

MINUTES
Observational Study Monitoring Board
For Framingham Heart Study
Meeting, December 11, 2014

PARTICIPANTS:

OSMB Members Present: Russell Luepker, Chair; Pamela Douglas, Phil Greenland, Svati Shah (by phone), Lewis Smith, Jason Umans (by phone), Alexander Wilson

OSMB Members Absent: James Neaton

Framingham Investigators: Vasam Ramachandran, PI; Dan Levy (NHLBI intramural), Adrienne Cupples, Caroline Fox (NHLBI Intramural), Joanne Murabito, Joseph Massaro

NHLBI Extramural Staff: Richard Fabsitz, Executive Secretary; Cashell Jaquish, Cheryl Jennings, George Papanicolaou, Phyliss Sholinsky, Elizabeth Zoller

INTRODUCTION

The regularly scheduled annual meeting was called to order at 8:58 am. No conflict of interest declarations were reported by the OSMB members in attendance, and all (including the absent Board member) were up to date on their conflict of interest forms prior to the meeting. Two new OSMB members were introduced: Dr. Svati Shah, a cardiologist and omics expert from Duke University, and Dr. Jason Umans, a hypertension, renal disease, and chemistry laboratory expert, with joint appointments at MedStar Health Research Institute and Georgetown University.

DESCRIPTION OF THE STUDY

The Framingham Heart Study (FHS) was initiated by NHLBI in 1948 and currently comprises three cohorts representing three generations that have participated in multiple exams over varying lengths of time and time intervals between exams. The Original cohort has been examined every two years since 1948. The Offspring cohort has been examined periodically since 1971. The third generation (Gen 3) has been examined twice since 2000. In 2009, the Omni Group 1 and Omni Group 2 cohorts, previously supported by grants, were integrated into the Framingham contract. Funding for FHS' current contract was continued in 2008 for seven years and is now in the process of renewal. A reexamination of all three cohorts, as well as the Omni cohorts, is part of the current contract. The second exam of Gen 3 and Omni Group 2 were completed in 2011, and the 32nd exam of the original cohort was also completed. The Offspring cohort exam 9 and Omni Group 1 exam 4 started in 2011 and are now complete. Plans for NHLBI support of the study will change significantly for funding beginning with the contract renewal in 2015. Current plans call for a reduced funding commitment for the next phase of the Framingham Heart Study with a focus on infrastructure and morbidity and mortality follow-up with the possibility for core exam funding for the Gen 3, Exam 3 if grant applications requiring an exam receive awards.

RESPONSE TO THE CONCERNS AND RECOMMENDATIONS OF THE PRIOR MEETING

Responses to the concerns and recommendations were addressed in an interim response delivered in mid-2014 and were not reviewed in detail at the meeting. The Board was very pleased with the response of the investigators to previous recommendations and thought all were thoroughly addressed. The Board was particularly pleased that the NHLBI revised its approach to funding the core examination in the current solicitation.

REPORT ON ADVERSE EVENTS

One adverse event was reported. One participant was found to have high blood pressure and talked with a physician regarding the finding. He was able to complete only part of the exam and was referred to his physician for follow-up. A total of 34 referrals were made as a result of the exam; 5 required urgent medical follow-up.

BRIEF DESCRIPTION OF AGENDA ITEMS COVERED

Dr. Vasam Ramachandran presented to summary report in his new role as Principal Investigator. Dr. Ramachandran indicated it was a year of transition with careful considerations from multiple perspectives on how the study operates. Reviews were provided by a group of outside experts and a consulting team. The goal is a more efficient process of conducting exams and boosting scientific productivity. Productivity of the study was excellent given the transition and focus on renewal of funding: 200 papers were published, 86 of which were genetically-focused and 25 of which were without FHS investigators (using shared data/samples). Exams were completed for the Offspring, Exam 9, the Omni cohort 1, Exam 4, and the original cohort, Exam 32. Accounting for home visits and other forms of contact, overall retention remains above 90%.

Dr. Ramachandran presented the pulmonary function measurement and analysis plans. He noted the progress with lung imaging and the automated lung density analysis based on pixel density. These images provide new measures that can be used in GWAS analyses, for example. Other imaging provides a measure of blood vessel volume from which total blood volume in the lungs can be derived. Finally, the second CT scans of the lungs include greater coverage with full thoracic CT – apex to base images.

Dr. Cupples provided a report on the DNA Committee, noting an increase in requests for DNA that is linked to the AHA funding opportunities initiated in 2014. Requests remain largely Boston-centric. Many requests for genetic data are now fulfilled by dbGaP and these come primarily from outside Boston. There were 10 proposals for biospecimens, 8 of which were approved. The AHA CVGPS program was responsible for a significant portion of the requests; AHA recently made 8 awards as a result of this program.

Dr. Ramachandran summarized the creation of the Boston University Service Center to request fees for data and sample sharing in the wake of funding reductions. Discussion by the Board centered on the equality of fees for requests from commercial and academic institutions and the size of the fee given the associated costs of managing such a system. FHS Investigators and the Board discussed early stage investigators and their potential inability to pay the fee structure.

Dr. Fox presented an innovative effort to increase the participation of early stage investigators in the Framingham Heart Study that included WebEx seminars, multidisciplinary journal club, invited speakers, theme-based sessions, innovation forums, professional boot camp and work-in-progress meetings. The Board was very pleased with this set of activities.

Dr. Cupples reported on the genetic and non-genetic sample sharing and data sharing activities. Efforts are currently underway to develop a living tissue/cell based distribution policy, promote the genomic data commons, expand collaborations with commercial entities, and develop a plan for return of whole genome sequencing results. Dr. Murabito presented on the latter and indicated it has proven difficult for many reasons including confidence in data quality, need for CLIA approval, evolving knowledge regarding variants that may offer clinical actionability, and

the cost of return. The investigators hope for further guidance from the NHLBI and/or the NIH as opportunities for data collections increase.

Dr. Levy reported on the progress of the SABRe study. Three of the four components had completed their lab work; the multiplex immunoassays project was slowed due to sequester cuts but progress is now more apparent. Presentation of results from the SABRe project suggests tremendous progress in discovery, consistency in findings between gene expression and methylation projects, and replication in other cohorts. A number of high profile papers were published. Integrative network analyses have been found to link previously unknown phenotype linkages. It was noted that three of the AHA CVGPS grants awarded were based on SABRe data.

Dr. Murabito reviewed the status of the ten ancillary study applications previously approved by the OSMB that were proposed for funding in association with the Framingham Heart Study renewal. It appears that several may have fundable scores. As a result it is expected that the NHLBI will likely support a basic exam of Gen 3 in the coming contract renewal. Two new proposals and six resubmissions may potentially be part of the exam as well. As a result, the Board was unsure of how to track the total burden of participants and requested a table be submitted as part of all ancillary study approvals that summarizes the existing and potential participant burden to allow the Board to better assess this issue in their review of new ancillary studies.

Scientific presentations were provided by Dr. Murabito on the genetics of age at natural menopause and by Dr. Fox on the validation of e-epidemiology as an alternate way to collect data in the Framingham Heart Study. Both were well-received by the Board.

The Board inquired as NHLBI moves to consortium cohorts, is there a way for individual study OSMBs to work with other study OSMBs to address common issues, tasks, etc. This possibility may be addressed at the expected cohort consortium planned for this spring.

RECOMMENDATIONS

The Board voted unanimously to continue the study.

The following specific recommendations to the NHLBI were provided:

- 1) The Board commends Dr. Ramachandran and the Framingham Heart Study investigators on an excellent transition of leadership and advancement of the ongoing and new science during the previous year.
- 2) The Board acknowledged the effort to generate additional ways to offset costs of managing and distributing data and specimens in the spirit of sharing but questioned the fee structure that treats academic and commercial interests equally and at a level that does not appear to be cost effective given the associated accounting burden.
- 3) The Board commended the investigators for accelerating the scientific productivity of the SABRe project and for the compelling scientific findings of this project.
- 4) The Board recognized the scientific opportunity of the successful application for whole genome sequencing in the Framingham Heart Study but questioned the value of initial efforts to conduct whole genome sequencing on six FHS trios across all sequencing platforms without a timely plan for analysis and action based on the results of that effort.
- 5) The Board recognized that that the Framingham Heart Study investigators were on the leading edge of addressing the questions of when and how to return of genetic research results and urged the investigators to provide a plan to address this issue.

- 6) The Board urged the NHLBI to explore opportunities to support the development of infrastructure for the Framingham Heart Study and other NHLBI-supported studies that would facilitate the sharing of the wide range of imaging data currently available.
- 7) The Board commended the investigators for expanding the pulmonary technologies currently being employed in the study and the outstanding science derived therefrom.
- 8) The Board requested that a table be routinely provided in OSMB meetings and with ancillary study reviews that provides current and potential participant burden for approved and pending ancillary studies.
- 9) The Board urged the investigators to be more proactive in marketing the opportunities for early stage investigators in the Framingham Heart Study, particularly for individuals outside Boston.
- 10) The Board urged the investigators to develop a plan for conducting functional studies to confirm the functional status of identified variants from the various discovery techniques.

NEXT MEETING

The next meeting is scheduled for Thursday, December 3, 2015.

SIGNATURES

Approved	Richard R. Fabsitz, Executive Secretary, FHS OSMB	12/16/2014
Approved	Russell Luepker, Chair, FHS OSMB	12/15/2014
Approved	Michael Lauer, Director, DCVS, NHLBI	12/17/2014