April 4, 2012

Guidelines for use of the Growing Up Today Study: External Collaborators.

A. Submitting a Proposal to the Advisory Committee.

1. Any investigator wishing to develop a collaboration with the Growing Up Today Study (GUTS) Research Group to use the GUTS data should first send a two-page description of the proposed analyses ("letter of intent") to Dr. Stacey Missmer, Principal Investigator (nhlaa @ channing.harvard.edu). If a project is judged feasible (given GUTS database resources), of substantial scientific interest, and is not currently under consideration by an GUTS 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 GUTS 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 GUTS 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 Growing Up Today Study (GUTS), rather than another data source, must be clearly described. Although GUTS is a unique resource, it is heavily used and added demands on investigator time must be clearly justified. Therefore, GUTS 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 GUTS investigators will not be considered for approval by the Advisory Committee, which provides ongoing input to the development of specific aims for GUTS 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 GUTS Investigators cannot take responsibility for missed deadlines.

B. Conducting Studies Using the GUTS 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 GUTS investigator, and a representative from each investigators institution. Use of data (or other covariate data) from the GUTS 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 Growing Up Today 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 GUTS 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 GUTS investigator at least two months prior to the application due date. This will allow the GUTS 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 Brigham and Women's Hospital, the final grant proposal must be reviewed by the Associate Co-Director of the Channing Laboratory (Meir Stampfer, M.D., Dr.P.H.) 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 GUTS investigators and cannot be circumvented. The primary GUTS investigator will provide a letter of support to the external investigator to be included in the application indicating Growing Up Today 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 Growing Up Today Study investigator may be included as a co-investigator (with appropriate time commitment) on any grant proposal where use of GUTS data is proposed. The level of effort will vary according to the size and complexity of the project but will usually be in the 5% to 10% FTE per year.

(d) To insure integrity of the Growing Up Today Study data, it is the policy of the GUTS that no data leave the Channing Laboratory. Secondly, because of the complexity of the database and the GUTS Investigators' knowledge of the strengths as well as the limitations of these data, substantial input is required of GUTS Investigators to insure both valid and maximal use of the available data. For these reasons, a data analysis center (NDAC) 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 GUTS investigator; these plans will be given to the NDAC 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 Brigham and Women's Hospital 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 Brigham and Women's 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 GUTS investigators and/or the Advisory Board would normally consult with the GUTS Ethical Advisory Committee prior to seeking approval from the Brigham and Women's Human Subjects Committee. Investigators should be aware that analyses, which identify women at very high risk of disease, are particularly problematic in this regard.

6. The programs used for analysis must be carefully reviewed and signed off on by an GUTS epidemiologist and statistician in addition to the study programmer and the external collaborating investigator. Importantly, the sign off must be by a GUTS investigator who understands how the cases and population for analysis are being defined, is familiar with GUTS 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 GUTS 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. GUTS 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 GUTS 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 GUTS 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 Growing Up Today Study. All primary data sets of laboratory results will be maintained on the GUTS Channing-SUN computer.

2. All data analyses will be conducted on the GUTS SUN computer (see section B.3.d above). The most efficient way for these analyses to be accomplished will be for the outside investigator and the collaborating GUTS 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 GUTS data analysis center will proceed to complete the analyses and return the completed tables to the collaborating investigator. In completing the analysis plan, the GUTS investigator also will work as needed with the statistician in supervising the GUTS programmer assigned to the project.

3. At least one member of the GUTS Investigative team may 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 GUTS 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 GUTS 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 GUTS 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 GUTS investigator in resolving any dispute. Final decisions rest with Dr. Missmer, the GUTS Principal Investigator, in consultation with the Advisory Committee.