15. The format of the proposal 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.

It is anticipated that the Advisory Committee's decision will be made within 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 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 NHS investigators cannot take responsibility for missed deadlines.

B. Conducting Studies Using the NHS Data Archive

B.1. Collaborative agreement: If the proposal is approved, a primary NHS investigator will be identified to work with the external collaborator to facilitate the research. The exact nature and scope of the project must be described in a written collaborative agreement and signed by the external collaborator and the primary NHS investigator. Use of data from the NHS cohort is limited to the defined, specific project for which 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 agreement, external collaborators also will be confirming that they have read the guidelines outlined in this document and both understand and agree to comply with them.

B.2. Preliminary data: An NHS investigator and programmer will provide approximate case numbers, exposure distributions, and other related data that may be used for preparing a grant application. Since no funds have been allocated to manage the development of these outside collaborative arrangements, all costs for this effort must be borne by the collaborating outside investigator's institution based on the time required to produce the data. No charge will be made for minimal effort.

B.3. Grant funding: Outside collaborators must provide a draft of any grant proposal (e.g., NIH grant) to the collaborating NHS investigator at least one month prior to the application due date. This will allow the NHS investigator an opportunity to provide feedback, and will provide time to obtain any additional data, as noted above, that will maximize the probability of funding for the proposal.

In keeping with the policies of the Brigham and Women's Hospital, the final grant proposal must be reviewed by Drs. Grodstein or Eliassen and Dr. Meir Stampfer, Co-Director of the Channing, at least 10 days before submission. Failure to meet this deadline will result in delay of submission. This institutional policy also is followed by all NHS investigators and cannot be circumvented. The primary NHS investigator will provide a letter of support to the external investigator to be included in the application indicating Nurses' Health Study interest in collaborating on the proposed study.

B.4. Study costs

(a) As noted above (section B.2), external collaborators must provide funds to cover the cost of initial programming by NHS staff, needed to identify cases, exposure distributions or other related data if necessary.

(b) Should substantial pilot research be needed, the cost of all pilot studies required to determine the feasibility and validity of the proposed project must be assumed by the external collaborator.

(c) Because of the complexity of the database and the NHS investigators' knowledge of the strengths as well as the limitations of these data, substantial input is required of NHS investigators to insure both valid and maximal use of the available data. Therefore, at least one NHS investigator must be included as a co-investigator on any grant proposal where use of NHS 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. For more complex investigations, funding for an NHS statistician may also be required.

(d) To insure integrity of the NHS data and comply with privacy commitments for our study participants, it is the policy of the NHS that no data are copied from the Channing computer. Therefore, all analyses must be conducted on our computer system. It is possible for all programming to be done by the external collaborator or a designated person at the collaborating institution. The programmer would need to learn our computer system, data files, and analysis methods, which may require a visit to the Channing for an introductory session. A Data Use Agreement would be signed and proof of Human Subjects certification (such as completion of the CITI course) must be submitted. The programmer would be issued a logon to the Channing computer for remote access. Inevitably, even if outside collaborators do their own programming, some input from Channing programmers is needed, and those costs would have to be covered by the outside collaborator. Alternatively, the external collaborator may pay for the cost of having an NHS programmer do all analyses, if one is available. The cost is dependent upon the complexity of the investigation but is typically about 20% FTE.

(e) The arrangement for payments will be through formal subcontracts with the Brigham and Women's Hospital, including full overhead.

B.5. Human subjects considerations: All projects must receive approval from the Brigham and Women's Hospital Human Subjects Committee prior to implementation. Also, all investigators who have access to NHS data on the computer must complete a Human Subject certification, such as the CITI course.

B.6. Study timeline: 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 NHS 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. NHS 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 NHS a proposed schedule for project completion and may contact the Project Director to discuss study progress.

B.7. Progress reports: The external collaborator must agree to keep the NHS 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.

C.1. Use of NHS Channing computer: As noted above (section B.4.d) , all primary data, computer programs, and analysis results must be maintained on the NHS Channing computer, and all data analyses will be conducted on this computer. SAS is typically used for data analyses. If an external collaborator needs to use a different programming language, this must be discussed with the NHS investigator before analyses begin.

C.2. Analysis plan and procedure: The most efficient way for analyses to be accomplished will be for the external investigator and the collaborating NHS investigator to agree on the

analysis plan in advance (to whatever extent possible). If analyses are being conducted by an NHS programmer, the external collaborating investigator will provide a set of data analysis requests and a series of empty tables that indicate how the results are to be presented. In completing the analysis plan, the NHS investigator will work as needed in supervising the NHS programmer assigned to the project. The external collaborating investigator should forward all analysis results to the NHS investigator for review and discussion.

C.3. Presentation of results: When data tables of results are finalized, these tables and a written abstract will be presented by the NHS investigator at a regular NHS study meeting. This provides an opportunity for other NHS investigators to comment and make suggestions for improvement. Based on the comments, additional analyses may be required. Presentation of results at a study meeting is required for all research that uses NHS data prior to submission for publication.

C.4. Review of computer programs: It is required that the programs used for analysis must be carefully reviewed by an NHS epidemiologist and/or statistician in addition to the study programmer and the external collaborating investigator. Importantly, the sign off must be by a NHS investigator who understands how the cases and population for analysis are being defined, is familiar with NHS variable definitions, and can understand the code generated by the programmer. This program review is required for all investigations that use NHS data, and a specific system is in place for such program review to ensure it is both accurate and timely.

C.5. Authorship and manuscript review: At least one member of the NHS 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. All manuscripts must also be submitted for review to Dr. Meir Stampfer, Co-Director of the Channing, and the Department of Medicine at the Brigham and Women's Hospital ("Channing Review") and approval must be obtained before a manuscript can be submitted to a journal for publication. This additional review is required of all NHS investigators.

C.6. Manuscript disputes: Any dispute regarding data interpretation may be brought to the External 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 NHS investigator in resolving any dispute. Final decisions rest with Dr. Francine Grodstein, NHS Director, and Dr. Heather Eliassen, NHSII Directory, in consultation with the Advisory Committee.