Framingham Heart Study OSMB Meeting
Jurys Washington Hotel, Washington, D.C.
December 14, 2006

OSMB members present: Drs. Boerwinkle, Cushman, Greenland, Luepker (Chair), Neaton, and Wilson

OSMB member absent: Dr. Rotimi

Investigators present: Drs. Atwood, D'Agostino, Vasan, and Wolf

NHLBI staff present: Drs. Olson (OSMB Executive Secretary), Aviles, Harman, Levy, and Sorlie; and Ms. Jennings

INTRODUCTION (CLOSED SESSION)

Potential conflict of interest issues had been addressed prior to the day of this regularly scheduled annual Framingham Heart Study OSMB meeting. Dr. Luepker opened the meeting at 8:30 am. Introductions were made. The minutes from the meeting of December 8, 2005 were approved. Dr. Olson announced that Dr. Weiss resigned from the Framingham OSMB last February. The Board members agreed that having additional genetic and pulmonary expertise would be of value to the Board and to the study. Dr. Sorlie summarized the reorganization of NHLBI's extramural program and the re-designation of NHLBI's Framingham staff to intramural status.

The Board discussed the responses to recommendations from the previous year's meeting. Members felt that the first response, concerning tracking of participants' biological samples, presented much information but still did not address how use of samples is being tracked and how use is prioritized as volumes get low. They also felt that a summary of the lengthy quality control results included in the report would be helpful. Concerning the response to the recommendation to conduct more analyses using longitudinal risk factor data, they thought that Framingham is in a position to act as a leader in developing the statistical methods needed for longitudinal analyses. They also observed that most collaborative projects continue to be with others in the Boston area; the study should make greater efforts to promote involvement from other researchers, such as through workshops for new investigators as has been done successfully in CHS. Such efforts should not focus solely on genome-wide association data, as Framingham still has much more to offer scientifically in addition to genetics.

OPEN SESSION

Framingham Committee reorganization (Drs. Wolf and Sorlie)

The Framingham Heart Study was originally conducted entirely by NHLBI staff; decisions about study conduct were initially made *ad hoc*, and current study procedures have evolved over time.
The study is now restructuring its committee organization and establishing procedures and processes that are more transparent and accountable to investigators both inside and outside of Framingham. The Executive Committee now comprises 3 members from Boston University, 3 from NHLBI, the Principal Investigator, Dr. Wolf, and the Project Officer from NHLBI. Additional subcommittee structures are being developed and subcommittee policies, procedures, and conditions for involvement will be made available on Framingham's website. Information about access to DNA samples is currently available but how to access other samples also needs to be posted, as does documentation of how requests for non-renewable resources (serum and plasma) are evaluated. Standard procedures for submitting and evaluating ancillary study and paper proposals are needed, as are systems for tracking proposals and approved projects.

General summary and response to OSMB recommendations (Drs. Wolf and Levy)
Events surveillance of all 3 generational cohorts is ongoing. The Offspring Exam 8 is underway with clinic attendance at or above target levels, and is on track to finish as scheduled by the end of December 2007. The Original cohort Exam 29, also underway, aims to complete approximately 200 exams by its end at the same time. About half of the Original cohort exams are performed in the clinic, with many conducted in nursing homes. Approximately 100 papers were published over the past year. NHLBI plans to distribute all study and ancillary study data to qualifying researchers as part of its Framingham SHARe project. The Genetics Laboratory continues to distribute DNA to requestors with applications approved by the DNA Committee.

The investigators and NHLBI Framingham staff responded to recommendations from the Board made at last year's meeting. Processes for labeling, tracking, and storing laboratory samples were described. The inventory includes approximately 650,000 biological samples stored both at the Framingham clinic and at an off-site location. Ongoing and recently completed manuscripts using longitudinal data were presented, and considerations for use of longitudinal data for risk factors in genetic analyses were discussed. The Board was pleased to learn about these efforts, and requested future presentations on methodological issues and more results using longitudinal data. Activities to increase broad sharing of genome-wide association data were summarized, including current distribution to outside investigators of the 100,000 SNP markers and accompanying phenotype data in the largest Offspring cohort families and the SHARe project's planned 550,000 SNPs to be made available later in 2007 through the National Center for Biotechnology Information (NCBI). A new robot was acquired to expedite the Genetics Lab's production of custom DNA plates to respond more quickly to investigators' requests. The Board advised that strict quality control procedures for this process should be in place. The Lab plans to perform random checks to be sure that the correct samples have been placed in the correct wells after plating is done. Increasing accessibility and sharing of Framingham data to outside investigators is being accomplished by publishing a collection of summary papers on genetic associations and linkage with the 100K SNP markers, sharing of genetic data from the 100K and SHARe projects, proposing an educational session on the availability of genetic data at the next American Society of Human Genetics meeting, and offering Framingham data for the 2008 Genetic Analysis Workshop.

The Board noted that its previous suggestion to hold a hands-on workshop on obtaining and using Framingham data has not yet been acted upon, and again encouraged that this be done. It was also noted that the number of proposals for DNA from outside of the Boston area has been fairly stable over the past 4-5 years, and that studies making use of non-genetic data also need to be encouraged. DNA quality control activities were moved away from the Genetics Lab to the Genetics Data Management Group in 2004.

Genetic Distribution (Dr. Atwood)
All applications for genetic materials and data are reviewed by the DNA committee. Dr. Atwood summarized the number of applications received, reviewed and approved in the past year. Fifty-six data sets were distributed. Data sets can be distributed the day that all approvals are in place with good advance planning and cooperation from the requesting investigators. Sixteen DNA plate sets were sent out this year.

Dr. Levy summarized activities for the SHARe project. Genome-wide scans of all consenting participants will be done using high-throughput technology. In addition to the genotype data, all available phenotypes from all generations will be made available. Participant privacy and confidentiality will be protected by de-identifying the data and by requiring an approved application, IRB approval from requestor's institution, and a signed DDA before data are distributed. Oversight is provided by the Framingham SHARe Oversight Committee, Framingham SHARe Steering Committee, Framingham Ethics Advisory Board, NHLBI review of applications, participant focus groups, and communications to participants about SHARe via the study's newsletter. It is hoped that analyses of these data will stimulate comparisons with other genome-wide association results, follow-up genotyping and re-sequencing activities, and similar efforts in other studies. NCBI will develop tools to facilitate data analysis. All genotype and phenotype data are expected to be available in NCBI's completed database by July 2007.

Board members commented that the participant newsletter announcing this project should describe details of privacy protection and data distribution (particularly the plan to share data via the Internet) and use less sophisticated language. In addition, the Institute should carefully consider the legal implications and consequences of data misuse and other potential violations of the data distribution agreement. When and how to alert affected participants when clinically meaningful associations are found should also be considered, addressing in particular whether outside investigators analyzing the data also bear responsibility for such reporting. Scientifically, the investigators were advised that the greatest benefit is likely to come not from hurrying to be the first to publish but from investigating in deep detail a selected few of the associations that are found.

Genetic Laboratory (Dr. Atwood)
Quality control activities and the status of preparation of customized plates were reviewed. Quality control efforts are considerable because of the unique genetic quality control challenges for family data. Much lab effort over the past year has been devoted to building plate sets for the Original and Offspring cohorts and a "precious" plate set of DNA with no cell line back-up; special permission is needed to use the latter. The total number of samples with cell line back-up will be approximately 8300. The amount of DNA distributed has increased since it began in 2003 but has leveled off since 2005; 16 plates were distributed this year. Preparing custom plates requires considerable effort and cost. The Board suggested that

since the DNA supply is unlimited with cell line back-ups and since genotyping costs are coming down, the lab should consider saving money by not producing custom plates. Genotyping of all samples in standard plates could be done more inexpensively, and accompanying phenotypic data could be provided only for cases and controls of interest.

Ancillary Studies (Dr. D'Agostino)
The status of existing ancillary studies, particularly those with participant burden, was reviewed. Most of the Offspring Exam 8 ancillary studies are funded as NIH R01 grants. Some involve additional data collection at the time of the exam, while others require call-backs of participants for the additional data collection. Ancillary studies requesting resources (biological samples) also impose considerable burden by having to address ancillary study investigators' questions, offering advice, performing sample selection, etc. The ancillary study proposal and review process is being revised to formalize the Research and Publications Committee structure, membership, review process, and timeline for publication of findings. The goals are to make the system more transparent for proposing investigators, to streamline the process, and to better determine the burden to the parent study.

Quality control from Offspring 8 Exam (Dr. D'Agostino)
An overview of quality control results for anthropometric, blood pressure, and spirometry data was presented. In general, measurements obtained were consistent with those expected. Quality control results are reported back to the technicians and re-training is done as needed. For laboratory assays, external quality control is done by sending selected samples to an outside laboratory that uses the same assay procedures. Control samples with known concentrations are assayed with every set of participant samples, and observed values are compared to those expected. The Board suggested that for outside laboratories receiving frozen Framingham samples for assays and returning the unused portions, Framingham laboratory staff should communicate clearly with the receiving laboratories about proper handling of samples to ensure their integrity. When possible, it is preferable to batch requests for samples and then thaw, aliquot, and distribute samples in the volumes required rather than to receive unused returned material. The Board requested to see genotyping blind duplicate results, suggested looking at the missing data rate as the Genetic Lab transitions from Taqman to SNPlex technology, and advised inspecting missing data from SNP chips by locus or individual as a way to assess the quality of the data obtained.

Plans for new contract period (Dr. Sorlie)
The new Framingham contract is planned to begin in one year, allowing 9 months of overlap with the current contract in order to continue the examination sequence without interruption. The Request for Proposal is expected to be released in January. The goals of the new contract are (1) to conduct a Generation 3 repeat exam followed by Offspring Exam 9 and Original cohort Exam 30; (2) continue funding for all genetics-related activities; and (3) support other requirements still to be determined concerning subclinical disease and laboratory questions relevant to these cohorts at this time. As a national resource, access to Framingham resources will continue to be made more accessible to the greater research community. Training issues, policies, and processes also need to be addressed. The contract renewal will be announced so that potential collaborating investigators can plan and submit proposals for ancillary studies to coincide with the cohort exams. No Generation 4 exam is planned at this time. The Board noted that Framingham will pave new ground as it addresses

the substantial analytic and methodological challenges it now faces and that adequate resources for biostatistics support should be a priority.

Scientific Presentations

Dr. Vasan: Antecedent blood pressure and body-mass index and risk of heart failure in the Original cohort

Dr. Levy: A 100K genome-wide analysis for hypertension candidate genes

Dr. D'Agostino: An updated cardiovascular risk function

The open session ended at 2:40 pm. Dr. Luepker thanked the Framingham staff for their time and excellent presentations.

CLOSED SESSION

The Board discussed a proposal from Dr. Lewis Kazis for an ancillary study on epilepsy involving participant burden, expressing a low level of enthusiasm. Board members unanimously and enthusiastically endorsed renewal of the Framingham Heart Study contract. They agreed that the study investigators continue to perform well, are highly productive, and have been very effective in retaining and examining study participants. They noted that with increasing interest to make it a national resource, Framingham will face growing burdens in addressing outside investigators' questions, responding to requests for data and specimens, etc., and advised the investigators to consider this carefully as they prepare their response to the Request for Proposal for contract renewal.

<u>Recommendations</u>:

1. Establish a more defined Coordinating Center that protects the time and value of the study's statistical experts, addresses growing needs to formalize processes for making and reviewing data and sample requests, handles the anticipated increased burden of questions concerning data analysis, and prioritizes use of study resources.
2. Give careful time and attention to thinking through the scientific and analytic challenges inherent in genome-wide association studies.
3. Establish clear policies for use of non-renewable biological samples, with an accompanying inventory of available phenotypes, bioassays, and available specimens.
4. Create opportunities to instruct outside investigators about Framingham data sets, study design, and analytic considerations, such as new investigator hands-on workshops as done in another large NHLBI-contracted observational study.
5. Continue making use of the study's rich data sets for longitudinal data analyses for both phenotypic and genomic risk factors and markers.
6. In the next OSMB report and meeting, the Board would like to see
    a) For each cohort by exam, the number and proportion of participants alive, retention goal and retention achieved
    b) How sample use is tracked and how distribution is prioritized as volumes get low
    c) Quality control results summarized in lieu of large sections
    d) Presentations on methodological issues and results
    e) Results from the Generation 3 exam, particularly those from data collected using advanced technological imaging and other procedures

The next Framingham OSMB meeting was scheduled for Wednesday, December 12, 2007.

Respectfully submitted,

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Russell Luepker, Chair Date

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Jean Olson, Executive Secretary Date