



HARVARD BIOMARKERS STUDY

Harvard Medical School
Brigham and Women's Hospital
Massachusetts General Hospital



Guidelines for Collaborators

INTRODUCTION

The HBS is designed for large-scale testing of well characterized assays. The study is not suitable for small studies aimed at assay development. Thus, assays should be developed, characterized for precision and retest reliability, and miniaturized first in pilot studies. Proposals to evaluate highly speculative hypotheses are not considered appropriate and will not be approved by the Biospecimens Request Access Committee (BRAC). Finally, analyses which are either already funded or have been proposed by NeuroDiscovery Biomarker Investigators will not be considered for approval by the BRAC.

Any investigator wishing to develop a collaboration with the Harvard NeuroDiscovery Center Biomarker Study (HBS) to use data and/or biospecimens should first send a one- to two-page description of the proposed analyses ("study proposal") to Dr. Yuliya Kuras, Project Manager. If a project is deemed feasible, of substantial scientific interest, and is not currently under consideration by a NeuroDiscovery biomarker investigator, the investigator will be invited to submit a detailed proposal to the BRAC. The format of study proposal is described below.

1. REQUIREMENTS

Study Proposal

Study proposals should briefly outline the hypothesis being proposed, its significance, the reason for proposing use of HBS biomarker specimens and required covariate data. Proposals are approximately one- to two- pages in length, and can be submitted at any time throughout the year. Within approximately 14 days, the applicant will be notified whether more information is required, or whether the project has been approved.

The format of the proposal should include specific aims, background and significance, preliminary studies, and methods. A copy of a pertinent NIH or Foundation grant applications can be submitted in place of the study proposal, if the following points are clarified. If biospecimens are requested, the following information must be included within the proposal:

Sample and Data Specifications:

- Type(s) and volume of the biospecimens
- Results of power analysis describing the sample size required, and the predicted effect size.
- A complete list of all required clinical data.
- A description of all covariates.
- Definitions for case and control participants, as well as the number of enrollment visit and follow-up visit data requested (i.e. will the project require biospecimen and/or clinical data from a single time-point, or across multiple study visits).

Assay Specifications:

- Stability of the biomarker for 4 hours in SST and EDTA tubes
 - Blood samples from biomarker participants are transported at room temperature to the HBS laboratory for processing within 4 hours of blood draw, centrifuged and aliquoted into plasma, packed red blood cells, buffy coat and serum and placed in -80°.
- Robust detectability of an RNA biomarker in RNA extracted from Paxgene tubes according to our protocol (e.g. if Taqman QPCR is used, CT values < 35 are mandatory).
 - Samples collected in PAXgene tubes are transferred at room temperature to the HBS laboratory and placed at -4° within 4 hours of the blood draw. RNA is processed within 3-5 days by the biospecimen manager using the PreAnalytix protocol.
- Collaborator assay to be used.
 - All assays must be conducted using the best available technology to insure the appropriate parameter is assayed, the plasma volume required is minimal and the reproducibility is maximized. The volume samples will be determined on a case by case basis. In general, a volume of $\leq 50\mu\text{l}$ will be considered acceptable.
- Reproducibility of the assay.
 - The laboratory conducting the analyses must be able to conduct the assay with a high degree of precision (i.e. low coefficient of variation). The evaluation should be recent and by the same technician who will be conducting the study analyses, if possible.
- Range of biomarker.
 - If there are many biomarkers of interest, knowledge of a usual range in an adult population will be sufficient (e.g., plasma antioxidant levels); in this instance the usual range, how it was determined and in what population should be described briefly. However, for assays where the range may vary substantially by population (e.g., plasma levels of DDE/PCBs), a pilot study may need to be conducted on the HBS samples prior to receiving approval for the final project.
- Stability of the biomarker over time in healthy controls is needed for progression marker candidates.
 - The HBS collects specimens at enrollment and at 2 annual visits. If data is not available on the stability of the biomarker at 2 time points, a pilot study may have to be conducted to assess the stability of the marker.

We ask the collaborators to conduct analyses as a single batch with appropriate masked QC samples added to the batch. If there are a large number of samples being assayed, the precision of the assay must be monitored on an ongoing basis using

masked QC samples. Results from the QC samples must be reported on a batch-by-batch basis to the HBS investigator who will be responsible for monitoring reproducibility.

2. BRAC DECISION

The decision of the BRAC to accept, accept pending revisions, or reject a proposal will be sent to the investigator within 2 weeks of the date the proposal was received. For either of the latter two outcomes, a summary of the reasons for the BRAC's decision will be provided as feasible. 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 BRAC.

3. APPROVED PROJECTS

A written collaborative agreement must be signed by the collaborator and the primary investigator of the HBS, detailing the nature and scope of the project (Appendix I). Use of specimens and covariate data from the HBS is limited to the defined, specific project for which BRAC approval was obtained. If specimens or data are required, the collaborator must obtain appropriate IRB approval for such activities and provide a copy to the HBS. In signing the collaborative agreement, collaborators also will be confirming that they have read these guidelines ("Guidelines for use of the Harvard NeuroDiscovery Center Biomarker Study data") and both understand and agree to comply with them. While HBS always strives to collect the most precise and informed data, this is an ongoing and active biomarkers study, and clinical data and samples may change. HBS provides data "as is," and is not responsible for differences between various data freezes, or changes due to cleaning, locking, or for any other reason.

4. COSTS

User-Pay: The HBS does not receive funds or does not have a mandate from any agency to operate as a tissue and/or data bank for the general research community. Funding for the HBS will be recouped as percentage of our operating costs by cost recovery charges for tissue and/or data transfer. These charges are essential for our continued operation. Tissue and/or data transfer charges are negotiated between the HBS and the requesting researcher and may take the form of a single fee or as a budget line in the researcher's grant-funded research.

- a) Collaborators must provide funds to cover the cost for amending our IRB, initial programming needed to identify cases and exposure distributions.
- b) The pilot studies required to determine the feasibility and validity of the proposed project must be conducted by the

potential external collaborator. A minimal group of specimens are available for pilot studies (see pilot study guidelines).

- c) If specimens are requested, funds must be provided to cover the costs for the biospecimen manager's time retrieving, aliquoting, labeling, barcoding, scanning and shipping of specimens. The level of effort will vary according to the size and complexity of the project. In the case of large studies, the HBS may ask the collaborator to provide temporary personnel to work with the biospecimen manager to aliquot and barcode the samples requested.
- d) At least one HBS investigator may be included as a co-investigator (with appropriate time commitment) on any grant proposal where use of specimens is proposed. The level of effort will vary depending on the size and complexity of the project. Usually the range is from 5% to 10% FTE per year.
- e) Invoice must be paid in full or a PO must be received before release of specimens and/or data. Payment options will be discussed. Wire transfers will not be allowed.

5. HUMAN SUBJECTS CONSIDERATIONS

- a) An amendment to the HBS protocol will be submitted to the Brigham and Women's Hospital (Partner's) Institutional Review Board for approval to share the specimens and/or data with the specific institution.
- b) Please send us your approved IRB protocol containing information regarding the use of de-identified Harvard Biomarkers Study data and biospecimens.
- c) Investigators within the Partner's system will request approval for a secondary use of data/research samples with the Institutional Review Board.
- d) 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.

6. DATA ANALYSIS AND PUBLICATION

The data used for analysis must be carefully reviewed and signed off on by the collaborating investigator and a HBS investigator who understands how the cases and population for analysis are being defined, is familiar with HBS variable definitions, and can understand the code generated by the programmer.

The collaborator must agree to keep the HBS investigator updated on the progress of the study by providing either a written or verbal report and a draft manuscript prior to submission. Failure to adhere to a reasonable progress schedule (as assessed by the BRAC) could lead to termination of the collaborative relationship.

- In order to enrich the HBS database, collaborators may be asked to provide subject data such as APOE genotype or vitamin D levels to be incorporated into the HBS database. Additionally, the HBS reserves the right to request data, such as GWAS, to be made publicly available 3 months after publication.
- Since 2003 the Harvard NeuroDiscovery Biomarker Study investigators have been investing considerable time effort and financial resources (e.g major funding by Harvard NeuroDiscovery Center, as well as major funding obtained by Drs. Scherzer and Hyman from a variety of funding agencies) in the collection, phenotypic characterization, quality control, tracking of biospecimens and clinical data, as well as the maintenance of the biobank. Furthermore, HBS investigators are contributing significant time, effort and expertise to each accepted collaboration to assure appropriate study design, matching, data cleaning, and biospecimen management. Key member/s of the HBS Investigative team will thus be coauthor/s 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.
- Additionally, a large team of neurologists, study coordinators, data managers and biospecimen managers are involved in the day-to-day operations of HBS. Thus, these will be acknowledged in the co-author byline as “The Harvard Biomarkers Study (HBS).” HBS funding information and a list of HBS study investigators and staff must be included in the acknowledgements section of manuscripts that results from this collaboration. The specific funding and personnel details will be made available to collaborators at the time of manuscript preparation.

7. DATA SHARING

Collaborators must return both raw and processed data to the HBS no later than at the time of manuscript submission. If no manuscript is submitted, collaborators must return data within 12 months. This data will enrich the HBS database, and may be used for

secondary analysis by HBS investigators, Harvard Medical School investigators, and outside collaborators.

8. PATENTS

The mission of the HBS is to develop new biomarkers and accelerate their translation into the clinic. Intellectual Property (IP) will be important for attracting diagnostics companies and future investors for developing the candidate biomarker into a clinically useful product.

IP and Patent filings will be governed by standard Partners institutional policies and U.S. Patent Law and reflect the collaborators' and the HBS' respective contributions.

9. REMAINING SAMPLES

Any sample remaining after the completion of the approved laboratory assays should be returned promptly to the HBS biobank.

I have read, understand and agree with these guidelines.

Signature

Date

Printed Name

Institution