OVERVIEW OF STUDY

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1. Study overview

The Multicenter Osteoarthritis Study (MOST) is a prospective epidemiological study of incident symptomatic knee osteoarthritis (OA), incident radiographic knee OA, and factors that lead to worsening of knee osteoarthritis. Using a population-based sampling frame, participants with frequent knee symptoms or at high risk of developing symptomatic knee osteoarthritis (based on known risk factors including age, gender, previous knee injury or operation and increased body weight) will be enrolled into the study.

Participants will be seen at one of the clinical centers for baseline examinations and the administration of questionnaires. At 15 months all participants will be contacted by telephone, for a telephone interview. Participants who report new frequent knee symptoms during the telephone interview will be asked to return to the clinic for the first follow up "case" clinic visit. In addition up to four randomly selected control participants per case knee will be asked to return to the clinic for the first follow up "control" clinic visit. At 30 months, all study participants will again be seen at one of the clinical centers for repeat examinations and administration of questionnaires.

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 (UI)
   - Clinical Center

3) The University of California, San Francisco (UCSF)
   - Coordinating Center, Data Management Center, DXA Quality Control 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
- Steering Committee
- Publications Committee
- Quality Assurance/Quality Control Committee
- Recruitment and Retention Committee

3.1 Executive Committee

The MOST Executive Committee is comprised of five voting members and one non-voting member. Voting members are the four principal investigators (Michael Nevitt, Ph.D. (UCSF), David Felson, MD (BU), Cora E. Lewis, MD (UAB), and James Torner, Ph.D. (UI), and a representative from the NIA Program Office, Chhanda Dutta, Ph.D. Jean Hietpas, 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 will convene by teleconference every other 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 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 every other month 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.

3.3 Publications Committee

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 joins the members of this committee during the regularly scheduled conference calls. BU serves as the primary Data Analysis Center, with additional data analyses conducted by investigators at each participating center using distributed data sets.

3.4 Quality Assurance/Quality Control Committee

This committee will be 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.

3.5 Recruitment and Retention Committee

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 Committee 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 Recruitment and Retention Committee with up-to-date recruitment statistics captured through the study website recruitment activity report (to be completed weekly by clinic staff) and through the digitally scanned study forms 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 Recruitment Committee will be transformed into the Retention and Follow Up Committee. As with recruitment, there will be a web-based retention and follow-up activity survey on the study web site. Statistics from this survey, and from the data system, on completion of follow-up contacts and visits will be posted on the website and reviewed by the Retention and Steering Committees during the regularly scheduled teleconference meetings.

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
  Cora E. Lewis, MD – Principal Investigator

- The University of Iowa (U of Iowa)
  College of Public Health
  Iowa City, Iowa
  Jim Torner, Ph.D. – Principal Investigator

The clinical sites are the interface with the study participants and are 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 3,000 study participants (1,500 at each site) in adherence to the study protocol

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

- sending DXA, X-ray, MRI, and biological specimens to the appropriate Reading Center or storage facility as scheduled

- 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 provide include:

Study-wide governance

The Coordinating Center assists committee chairs to carry out the Executive Committee, Steering Committee, Publications Committee, Quality Assurance/Quality Control Committee and Recruitment and Retention Committee responsibilities.

Protocol and measurement development

In collaboration with the Steering Committee and the Quality Assurance/Quality Control 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 Steering Committee, Quality Assurance/Quality Control 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 (at least once per year) to assess protocol adherence, to provide training when needed, and to encourage exchange of strategies and techniques between clinical sites. The Quality Assurance/Quality Control and Steering Committees review a written site visit report.

Administer subcontracts

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

- Synarc for MRI consulting
- Biomedical Research Institute (BRI) for specimen storage
- New England Research Institute (NERI) for use of the PASE measurement

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 working groups 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/Quality Control 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.

DXA quality control

Quality control for DXA is performed by the Coordinating Center. Procedures outlined in the operations manual will be followed. The Coordinating Center is responsible for training densitometry operators, on-going monitoring of scans, periodic site visits to review densitometry procedures and, if necessary, providing additional training. The Coordinating Center is responsible for maintaining a complete scan database and distributing regular reports on operator certification, machine maintenance and repair, flagged and random sample scan review, ID verification/correction analyses, data distribution and outlier analyses, cross-calibration, and longitudinal quality control data.

Adjudication of clinical outcomes

The Coordinating Center is responsible for the development of a protocol for the adjudication of cases of incident symptomatic knee and hip OA, 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 retrieval of samples archived at Biomedical Research Institute (BRI).

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 University of California, San Francisco. 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 bimonthly MRI scan quality control reports, and sending the quality control database to the Coordinating Center.

Knee X-ray Reading Center
The Boston University X-ray Reading Center will be responsible for protocol and operations manual development, training, certification, quality assurance, and central image review of study knee X-rays. BU is responsible for maintaining a scan database, distributing bimonthly knee x-ray quality control reports and sending the quality control 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 Biomedical Research Institute (BRI) for biological specimen storage. Clinical sites are responsible for regularly shipping frozen baseline samples (two times/month) to BRI by overnight Federal Express. Shipping details are contained in the Laboratory Processing Operations Manual

Chapter. BRI 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 BRI and for retrieving samples from the archive.

Appendix 1 MOST Measurements

MEASUREMENTS	SCREENING INTERVIEW	ENROLLMENT CLINIC VISIT	FIRST FOLLOW-UP VISIT	SECOND FOLLOW-UP VISIT
TELEPHONE INTERVIEW QUESTIONS				
I. Telephone Interview:				
age	X			
gender	X			
ethnicity/race	X			
self-reported weight	X			
knee symptoms	X		X	x
knee injury	X		X	
knee surgery	X		X	
cancer screen	X			
disability question	X		X	
general health questions	X			
RA & inflammatory arthritis screen	X			
relocation screen	X			
hip pain			X	
hip surgery			X	
fracture history			X	
clinic visit eligibility			X	
contact information			X	x
MRI Prescreen			X	x
QUESTIONNAIRES / INTERVIEWS				
II. Self-Administered Questionnaire-Home:				
contact information		X		
ethnicity/race/marital status/education		X		
weight & height history		X		
joint pain, aching and stiffness (homunculous)		X		x
back pain & function (homunculous)		X		x
arthritis diagnosis/family history of arthritis		X		Diagnosis only/not family hx
health history & medical conditions (modified Charlson co-morbidity)		X		x
fracture history		X		x
tobacco use		X		
current employment /work history		X		x
health survey (SF-12 and CESD)		X		x
Modified Late Life FDI - Disability		X	(see SAQ-Clinic)	x
III. Self-Administered Questionnaire-Clinic:				
joint pain, aching and stiffness (homunculous)			x (Cases + Controls)	
knee symptoms (WOMAC, KOOS, VAS)		X	x (Cases + Controls)	x
physical difficulty (WOMAC)		X	x (Cases + Controls)	x

hip symptoms (WOMAC-hip)		x	x (Cases + Controls)	x
Modified Late Life FDI - Disability			x (Cases + Controls)	
health survey (SF-12)		(see SAQ-Home)	x (Cases + Controls)	(see SAQ-Home)
IV. Clinic Interview:				
physical activity (PASE)		x		
flights of stairs climbed in past 7 days		x		
knee symptoms		x	x (Cases + Controls)	x
knee buckling		x		x
knee injury &/or surgery		x		x
hip pain/surgery		x		x
shoe heel height		x		
medication use / history / medication inventory (MIF)		x	x (Cases + Controls); targeted medications only	x
pregnancy screen / menstrual history				x
MEASUREMENTS	**SCREENING INTERVIEW**	**ENROLLMENT CLINIC VISIT**	**FIRST FOLLOW-UP VISIT**	**SECOND FOLLOW-UP VISIT**
V. Clinic Visit				
blood pressure		x		x
height		x		
weight		x	x (Cases + Controls)	x
fasting specimen collection / processing		x		(subset)
20-meter walk		x		x
chair stands		x		x
isokinetic strength (Cybex)		x		
leg length		x		
knee height		x		
laxity		x		
proprioception		x		
hand exam		x		
knee and hip joint exam		(subset)	x (Cases)	(subset)
MD knee and hip joint exam		(subset)	x (Cases)	
knee pain diagram			x (Cases)	
knee flexion contracture		x		
DXA: hip & whole body		x		
knee x-ray		x	x (Cases)	x
full-limb x-ray		x		
1.0-T knee MRI		x	x (Cases 2 knees and Controls 1 knee)	x
1.5-T knee MRI		(subset)		(subset)
MRI Validation Study				(subset)