OVERVIEW OF STUDY

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1. Study overview

The Multicenter Bone and Joint Health Study (MOST) is a longitudinal, prospective, observational study of knee osteoarthritis (OA) in older Americans with knee OA disease or at increased risk of developing it. The overall goals of the grant are to expand opportunities for prevention and treatment of knee osteoarthritis (OA) by studying new potentially modifiable risk factors for disease especially among those with early or mild knee symptoms and by exploring for the first time modifiable factors involved in potentially major consequences of disease.

This study will involve enrollment of two cohorts for longitudinal study: approximately 1,500 returning participants in the original MOST cohort, and recruitment of 1,500 participants into a new cohort approximately equally distributed between the two MOST clinical sites in Birmingham, AL and Iowa City, IA. Potential participants in both cohorts will be administered a screening telephone interview to determine interest in enrollment and eligibility. The new cohort will also attend an in-clinic screening visit to determine eligibility. Participants in both cohorts will have a baseline clinic examination, 2 interim phone contacts at 8, and 16 months after enrollment and a follow-up clinic visit at 24 months. For the returning members of the original cohort, these will be a 144-month clinic visit, 152- and 160-month telephone contacts, and a 168-month clinic visit.

Surviving participants in the original cohort who have not withdrawn consent will be eligible and contacted by mail and telephone, and invited to participate. Of the 3,026 participants enrolled from 2003-5, we anticipate that approximately 1,500 surviving participants will be enrolled in the new study. The estimate is based on approximately 80% participation rate among the 1,890 subjects who attended the 84-month follow-up clinic visit and are eligible for the new study.

A new cohort will be recruited, screened to determine study eligibility, and enrolled into the study. The new cohort will consist of subjects without knee OA or with early stage knee OA, when prevention and treatment opportunities are more likely to offer success. The new cohort will consist of 1,200 subjects with knee pain, aching or stiffness at baseline and 300 participants without any knee symptoms in the previous 30 days.

The MOST Study Protocol provides detailed information about MOST study objectives, study design, population studied, data management, study organization, measurements, and study timeline.

2. Study organization

MOST is a cooperative grant funded by the National Institute of Aging (NIA), an institute within the National Institutes of Health (NIH). The study has been developed with full participation of all principal investigators. The investigators are committed to the study being conducted in a uniform manner, adhering to procedures described in the MOST operations manual. Standardization, supervision, and coordination of all procedures will be ensured through quality-control mechanisms.

The four participating sites in this research study are:

1) The University of Alabama at Birmingham (UAB)
   - Clinical Center

2) The University of Iowa (U-Iowa)
   - Clinical Center

3) The University of California, San Francisco (UCSF)
   - Coordinating Center, Data Management Center, and MRI Reading Center

4) Boston University (BU)
   - X-ray Reading Center and Data Analysis Center

3. MOST committees

The organization of MOST includes the following committees:
- Executive Committee
- Quality Assurance Committee and Recruitment/Retention Subcommittee
- Steering Committee
- Publications Committee and Data Analysis Subcommittee

3.1 Executive Committee

The MOST Executive Committee is comprised of seven voting member and one non-voting member. Voting members are principal and co-principal investigators [Michael Nevitt, Ph.D. (UCSF), David Felson, MD, MPH (BU), Cora E. Lewis, MD, MSPH (UAB), James Torner, Ph.D. (U-Iowa), Tuhina Neogi, MD, PhD, Neil Segal, MD, and a representative from the NIA Program Office, Lyndon Joseph, Ph.D]. Jean Hietpas, MSW, OTR, MOST Project Director (UCSF) is a non-voting committee member.

The Executive Committee is responsible for overall study design, coordination, and governance including:

- ✓ Final approval of all major changes in study design
- ✓ Budgetary decisions
- ✓ Final approval of all study policies
- ✓ Approval of all study ancillary studies
- ✓ Development of ancillary studies and publications guidelines

The Executive Committee convenes by teleconference every month. Members meet in person annually.

The Coordinating Center manages all operations of the Executive Committee, including arrangements for meetings and conference calls under direction of the committee chair.

3.2 Quality Assurance Committee and Recruitment/Retention Subcommittee

This committee is responsible for developing methods to assure the highest possible quality of study data. The project director of the Coordinating Center (in charge of QA) and the clinical center investigators will serve on this committee to oversee the quality of procedures and data. The membership of this committee will include the QA officers of each clinical center and the Coordinating Center data manager and research associates. This committee will convene monthly by teleconference to review QA policies and procedures, to review all aspects of the data management system, and resolve any problems or issues related to the data systems.

The MOST Recruitment and Retention Committee will be chaired by an investigator or a senior recruitment staff person from one of the clinical centers. The Coordinating Center project director will also serve on this committee.

The Recruitment and Retention Subcommittee is responsible for formulating recruitment and retention plans, monitoring the success of meeting specific recruitment goals at each clinic, and advising the Steering Committee about ways to meet these goals. Problems and successes will be reported to the Steering Committee. The Coordinating Center will provide the subcommittee with up-to-date recruitment statistics captured through the study website recruitment activity report (to be completed weekly by clinic staff) and through the electronic data capture (REDCap) and digitally scanned study forms (TELEForm) into the MOST data system. This will allow the committee to track enrollment within specific age, gender, and risk groups.

The Committee will meet monthly, and additionally as needed, by teleconference during study recruitment.

After recruitment ends, the subcommittee will focus on study retention. As with recruitment, there will be web-based retention tracking reports on the study web site. The reports will be reviewed by the subcommittee during the regularly scheduled Quality Assurance Committee teleconference meetings.

3.3 Steering Committee

The Steering Committee is responsible for overall study design, coordination, and governance including:

- ✓ Drafting of the study design
- ✓ Oversight of performance of all study sites including the Clinical Centers and the Coordinating Center
- ✓ Designation of subcommittee membership
- ✓ Oversight of the Recruitment and Retention Committee and Quality Assurance/Quality Control Committee

The Steering Committee convenes by teleconference monthly during the first 24 months of the study and quarterly thereafter. Members meet in person annually.

The Coordinating Center manages all operations of the Steering Committee, including arrangements for meetings and conference calls under the direction of the committee chair.

3.4 Publications Committee and Data Analysis Subcommittee

This committee will be responsible for coordinating and approving analysis plans and priorities, and monitoring abstracts, presentations, and publications. The Coordinating Center supports the Publications Committee activities. The Coordinating Center tracks all analysis plans, communications, submissions, presentations and publications, and provides timely reports of these activities via the study website. The Coordinating Center project director and publications coordinator join the investigators from each site and the senior statisticians and data analysts from the Analysis Center and Coordinating Center every other month via teleconference and webinar. BU serves as the primary Data Analysis Center, with additional data analyses conducted by investigators at each participating center using distributed data sets.

4. Participating study sites

4.1 Clinical study sites

There are two clinical centers participating in the MOST study:

- The University of Alabama at Birmingham (UAB)
  Division of Prevention Medicine
  Birmingham, Alabama

- The University of Iowa (U-Iowa)
  College of Public Health
  Iowa City, Iowa

The clinical sites are the interface with the study participants and responsible for conducting the study according to procedures described in the MOST Operations Manual, and with the highest regard to participant safety at all times. The clinical sites are responsible for:

- recruiting, screening, evaluating, and conducting follow-up of study participants in adherence to the study protocol

- timely electronic transmission of the study data to the Coordinating Center with the lowest error rate possible

- sending X-ray, MRI, CT images and biological specimens to the Coordinating Center or biorepository facility as scheduled

- uploading electronic exam data to the Coordinating Center secure data transfer network

- timely completion of study quality assurance documents

- participation in the scientific aspects of the study including design, analysis, and publications
- alerting the Coordinating Center to any problems that may arise during the study

The Principal Investigator at each clinical center is responsible for the conduct of the study at their site in accordance with procedures described in the MOST operations manual and all additional relevant study documentation. Additionally adherence to all regulatory requirements will be followed according to institutional guidelines.

4.2 Coordinating Center

The UCSF Coordinating Center will coordinate the study under the direction of the Executive Committee, the Steering Committee and the Project Office. The Coordinating Center serves as the data and quality control center, and oversees the communications and governance of the research study.

The functions and services that the Coordinating Center provides include:

Study-wide governance
The Coordinating Center assists committee chairs to carry out the Executive Committee, Steering Committee, Publications Committee, and Quality Assurance Committee responsibilities.

Protocol and measurement development
In collaboration with the Executive Committee, Steering Committee and the Quality Assurance Committee, the Coordinating Center develops measurement protocols and scientific priorities. The Coordinating Center is responsible for developing and maintaining the study operations manual.

Develop data collection forms
Data collection forms are designed by the Coordinating Center with guidance from the Executive Committee, Steering Committee, Quality Assurance Committee and study site personnel. The forms are reviewed, tested and integrated into an electronic data collection system by the Coordinating Center.

Manage the data management system
The remote data entry system is designed, tested, maintained, and managed by the Coordinating Center. The study database is maintained at the Coordinating Center.

Training
The Coordinating Center develops training sessions to teach examiners procedures described in the operations manual. Interviewers and examiners are taught to administer tests in a reliable, standardized fashion. The Coordinating Center is responsible for organizing centralized training sessions, training conference calls, and ensuring staff certification.

Coordinate study activities
The Coordinating Center tracks all study activities, creates and monitors study timelines, and arranges and maintains the documentation of committee conference calls and meetings on the study website.

Clinical site visits
The Coordinating Center periodically conducts site visits to assess protocol adherence, to provide training when needed, and to encourage exchange of strategies and techniques between clinical sites. The Quality Assurance, Executive and Steering Committees review a written site visit report.

Administer subcontracts
The Coordinating Center is responsible for administering several subcontracts, consulting agreements and vendor agreements. The Coordinating Center develops and implements systems for disbursement of funds to subcontractors. Subcontracts administered by the Coordinating Center include:

- Radiologists for MRI reading
- Fisher BioServices for specimen storage
- New England Research Institute (NERI) for use of the PASE measurement
- QualityMetric Incorporated for use of the SF-12 and/or SF-36
- iMorphics for bone segmentations of the knee from CT (to be used for local BMD readings)
- University of Saskatchewan for local bone density readings from knee CT

Communication
Teleconferences and face-to-face meetings play an important part in keeping the elements of a multicenter collaborative study in touch. The Coordinating Center makes arrangements, sends notification, and distributes minutes for MOST committees and subcommittee teleconferences and face-to-face meetings.

The Coordinating Center develops and maintains a password-protected web-based system for communication that includes the study directory, memo archive, meeting schedules, study documents, data inventory, data entry totals, audit trail, data queries, questions and answers, reports, analysis plans, publications, and ancillary studies.

Quality assurance (QA)
Quality assurance is monitored by the Coordinating Center. The Quality Assurance Committee meets monthly via teleconference and oversees adherence to study operations manual. This committee oversees training, certification, and surveillance of all study protocols, procedures, and data collection.

Adjudication of clinical outcomes
The Coordinating Center is responsible for the development of a protocol for the adjudication of total joint replacement for OA (knee and hip), and other outcomes designated by the Steering Committee. The Coordinating Center will manage report of death documentation but will not adjudicate deaths.

Specimen tracking
The Coordinating Center is responsible for tracking specimen storage and coordinating retrieval of samples archived at Fisher BioServices.

Analysis and publications
The Coordinating Center will collaborate with the Publications Committee, Executive Committee, Steering Committee, investigators, and the BU Data Analysis Center to develop publications and presentations; provide analyses of data in accord with the policies and priorities of the Publications Committee; and track and file all analyses, presentations, and publications arising from the study.

4.3 Reading Centers

Knee MRI Reading Center
Protocol and operations manual development, training, and quality assurance for knee MRI imaging will be performed by the UCSF Coordinating Center. UCSF is responsible for a quality control program for MRI with components similar to that for radiography, including detailed operations manuals, designation of lead technicians, local training, certification, and central image review. UCSF is responsible for maintaining a scan database, distributing quarterly MRI scan quality control reports, and maintaining the quality control database.

X-ray Reading Center
The Boston University X-ray Reading Center is responsible for protocol and operations manual development, training, certification, quality assurance, and central image review of study knee and full-leg X-rays. BU is responsible for maintaining a scan database, distributing quarterly x-ray quality control reports, and sending the quality control and reading center database to the Coordinating Center.

4.4 Data Analysis Center

The Boston University Data Analysis Center is responsible for developing publications and presentations; providing analyses of data in accord with the policies and priorities of the Publications and Steering Committees; and working with the Coordinating Center to track and file all analyses, presentations, and publications arising from the study. BU will serve as the primary Data Analysis Center. Additional data analyses will be conducted by investigators at each participating center using distributed data sets.

4.5 NIH / NIA

NIA is the primary funding source for the study. Representatives from NIA are responsible for working with the Executive and Steering Committees to assure the scientific integrity and value of the study. NIA is also responsible for working with the four study sites to track the respective study budgets.

5. Specimen storage

The UCSF Coordinating Center will establish and maintain the subcontract with the Fisher BioServices for biological specimen storage. Clinical sites are responsible for regularly shipping frozen baseline samples (2 times/month) to Fisher by overnight Federal Express or UPS. Shipping details are contained in the Laboratory Processing Operations Manual Chapter. Fisher is responsible for preparing a biological specimen database, maintaining a specimen inventory, and storing study specimens. The Coordinating Center is responsible for the subcontract with Fisher for sample storage and coordinating sample retrievals for funded ancillary studies