

November 10, 2004

NHLBI Framingham Heart Study

Data and Materials Distribution Agreement

The undersigned parties hereby enter into this Distribution Agreement as of the date specified on the final page hereof.

PRELIMINARY STATEMENT

The National Heart, Lung, and Blood Institute (NHLBI), in collaboration with Boston University, has supported collection of blood samples and clinical data from participants in the Framingham Heart Study since 1948. This clinically and genetically well-characterized population is a valuable scientific resource that is maintained under the joint stewardship of Boston University and the NHLBI. Promoting use on a national scale of such a resource will require a large and concerted effort that may exceed the research capacity of currently available investigators in Framingham and other individual study locations. The NHLBI and the researchers it supports have a responsibility to the public, and the scientific community in particular, to encourage as rapid scientific progress as possible using these resources, subject to appropriate terms and conditions. In order to take full advantage of such resources and maximize their research value, it is important that samples and data collected with public funds be made available, on appropriate terms and conditions, to the largest possible number of qualified investigators in a timely manner.

Blood samples and clinical data collected by the Framingham Heart Study have been stripped of all personal identifiers but the confined nature of the geographic area from which these subjects were drawn and the wealth of data available on them in publicly available records would make less difficult the individual identification of some subjects. To protect the confidentiality and privacy of these participants and their families, investigators granted access to these data and materials must adhere to the requirements of this Distribution Agreement. Failure to comply with this Distribution Agreement could result in denial of further access to Framingham samples and data. Violation of the confidentiality requirements of this agreement may leave requesting investigators liable to legal action on the part of Framingham Study participants, their families, or the U. S. Government.

The Framingham investigators (both from Boston University and the NHLBI) have made a substantial long-term contribution in establishing and maintaining the clinical database and the genetic database and samples. The NHLBI and Boston University seek to encourage appropriate collaborative relationships by outside investigators with the Framingham investigators and to ensure that the contribution of the Framingham investigators is appropriately acknowledged.

The NHLBI and Boston University further seek to promote the development of valuable discoveries and inventions beneficial to the public health based upon use of this Framingham Study repository.

DEFINITIONS

For purposes of this agreement,

"Clinical Data" refers to data, and associated records, collected and recorded from Framingham Study subjects through the periodic examinations conducted pursuant to Boston University's contract with the NHLBI.

"Biological Materials" refers to blood samples and products thereof including immortalized lymphocytes and extracted DNA collected and prepared pursuant to Boston University's contract with the NHLBI.

"Genetic Analysis Data" refers collectively to "Molecular Genetic Data" and "Statistical Analysis Data" as these terms are defined below.

"Molecular Genetic Data" consists of data derived from analyses of DNA samples contained in Biological Materials including but not limited to genotyping analysis, anonymous marker polymorphisms, DNA sequence information, mutation analysis and other genetic analyses.

"Statistical Analysis Data" consists of data derived from statistical analyses linking Molecular Genetic Data with Clinical Data including but not limited to genetic linkage analysis, genetic association analysis, transmission disequilibrium analysis, haplotype relative risk analysis and other statistical genetic techniques.

RECIPIENT

_____, a [non-profit] OR [for-profit] corporation organized under the laws of the State of _____ with a principal address at _____

("Recipient") requests access to Framingham Clinical Data, Genetic Analysis Data and Biological Materials at its sole risk.

AGREED TERMS AND CONDITIONS

It is mutually agreed as follows:

1. Biological Material. Boston University and NHLBI, agree to transfer to Recipient Biological Materials described below for use by the Recipient's principal investigator named below ("Principal Investigator") to conduct the research described in paragraph 4 below. These Biological Materials (including numbers of samples and whether samples are unique or immortalized) are described as follows:

2. Clinical Data. Boston University and NHLBI, agree to provide Recipient with Clinical Data described as follows:

3. Genetic Analysis Data. Boston University and NHLBI, agree to provide Recipient with Genetic Analysis Data, if available, described as follows:

_____ Boston University will provide Recipient with the name and address of any and all other Investigator(s) who generated such "Genetic Analysis Data."

4. Research Project.

4.1 The Biological Material, Clinical Data and /or Genetic Analysis Data will be used by Recipient's Principal Investigator solely in connection with the following research project ("Research Project"), specifically described below or in an attached Exhibit A: _____

4.2 This Distribution Agreement covers only the above-described Research Project. Recipient must complete and submit a separate Distribution Agreement for each research project for which Clinical Data and Biological Materials are requested.

5. Non-transferability. This Agreement is not transferable. Recipient agrees that substantive changes made to the Research Project described above, and/or appointment by Recipient of another Principal Investigator to complete the Research Project, require execution of a new Agreement in which the new Principal Investigator and/or new Research Project are designated. Recipient may not distribute Clinical Data, Biological Materials, Genetic Analysis Data, Molecular Genetic Data or Statistical Analysis Data to any other individual or entity, regardless of the intended use of such data or materials, except in connection with the publication of Project results through the usual channels of scientific publication.

6. Conduct of Research Project. The Principal Investigator is responsible for the conduct of the Research Project, and shall be responsible for assuring that all co-investigators comply with the terms of this Agreement.

7. Publication. Prompt publication of the results of the Research Project is encouraged. Recipient agrees to provide to Boston University and NHLBI a copy of any abstract ten (10) days in advance of submission for publication and any manuscript thirty (30) days in advance of submission for publication, in order to permit review and comment and ensure compliance with

the confidentiality requirements of this Agreement.

8. Acknowledgments. Recipient agrees to acknowledge the contribution of Boston University and NHLBI Framingham staff in any and all oral and written presentations, disclosures, and publications resulting from any and all analyses of Clinical Data and Biological Materials.

8.1 Collaborations/Acknowledgments. If the Research Project involves collaboration with Boston University co-investigators, then Recipients will acknowledge Boston University co-investigators as co-authors, as appropriate, on any publication. In addition, the manuscript will be reviewed by NHLBI and by the Boston University/Framingham Study manuscript review process.

8.2 Other Studies/Acknowledgments. If the Research Project does not involve a collaboration with Boston University co-investigators, then the manuscripts, upon submission pursuant to paragraph 7 above, will be reviewed by Boston University and NHLBI for scientific content and consistency of data interpretation with previous Framingham publications. The manuscript shall include the acknowledgement below. [The process for review of manuscripts by Boston University and NHLBI is described in Attachments 1 and 2, respectively.]

"The Framingham Heart Study is conducted and supported by the National Heart, Lung, and Blood Institute (NHLBI) in collaboration with Boston University. This manuscript was not prepared in collaboration with investigators of the Framingham Heart Study and does not necessarily reflect the opinions or views of the Framingham Heart Study, Boston University, or NHLBI."

8.3 Acknowledgments/Genetic Analysis Data. If Genetic Analysis Data are received, the Recipient agrees to acknowledge the contribution of Boston University staff (Framingham Heart Study) and/or the Investigator(s) who derived such data in any and all oral and written presentations, disclosures, and publications resulting from any and all analyses of such Genetic Analysis Data.

9. Non-Identification. Recipient agrees that Biological Material and Clinical Data will not be used, either alone or in conjunction with any other information in any effort to determine the individual identities of any of the subjects from whom Clinical Data or Biological Materials were obtained.

10. Use Limited to Research Project. Recipient agrees that Biological Materials, their progeny, or unmodified or modified derivatives thereof and data derived from statistical analyses of Clinical Data or Genetic Analysis Data will not be used in any experiments or procedures that are not disclosed and approved as part of the Research Project.

11. Use in Human Experimentation Prohibited. Recipient agrees that Biological Materials, their progeny, or unmodified or modified derivatives thereof will not be used in human experimentation of any kind.

12. Compliance with Subjects' Informed Consent. Recipient agrees that Biological Materials, their progeny, or unmodified or modified derivatives thereof will not be used for any purpose

contrary to a subject's applicable signed informed consent document(s). It is the responsibility of the Recipient's Principal Investigator to consult with the Framingham investigators and ascertain, specifically and in detail, the terms and conditions of applicable Framingham Study informed consent documents.

13. No Distribution, Avoidance of Waste, Return of Materials. Recipient agrees to retain control over Clinical Data, Genetic Analysis Data, other statistical analyses data and Biological Material, their progeny, and unmodified or modified derivatives thereof, and further agrees not to transfer Clinical Data, Genetic Analysis Data or Biological Material, their progeny, and unmodified or modified derivatives thereof, with or without charge, to any other entity or any individual. Recipient agrees, in handling the Biological Materials, to make reasonable efforts to avoid contamination or waste of the samples. Recipient agrees not to distribute any results of the Research Project other than through the usual channels of scientific publication and agrees not to distribute any unpublished statistical results of the Research Project. When the Research Project is completed, or three (3) years have elapsed from the effective date of this Distribution Agreement, whichever occurs first, the Biological Material will be returned to Boston University and NHLBI, unless an extension of this Agreement is obtained.

14. Recipient's Resulting Genetic Analysis Data to be Provided to NHLBI/Boston University. Recipient agrees to provide Boston University and NHLBI with a report every twelve (12) months during the term of this Agreement containing Genetic Analysis Data derived by Recipient, in the performance of the Research Project. Such report will cover all Genetic Analysis Data derived by Recipient up to six (6) months before the reporting date. Recipient agrees that Boston University and NHLBI may distribute these data to qualified scientific investigators requesting access through established NHLBI procedures and completing a signed Distribution Agreement comparable to this Agreement. Recipient will provide Genetic Analysis Data, indexed by genotyping ID number in the precise electronic format specified by NHLBI or Boston University. When genotyping has been conducted, DNA marker names and genotype data will be provided for each individual subject as indexed by the Framingham subject ID number; descriptive information about each typed marker that includes standard marker and allele names, absolute distances in Megabases and in Centimorgans, and the source of information used to determine map location will also be provided referenced to the NCBI database, if available. Recipient also agrees to submit all data relevant to errors in family structure, especially paternity, at the time such determinations are made, and to refrain from any disclosure of such data to anyone other than the Framingham Principal Investigator.

15. Costs/No Warranties. Cost for DNA distribution will be borne by the NHLBI at no cost to the recipient for quantities of DNA between 10ng to 10ug per sample, depending upon the needs of the study. Costs are subject to change following written notification from Boston University with the approval of NHLBI. NO WARRANTIES, EXPRESS OR IMPLIED, ARE OFFERED AS TO THE MERCHANTABILITY OR FITNESS FOR ANY PURPOSE OF THE BIOLOGICAL MATERIALS, GENETIC ANALYSIS DATA AND CLINICAL DATA PROVIDED TO RECIPIENT UNDER THIS AGREEMENT, OR THAT THE BIOLOGICAL MATERIALS, GENETIC ANALYSIS DATA OR CLINICAL DATA MAY BE EXPLOITED WITHOUT INFRINGING THE INTELLECTUAL PROPERTY OR PROPRIETARY RIGHTS OF ANY THIRD PARTIES.

16. Recipient's Responsibility for Handling Biological Materials. Recipient acknowledges that Biological Materials may carry viruses, latent viral genomes, and other infectious agents. The Recipient agrees to treat Biological Materials as if they are not free of contamination, and that Biological Materials will be handled only by trained persons under laboratory conditions that afford adequate biohazard containment. By accepting Biological Materials, Recipient assumes full responsibility for their safe and appropriate handling.

17. Non-Endorsement, Indemnification. Recipient agrees not to claim, infer, or imply Governmental endorsement of the Research Project, the entity, or personnel conducting the Research Project or any resulting commercial product(s) except as described in paragraph 8. To the extent permitted by law, Recipient agrees to hold the United States Government, Boston University, and all other investigator(s) who generated Genetic Analysis Data, and the agents and employees of each of them, harmless and to defend and indemnify all such parties for all liabilities, demands, damages, expenses, and losses arising out of Recipient's use for any purpose of Clinical Data, Genetic Analysis Data, and Biological Materials, their byproducts, or modified or unmodified derivatives.

18. Accuracy of Data. Recipient agrees that the United States Government, Boston University, and the other investigator(s) who generated Genetic Analysis Data are not responsible for the accuracy of Genetic Analysis Data provided by other Recipients. The United States Government and Boston University are not responsible for the accuracy of Clinical Data or Biological Materials provided.

19. Recipient's Compliance with IRB Requirements. Recipient acknowledges that the conditions for use of the data and/or Biological Materials have been approved by the Recipient's Institutional Review Board (IRB) in accordance with Department of Health and Human Services regulations at 45 CFR Part 46. Recipient agrees to comply fully with all such conditions and with the subjects' informed consent documents, and any additional conditions that may be imposed by the Boston University Medical Center Institutional Review Board (BUMC IRB). Recipient acknowledges that this project is not eligible for exemption from IRB review. Recipient agrees to report promptly to the BUMC IRB and the NHLBI any proposed change in the research project and any unanticipated problems involving risks to subjects or others. Recipient remains subject to applicable State and local laws and regulations and institutional policies that provide additional protections for human subjects.

20. Amendments. Amendments to this Distribution Agreement must be made in writing and signed by authorized representatives of both parties.

21. Termination. This Distribution Agreement shall terminate three (3) years after the Effective Date unless Boston University, NHLBI and Recipient agree in writing to extend the Agreement. Boston University, in consultation with NHLBI, may terminate this Distribution Agreement if Recipient is in default of any of its conditions and such default has not been remedied within 30 days after the date of written notice by NHLBI and Boston University of such default. Upon termination of this Distribution Agreement, Recipient agrees to return all unused Biological Materials, Genetic Analysis Data and Clinical Data to Boston University. Upon termination of this Agreement Recipient's right to publish the results of the Research Project shall terminate immediately, unless otherwise agreed to in writing by NHLBI and Boston University.

22. Disqualification, Enforcement. Failure to comply with any of the terms specified herein may result in disqualification of Recipient from receiving additional Clinical Data, Biological Materials, and/or Genetic Analysis Data. The United States Government and/or Boston University shall have the right to institute and prosecute appropriate proceedings at law or in equity against the Recipient for violating or threatening to violate the confidentiality requirements of this agreement, the limitations on the use of the data or materials provided, or both. Proceedings may be initiated against the violating party, legal representatives, and assigns, for a restraining injunction, compensatory and punitive damages, mandamus, and/or any other appropriate proceeding in law or equity, including obtaining the proceeds from any intellectual property or other rights that are derived in whole or in part from the breach of the confidentiality requirements or use limitations of this agreement. In addition, Recipient acknowledges that a breach or threatened breach of the confidentiality requirements or use limitations of this agreement may subject Recipient to legal action on the part of Framingham Study subjects, their families, or both.

23. Accurate Representations. Recipient expressly certifies that the contents of any statements made or reflected in this document are truthful and accurate.

24. Prior Distribution Agreements. The following two paragraphs apply only to Recipients that have entered into a previous Distribution Agreement:

24.1. Execution of this Distribution Agreement is contingent upon Recipient's compliance with all terms and conditions of existing Distribution Agreements with Boston University and NHLBI, excluding the requirements stated in paragraph 4 of the previous Distribution Agreement.

24.2. If Recipient has executed a previous Distribution Agreement, Recipient agrees to provide Boston University and NHLBI with a report in the format described in section 14 of this Distribution Agreement every twelve (12) months during the term of such prior Distribution Agreement containing Genetic Analysis Data derived by Recipient from any Clinical Data and Biological Materials previously received from Boston University. Such report will cover all Genetic Analysis Data derived by Recipient up to six (6) months before the reporting date. Recipient agrees that Boston University and NHLBI may distribute these data to qualified scientific investigators requesting access through established NHLBI procedures and completing a signed Distribution Agreement comparable to this Agreement. If the effective date of such previous Distribution Agreement was more than twelve (12) months before the time of the current request for Clinical Data and Biological Materials, and Recipient has not provided to Boston University Genetic Analysis Data derived from any Clinical Data and Biological Materials previously received from Boston University, Recipient agrees that provision to Boston University and NHLBI of such Genetic Analysis Data is a precondition for consideration of the current Distribution Agreement.

This Distribution Agreement is entered into as of: _____(Effective Date)

RECIPIENT:

Name of Recipient Entity:

Name and Title of Recipient's Authorized Representative:

Signature and Date of Recipient's Authorized Representative:

Date: _____

PRINCIPAL INVESTIGATOR:

Principal Investigator's Name and Title:

Principal Investigator's Surface Mail Address:

Principal Investigator's Email Address:

Principal Investigator's Telephone Number:

Principal Investigator's Fax Number:

Signature and Date: Principal Investigator:

_____ Date: _____

TRUSTEES OF BOSTON UNIVERSITY (BOSTON UNIVERSITY):

Name and Title of Boston University's Authorized Representative:

Signature and Date of Boston University Authorized Representative:

Date: _____

NHLBI:

Name and Title of NHLBI's Authorized Representative:

Signature and Date of NHLBI Authorized Representative:

Date: _____