Multicenter Osteoarthritis Study (MOST) Protocol
July 2023

IMPORTANT INFORMATION FOR MOST STUDY DATA USERS, July 2023

The MOST Protocol is provided as background information for investigators who are obtaining MOST public use data and materials through the National Institute on Aging's AgingResearchBiobank. https://agingresearchbiobank.nia.nih.gov/.

The information in the protocol is current as of January 2020, with minor editing performed in July 2023. Some of the information in the protocol may be out of date and/or no longer applies. The MOST study ended in May 2021 and the MOST research sites are no longer involved in public sharing of MOST data and materials. MOST data and materials are currently only available through requests to the AgingResearchBiobank, whose terms and conditions govern access to and use of the data.

The MOST protocol includes descriptions of some measurements and data that may not be available for public sharing through the AgingResearchBiobank. Some of these data and materials may be available for public sharing in the future. For availability of data for public sharing, consult the information for MOST on the AgingResearchBiobank website.

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I. INTRODUCTION AND OVERVIEW

The Multicenter Osteoarthritis Study (MOST) is a longitudinal, prospective, observational cohort study with a focus on knee osteoarthritis (OA) in older Americans. The broad overall aim of the study is to identify novel and modifiable biomechanical, bone and joint structural, genetic, nutritional-biochemical, physical activity and body composition risk factors for the incidence and progression of knee symptoms, radiographic and symptomatic knee osteoarthritis (OA) and functional limitations and disability, with the intention that this will lead to new approaches for preventing the development and worsening of the disease. MOST is a pioneering study in its use of both MRI and radiograph to assess knee structural disease severity and outcomes. In addition to knee OA, MOST has a secondary focus on risk factors for, and outcomes of, radiographic and symptomatic hip OA.

MOST is a National Institute on Aging (NIA) funded U01 Cooperative Agreement research study comprised of two clinical centers that enrolled, examined and followed participants (the University of Alabama at Birmingham and the University of Iowa), a data coordinating center (University of California, San Francisco), and a science and analysis center (Boston University). NIA program officers (currently Lyndon Joseph, PhD, formerly Chhanda Dutta, PhD) for the Cooperative Agreement have taken an active role in the scientific development and governance of the study.

Table 1. NIH/NIA Award and Local IRB FWA Numbers

Investigator	U01 Award	University	FWA Numbers
Cora E. Lewis	AG18947	UAB	00005960
James C. Torner	AG18832	UI	00003007
Michael C. Nevitt	AG19069	UCSF	00000068
David T. Felson	AG18820	BU	00000301

The MOST study population, which is comprised of two separately recruited cohorts, is a community-based sample of older adult men and women including three subgroups of participants who at the time of their enrollment in the study: 1) had knee OA disease, or 2) were at increased risk of developing knee OA due to the presence of knee pain or risk factors, or 3) did not have knee pain or knee OA.

There have been three funded grant cycles of the MOST study, starting in 2001, with the Third Cycle ending in 2020. Each grant cycle has consisted of a baseline clinic visit to assess risk factors and follow-up clinic visits and phone contacts to assess outcomes. The particular baseline measurements and follow-up outcome data collected at the respective baseline and follow-up time-points of each grant cycle were determined by the specific aims of that cycle. In the second and third grant cycles, additional baseline risk factor measurements were introduced in order to address new specific aims. In addition, during the later cycles follow-up continued for outcomes related to the aims of the previous grant cycles. Knee MRIs and knee radiographs have been obtained at all clinic visits in each cycle.

See Section III, Figure 1 for a timeline showing the baseline and follow-up time-points of each cycle, and Section IV, Tables 2 and 3 for a detailed list of measurements obtained at each time-point during the grant cycles.

1) First Cycle

In the First Cycle (2001-2007), MOST enrolled an Original Cohort of 3,026 participants ages 50-79 (60.1% women, 15.2% African American) who either had radiographic symptomatic knee OA, or were at increased risk for developing knee OA based on the presence of knee symptoms, a history of knee injury or surgery, or being overweight. The primary aims of this cycle were to evaluate the effects of four groups of factors on the risk for incidence and worsening of radiographic and symptomatic knee OA:

a) biomechanical factors (including muscle strength, physical activity-related and joint loading factors);
b) bone and joint structural factors (including those assessed by MRI, radiograph and Dual Energy X-ray Absorptiometry - DXA);
c) nutritional factors assessed by biochemical assay from baseline serum and plasma samples; and
d) future studies of biochemical and genetic risk factors and biomarkers using archived plasma, serum, DNA, and urine samples collected during the baseline examination.

Radiographic and MRI structural outcomes, and knee symptom, physical function (including performance measurements) and disability outcomes were obtained at 15- and 30-month follow-ups.

2) Second Cycle

In the Second Cycle (2008-2014), all surviving members of the Original Cohort were invited for a clinic visit that occurred approximately 60 months after each participant's baseline assessment in the First Cycle. The aims of this cycle focused on advancing understanding of the effects of the following factors on the risk for incident and worsening knee OA, pain and functional disability:

a) spatiotemporal parameters of gait and foot pronation-supination;
b) muscle function and activation patterns;
c) physical activity assessed by accelerometry;
d) altered pain sensitivity; and
e) knee instability symptoms and fear of falling.

The baseline examination (occurring at approximately 60 months after each participant's baseline assessment in the First Cycle) included measures of these risk factors and collection of serum and plasma samples for the specimen bank. Twenty-four month follow-up radiographic and MRI structural outcomes were obtained at a follow-up clinic visit (occurring at approximately 84 months after each participant's baseline assessment in the First Cycle). Knee symptoms, physical function and disability outcomes were assessed at a follow-up phone contact at the 72-month time-point, and at the clinic visit (including performance-based measurements of function) and phone contact at the 84-month time-point.

3) Third Cycle.

In the Third Cycle (2015-2020), MOST added a focus on factors contributing to the development of early knee OA, with the goal of identifying modifiable risk factors for prevention in persons who show early or mild signs of knee OA, a stage of disease that is likely more amenable to intervention than more advanced disease. To address this goal, the study enrolled a New Cohort of 1,525 participants, including those who had early or mild symptoms or radiographic findings, as well as a control group of persons who did not have either knee pain or radiographic knee OA. Risk factors for the development of early OA assessed at the baseline examination of the New Cohort included:

a) calcium crystal deposition and depth-specific 3D bone density assessed from CT scans of the knee;
b) impact loading of the knee during heel strike assessed using force plates;
c) hip abductor and quadriceps weakness;
d) additional measures of pain sensitivity; and
e) gait abnormalities and physical activity assessed by accelerometry in both the clinic and the community settings.

Plasma, serum, DNA, and urine samples were collected and stored for future research.

Also in this cycle, the surviving members of the Original Cohort were invited to attend a clinic visit examination (occurring at approximately 144 months after each participant's baseline assessment in the First Cycle) that included the assessments being obtained in the New Cohort, but with a focus on the role of these factors on function loss and other age-related consequences of knee OA and knee pain.

For follow-up for outcomes, both the New and the Original Cohorts had a 24-month clinic visit exam (occurring at approximately 168 months after the baseline exam of the Original Cohort in the First Cycle) to assess MRI, radiographic, pain, and physical function (including performance measurements) and disability outcomes. Pain and function outcomes were also assessed in both cohorts at up-to two interim telephone contacts between the 144- and 168-month study timepoints.

4) Overall

Details of the background and rationale, aims, measurements obtained, recruitment and enrollment methods, participant characteristics, and retention of the cohort for each grant cycle are described below.

Over 150 articles have been published using MOST data addressing the specific aims of the study and related questions (Appendix A, MOST Bibliography). These publications include a wealth of detailed information about the design and methods of MOST and the data collected.

In addition to its focus on OA, MOST data is being used to investigate questions of broad relevance to aging. These include the determinants of functional decline in elders with joint symptoms, the impact of joint symptoms and arthritis on daily physical activity, exercise and frailty, and the role of sarcopenic obesity, pain sensitization and gait abnormalities in musculoskeletal aging.

MOST has provided an opportunity for a range of ancillary studies addressing questions of relevance to OA and aging. A variety of bioassays have also been performed using the MOST biospecimen archive for analyses relating to the aims of the parent grants as well as to the aims of several ancillary studies (Appendix C, MOST Bioassay Measurements).

MOST has also provided non-MOST investigators with access to selected data obtained during the first two grant cycles through the public data sharing procedures detailed on the MOST public website (http://most.ucsf.edu). Over 100 investigators have obtained MOST public data sets.

II. SIGNIFICANCE, BACKGROUND AND RATIONALE

Osteoarthritis (OA) is the most common form of arthritis and remains one of the few chronic diseases of aging for which there is little if any effective treatment and few preventive strategies. It accounts for more mobility disability in elders than any other disease,[1,2] and contributes annually to an estimated $186 billion in excess health care costs.[3] The knee is the weight bearing joint most commonly affected by OA. Frequent knee pain affects 25-30% of adults and in persons age ≥45 is usually due to OA.[4,5] Knee OA, whose prevalence is increasing, is the most common cause of mobility disability and a major cause of function limitations for millions of Americans; 16% of adults over age 45 years will develop symptomatic knee OA at some point in their lives.[6] For adults who are obese, the lifetime risk of knee OA increases to 2 in 3,[7] accounting for many of the 27 million adults who have knee OA in the United States. Despite medical advances, knee OA remains for many of those affected a major source of pain and function limitation. The markedly increasing rates of knee replacement now causing an economic burden to our society[8,9] reflect the failure of rehabilitative and medical strategies to affect the course and impact of this disease.

Unlike most chronic diseases, we still understand little about risk factors for developing OA and its progression and we have few, if any, preventive strategies to offer persons who are affected or at high risk of disease. [10-12] The central goal of MOST is to identify modifiable and preventable risk factors. Although determining means of prevention is of paramount importance, there also is an urgent need to minimize disablement in those with existing OA.[1] MOST addresses this need by also investigating modifiable factors that affect the risk of functional limitation and disability in those with knee OA.

To approach these broad goals required that MOST be a comprehensive epidemiologic study of OA, incorporating a substantial amount of information on joint structural abnormalities, symptoms, physical function, disability and risk factors, and utilizing a variety of conceptual and methodological approaches. Many of these features of MOST represent new and substantial departures from previous epidemiological and observational studies of OA.[13,14] These novel features of MOST are described below.

1) Full Spectrum of OA Disease

MOST is the first large scale observational study to focus on persons both with, and at high risk of developing, knee OA. Previous epidemiological studies of OA drew from population samples that included large numbers without disease and at low risk of OA, resulting in limited power for both disease incidence and disease progression endpoints. Targeting both those with, and at high risk of developing, knee OA is both practical - they provide sufficient cases of disease to perform an efficient longitudinal study - and relevant - they are the subjects who will be the focus by treatment and preventative interventions, and are the individuals who are most personally interested in preventing disease or its worsening. Risk factors and intervention strategies for prevention of OA onset may differ from those intended to slow the course of disease, and the inclusion of those with, and at risk for, knee OA allows the study of both.

By the time people develop chronic symptoms of knee OA they usually have advanced structural findings of disease, such as meniscal tears and cartilage loss on MRI and mechanical malalignment of the knee, which drive further structural deterioration and limit intervention opportunities.[10,11] This underlines the importance of focusing on incidence of new disease in order to develop prevention strategies in those at risk.

Furthermore, in the Third Cycle, MOST recruited a New Cohort of individuals with early signs and symptoms of disease and at an even earlier stage than was possible in the Original Cohort, and when both prevention and

treatment opportunities are more likely to offer success as opposed to studying progression in those who already have advanced structural disease or chronic pain.[15-17]

2) Symptomatic OA

Previous epidemiologic studies of OA have mostly targeted OA assessed by radiograph, the most widely used imaging modality for assessing structural damage in the joint. In addition to studying radiographic OA, MOST pioneered a focus on risk factors for the development of symptomatic OA (characterized by the combined presence of joint symptoms and evidence of OA pathology in symptomatic joints) an approach that corresponds to a clinical diagnosis of OA[18] and enhances the clinical and public health relevance of MOST. Symptomatic OA is the disease that causes disability and has formidable societal and public health impacts and the one we genuinely want to prevent.[19]

3) Comprehensive Joint Imaging, including MRI and X-ray

MOST incorporated more comprehensive and reproducible imaging than has been used in previous epidemiological studies of OA, which typically used x-rays as the only modality to image pathology. While x-rays accurately reflect advanced bony changes of OA, and provide indirect evidence about cartilage loss, they provide no information about critical intraarticular soft tissue damage, meniscal lesions, and bone marrow edema that are common in OA and that propel both incident and progressive disease.[20-22] MOST pioneered the application in a large-scale, community-based cohort study of serial MRI to accurately image all of the key structures of the knee joint over time. To obtain high quality MR imaging of the joints affordably and efficiently, dedicated 1.0 Tesla MRI extremity scanners were installed in the MOST clinics at the start of the study. For the Third Cycle MOST clinics upgraded to dedicated 1.5T extremity scanners. This has allowed the study to employ far more, and more frequent, MR imaging than would otherwise be affordable, while maintaining a high level of image quality and tight control over scheduling.

In addition, the radiographic imaging in previous knee OA studies had largely relied on outmoded fully extended, and frequently non-weight-bearing, views of the tibiofemoral (TF) joint. MOST was one of the first large-scale epidemiological studies to use the more accurate and reproducible weight-bearing fixed-flexion view of the tibiofemoral joint.[23] In addition, the radiographic assessments in MOST were more comprehensive than in previous studies, and included standardized views of the patellofemoral (PF) joint, an important but often overlooked source of pathology, pain and disability.[24,25] In addition, full limb views of the lower extremity have been acquired for assessment of alignment of the hip-knee-ankle axis, a key determinant of knee OA worsening.[26-28] MOST investigators have also made novel use of the full limb radiographs to assess, and investigate risk factors for hip OA.[29]

The comprehensive joint imaging in MOST allows for the investigation of risk factors and outcomes (e.g. pain) specific to individual structural features of OA, such as loss of joint space, cartilage damage, meniscus damage, bony lesions and malalignment. In addition, MR imaging of the knee and x-ray imaging of all knee compartments allows investigation of the association of risk factors with the specific location of joint tissue damage (e.g. knee compartment-specific cartilage damage), which is particularly important for understanding the role of biomechanical loading factors during weight bearing in knee OA.[28,30]

All radiographic and MR images in MOST have been read at central core labs using standardized and validated protocols for structural disease assessment and rigorous quality control programs.[26,31-36]

4) Clinical Outcomes of OA

MOST assessed the full spectrum of longitudinal measures of clinical outcomes of knee OA using widely recommended, validated and reliable measures of joint pain and physical function[37,38] performance-based assessments of functional status[39] and disability.[40] (See Tables 2 and 3 for a detailed list.)

Pain is the critical symptom of OA, and in early disease is more often mild or intermittent than severe and continuous. Prevention and treatment might entail identifying factors that increase the frequency, severity and chronicity of knee pain. To study the transition from mild and intermittent knee pain to severe, continuous and chronic knee pain, MOST incorporated measures specifically designed to describe and capture this transition[41,42] thus allowing investigation of the factors influencing the evolution of chronic knee pain.

In addition, MOST is one of the first large cohort studies of knee OA to use accelerometer-based measures of objective physical activity as a disease outcome.[43]

Knee pain is not the only symptom experienced in persons with knee OA. Knee buckling, episodes of joint instability involving a sudden loss of postural support across the knee upon weight acceptance, is highly prevalent in persons with knee OA and contributes to significant functional limitations.[44] Prevention of joint instability through neuromuscular training is a potential focus for interventions to prevent falls and functional limitations in people with, or at risk for, knee OA. Measures of knee joint instability and buckling in MOST have facilitated investigation of the impact of these common OA symptoms on falls,[45] fear of falling and functional limitation[46] and of modifiable risk factors for joint instability MOST.[47,48]

The Original MOST Cohort participants have been followed for outcomes for up to 14 years at multiple time-points, providing a unique opportunity to gain a better understanding of the long-term outcome trajectories of knee OA, especially functional limitation/disability, and the relationship of progression of structural damage in the joint to these outcomes. Whether progressive cartilage loss and other joint tissue damage predicts long-term pain and functional outcomes is key to the validation of imaging biomarkers of knee OA progression.[21,49,50] The comprehensive assessment of risk factors in MOST (see below) has enabled investigation of the long-term outcomes of knee OA and of factors like physical activity that influence these trajectories.[51-57]

5) Comprehensive Assessment of Risk Factors for the Development, Progression and Functional Impact of OA

MOST has assessed a comprehensive range of risk factors for OA, including many modifiable ones. The causes of knee OA are likely to be multifactorial with many local and systemic factors playing a major or minor role in causing disease. Inclusion of a broad range of risk factors adds to a comprehensive understanding of how OA is caused both from the perspectives of systemic predisposition and of local mechanical factors and joint injury. Taking advantage of three funded grant cycles, MOST has incorporated assessment of many novel and diverse risk factors using recently available measurement tools, often applying these for the first time in a large-scale cohort study. These have included computerized dynamometry to assess extremity muscle strength, force plates to assess joint loading, pain sensitization as a factor in development of chronic OA pain, accelerometry-based measures of physical activity and gait abnormalities, CT of the knee to assess peri-articular calcium crystals and 3D bone mineral density, and many others.

5a. MRI and CT of the Knee to Assess Intra-articular Lesions as Risk Factors and Causes of Knee OA and Knee Pain. MOST has evaluated intra-articular lesions seen on MRI, but not visible on x-ray, as risk factors and causes of knee OA and knee pain. The meniscus acts to distribute weight-bearing force and to stabilize the knee.[58] Removal of the meniscus causes OA.[59] Meniscal damage is very common in the general population of people both with, and without, knee OA,[60] and the effect of meniscal damage, such as tears and extrusion, on the development and progression of OA has been uncertain.[61] Subchondral bone marrow edema-like lesions, visible as areas of hyperintensity on T2 weighted MR images with fat suppression, and often co-located with areas of excessive mechanical load and cartilage and meniscus degeneration, may represent mechanical osseous trauma and increased localized bone turnover. These lesions have long been suspected of playing a role in both pain and faster progression of OA.[62,63] Cartilage lesions visible on MRI in knees with no, or little, radiographic findings of OA[20] may constitute early evidence of OA and predict the development of full blown radiographic and clinical OA. Inflammation in the joint, seen with conventional MRI as excessive synovial fluid volume and synovitis (hyperintensity) in Hoffa's fat pad,[64] may indicate active degradation of joint tissues, and may be a direct cause of cartilage damage and knee pain.[65-67]
MOST investigators have used data from the study's MR images to extensively evaluate the role of MRI-detected meniscus damage,[22,68-71] bone marrow lesions,[72-74] inflammation and cartilage damage[70,75-77] in the development and progression of knee OA and knee pain, which has helped establish their importance in OA pathogenesis.

Calcium crystals form frequently in the knees of older persons, especially those with OA.[78] These can be visualized as calcifications in the soft tissues on radiographs, called chondrocalcinosis (CC). Animal studies suggest that calcium-containing crystals play an important role in both the onset and worsening of OA.[79] The prevalence of CC on plain x-ray is 7% in those age ≥40[80] and is higher in older persons and in knees with OA. However, the use of plain radiography grossly underestimates the frequency of CC[81,82] and does not permit identification of which joint structures contain calcium crystals. CT scans are an ideal method to assess CC

with high sensitivity and accurate spatial localization.[82] Prior to MOST there are no large-scale OA studies using CT of the knee. Calcium crystal deposition in the joint offers a treatment opportunity for medication to reduce intra-articular mineralization. Use of CT in MOST to assess calcium crystal deposition in knees is the first use in a large scale study of OA of a technique that promises, like MRI, to yield new insights into disease pathophysiology.

5b. Biomechanical Risk Factors. OA is a mechanically driven disease and in its early stages OA pathology is focal and does not involve the entire joint, reflecting the location-specific impact of mechanical abnormalities and risk factors. Nearly all knee pain is provoked by some kind of weight-bearing activity. This indicates that sensitivity to mechanical load is a common feature of the most frequently symptomatic knee tissues. Biomechanical risk factors are likely to be both strongly associated with disease risk and modifiable. Over the course of three funding cycles, MOST has studied a substantial number and variety of biomechanical risk factors, including several that have been pioneering applications of state of the art laboratory methods in a large-scale epidemiological study.[83]

5b1. Physical Activity. Compression of cartilage by loading in a dynamic (and not static) way is necessary for cartilage turnover and synthesis of new matrix.[84,85] However, it is likely that too much loading (too frequent or too great a force or not sufficiently dynamic a force) as well as focal excessive loading due to biomechanical abnormalities may damage or degrade cartilage and other joint tissue.[86]

MOST investigators have assessed the self-reported frequency of common weight-bearing activities suspected as risk factors for knee OA,[87-89] including squatting, kneeling, knee bending, lifting and going up and down stairs, as potential risk factors for knee OA. In addition, the cumulative frequency of joint loading cycles during daily activity has been assessed objectively in MOST using accelerometers to determine the number of steps (weight-bearing cycles) per day and overall physical activity, allowing investigation of the potential role of both joint under-loading and overloading as factors in disease incidence and progression.[90-92] Objective measures of daily physical activity in MOST have also been evaluated as risk factors in the development of functional limitation.[54,93]

5b2. Foot Dynamics. In gait, the foot pronates (flattens) with initial impact, and supinates (arches) during midstance. When foot pronation/supination occurs during weight-bearing it is manifest throughout the closed kinematic chain as changes in the medial longitudinal arch, eversion of the calcaneus, abduction of the knee, and internal rotation of the tibia and femur.[94] There is strong biomechanical evidence that abnormal foot pronation/supination contributes to altered mechanics and pain in the patellofemoral joint, and that these abnormalities include adaptations made during gait to lessen medial tibiofemoral knee pain.[95-98] Direct measurements of dynamic loading of the foot during gait have been acquired in MOST using state of the art pedobarographic (plantar pressure) devices, [99-101], making it possible for the first time to investigate their association with patellofemoral and tibiofemoral knee OA pathology and pain in a large cohort.[100]

5b3. Altered Gait and Walking Patterns. Aberrant joint loading during gait is a potential mechanism for development and progression of joint tissue damage and OA. Persons with symptomatic knee OA alter their walking pattern in a way that is consistent with an attempt to redistribute load and reduce pain.[98] Even subtle changes in walking pattern, by affecting location-specific loading across the knee, may profoundly limit or intensify exposure to stresses known to accelerate OA progression.[102] Individuals with knee OA and knee pain walk more slowly, with a reduced step rate and smaller steps[103] and with an increased ratio of double to single limb support time,[104,105] all of which alter joint-specific loading.[106-108] In addition, by walking in a “toe out” posture, people with medial tibiofemoral OA achieve a desirable reduction of the knee adduction moment[109] but also increase foot pronation and risk overloading the lateral patellofemoral joint. Spatiotemporal parameters of gait have been assessed in MOST using a pressure sensitive walkway[110] and evaluated as predictors of knee OA worsening.[106,107]

Lower extremity musculoskeletal impairments may lead to asymmetry in key gait parameters, including stride, stance and swing times, cadence and range of motion.[111-114] Whether gait asymmetries contribute to risk for development of pain and pathology in joints in the kinetic chain is uncertain.[113] When one knee is painful, gait is often asymmetrical; attempts to reduce loading in the symptomatic knee may cause injurious loading of the contralateral limb and other joint.[111,114] If gait asymmetry has adverse consequences, rehabilitation strategies

aimed at reducing asymmetry may need to be designed. In addition, a stable gait relies on adaptability in the neuromuscular control system. Decrease in motion pattern options, or loss of "gait complexity",[115] is a consequence of a disease-associated decrease in compensatory reserve of the system.[116,117] Reduced gait complexity has been reported in persons with low back pain[118] and foot impairments.[119] The study of physiological complexity has shown great promise for improving understanding of aging and evaluating novel interventions that treat age-related disease.[120] MOST has taken advantage of recent advances in wearable accelerometry-based assessment and extraction of gait parameters from accelerometry data.[119,121-126] This has allowed MOST to assess gait asymmetry and complexity in order to evaluate their potential role in OA progression and functional outcomes.

Given the importance of mechanical loading to OA etiology, repeated exposure to impact loads, such as occurs from heel strike during walking, could increase risk of OA.[127] For weight-bearing joints like the knee, each heel strike imparts a sudden axial force that is transmitted proximally as a shockwave. Animal experiments confirm that even moderate loads comparable in magnitude to those incurred at heel strike during walking, if applied suddenly and repeatedly, can result in pathological changes that closely parallel those of early OA.[128,129] Despite inter-subject variability in footfall parameters[130] and evidence of higher tibial deceleration and rate of impact loading during gait among adults with knee OA,[131,132] little investigative attention has been paid to the possible consequences of an increased loading rate during heel strike among older persons at risk for OA and the value of impact-lessening footwear for treatment and prevention of OA. MOST is the first large-scale cohort study to examine the association of impact loading rate during walking, assessed using a high-frequency force plate (1000 Hz) without need for an instrumented gait laboratory,[133] with the risk of pain and structure worsening in early knee OA.

5b4. Lower Extremity Sensory Function. Proprioception, the perception of body position, joint loading and limb movement[134] relies on input from visual and vestibular systems, articular, cutaneous and muscle mechanoreceptors, and contributes to dynamic knee joint stability by coordinating the actions of the quadriceps, hamstrings, and associated muscles. Impaired proprioceptive acuity may result in poorly controlled, excess loading to the knee during gait, initiating or accelerating joint degeneration.[134-138] Another lower extremity sensory modality, vibratory acuity, appears to travel through similar neurological pathways as proprioception, has been shown to be associated with dynamic loading of the knee and is altered in lower extremity OA.[139,140] Peripheral neuropathy involving the foot is another common lower extremity sensory deficit that may alter loading during gait. Lower extremity sensory measurements in MOST include goniometer-assisted joint position sense MOST[141,142] quantitative vibratory perception threshold using a biothesiometer[47] and peripheral sensory deficits using mechanical stimulation of the foot with von Frey filaments.

5b5. Muscle Weakness and Co-activation. Stability at the knee joint requires internal forces of sufficient magnitude to counteract external forces acting at the knee. The quadriceps muscle absorbs loads and provides dynamic stability. Weakness of the quadriceps may alter local contact stress in a manner detrimental to articular cartilage[143,144] and may also lead to increased impulse loading, increasing the risk of knee pain knee and OA.[145,146] Patients with knee OA have weaker quadriceps than age-matched controls and quadriceps weakness is correlated strongly with knee joint pain and dysfunction.[147,148] Women who developed knee OA have been found to have weaker quadriceps at baseline than women not developing OA.[149] Adults with knee OA also frequently have significant hip abductor weakness.[150] This is consistent with the importance of the hip abductors in affecting pelvis orientation during gait and rotation of the femur,[151] both of which affect knee biomechanics. Hip abductor weakness may influence OA worsening in the medial knee compartment due to a greater external knee adduction moment[150] and greater knee joint contact forces during gait.[152] Because of its role as an external rotator of the femur, hip abductor weakness may also be instrumental in the development of patellofemoral pain and OA.[153-155]

Co-activation of the hamstrings during quadriceps contraction is necessary for joint stability, serving to dynamically counteract the anterior pull of the quadriceps on the tibia, assisting the passive stabilization by the anterior cruciate ligament.[156-159] Older adults with knee OA demonstrate higher levels of muscle co-activation around the knee than those without OA, as well as reduced knee range of motion during gait.[160,161] Both co-activation and reduced range of motion may be compensations intended to "stiffen" the joint, particularly for those with a sense of knee instability.[160,162,163] It is unknown whether abnormal levels of co-activation are

adaptive for inducing a sense of joint stability, or maladaptive by elevating peak contact pressure in the knee the joint and reducing the net knee extensor torque, precipitating instability.[156]

MOST investigators have measured quadriceps, hamstring and hip abductor strength at multiple time-points over three cycles, using both isokinetic and isometric dynamometry, and quads/hamstring co-activation using surface EMG, and have evaluated the association of muscle strength and co-activation on the incidence and progression of structural OA, symptoms and functional limitation.[47,48,164-169]

5b6. Obesity and Body Composition. Obesity, a state of excess weight and adiposity, has long been established as a major risk factor for new onset knee OA.[170] But prior studies are conflicting about the effect of obesity on worsening of existing OA.[171] The design of MOST has allowed comparison of the role of obesity in incidence and progression of OA, and factors such as knee malalignment that can explain differences in these associations.[172] Prior studies of obesity and knee OA have mostly defined obesity using anthropometric measures, such as body weight or body mass index (BMI). However, anthropometric measurements are not exclusive measures of adiposity, but instead reflect the composite of fat, muscle, and bone mass. Thus, it is not clear whether the effects of "BMI," typically interpreted as effects of obesity, are truly due to excess adiposity rather than to overall loading due to the combined weight of body mass. DXA-derived body composition and muscle measurements in MOST have been used to better understand how adiposity and muscle mass, as opposed to body mass and BMI, leads to knee OA.[173-175]

5b7. Bone. While OA has traditionally been considered a disease of cartilage, changes in subchondral bone occur early in the course of OA concurrent with, or preceding, cartilage abnormalities.[128,171,176-180] The density and quality of subchondral bone and its capacity to respond to various stresses, including changes in loading forces caused by altered biomechanics, may influence whether osteoarthritis develops, and if OA is present, either stabilizes or progresses. Subchondral bone in OA is thought to have increased density and stiffness, making it less able to deform under loading, thereby transferring more energy to the overlying cartilage, leading to its degeneration.[128] Subchondral bone may also influence pain as bone is richly innervated. Alterations in trabecular density and architecture may influence deformation under load, and alter intraosseous pressure distribution, which is hypothesized to contribute to pain.[181]

Different patterns of subchondral trabecular bone texture detected from plain radiographs of the knee are thought to reflect variation in response to biomechanical stress and have been found to differ between knees with, and without, cartilage defects and OA.[182,183] Subchondral trabecular bone texture has been measured from MOST knee radiographs using fractal signature analysis and investigated as a predictor of OA onset.[184] In addition, the study's knee MRI data have been used to investigate the spatial co-location of areas of subchondral bone attrition with cartilage damage and bone marrow edema.[185,186] Measures of systemic bone density acquired using DXA in MOST have demonstrated a strong relationship between elevated hip and whole body BMD and the onset of OA and cartilage loss.[187]

Radiographs (e.g., as used in fractal signature analysis) and DXA rely on 2D evaluations of 3D density distributions and do not have the ability or resolution needed to discern spatial distributions of bone that may have specific local effects with implications for the overlying/underlying structures (e.g., cartilage, meniscus, BMLs).[188,189] CT topographic mapping of subchondral density is a 3D imaging tool that precisely measures depth-specific subchondral cortical and trabecular BMD.[181,190] This technique has identified several qualitative and quantitative differences at different depths and regions between OA and normal knees, including greater focal densities and higher density at deeper layers in OA.[191,192] CTs of the knee of the knee for 3D bone density have been acquired in MOST, providing the first opportunity for this measure to be assessed as a risk factor for knee OA.[181,190]

5c. Pain Sensitization. Causes of pain in knee osteoarthritis (OA) remain poorly understood despite pain being the primary symptom and cause of disability in OA. The structure-symptom discordance in knee OA[193,194] suggests that structural pathology alone cannot account for the variation in pain frequency and severity experienced.[195] Alteration in the neurologic processing of nociceptive signaling leading to enhanced pain facilitation may be an important factor in determining the pain experience in OA.[196] The initial symptoms in OA are weight-bearing, thought to reflect nociceptive pain. In later stages, the increase in pain at rest and chronic pain are likely indicative of alterations in central pain processing. An increased responsiveness (sensitization)

of peripheral or central nociceptive neurons leads to heightened pain sensitivity and is a potential mechanism by which pain in knee OA may become severe, chronic and persistent.[197] Pain sensitization, as assessed by quantitative sensory testing, has been associated with painful knee OA when compared with pain-free controls,[196,198-200] and with pain severity independent of knee OA severity.[201,202] To investigate this critical area, MOST is the first large cohort study of knee OA to include serial quantitative sensory testing, including pressure pain threshold (PPT) using pressure algometry, a measure of sensitivity to pain evoked by mechanical stimulation of nociceptors,[195,199,203-205] and mechanical temporal summation, a measure of central pain amplification and a feature of central sensitization.[195,199,201] MOST has also tested for abnormal conditioned pain modulation, a measure that reflects lack of appropriate modulation in the pain inhibitory capacity of the descending inhibitory pathways.[206,207] Pain sensitization measures in MOST are being evaluated as risk factors for increasing severity and frequency of joint pain and the transition from acute to chronic pain.

5d. Nutritional Factors. Many nutrients in food and dietary supplements have been hypothesized to influence the development of OA. Supplement use is popular among persons with OA in the hope that this may help ameliorate or prevent disease. For some nutrients, biological evidence points to the potential for treatment effects. But evidence from rigorous studies on the relation of nutrients in food and supplements to OA outcomes is badly needed.

5d1. Vitamin C and E. Oxidant damage from reactive oxygen species (ROS), a natural product of metabolism, has been implicated in a variety of human diseases including cancer, coronary disease and cataracts. In joints, chondrocytes and other cells produce ROS and oxidant damage may adversely affect the structural integrity of collagen and hyaluronic acid,[208-210] effects which may be prevented by antioxidant enzymes.[209] Because of their antioxidant properties, as well as important non-antioxidant effects on cartilage metabolism,[211,212] both vitamins C and E have been investigated in MOST and other studies for a potential role in protecting joints from the development and progression of OA.[213-219]

5d2. Vitamin D. Vitamin D is a critical hormone that regulates the transition from growth plate cartilage to bone. Hypertrophic chondrocytes present in OA can redevelop vitamin D receptors mimicking the phenotype present in the growth plate and synthesize an excess of type X collagen that may contribute to calcification of cartilage matrix (e.g. the tidemark).[220] OA articular cartilage is sensitive to the effects of vitamin D, although its exact effects on matrix synthesis and degradation are unclear. Vitamin D sufficiency is necessary for bone health[221] and vitamin D might also affect OA activity through the density and quality of periarticular bone. Studies of 25-OH vitamin D status and incidence and progression knee and hip OA have been conflicting.[222-224]

5d3. Vitamin K. Because of vitamin K's important role in regulating bone and cartilage mineralization[225] and the inadequate intake of vitamin K in the general population,[226] it has potential to be a preventative option for osteoarthritis. Cross-sectional observational studies have found an association of low vitamin K status, assessed by both a biochemical measure (plasma phylloquinone concentration) and dietary intake, with knee OA.[227,228]

5d4. Lipids. OA is thought to be an inflammatory disorder, with low grade inflammation affecting the synovium and inflammatory cytokines contributing to cartilage damage,[65] which is the signature pathologic feature of the disease. Omega-6 and omega-3 polyunsaturated fatty acids (n-6 and n-3 PUFAs) are directly linked to inflammation *via* their role as precursors for a family of compounds known as eicosanoids that are mediators and regulators of inflammation.[229] High levels of pro-inflammatory Omega-6 and low levels of anti-inflammatory Omega-3 fatty acids may increase the risk of joint inflammation and knee OA.[230,231]

5d5. Magnesium. Magnesium (Mg^{++}) is an abundant cation in the body's intracellular and extracellular spaces. Dietary ingestion plays a major role in determining magnesium levels. Low dietary intakes enhance inflammatory responses, leading to elevations in CRP levels.[232,233] Mg^{++} also blocks articular glutamate receptors which induce pain when stimulated.[234] Magnesium deficiency may accelerate the development of OA.[235] In two cross-sectional human studies, there were trends for low magnesium intake to be associated with higher than expected rates of radiographic OA.[236,237] In addition to potential effects on OA, magnesium inhibits calcification of cartilage and studies have suggested that low levels of magnesium are associated with cartilage calcification (chondrocalcinosis) which may itself cause episodic joint pain.

MOST investigators have utilized the resources of the study's biospecimen archive to examine the role of vitamins C and E,[238], vitamin D,[239] vitamin K,[240] and lipids[241] in OA development and progression.

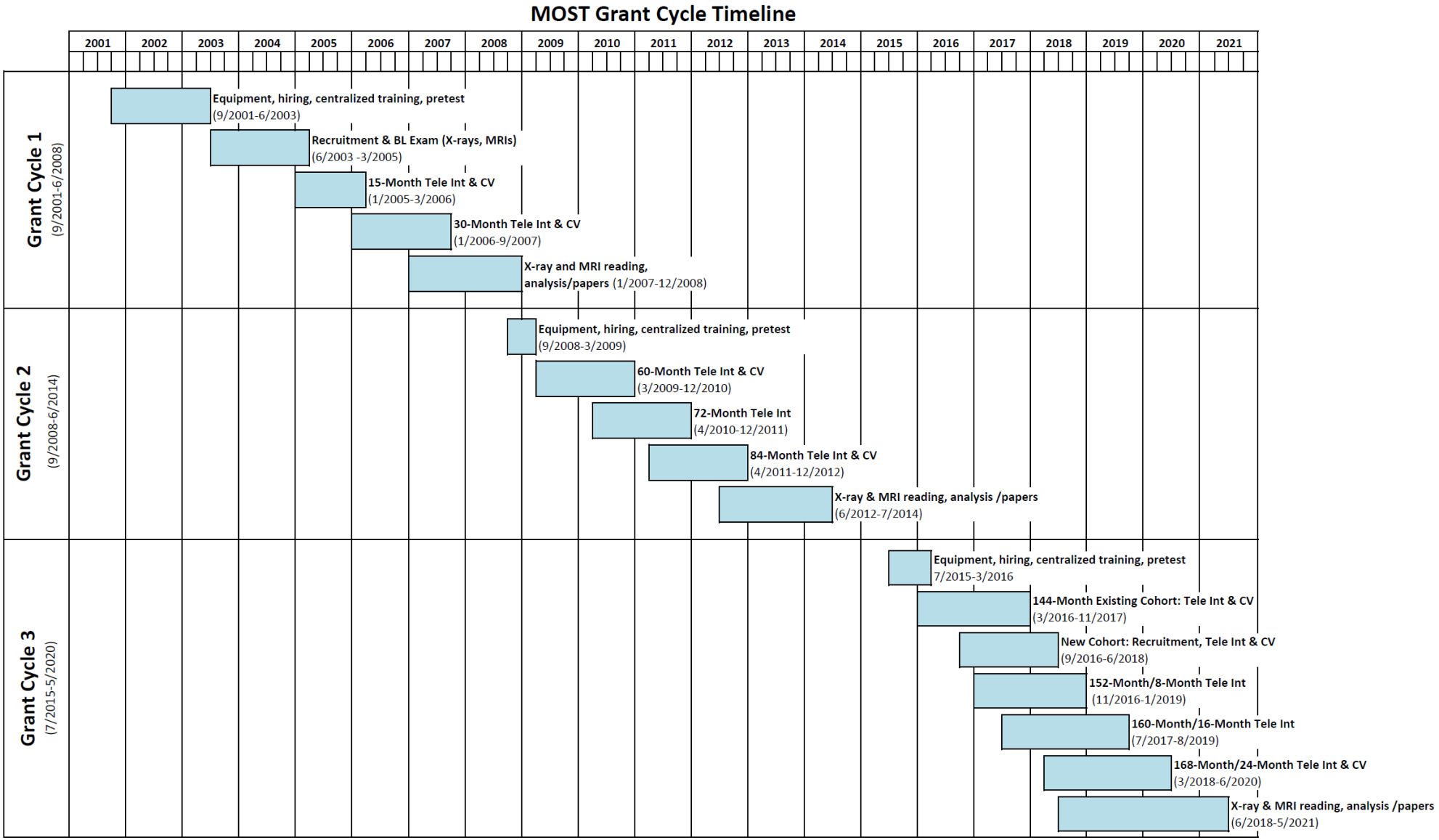
6) Biospecimen Archive

MOST has collected serum, plasma, urine and DNA at multiple time-points and created a specimen bank for use in future studies of biochemical and genetic markers of OA and nutritional factors relevant to OA. While biomarkers are being developed and a variety of genetic polymorphisms tested for their association with osteoarthritis currently, in many instances those fields have not advanced far enough to warrant testing candidates. Therefore preserving biospecimens and DNA provides a potentially high impact opportunity for future OA biomarker studies given the high quality phenotype data on large numbers of individuals available in MOST.

III. STUDY TIMELINE SCHEMA AND SUMMARY OF SPECIFIC AIMS FOR EACH GRANT CYCLE

1) MOST Grant Cycles and Timeline

Figure 1



2) Cycle 1 Specific Aims

- To longitudinally evaluate the effects of three groups of risk factors: biomechanical factors, bone and structural factors and nutritional factors on the occurrence and progression of symptomatic knee OA and radiographic knee OA in a population-based sample of men and women aged 50 to 79.

    - *Biomechanical Factors: Squatting, kneeling and stair climbing, quadriceps weakness, and impaired proprioception;*
    - *Bone and structural factors: Bone marrow edema and meniscal damage on MRI and higher bone density by DXA;*
    - *Nutritional Factors: Low blood levels of vitamin C and E, moderate and low serum levels of 25-OH vitamin D and high levels of PTH.*
- To determine whether factors that increase the risk for incident disease differ from factors affecting progression of existing disease, and whether factors that are associated with joint space loss and cartilage loss differ from factors that influence osteophyte growth.
- To collect plasma, serum, DNA and urine samples and create a specimen bank for future biochemical and genetic studies of biomarkers in OA.

3) Cycle 2 Specific Aims

- To evaluate the influence of variations in biomechanical loading factors during walking and weight-bearing on compartment-specific worsening in knees with OA (defined as compartment-specific cartilage loss based on semi-quantitative MRI reading) and on knee pain with specific activities. Specifically the association of:
    - *high levels of foot pronation with worsening OA in the lateral patellofemoral compartment and knee pain during stair climbing;*
    - *high levels of foot supination with worsening OA in the medial compartment of the tibiofemoral joint, and knee pain while walking;*
    - *increased walking velocity and increased ratio of single to double limb support time with worsening OA in the tibiofemoral compartments;*
    - *increased toe out angle with worsening OA in the medial tibiofemoral joint and the lateral patellofemoral joint*;
    - *greater co-activation of knee extensor and flexor muscles with the risk of worsening OA in the medial tibiofemoral compartment.*
- To study risk factors associated with, and consequences of, knee instability and buckling. Specifically the association of:
    - *quadriceps weakness, poor vibratory sensation and poor balance performance with an increased risk of knee instability and buckling;*
    - *knee instability and buckling with an increased risk of subsequent falls, injurious falls and fractures;*
    - *knee instability and buckling with fear of falling, decreased balance confidence and physical function limitation.*
- To evaluate the relation of abnormal pain sensitivity with the presence of knee pain at baseline, with new development of knee pain at follow-up, with the severity of knee pain at baseline, and with change in severity of knee pain at follow-up. Specifically the association of these outcomes with:
    - *greater pain sensitivity at the knee (indicating peripheral sensitization)*
    - *abnormal pain sensitivity at the tibial tuberosity (indicating central sensitization);*
    - *abnormal pain sensitivity at the elbow (indicating an underlying predisposition to pain independent of the diseased joint).*

- To study the trajectories of knee-related physical function and cartilage loss over 7 years, and factors affecting these trajectories. Specifically:
    - *the influence on these trajectories of physical activity, knee pain, knee or hip replacement, use of assistive technologies, age, female gender, pain in multiple joints, obesity, and higher levels of pain and depressive symptom;*
    - *the association of short-term cartilage loss with longer-term functional loss.*

4) Cycle 3 Specific Aims

- To evaluate novel risk factors for knee pain and structural deterioration that promise to yield new insights into disease biology and new opportunities for treatment and prevention, including:
    - *calcium crystal deposition within the knee joint (assessed using CT);*
    - *increased local 3D depth-specific bone density in the knee (assessed using CT);*
    - *increased slope of the force at heel strike (assessed using a force plate);*
    - *hip abductor weakness.*
    - *pain sensitivity assessed by quantitative sensory testing and conditioned pain modulation with the risk of worsening knee pain and the transition from acute to chronic pain;*
- To track the longitudinal trajectories of pain sensitization for up to 9 years.
- To evaluate novel risk factors for function loss, knee buckling, falls and development of multiple joint pain, including:
    - *gait asymmetry and gait complexity (assessed using accelerometers in the clinic and in the community).*

IV. SCHEDULE OF MEASUREMENTS

Table 2. Measurement Schedule for MOST Grant Cycles 1 and 2.

Measurements & Instruments Questionnaire and Interview Measures	Screening	Baseline	Follow-up Visits				
			15mo	30mo	60mo (Cycle 2 Baseline)	72mo	84mo
SCREENING / DEMOGRAPHICS							
- Age and gender	X[4]						
- Ethnicity, racial background, level of education		X[5]					
- Marital status[a] and live alone or with others[b]		X[a,b,5]			X[b,5]		X[a,b,5]
- Employment, current and past		X[5]		X[5]	X[5]		X[5]
- Household: Ability to pay monthly bills					X[5]		X[5]
- Screening exclusion: Inflammatory arthritis	X[4]						
KNEE SYMPTOMS							
- Knee symptoms, past 12 months and past 30 days	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]
- First knee symptoms, how many years ago							X[4]
- Knee pain visual 0-100 rating scale, past 30 days		X[5]	X[2,3,5]	X[4]	X[4]		X[4]
- WOMAC knee pain, past 30 days	X[4]	X[5]	X[2,3,5]	X[5]	X[5]		X[5]
- WOMAC knee stiffness, past 30 days	X[4]	X[5]	X[2,3,5]	X[5]	X[5]		X[5]
- Initial pain at clinic visit					X[4]		
- Constant and intermittent pain (ICOAP), past 7 days					X[4]		X[4]
- Knee pain map			X[1]		X[4]		X[4]
- Knee buckling		X[4]		X[4]	X[4]	X[4]	X[4]
KNEE-RELATED FUNCTION AND QOL							
- WOMAC physical function - past 7 days		X[5]	X[2,3,5]	X[5]	X[5]		X[5]
- KOOS function/sports/recreation, past 30 days		X[5]	X[2,3,5]	X[5]	X[5]		X[5]
OTHER JOINT SYMPTOMS							
- Hip symptoms, past 30 days		X[5]	X[4]	X[4]	X[4]	X[4]	X[4]
- WOMAC hip symptoms, past 30 days		X[5]	X[2,3,5]	X[5]			
- Hip surgery (THR)		X[4]	X[4]	X[4]	X[4]	X[4]	X[4]
Joint pain (homunculus diagrams), past 30 days							
- Body: shoulders, elbows, hips, wrists, hands, knees, ankles, neck		X[5]	X[2,3,5]	X[5]	X[5]		X[5]
- Feet and/or hands		X[5]			X[5]		X[5]
- Back pain and function, past 30 days		X[5]		X[5]	X[5]		X[5]
GENERAL HEALTH							
- Arthritis diagnosis		X[5]	X[2,3,5]	X[5]	X[5]	X[4]	X[5]
- SF-12		X[5]	X[2,3,5]	X[5]	X[5]		X[5]
- CES-D (depressive symptoms)		X[5]		X[5]	X[5]		X[5]
- Cognition (Fillit[a] or Callahan 6-Item Screener[b])					X[a,4]		X[b,4]
- Comorbidity Index		X[5]		X[5]	X[5]		X[5]
- Pittsburg Sleep Quality Index and fatigue, past 7 days					X[5]		X[5]
- Medical care and insurance							X[5]

Table 2 (*Continued*) Measurement Schedule for MOST Grant Cycles 1 and 2.

Measurements & Instruments: Questionnaire and Interview Measures	Screening	Baseline	Follow-up Visits				
			15mo	30mo	60mo (Cycle 2 Baseline)	72mo	84mo
FUNCTIONAL STATUS AND DISABILITY							
- Mobility: Assistive technology / devices (HAQ)					X[5]		X[5]
- Disability: Walk by self without help / walker			X[4]				
- Limitation of activity due to pain, past 30 days		X[4]	X[4]	X[4]	X[4]	X[4]	X[4]
- Late-life FDI: Disability Component		X[5]	X[2,3,5]	X[5]	X[5]		X[5]
- Physical Activity Scale for the Elderly (PASE), past 7 days		X[4]					X[1,4]
- PF-10 Scale of SF-36					X[5]		X[5]
- Stair flights climbed, past 7 days		X[4]					X[1,4]
MEDICATION							
- Medication inventory (Rx and/or non-Rx), past 30 days		X[4]	X[2,3,4]	X[4]	X[4,7]		X[4,7]
- Vitamins E and C supplements		X[4]	X[2,3,4]	X[4]			
- Vitamin D supplements					X[4]		X[4]
Selected medications, self-reported							
- Salicylates/NSAIDs/opioids, current use		X[5]		X[5]	X[5]		X[5]
- Bisphosphonates/estrogens, past 12 months		X[4]		X[4]	X[4]		X[4]
- Knee injections for arthritis, past 6 months		X[5]		X[4]	X[4]		X[4]
HEALTH BEHAVIORS AND OA RISK FACTORS							
- Knee injury history		X[4]	X[2,3,4]	X[4]	X[4]	X[4]	X[4]
- Knee surgery history (for TKR, see Misc. below)	X[4]	X[4]	X[2,3,4]	X[4]	X[4]	X[4]	X[4]
- Family history of arthritis		X[5]					
- Height and weight history		X[5]					
- Shoe heel height		X[4]					
- Fracture history (after age 45)		X[5]					
- Injury, fractures, falls, past 12 months or since last contact			X[2,3,4]	X[5]	X[5]	X[4]	X[5]
- Falling (fear of)					X[5]	X[4]	X[5]
- Activities-specific Balance Confidence Scale (ABC)					X[5]		X[5]
- Tobacco use history		X[5]					
- Tobacco use, current							X[5]
- Coping Strategies Questionnaire (CSQ) - Pain Catastrophyzing subscale elements					X[5,6]		X[5,6]
- Accelerometer questionnaire (knee pain, sleep, and fatigue during 7-day collection)							X[1]
- Female history – pregnancy history, childbirth, hysterectomy				X[5]			
MISCELLANEOUS							
Outcomes							
- Knee/hip replacement			X[8]	X[8]	X[8]	X[8]	X[8]
- Knee/hip replacement pre-operative diagnosis			X[9]	X[9]	X[9]	X[9]	X[9]
- Confirmation of death by public records			X	X	X	X	X

Table 2 (*Continued*) Measurement Schedule for MOST Grant Cycles 1 and 2.

Measurements & Instruments: Examination Measures	Screening	Baseline	Follow-up Visits				
			15mo	30mo	60mo (Cycle 2 Baseline)	72mo	84mo
Blood collection, fasting						No clinic visit	
- Serum and EDTA plasma		X[11]		X[1,11]	X[11]		
- EDTA Supernatant		X[12]					
- Buffy coat for DNA		X[13]					
Urine collection							
- Second AM void		X[11]		X[11]	X[11]		
Height, standing		X			X		
Weight	X[4]	X	X[2,3]	X	X		X
Leg length		X					
Knee height		X					
Knee laxity		X					
Leg proprioception		X					
Knee flexion contracture		X					
Hand exam		X					
Pain sensitization (i.e. von Frey filaments, pressure algometer)					X		X
Peripheral neuropathy					X		
Vibration perception threshold					X		
Knee range of motion							X
Knee joint examinations							
- Trochanteric bursitis		X[1]	X[2]	X[1]			
- Iliotibial band friction syndrome		X[1]	X[2]	X[1]			
- Anserine bursa tenderness		X[1]	X[2]	X[1]			
- Medial knee fat pad and other tenderpoints		X[1]	X[2]	X[1]			
- Hip internal rotation (pain and range of motion)		X[1]	X[2]	X[1]			
- Tenderpoint exams		X[1]	X[2]	X[1]			
Blood pressure		X		X	X		X
Performance Measures							
- 20-meter timed walk		X		X	X		X
- Chair stands, timed		X		X	X		X
- Balance exams (rapid step ups, maximum step length)					X		
- Isokinetic upper leg concentric strength		X[10]			X[10]		
- Surface EMG, muscle co-activation (during isokinetic strength)					X		
- Plantar Pressure					X		
- Gait assessment (GAITRite)					X		
- Accelerometer (7-day collection)					X[1]		X[1]
MRI							
- 1.0T MRI (Coronal, Sagittal, Axial)		X[10]	X[2,3,10]	X[10]	X[10]		X[10]
- 1.0T MRI 3-Point Dixon sequence		X[1,10]			X[1,10]		
- 1.5T MRI (Laxity Ancillary Study)		X[1]		X[1]			
- 1.5T MRI (Gadolinium Ancillary Study)				X[1]			
X-ray							
- Knee (PA and lateral)		X[10]	X[2,10]	X[10]	X[10]		X[10]
- Full-limb		X			X		
DXA Bone Density							
- Hip		X		X[1]			X
- Whole body		X		X[1]			X

Footnotes to Table 2 (MOST Grant Cycles 1 and 2).

[1] Subset of participants
[2] Subset of participants: 15-month potential cases
[3] Subset of participants: 15-month controls
[4] Measured by interview
[5] Measured by self-administered questionnaire (SAQ)
[6] Subset of questions
[7] Rx medications only
[8] Self-reported or physician adjudicated by x-ray or surgery records, if available
[9] Pre-op diagnosis derived from surgery records, if available
[10] Bilateral or unilateral
[11] MOST samples available through NIA Aging Research Biobank (https://agingresearchbiobank.nia.nih.gov/)
[12] EDTA Supernatant samples used for parent study or destroyed (limited shelf life)
[13] DNA extracted from baseline buffy coat samples

Table 3. Measurement Schedule for MOST Grant Cycle 3.

Measurements & Instruments Questionnaire and Interview Measures (measurement methods)	Screening	Baseline (144mo)	Follow-up Visits		
			8mo[4] (152mo)	16mo[4,5] (160mo)	24mo (168mo)
SCREENING / DEMOGRAPHICS					
- Age and gender	X[1]				
- Education		X[1]			
- Ethnicity, racial background	X[1]				
- Marital status and live alone or with others		X			X
- Current Employment		X			X
- Household: Ability to pay monthly bills		X			X
- Screen: Pregnancy and female history (menstrual history, childbirth, hysterectomy, menopause)	X[1]				
- Screen: Walk without a walker	X[1]				
- Screen: Inflammatory arthritis	X[1]				
- Screen: Cancer / health	X[1]				
- MRI and/or CT eligibility	X[1]	X[2]			X
KNEE SYMPTOMS					
- Knee symptoms, past 12 months and past 30 days	X[1]	X	X[4]	X[4]	X
- Knee pain visual 0-100 rating scale, past 30 days		X			X
- WOMAC knee pain, past 30 days		X	X[4]	X[4]	X
- WOMAC knee stiffness, past 30 days		X	X[4]	X[4]	X
- ICOAP (Constant and intermittent pain)		X	X[3,4]	X[3,4]	X
- Knee pain location		X			X
- Knee buckling		X	X[4]	X[4]	X
KNEE-RELATED FUNCTION AND QOL					
- WOMAC physical function - past 7 days		X	X[4]	X[4]	X
- KOOS function/sports/recreation, past 30 days		X[1]			X[1]
OTHER JOINT SYMPTOMS					
- Hip symptoms, past 30 days		X			X
- Hip surgery		X	X[4]	X[4]	X
JOINT PAIN (homunculus diagrams), past 30 days					
- Body: shoulders, elbows, hips, wrists, hands, knees, ankles, neck		X	X[4]	X[4]	X
- Feet and/or hands		X			X
- Back pain and function, past 30 days		X	X[3,4]	X[3,4]	X
GENERAL HEALTH					
- Arthritis diagnosis		X			X
- SF-12 (health survey)		X			X
- CES-D (depressive symptoms)		X			X
- Modified Charlson Comorbidity Index		X			X
- Pittsburg Sleep Quality Index (PSQI) and fatigue		X[1]			X[1]
- 7-day sleep and fatigue		X			X
- Physical therapy		X			X
- Medical care and insurance		X			X
- Major hospitalizations		X	X[4]	X[4]	X

Table 3 (*Continued*) Measurement Schedule for MOST Grant Cycle 3.

Measurements & Instruments: Questionnaire and Interview Measures	Screening	Baseline (144mo)	Follow-up Visits		
			8mo (152mo)	16mo (160mo)	24mo (168mo)
FUNCTIONAL STATUS AND DISABILITY					
- Helpful aids/devices (Stanford HAQ)		X[2]			X[2]
- Late-life FDI: Disability Component		X[2]			X[2]
- Pain DETECT		X			X
- PROMIS function (pain behavior and interference)		X			X
- Physical Activity Scale for the Elderly (PASE), past 7 days		X			
- PF-10 Scale of SF-36		X			X
- Life-Space Assessment		X[2]			X[2]
MEDICATION					
- Medication inventory (Rx), past 30 days		X			X
- Vitamin D supplements, calcium, magnesium		X			X
Selected medications, self-reported					
- Joint pain medications		X			X
- Salicylates/NSAIDs/opioids, current use		X			X
- Bisphosphonates/estrogens, past 12 months		X			X
- Knee injections for arthritis, past 6 months		X			X
HEALTH BEHAVIORS AND OA RISK FACTORS					
- Knee injury history		X	X[4]	X[4]	X
- Knee surgery history (for TKR, see Misc. below)		X	X[4]	X[4]	X
- Family history of arthritis		X[1]			
- Weight history		X[1]			
- Fracture history (after age 45)	X[1]				
- Fracture since last contact		X	X[4]	X[4]	X
- Falling (fear of)		X			X
- Tobacco use history		X[1]			
- Tobacco use, current		X[2]			X
- Coping Strategies Questionnaire (CSQ) - Pain Catastrophyzing subscale elements		X			X
- Accelerometer questionnaire (knee pain, sleep, and fatigue during 7-day collection)		X			
MISCELLANEOUS					
Outcomes adjudication					
- Knee/hip replacement		X	X	X	X
- Knee/hip replacement pre-operative diagnosis		X	X	X	X
- Confirmation of death by public records		X	X	X	X

Table 3 (*Continued*) Measurement Schedule for MOST Grant Cycle 3.

Measurements & Instruments: **Examination Measures (methods references)**	**Screening**	**Baseline** (144mo)	**Follow-up Visits**		
			8mo (152mo)	**16mo** (160mo)	**24mo** (168mo)
Blood collection, fasting			No clinic visit	No clinic visit	
- Serum and EDTA plasma		X[1]			
- Buffy coat for DNA		X[1]			
- Paxgene		X[1]			
Urine collection		X[1]			
Height, standing		X			
Shoe hardness		X			
Foot length		X			
Weight	X[1]	X[2]			X
Hand photo		X			
Hip internal rotation (pain and range of motion)		X			
Blood pressure		X			X
Performance Measures of Function					
- 20-meter timed walk		X			X
- Chair stands, timed		X			X
- Timed Up and Go (TUG) Test		X[2]			X[2]
- 6 Minute Timed Walk (6MTW)		X			X
Biomechanical Measures					
- Quadriceps power and hip strength		X			
- Gait asymmetry, complexity OPAL		X			
- Force of heel strike		X			
- Objective physical activity (7-day accelerometer data w/ AX3)		X			
- Postural sway (Opal monitor)		X			
Quantitative Sensory Testing					
- Conditioned pain modulation		X			X
- Pressure pain threshold		X			X
- Temporal summation		X			X
- Peripheral neuropathy		X			X
Knee CT (chondrocalcinosis and local BMD)		X			
Knee MRI (1.5T - Extremity)		X			X
X-ray					
- Knee (PA and lateral)	X[1]	X[2]			X
- Full-limb		X[1]			
Cognitive Assessment: MoCA (>65 yrs)		X[2]			X

Footnotes to Table 3 (MOST Grant Cycle 3).
[1] New Cohort only
[2] Original Cohort only
[3] Subset of questions
[4] Interim TI collected in participants who had CV at 144M

V. SUBJECTS

Va. SUBJECTS – MOST ORIGINAL COHORT (FIRST CYCLE)

Recruitment and Enrollment for the First Cycle: Baseline Clinic Visit

MOST recruited a community-based sample of older men and women, drawn from the general population but selected so as to be likely to either have preexisting knee OA (about one third) or to be at high risk for knee OA (about two thirds) based on the presence of risk factors for knee OA, while maintaining a distribution of age and gender in proportion to the U.S. population.

Inclusion Criteria

- Ages 50 to 79
- Women and men
- All ethnic/racial groups
- Frequent knee pain, defined as knee pain on most days of the past month, reported at both the screening telephone call and about one month later at the baseline clinic visit
- In those without frequent knee pain, one or more of the following risk factors for knee OA:
  - Overweight: above the age- and gender-specific median weight in the Framingham Study
  - A history of knee injury that resulted in limited ability to walk for at least 2 days
  - A history of knee surgery, including meniscus and ligament repair and unilateral total joint replacement

Exclusion Criteria

- Unable to walk without the assistance of another person
- Unable to come to clinic for the baseline examination
- Total knee replacement (TKR) in both knees, or TKR in one knee with plans to have other knee replaced within the next year
- Not competent to provide informed consent
- Plans to move out of the area during the next 3 years
- Active life-threatening cancer or other life-threatening illness that made survival to follow up unlikely
- Rheumatoid arthritis (RA) or other forms of inflammatory arthritis, based on self-report of MD diagnosis confirmed using a connective tissue screening questionnaire with high sensitivity and specificity for RA,[242] and by self-reported use of specific medications used primarily for these forms of arthritis: e.g., gold, methotrexate, leflunamide, plaquenil and various biologics.

Recruitment and Enrollment

Recruitment and enrollment were conducted in 2003-5. Participants were recruited and enrolled at two clinical centers, one located at the University of Iowa (UI) and the other at the University of Alabama at Birmingham (UAB). Both centers had an established track record of enrolling and retaining large cohorts for epidemiological and clinical studies.

Potential participants were initially contacted through mass mailings, along with a variety of community outreach and media activities, including press releases, paid advertisements, and presentations at community health fairs and to community groups. Mass mailing databases were specific to those most useful at each clinical center, and included department of motor vehicles records, population-based voter registration listings, and other databases maintained by the UAB and UI recruitment and retention shared facilities.

Each center had target enrollment goals stratified by decile of age and gender according to their proportion of the U.S. population age 50-79 years, based on the 2000 U.S. census data when MOST was proposed, and by racial/ethnic minority status according to their representation in the recruitment area communities. This was anticipated to result in a sample of primarily non-Hispanic whites and African Americans. The UAB site, recruiting from the Birmingham metro area, aimed to recruit about 30% African American participants and completed recruitment with 29.8%. Although the Iowa City metro area had only 13.1% nonwhite ethnic minorities, the surrounding rural population was specifically targeted to represent the regional, agricultural Iowa City area.

Recruitment and enrollment at baseline had three stages:

- Initial Contact. Mass mailing of brochures describing the study and requesting return of a postage-paid postcard or phone contact indicating interest in the study, supplemented with outreach and media activities.
- Screening Telephone Interview. Potential participants who contacted the clinic expressing interest were called and administered a screening interview over the phone covering inclusion and exclusion criteria, including a question about the occurrence of knee pain on most days of the past month, and contraindications for knee MRI scans.
- Enrollment visit (initial MOST baseline visit). Those who were eligible after the screening interview were invited to attend an enrollment clinic visit to occur within approximately one month of the screening interview. Self-administered questionnaires were mailed to eligible screenees and completed questionnaires brought to the clinic visit. At the clinic visit the question about the occurrence of knee pain on most days of the past month was repeated. Eligibility on the basis of frequent knee pain required a positive answer to this question on the Screening Interview. The initial baseline visit consisted of interviews, self-administered questionnaires, joint imaging, other physical and risk factor examinations and biospecimen collection.

For a complete inventory of the measurements obtained at the screening telephone interview and the baseline clinic visit, see Table 2. In general, all measurements were obtained in participants who attended the clinic visits except when they met exclusion criteria specific for a measurement. For example, some participants were unable undergo an MRI scan of the knee, either because they had contraindications to MRI scans or their knees did not fit in the bore of the dedicated extremity scanner used in MOST. Ability to have knee MRI scans was not a requirement for enrollment, and 14% of the 3,026 enrolled participants (12% of women and 17% of men) did not have a knee MRI scan at baseline.

Characteristics of the MOST Original cohort at baseline

3,026 participants had a baseline clinic visit examination and were enrolled, 1,507 at the University of Iowa and 1,519 at the University of Alabama at Birmingham. Baseline characteristics are in Table 4.

Table 4. Characteristics of Enrolled Participants at Baseline of the First Cycle		
Characteristic	N=3026	Percent
Age 50 – 59	1167	38.6%
Age 60 - 69	1174	38.8%
Age 70 - 79	685	22.6%
Female	1820	60.1%
Male	1,206	39.0%
White	2,509	82.9%
AA	461	15.2%
Hispanics	19	0.6%
Other	37	1.2%
BMI < 25	447	14.8%
BMI 25 to 30	1,093	36.1%
BMI 30 plus	1,486	49.1%
Frequent knee pain either knee (at both screening call and clinic visit),	1,272	42.0%
X-ray OA either knee (K/L grade ≥ 2 or KR)	1,607	53.1%
Symptomatic OA either knee (frequent pain and x-ray OA in same knee)	799	26.4%
History of knee injury or surgery in either knee		
Injury	1,270	42.0%
Surgery	671	22.2%
Injury or surgery	1,458	48.2%
Injury and surgery	335	11.1%
Baseline MRI in >=1 knee	2,600	85.9%

Vb. SUBJECTS – MOST ORIGINAL COHORT (SECOND CYCLE)

Recruitment and Enrollment for the Second Cycle: 60 Month Time-Point Clinic Visit (Baseline for the Second Cycle)

To address the specific aims of the Second Cycle of MOST, all surviving participants were invited to participate in clinic visit examinations and phone interviews. Data collected at the 60-month time-point serves as the baseline assessment for the aims of the Second Cycle. In addition, joint imaging and joint pain, function and other data was collected that served as outcomes for the aims of the First Cycle of MOST.

Recruitment and enrollment were conducted in 2009-2010 and had two stages.

- Initial phone contact and interviews. Participants were contacted by telephone to determine willingness to participate in the Second Cycle of interviews, clinic visits and examinations, and if willing, they had a brief phone interview to assess knee symptoms and MRI eligibility. Willing participants were invited to attend a clinic visit at the time-point 60 months after baseline clinic visit of the First Cycle, which serves as baseline for the Second Cycle aims. Potential participants who were willing to continue in the study but not willing to have a clinic visit, were asked to complete a missed clinic visit telephone interview, which collected additional follow-up data for self-reported outcomes related to the First Cycle of MOST, including joint symptoms, arthritis treatments, physical function and disability and updated key covariates such as comorbidities and OA treatments.
- Clinic Visit (baseline visit for Second Cycle). At the clinic visit exam, eligibility and willingness for a knee MRI were confirmed, and participants had joint imaging, interviews, self-administered questionnaires, examinations, and biospecimen collection.

A detailed inventory of the measurements obtained during the telephone contacts and clinic visit at the 60 month time-point are in Table 2.

Participation rates in the 60 month clinic visit were high at both UI and UAB, with 81% and 78% of survivors, respectively, attending a clinic visit exam. 2,330 participants attended the Second Cycle baseline clinic visit at the 60 month time-point, 1,197 at UI and 1,133 at UAB. Characteristics of the cohort who had a 60-month clinic visit are in Table 5.

Table 5. Characteristics of Participants at the Second Cycle Baseline Clinic Visit (60 month time-point after enrollment in MOST)

Characteristic	N=2,330	Percent
Age 50 – 59	511	21.9%
Age 60 - 69	891	38.2%
Age 70 - 79	764	32.8%
Age 80 plus	164	7.1%
Female	1409	60.5%
Male	921	39.5%
White	1956	83.9%
AA	334	14.3%
Hispanics	13	0.6%
Other	27	1.2%
BMI < 25	341	14.6%
BMI 25 to 30	834	35.8%
BMI 30 plus	1155	49.6%
Frequent knee pain either knee (at both screening call and clinic visit),	832	35.7%
X-ray OA either knee (K/L grade ≥ 2 or KR)	1481	63.6%
Symptomatic OA either knee (frequent pain and x-ray OA in same knee)	563	24.2%
History of injury and surgery in either knee		
Injury	1120	48.1%
Surgery	758	32.5%
Injury or surgery	1374	59.0%
Injury and surgery	504	21.6%
60m MRI in >=1 knee	1654	71.0%

Vc. SUBJECTS – MOST NEW COHORT (THIRD CYCLE)

Recruitment and Enrollment for the Third Cycle Baseline Clinic Visit

For the Third Cycle, MOST added a focus on the development of early knee OA, with the goal of identifying modifiable risk factors for prevention in persons who have early or mild symptoms and signs of knee OA, a stage of disease that is likely to be more amenable to intervention than more advanced disease. To do so, the study enrolled a New Cohort consisting of two subgroups:

1) individuals who had early or mild knee symptoms and no, or early, radiographic findings of knee OA; and

2) control group who had no knee pain and had no, or mild, radiographic knee OA.

The overall enrollment goal was 1,500 subjects, with approximately 80% with knee pain and 20% without knee pain.

As in the First Cycle, MOST recruited a community-based and racially diverse sample of men and women, drawn from the general population, but selected based on screening for knee symptoms and radiographic knee OA, with an emphasis on enrolling African Americans and Hispanics.

Eligibility criteria were determined at the Telephone Screening Interview unless otherwise noted.

Inclusion Criteria:

1. Knee pain and no knee pain subgroups

- Ages 45 to 69
- Women and men
- All ethnic/racial groups, with an emphasis on recruitment of Hispanics and African Americans
- Both knees with KL grades of radiographic OA of 0, 1, or 2 in the tibiofemoral and patellofemoral compartments (determined by radiograph during the Screening Visit)

2. Knee pain subgroup

- Report of any pain, aching or stiffness in one or both knees in the past 30 days
- Both knees with KL grades of radiographic OA of 0, 1, or 2 in the tibiofemoral and patellofemoral compartments (determined by radiograph during the Screening Visit)

3. No knee pain subgroup

- Both knees without any knee pain, aching, or stiffness in the previous 30 days

Exclusion Criteria:

1. Knee pain subgroup

- Constant pain of severe or greater intensity in either knee, assessed with the ICOAP questionnaire[41]

2. Knee pain and no knee pain subgroups

- Knee joint replacement surgery in either knee
- Unwilling or ineligible at baseline to have all four baseline imaging exams (knee x-rays, full-limb x-rays, extremity MRI scan and CT scan of the knees) and the 24-month follow-up imaging (knee x-rays and extremity MRI scan)
- Not able to walk without the aid of a person, walker, cane, prosthesis, or assistive device
- Neither knee fits in the MRI knee coil (determined during Screening Visit).
- Advanced structural tibiofemoral or patellofemoral knee OA disease (KL grade 3 or 4) in either knee (determined by radiograph during Screening Visit)
- Rheumatoid or inflammatory arthritis (based on self-report and use of medications specific to these conditions)
- Serious health condition e.g., end-stage renal disease, etc. that would likely limit follow-up to less than 2-3 years
- Plan to relocate out of geographic region in next 3 years
- Not competent to give informed consent

Recruitment and Enrollment

Recruitment and enrollment were conducted in 2016-2018 at the UI and UAB MOST clinics.
As with the MOST Original Cohort, a community-based sample was recruited for the Third Cycle. Enrollment targets were stratified by gender and by decile of age according to their proportion of the U.S. population age 45-69 years in (2010 U.S. Census). In addition, MOST intended to over-recruit Hispanic participants compared to their representation in the recruitment area communities, with a goal of 8% (60 participants) at UAB and

10% (80 participants) at UI, and to over-recruit African Americans with a goal of 40% (300 participants) at UAB and 5% (37 participants) at UI.

Potential participants were initially contacted through mass mailings, along with various community outreach and media activities, including press releases, paid advertisements, and presentations at community health fairs and to community groups. Mass mailing databases again included department of motor vehicles records, population-based voter registration listings, and databases maintained by the UAB and UI Recruitment and Retention Shared Facilities.

Recruitment and enrollment had four stages:

- Initial contact. Mass mailing of postcards describing the study and requesting a return phone call indicating interest in the study, supplemented with outreach and media activities.
- Telephone Screening Interview. Potential participants who contacted the clinic expressing interest were called and administered a screening interview over the phone that assessed interest in participating in the study, inclusion and exclusion criteria and eligibility, and willingness to have joint radiographs, knee MRI and CT of the knees.
- Screening Clinic Visit. Willing participants who were eligible after the Telephone Screening Interview were invited for a brief screening visit, to occur within approximately one month of the Screening Interview, to assess knee pain, eligibility and contraindications for knee MRI scans, and radiographs to determine the presence and severity of OA of the tibiofemoral and patellofemoral joint.
- Enrollment Clinic Visit (New MOST Cohort baseline visit). Those who were eligible after the Screening Visit were invited to attend an enrollment clinic visit, to occur within approximately one month of the Screening Visit. At the Clinic Visit, eligibility and willingness for MRI, radiograph and CT imaging and other eligibility criteria were confirmed, and those eligible had a baseline assessment consisting of knee MRI and CT, interviews, self-administered questionnaires, examinations, and biospecimen collection.

For a detailed inventory of the measurements and biospecimens obtained at the Telephone Screening Interview, Screening Visit and Enrollment Visit, see Table 2.

Characteristics of the MOST New Cohort at baseline

1,525 participants were enrolled in the New Cohort and had a baseline clinic visit examination, 747 at UI and 778 at UAB. Subjects with knee pain comprised 74% of the cohort and 26% had no knee pain at baseline. Table 6 shows selected characteristics of the New Cohort at their baseline visit.

Table 6. Characteristics of MOST New Cohort Participants at the Baseline Clinic Visit		
Characteristic	**No knee pain** N=401 (100%)	**Knee pain** N=1124 (100%)
Age 45 - 49	81 (20.2%)	213 (19.0%)
Age 50 – 59	160 (39.9%)	527 (46.9%)
Age 60 - 70	160 (39.9%)	384 (34.1%)
Female	241 (60.1%)	606 (53.9%)
Male	160 (39.9%)	518 (46.1%)
White	250 (62.3%)	867 (77.1%)
AA	113 (28.2%)	201 (17.9%)
Hispanics	21 (5.3%)	36 (3.2%)
Other	17 (4.2%)	20 (1.8%)
BMI < 25	142 (35.4%)	288 (25.6%)
BMI 25 to 30	137 (34.3%)	442 (39.3%)
BMI 30 plus	122 (30.4%)	394 (35.1%)
Frequent knee pain (at both screening call and clinic visit, either knee)	0	363 (32.3%)
X-ray OA either knee (K/L grade = 2)	8 (2%)	88 (7.8%)
Symptomatic knee OA (frequent knee pain AND x-ray OA, either knee)	0	31 (2.8%)
History of knee injury or surgery in either knee		
Injury	50 (12.5%)	312 (27.8%)
Surgery	12 (3.0%)	102 (9.1%)
Injury or surgery	56 (14.0%)	340 (30.3%)
Injury and surgery	3 (0.8%)	47 (4.2%)
Joint Imaging		
MRI in >=1 knee*	392 (97.8%)	1119 (99.6%)
CT scan of knees**	388 (96.8%)	1085 (96.5%)
* MRIs may be missing due to technical problems with scanner or new contraindications. ** CTs may be missing due to failure to return for a separate CT scan visit after enrollment.		

Vd. SUBJECTS –MOST ORIGINAL COHORT (THIRD CYCLE)

Recruitment and Enrollment for the Third Cycle Baseline Clinic Visit (144-month time-point after enrollment of the MOST Original Cohort)

Surviving participants of the Original Cohort who had not withdrawn consent were eligible to participate in the Third Cycle of MOST. However, not all participants were eligible for the Third Cycle baseline clinic visit examination. Those who had bilateral TKRs (total knee replacements) were not eligible for the baseline clinic visit examination, but were eligible for a telephone interview. (These participants were being followed in a separate ancillary study of TKRs.) In addition, individuals who had bilateral endstage disease knee OA, defined as bilateral K-L grade 3-4 OA in both knees, or KL-3-4 in one knee and TKR in the other knee, were eligible to attend the clinic exam but would not undergo joint imaging exams (radiograph, MRI or CT) because they would not contribute useful information about joint structural outcomes of early disease, which were a primary focus of the Third Cycle aims.

Inclusion criteria:

- Surviving member of the Original MOST cohort (enrolled 2003-2005)
- Willing to participate in the Third Cycle clinic examinations and/or telephone interviews

Exclusion criteria:

- Consent previously withdrawn
- Not competent to give informed consent
- Developed rheumatoid or inflammatory arthritis since enrollment in MOST

Exclusion criteria for baseline clinic visit exam (eligible for a baseline phone interview):

- Bilateral TKR at the baseline time-point

Exclusion criteria for imaging at the baseline clinic visit exam (eligible for a baseline clinic visit):

- Bilateral end-stage knee OA, defined as K-L grade 3-4 OA in both knees, or in one knee and TKR in the other knee (K-L grade based on the most recent radiograph from a prior clinic visit)

Recruitment and enrollment had two stages:

- Initial telephone contact and interview. Participants were contacted by telephone to determine willingness to participate in the Third Cycle interviews and examinations, and if willing had a brief interview to determine eligibility for a clinic visit, MRI eligibility, knee symptoms and general health.
  Potential participants who were not eligible for the clinic visit (e.g., bilateral TKR), or who were eligible but were not willing to have a clinic visit, were asked to complete a missed clinic visit phone interview. The interview collected additional follow-up data for PROs (patient-reported outcomes) related to the First and Second Cycles of MOST, including joint symptoms, arthritis treatments, physical function and disability and updated key covariates such as comorbidities and OA treatments.
- Clinic Visit (baseline visit for Third Cycle Aims). Those who were eligible based on the initial phone contact were invited to attend the enrollment clinic visit, to occur within approximately one month of the telephone interview. At the clinic visit exam, participants had a baseline assessment for measurements related to the aims of the Third Cycle, consisting of joint imaging, interviews, self-administered questionnaires, and examinations.

For a detailed inventory of the measurements obtained during the Telephone Interview and Clinic Visit, see Tables 2 and 3.

Characteristics of the MOST Original Cohort at the 144 Month Time-point (Third Cycle Baseline)
1,309 members of the Original Cohort (49% of survivors), 731 at UI and 578 at UAB, had a baseline clinic visit examination for the Third Cycle. Another 23% completed a missed clinic visit telephone interview (MCVTI) and 10% completed the brief phone interview. Table 7 shows selected characteristics of the Original Cohort at 144 months.

Table 7. Characteristics of Original MOST Cohort Participants at the Baseline of the Third Cycle (144-month time-point after enrollment in MOST)		
Characteristic	**Clinic Visit** N=1309 (100%)	**Telephone Contact Only** N=868 (100%)
Age 60 - 69	529 (40.4%)	215 (24.8%)
Age 70 - 79	534 (40.8%)	342 (39.4%)
Age 80 plus	246 (18.8%)	311 (35.8%)
Female	773 (59.1%)	587 (67.6%)
Male	536 (40.9%)	281 (32.4%)
White	1116 (85.3%)	738 (85.0%)
African American	170 (13.0%)	114 (13.1%)
Hispanics	9 (0.7%)	5 (0.6%)
Other	14 (1.0%)	11 (1.3%)
BMI < 25	206 (15.7%)	n/a
BMI 25 to 30	447 (34.2%)	
BMI 30 plus	656 (50.1%)	
Frequent knee pain (at both screening call and clinic visit, either knee)	343 (26.2%)	n/a
X-ray OA (K/L grade ≥ 2 or KR)*	855 (65.3%)	641 (73.8)
Symptomatic knee OA (frequent knee pain AND X-ray OA, either knee)*	246 (18.8%)	
History of knee injury or surgery in either knee		
Injury	688 (52.6%)	475 (54.7%)
Surgery	421 (32.2%)	471 (54.3%)
Injury or surgery	825 (63.0%)	630 (72.6%)
Injury and surgery	284 (21.7%)	316 (36.4%)
Joint Imaging**		
144m knee X-ray	1020 (77.9%)	
144m MRI in >=1 knee	836 (63.9%)	
144m knee CT scan	635 (48.5%)	
*X-ray OA status based on adjudicated x-ray readings BL-84m or on quality assurance assessment of x-rays obtained at 144m. ** Participant with bilateral end-stage knee OA (K/L grade 3-4 or TKR in both knees) did not have joint imaging. MRIs may be missing due to technical problems with scanners or MRI contraindications, and CTs may be missing due to unilateral TKR or failure to return for a separate CT scan visit.		

VI. FOLLOW-UP AND RETENTION

VIa. MOST ORIGINAL COHORT IN FIRST AND SECOND CYCLES

Follow-up Schedule and Measurements

Follow-up data for all outcomes of the specific aims in the First Cycle were collected at 15-month and 30-month time points, with continued follow-up for primary outcomes taking place during the Second Cycle at the 60-month, 72-month and 84-month clinic visits and phone contacts. Follow-up data for outcomes of the specific aims in the Second Cycle were collected at 72-month phone contacts and 84-month clinic visits. (Fig. 1, MOST Grant Cycles and Timeline.) Outcomes obtained at clinic exams include incidence and progression of structural knee OA assessed by reading centers from the study radiographs and MRIs, performance-based measures of physical function, patient-reported outcomes (PROs) for joint pain, physical function and disability, joint

replacements and other examinations. In addition, PROs were assessed by phone interview in all participants at 15-month and 72-month time-points (See Tables 2 and 3 for a complete inventory of measurements obtained at each follow-up time-point).

At the 15-month follow-up time-point a nested case-control study of incident frequent knee pain that included a telephone interview and a clinic visit exam was performed in a subset. All participants were contacted by phone at 15 months and asked about frequent knee pain. Those who reported frequent knee pain but who did not have it at baseline, and a group of matched controls without frequent knee pain at either baseline or the 15-month contact, were invited to attend a clinic visit for a study of factors associated with incident frequent knee pain, with a focus on changes from baseline in knee tissue damage assessed by MRI. Knee MRIs, knee radiographs and selected additional measures of knee pain, physical function and key covariates for incident knee pain were assessed at the clinic visit in this subset. (Table 2)

Retention

Retention activities include follow-up phone contacts between clinic visits, periodic study newsletters, individualized reports for participants of results from selected study measures (e.g., radiographic knee OA, height, weight and BMI, blood pressure, longitudinal performance measurements - 20 meter walk and chair stands, activity step counts, longitudinal changes of knee pain and knee OA), transportation assistance and convenient parking, birthday cards, and social events.

Overall retention has been excellent. Among those enrolled at the First Cycle baseline: at 30 months 90% of survivors had a clinic visit and 99% provided PRO outcome data; at 60 months 79% of survivors had a clinic visit and 94% provided PRO data, and; at 84 months 74% of survivors had a clinic visit and 92% provided PRO data. At the 84 month time-point only 8% of survivors of the Original Cohort could not be contacted or had withdrawn from the study. Among the 2,330 who had a Second Cycle baseline clinic visit at the 60 month time-point, at 84 months 87% had a follow-up clinic visit and 97% provided PRO data. Deaths and the follow-up status of the surviving members of the Original MOST Cohort at each follow-up time-point, by type of contact and demographic characteristics, are in Tables 8-10.

Table 8. Contact Status at 30M, 60M, 84M (Percentages among participants alive at each time point)*

	Alive at 30M			Alive at 60M			Alive at 84M		
	UAB	**U-Iowa**	**Total**	**UAB**	**U-Iowa**	**Total**	**UAB**	**U-Iowa**	**Total**
	1502	**1496**	**2998**	**1461**	**1475**	**2936**	**1426**	**1457**	**2883**
CV done	1326 (88)	1387 (93)	2713 (90)	1133 (78)	1197 (81)	2330 (79)	983 (69)	1163 (80)	2146 (74)
Only TI done	35 (2)	6 (0)	41 (1)	63 (4)	63 (4)	126 (4)	33 (2)	15 (1)	48 (2)
MCVTI done	123 (8)	92 (6)	215 (7)	150 (10)	162 (11)	312 (11)	280 (20)	164 (11)	444 (15)
Missed contact (TI not done)	18 (1)	6 (0)	24 (1)	104 (7)	11 (1)	115 (4)	80 (6)	7 (0)	87 (3)
Withdrew/ discontinued	0 (0)	5 (0)	5 (0)	11 (1)	42 (3)	53 (2)	50 (4)	108 (7)	158 (5)
Had a TI or CV (% of alive)	1484 (99)	1485 (99)	2969 (99)	1346 (92)	1422 (96)	2768 (94)	1296 (91)	1342 (92)	2638 (92)

Table 9. Contact Status at 30M, 60M, 84M (Percentages among participants alive at each time point)*									
	Alive at 30M			**Alive at 60M**			**Alive at 84M**		
	Non-white	**White**	**Total**	**Non-white**	**White**	**Total**	**Non-white**	**White**	**Total**
	499	2499	**2998**	480	2456	**2936**	468	2415	**2883**
CV done	420 (84)	2293 (92)	2713 (90)	367 (76)	1963 (80)	2330 (79)	329 (70)	1817 (75)	2146 (74)
Only TI done	11 (2)	30 (1)	41 (1)	23 (5)	103 (4)	126 (4)	11 (2)	37 (2)	48 (2)
MCVTI done	56 (11)	159 (6)	215 (7)	40 (8)	272 (11)	312 (11)	80 (17)	364 (15)	444 (15)
Missed contact (TI not done)	12 (2)	12 (0)	24 (1)	47 (10)	68 (3)	115 (4)	32 (7)	55 (2)	87 (3)
Withdrew/ discontinued	0 (0)	5 (0)	5 (0)	3 (1)	50 (2)	53 (2)	16 (3)	142 (6)	158 (5)

Table 10. Cumulative Number Deceased at 30M, 60M, 84M (Percentages among participants enrolled at baseline)*									
	30M			**60M**			**84M**		
	UAB	**U-Iowa**	**Total**	**UAB**	**U-Iowa**	**Total**	**UAB**	**U-Iowa**	**Total**
Deceased (% of enrolled at BL)	17 (1)	11 (1)	28 (1)	58 (4)	32 (2)	90 (3)	93 (6)	50 (3)	143 (5)

* CV = clinic visit; TI = telephone interview; MCVTI = missed clinic visit telephone interview

VIb. MOST NEW AND ORIGINAL COHORTS IN THIRD CYCLE

Follow-up Schedule and Measurements

Outcome data for the specific aims in the Third Cycle were collected by phone interview after 8 months (152-month time-point after enrollment in MOST) and 16 months (160 month time-point), and at a clinic visit or phone contact at 24 months following the Third Cycle baseline contact (168 month time-point). (Figure 1) PROs for joint pain and function, disability and knee replacements were assessed at all three follow-up contacts. At the follow-up clinic visit, incidence and progression of structural knee OA was assessed by MRI and radiograph and performance-based measures of physical function and pain sensitization were assessed. (See Table 3 for a detailed inventory of measurements obtained at each follow-up time-point.)

Retention

A detailed Participant Results Reports is given to participants describing their clinical measurements, including blood pressure, height, weight, body mass index, knee pain score, 20-Meter Timed Walk, 6MWT (six minute walk test) distance, Timed Chair Stands, quadriceps muscle power, hip muscle strength, and knee OA status from knee x-ray readings.

VII. ORGANIZATION AND GOVERNANCE

VIIa. FUNDING

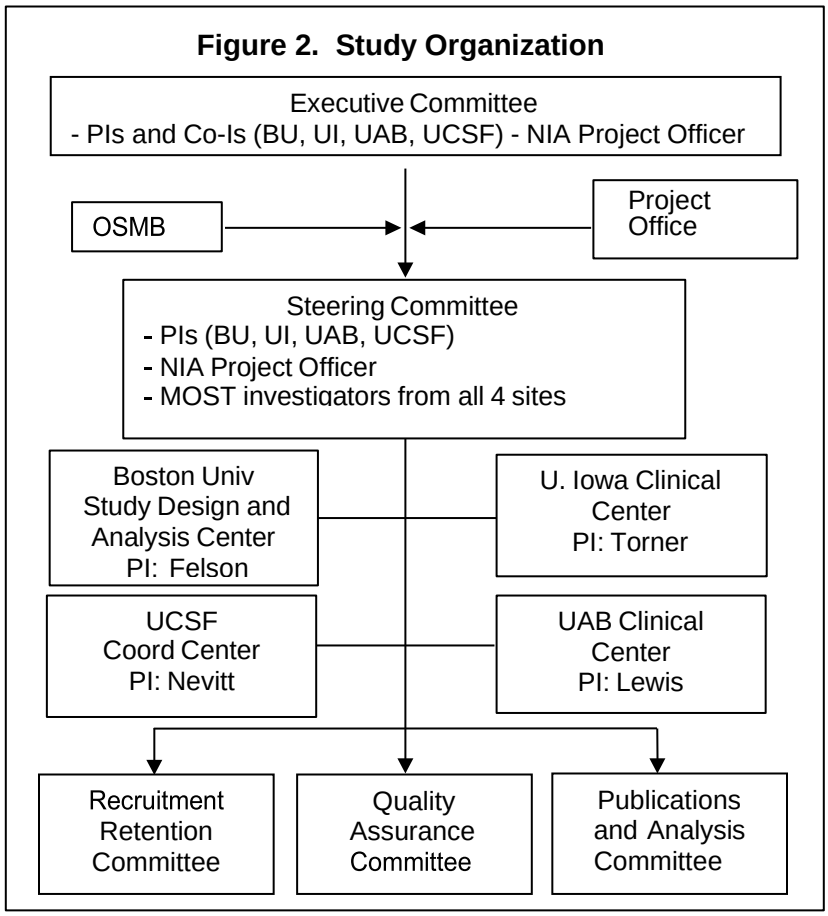
MOST is a U01 Cooperative Agreement multicenter research study funded by the National Institutes of Health (NIH)/National Institute on Aging (NIA). MOST was initially funded in 2001 for 7 years and competitively renewed in 2008 for 6 years and for 5 years in 2015. Funding to support ancillary studies and career development awards based on MOST has been provided by the NIA, the National Center for Medical Rehabilitation Research-NICHD, the National Institutes for Arthritis, Musculoskeletal and Skin Diseases, the American College of Rheumatology, The American Geriatrics Society, the Arthritis Foundation, Merck Pharmaceuticals, Foundation for Physical Therapy, Swedish Research Council, American Physical Therapy Association, and others.

VIIb. ORGANIZATION

There are two clinical centers: the University of Alabama at Birmingham (UAB) and the University of Iowa (UI) at Iowa City. Boston University (BU) is the science, study design and data analysis center.

The University of California San Francisco (UCSF) is the data coordinating center for this multicenter study. The NIA project officer for the Cooperative Agreement, Dr. Lyndon Joseph, takes an active role in governance of the study.

Figure 2. Study Organization



VIIc. ROLES OF THE CENTERS

The clinical centers at UAB and UI are responsible for enrolling and following participants, data collection, imaging acquisition and on-site data management.

The science, study design and analysis center at BU is responsible for methodological aspects of study design and measurements, performs the bulk of data analyses for abstracts and publications in collaboration with lead authors affiliated with all of the study units, and is the radiography and CT chondrocalcinosis reading center.

The UCSF Coordinating Center (CC) has responsibility for overall study management, coordination and quality assurance (QA) activities and data management (See Section VIII for details).

VIId. OVERSIGHT AND GOVERNANCE

Committees. The study is directed and governed by an Executive Committee consisting of the four center PIs and the NIA project officer. The Executive Committee has responsibility for overall scientific direction and oversight, and ensures scientific progress by identifying important new areas of investigation, prioritizing resources to accomplish aims and finding solutions to problems. The Executive Committee also oversees the review and approval of ancillary study and analysis proposals in accordance with written guidelines.

Other standing study committees draw their members from the investigators and staff of the participating centers. A study-wide Steering Committee is comprised of investigators and key staff from all study units. Steering Committee members provide reviews of analysis proposals, abstracts and manuscripts. Ancillary proposals are reviewed by the Executive Committee. The Recruitment and Retention and Quality Assurance Committees are composed of the clinic project directors and key staff and the CC project director and QA staff. The Publications and Data Analysis Committee is comprised of study investigators from each site and the senior statisticians and data analysts from BU and the CC.

Publications and ancillary studies are governed by written guidelines and policies that are available on the MOST internal investigator website.

Observational Study Monitoring Board (OSMB). The MOST OSMB was instituted in 2008. In twice annual meetings the Board reviews study progress and advises the Executive Committee (EC) and NIA with respect to the scientific direction and progress of the study. The OSMB has a written charter outlining areas where it is asked to make recommendations, including:

- participant safety and burden;

- adherence to protocol requirements;
- completeness and quality of data;
- amendments to the study protocol and consent forms;
- performance of individual centers;
- emerging scientific opportunities that could be addressed within the context/scope of the MOST study.

After each meeting the OSMB provides recommendations to the NIA project office and the EC.

VIII. COORDINATION AND MANAGEMENT

VIIIa. UCSF Coordinating Center

The UCSF Coordinating Center (CC), under the guidance of the Executive Committee, has operational responsibilities for the implementation, coordination, data management and monitoring of the MOST study. The UCSF CC has successfully carried out these complex and multifaceted tasks since the beginning of MOST in 2001, as evidenced by the timely completion of all study goals and milestones and the provision of high quality data for analysis and publication by MOST investigators and by the general osteoarthritis research community through the public release of data on the MOST public website (http://most.ucsf.edu/).

Specific operational responsibilities of the UCSF CC in MOST include:

Start-up and Implementation

- protocols and operations manuals, data collection forms, recruitment brochures, newsletters;
- scannable form and web-based data entry and management systems;
- systems for electronic transfer of MR Images, CTs and X-rays from the clinical centers to the CC and to, and from, the reading centers;
- systems for electronic transfer of raw digital exam data (e.g., accelerometry, force plate, etc.) from the clinics to the CC and to, and from, reading centers;

Quality Assurance Activities

- training and certification of clinic personnel, site visits and monitoring staff performance;
- monitoring study progress (recruitment, retention, data collection);
- tracking completeness of data collected including endpoint adjudication;
- design and implementation of reliability studies of data collected;
- analysis and reporting on data quality issues;

Communication and Coordination

- study website and communications systems;
- teleconferences and meetings;
- electronic archive of committee activities, meeting minutes and study communications;
- report on study progress to the Executive and Steering Committees and the OSMB;
- coordinate the activities of consultants, subcontractors, reading centers, core labs and central resources;
- publications and ancillary study review and approval processes;

Data Management

- manage and clean all study data using real-time web-based systems;
- digital archive of all study images;
- access, blind, and distribute images and electronic data to reading centers and investigators;
- manage and clean reading center-derived data;
- prepare data analysis files and documentation;
- manage and track biospecimen archive inventory and availability; request specimen retrieval and shipment;
- endpoint (joint replacement) adjudication and death confirmation;
- provide a public data release website and distribute datasets to public users.

VIIIb. DATA MANAGEMENT SYSTEMS

The CC's distributed data management system for MOST combines decentralized data submission, centralized and remote data editing, and a centralized database structure designed to collect, transfer, and store data for large-scale multicenter clinical studies. In this system, data are collected and transmitted electronically by web entry, fax and scan to the CC by remote clinical sites. A schematic representation of the data system is shown in the Figure below.

Data are entered at the clinical sites in two ways: 1) electronic form web entry on secure mobile or desktop computing devices using REDCap; and 2) fax entry of manually completed scannable forms (using Cardiff Teleform and Verifier software). Data is transferred to the CC via secure transfer. Electronic data are received at the CC and assessed by both automated and visual (images of scanned Teleform forms are compared to Verifier software interpretation) verification processes before being entered into a study-wide SQL database. Once in the database, additional queries (data discrepancies) are generated (hourly during business hours) to identify potential errors in the study data and are immediately accessible via the secure study website so that clinic staff can resolve them in a timely manner. When appropriate, sites can audit data in real-time via the web site, which automatically generates a full audit trail.

A secure, password-protected MOST internal investigator website is the communications hub for the study. The remote centers' computers access a private, secure UCSF CC web server that provides real-time reports reflecting the data as it is acquired, and provides the central means by which error-checking and queries are processed. All reports available on the website are generated on demand from current study data. The web site also provides a central repository for memos, manuscripts, publication and ancillary study proposals, data collection forms, and operations and user manuals.

Electronic transfer of images from clinics to the CC and from the CC to reading centers. MRI, CT and x-ray images are loaded daily into DICOM software on dedicated image transfer PCs at the clinical centers. DICOM is used, along with a secure network connection, to automatically transfer images to dedicated DICOM servers at UCSF. Radiographs are automatically forwarded using similar, secure methods from UCSF to the radiograph QC and reading center at BU. MRIs and CTs are automatically forwarded upon receipt to a dedicated viewing workstation at the CC to ensure prompt QC of the images. Receipt of all image types and completeness of acquisitions are automatically evaluated daily against acquisition tracking data recorded by the clinics in the study database. Clinics are notified immediately via the study web site of missing or incomplete images. For rapid screening of knee radiographs, images received at the CC are sent daily, via a secure DICOM transfer, to a viewing workstation at the radiologist's reading location in Boston.

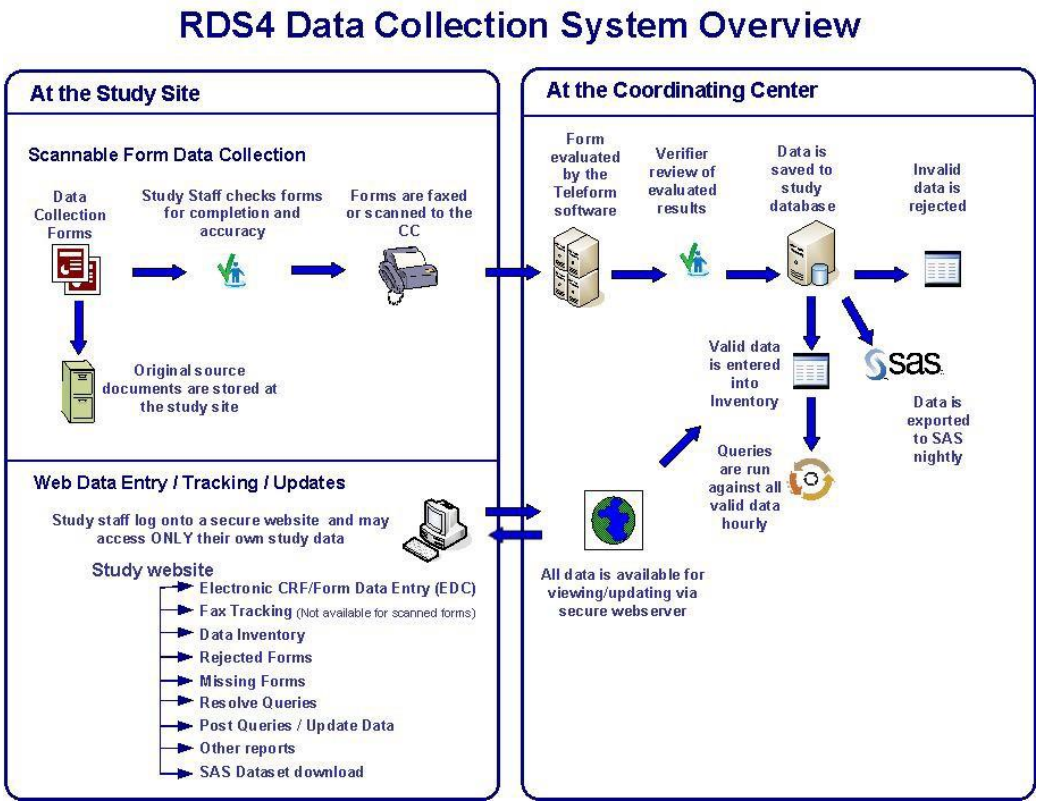
Electronic transfer of digital exam and reading center data. Digital examination data (e.g., force plate, accelerometry) are transferred weekly from the clinics to the UCSF CC over the internet using a secure data transfer web gateway and following data transfer SOPs detailing responsibilities of the sender and recipient. At the CC, receipt and completeness of reading center data are evaluated against measurement acquisition tracking data recorded by the clinics in the study database. The CC notifies reading centers regarding data that has passed quality assurance checks and is ready for the reading center to download from the secure data gateway. Reading centers upload results of their analyses to the secure gateway on a regular schedule for integration into the study database.

Internal MOST website. The CC maintains a limited access secure web site for administrative coordination and data management including the following components:

- study directory;
- meeting and conference call calendar, dial-in information;
- searchable memo archive;
- document archive: operations manuals, data collection forms and policy documents;
- protocol Q & A submission and searchable Q & A archive;
- staff certification tracking log;
- publications and ancillary studies tracking logs, guidelines and forms;
- automated enrollment and retention reports;
- visit scheduling reports (lists individual participant due dates and windows);
- data from prior visits report (lists information needed for individual participant visits);

- tracking reports (lists imaging, biospecimen, endpoint package receipt status for individual participants);*
- expected forms listing (RedCap) and fax tracking tools (Teleform);
- data query and edit tables and missing and rejected forms listing;
- data inventory, data summary report and audit trail;
- biospecimen inventory, encumbrance and use;
- reading and QA center reports;
- downloadable SAS analysis datasets and documentation.

Figure 3. Data System Schema



VIIIc. COMPUTER AND DATA SECURITY

The MOST Coordinating Center IT support staff in the Department of Epidemiology and Biostatistics (DEB) at UCSF follow standard operating procedures for computer system security to ensure the confidentiality and validity of study data. The network-based computing environment includes a private, secure network infrastructure located within a secure data center that meets all security and safety requirements, and a backup and disaster-recovery failover site for critical functions co-located in a separate building outside of the local earthquake zone. The DEB currently operates a private cloud infrastructure built on OpenStack technology and Microsoft Hyper-V where resources are accessed via remote desktop services client via secure HTTPS Proxy supporting all known major operating system platforms and web browsers.

Services to MOST provided by the DEB IT staff include:

- engineering and maintenance of multiple Openstack environments;
- nightly server and database backups, failover site for mission critical servers and data access;
- engineering and maintenance of remote desktop services and shared network storage space;
- physical server/infrastructure (switch/firewall/router) installation and configuration;

- engineering and maintenance for housed database systems, workflow processing, document management, communication services (email, social collaboration) and websites across multiple OS platforms;
- infrastructure support for HIPAA compliance (FISMA compliance);
- computing resources
  - 1876+ CPU cores
  - 12.1 TBs of RAM
  - 12.8 TBs of NVMe Storage
  - 70 TBs of SSD storage
  - 1250 TBs of high-speed magnetic storage (SAS).

VIIId. QUALITY ASSURANCE FOR CLINICAL DATA

The overall goal of quality assurance in MOST is to provide complete and accurate data to address the study specific aims. To ensure the highest quality of data, the following quality control policies and procedures are followed:

- Oversight of quality control rests with the MOST Quality Assurance (QA) Committee, utilizing data and reports on the website or provided by the CC.
- A QA officer is designated from each site, and participates in QA Committee conference calls. S/he is responsible for adherence to protocols and the integrity of locally collected data.
- Protocols for measurements are thoroughly pretested prior to examiner training.
- Final protocols and operations manuals incorporate feedback from the training and certification processes.
- Examiner training, certification and ongoing examiner performance for selected measures are monitored.
- Examiners participate in cross-site quality control site visits approximately 3-4 months after start-up of clinic visits to ensure that interviewers and examiners are following protocols in a uniform manner at each site.
- Equipment is calibrated and monitored for the duration of the data collection time period as described in the operation manuals and logged in tracking databases.
- Master examiners (typically the investigator most familiar with a measurement protocol and its “prime mover”) are designated for complex measurements (e.g. quantitative sensory testing, force plate exams)
- Master examiners and prime movers for each measurement review the data being generated by the protocol, assess the distribution of data values and identify outliers.

MOST performs formal test-retest and inter-examiner reliability assessments for selected clinic exams and measurements that have been introduced during each funding cycle. Clinic measurement reliability studies are conducted according to written protocols for subject selection and predetermined sample sizes. To the extent possible, examiners are blinded to the results from prior measurements.
Formal test-retest and inter-reader reliability assessments are performed for data obtained by reading centers. In general, previously read images and raw data are fed back to readers who are blinded to the purpose of the reading and to all prior results.

VIIIe. QUALITY ASSURANCE FOR MUSCULOSKELETAL IMAGING

MRI scanners. The MOST clinics own the MRI extremity scanners used in the study. This arrangement has distinct advantages over buying time on a scanner operated by university or hospital departments, including: uniform scanner hardware and software across clinical sites; control over hardware and software upgrades during the study; control over participant scheduling and throughput; greater convenience for participants who

do not need to go to another location for scanning; control over which technologists acquire images; and lower costs per image acquired.

GE OrthOne 1.0T extremity scanners were used during the first two funding cycles[35] and GE Optima MR430s 1.5T extremity scanners during the third funding cycle. The OrthOne scanner was discontinued in 2013 and repair and supplies are no longer supported or provided by GE. In collaboration with GE, MOST developed an acquisition protocol for the 1.5T scanner that provides knee images in 2/3 the scan time (reducing movement artifacts) with similar contrast and improved resolution and signal, and a larger effective field of view allowing better imaging of the entire knee compared to the older scanner. A scanner comparability study of the two scanner models was performed on MOST participants scanned with the existing 1.0T scanner at the UAB MOST clinical center and an Optima 1.5T scanner located at UAB Highlands Hospital. Images were read for OA abnormalities on both sets of scans by the MRI reading center. All abnormalities previously detected were readily seen with the Optima scanner.

Acceptance testing of new scanners was performed using the manufacturer's standard procedures and additional testing procedures specific to MOST using special phantoms. Testing evaluated whether center resonant frequency, magnetic homogeneity, intensity uniformity, signal to noise ratios, fat suppression level, slice location and thickness, spatial linearity, image resolution, and levels of magnetic and radiofrequency shielding were within tolerances and stable prior to scanning participants.

Ongoing MR system performance is continuously monitored during the study using several different phantoms and regular performance tests, including daily quality assurance scans of manufacturer provided phantoms to test that the performance of the scanner falls within specified tolerances for: (a) transmitter gain, (b) receiver gain, (c) signal to noise ratio, and (d) artifact to noise ratio. Oil-water phantom images are obtained weekly to check fat suppression imaging and scanner field homogeneity. Geometric checks on MR scanner images are performed monthly using a specially designed phantom containing spheres of known dimensions.

QA phantom images are transferred electronically to the CC where the results of the MR sites' image analysis for the QA parameters are archived and monitored for drifts in scanner performance, a sensitive indicator of performance deterioration. Phantom images are analyzed at the CC for signal to noise ratios, contrast ratios and ghosting. Fluctuations in room temperature within the magnet room, which may alter the scanner's static magnetic field, is closely monitored at the clinical centers. Routine scanner maintenance is performed on a schedule defined in the service contracts, and as needed whenever the scanner fails routine QA checks.

CT scanners. CT images of the knee are obtained on a 64-slice GE CT scanner in the Radiology Department at UAB, and a Siemens 64-slice CT scanner in the Department of Biomedical Engineering at UI. American College of Radiology/American Association of Medical Physicists technical standards for performance monitoring of CT equipment are applied at each site using special phantoms and measurement methods to monitor parameters such as image localization, table positioning accuracy, radiation beam collimation, reconstructed image thickness, image quality (resolution, uniformity, noise artifacts), HU accuracy, and radiation dose. The Mindways QCT phantoms, used to convert HU to mineral density values, are visible in all MOST knee CT scans, and monitored for stability of conversion factors over time.

VIIIf. QUALITY ASSURANCE OF IMAGES

Training, certification and QA monitoring of imaging technologists. Acquisition protocols are detailed in operations manuals. Radiography and MR imaging are performed by dedicated technologists trained and certified on site by the CC imaging QA staff. Technologists' performance is monitored in monthly reports detailing the number of exams performed by each technologist and the percentage of those acquired which fail QA criteria. Technologists with higher than normal rates of QA failure undertake refresher training and recertification. Knee CT exams are only acquired by technologists who have been trained and certified by the CC to perform the MOST CT scans.

Ongoing QA of radiographs. Automated QA for PA knee films by the CC includes checking the beam angle used for acquisition using custom programs for analyzing offsets of the metal beads within the Synaflexer frame, which indicate beam angle at the knee joint space.[243] Radiographs with incorrect beam angles are flagged for review. Radiographs undergo further QA checks at the BU center, examining positioning, joint

space visualization, adequate penetration and the appropriateness and success of repeat films. The baseline PA knee x-rays are acquired using 5, 10 and 15 degree caudal beam angles for each subject. The BU QA center selects the optimum beam angle for visualization of the medial joint space during central QA review and this angle is used for follow-up radiographs. Full limb films are assessed for quality including inclusion of all anatomic sites on the film (hips/ankles/knees) and acceptable visualization of all joints. When radiographs fail QA criteria, the clinic is notified, changes suggested and the participant asked to return for a repeat radiograph.

Ongoing QA of MR images. The CC performs automated checks of the scanner and acquisition parameters based on DICOM header information to ensure protocol adherence. Each knee MRI is visually evaluated and those with poor anatomical coverage, motion artifacts or other problems severe enough to prevent semiquantitative assessment of OA are flagged for repeat and the clinic notified.

Ongoing QA of knee CT. CT scans are checked at the CC to ensure that the Mindways QCT phantom is visible within the scan volume, and that all knee anatomy is visible in the relevant reconstruction. Automated checks of the scanner and reconstruction parameters are performed based on DICOM header information to ensure protocol adherence. Scans acquired with the incorrect protocol, with the QCT phantom not visible, or with motion artifacts in the image are flagged for repeat.

Image reading and quality assurance. Knee MRIs are read blinded to all subject data using semi-quantitative scoring of OA features[244-246] at the Boston Imaging Core Lab, at BU Medical Center. This is facilitated by custom reading software developed at the CC utilizing Windows [7] running eFilm viewing software that feeds the images to the reader. Images from different pulse sequences and time points are displayed concurrently. Readers perform cross-calibration exercises prior to starting/restarting using a training set of images from previously read MOST knee MRIs.

Knee radiographs are read blinded to all subject data using Kellgren-Lawrence grades[247] and the OARSI atlas for individual radiographic features[248] by a team of radiologists and rheumatologist at the BU MOST center.[31] Custom reading software developed at the CC utilizing Windows [7] running eFilm viewing software feeds the images to the readers and displays films from multiple time-points of the same subject. Prior to starting/ restarting readings the readers perform cross-calibration exercises compared to each other and to previous readings using previously read images. Radiographs are scored independently by two readers. Meaningful discrepancies in scores (e.g., OA is present vs. not present; JSN progression is present vs. not present) are adjudicated by consensus of the three readers.

Test-retest and inter-reader reliability for all image readings are formally tested by blindly feeding a predetermined percentage of previously read images to readers.

IX. SUBJECT CONSENT AND CONFIDENTIALITY

MOST is conducted in accordance with U.S. Dept. of Health & Human Services Protection of Human Subjects regulations (45 CFR part 46) and the Privacy Rule of the Health Insurance Portability and Accountability Act (HIPAA) of 1996. Research data and image sets available for public use are de-identified in accordance with regulation 45 CFR 164.514(e) relating to limited datasets.

The informed consent procedures and study protocol are approved by the Institutional Review Board Committee on Human Research at the participating institutions, including the two clinical centers at UAB and UI, the UCSF Coordinating Center and MRI reading center, and the Boston University analysis and x-ray QA and reading center.

Federal-wide Assurances (FWAs) are held by Institutional Review Boards at the four of the MOST centers.

FWA00000068 University of California, San Francisco

FWA00000301 Boston University

FWA00005960 University of Alabama at Birmingham

FWA00003007 University of Iowa

Written consent is obtained from all participants at the beginning of a clinic visit at the clinical center. The consent covers all data collection scheduled for each grant cycle. Verbal consent is obtained for telephone

interviews. Participants give written permission for clinical centers to obtain medical records needed for documentation of joint replacement surgery. For Hispanic participants, Spanish speaking staff conduct phone interviews and informed consent in the two clinical centers as determined by participant preference.

Participant confidentiality is protected through a multi-tiered approach. The disclosure of individual health information complies with local, state, and federal laws and regulations (including the Privacy Rule under the Health Insurance Portability and Accountability Act [HIPAA] of 1996) relating to the privacy, security and confidentiality of health information collected for research purposes. Participant information is kept as confidential as possible through the use of coded unique identifiers on all electronic and paper forms and in all data analysis programs. Separate documentation linking direct participant identifiers (name, address, contact names and addresses, social security numbers, etc.) to coded identifiers will be maintained in a secure location at each clinical center. No data key linking coded identifiers to subject identifiers exists, other than the clinical center source documents. Paper forms are stored at the clinic centers in locked filing cabinets and in offices locked outside of work hours and when unoccupied during office hours. The Coordinating Center, the biological specimen repository, participating processing laboratories and imaging QA and reading centers will not receive any direct subject identifiers. Biological samples are further de-identified with a unique specimen code before being sent to the biospecimen repository.

All data, including image data, are electronically transmitted from the clinics to the UCSF Coordinating Center via secure network connection. The Coordinating Center does not receive any paper forms in the process of data submission. Images are labeled at the clinics with unique identifiers, the date, time, clinical center and unique scan number. There are no other identifiers on the images. UCSF removes any ePHI from the images prior to transferring images to reading centers for measurements. Data transmission by FTP is encrypted using a Virtual Private Network (VPN), an established method for secure transfer. SOPs for Data Transmission Agreements (DTA) detail transfer-specific conditions and security requirements for transmission of data from outside entities e.g., reading centers or laboratories to UCSF.

Standard operating procedures (SOPs) for computer system security ensure the confidentiality and validity of study data. The SOPs are designed to prevent unauthorized access, limit authorized access to our computer systems and are in compliance with established standards for Information Technology Security. Coded electronic records are kept at UCSF on a secured, password protected network accessible by UCSF investigators and staff. All study data tracking, cleaning and reporting are done via a secure study web site housed on a UCSF Coordinating Center web-server running Internet Information Server. Study data reside on a dedicated SQL server with a defined database or dedicated-mirrored image servers with daily electronic back-up to ensure data integrity. Access to study data within the system is granted on an as-needed basis and further restricted by defined user roles. User authentication is by unique username and password. Study website and database access requires a network domain account with appropriate account-specific permissions on the database. Study coordinators and examiners at the clinical centers are able to view, update and edit only the data that they have submitted using the website, which is secured with a 128-bit SSL.

X. PUBLICATIONS AND DATA SHARING

Use of MOST data for abstracts, presentations and articles is governed by written publications policies administered by the Executive and Publications Committees. The goals of the policies are to encourage high quality publications and presentations produced in a timely fashion, broad participation by MOST investigators in publications and presentations and creative use of the MOST data. The publications policies are available on the MOST internal investigator website.

As of December, 2019 MOST data has been used in over 150 peer-reviewed publications (Appendix A), with primary authorship both by investigators affiliated with the MOST study and by users of the MOST public data resources (see below).

Xa. ANALYSIS DATA SETS

The MOST CC creates, distributes and maintains analysis data files consisting of SAS datasets and comprehensive documentation for both original study data and derived variables. Study data is extracted for analysis data sets from the source SQL database and processed through a series of SAS programs to a

second locked database which is used for reporting and analysis. This is a one way automated process, so that the SQL source data remains pristine irrespective of the nature of the transformation process. Reading center data streams enter the UCSF system in a similar manner, as they are transformed from their native format to SAS datasets via SAS programs.

Analysis data sets are accompanied by comprehensive documentation, describing the contents of the data file from the perspective of a data analyst, that can be easily understood by researchers and analysts. The documentation includes a general description of the data, information on the source of each variable, information on the data set structure and contents, data set index formulation and key variable mapping, and general strategies for manipulating and merging the data. It also includes descriptive statistics for each variable and data forms annotated with the corresponding field names. For computed variables, the documentation includes a written description of the variable, a listing of the SAS program statements used in its calculation.

The CC releases analysis-ready datasets to the BU analysis center and other MOST investigators with Publications Committee approved analysis plans, for statistical analysis purposes. Standard Operating Procedures are in place to regulate access to analysis data sets, which contain only coded identifiers. All MOST investigators who receive or use MOST datasets must have a signed Data Use Agreement on file. Analysis data sets do not contain names, social security numbers, addresses, phone numbers, health care records, dates, geographic identifiers smaller than state, and similar PHI and have an anonymous study ID that is linked to an individual only in the participant records that are kept in locked files at the clinical centers.

Xb. PUBLIC DATA SHARING AND PUBLIC WEBSITE

As per the terms and conditions of the MOST Grant Awards, UCSF develops resources to facilitate sharing of the MOST clinical and imaging data and research resources with the outside scientific community. The MOST Public Data Sharing website (http://most.ucsf.edu) was launched November 2009.

Xc. PUBLIC RELEASE DATA SETS

The MOST CC shares with public data users a Limited Data Set that includes the following Protected Health Information (as defined in the Health Insurance Portability and Accountability Act of 1996, Public Law 104-191, and implementing regulations promulgated by the United States Department of Health and Human Services at 45 CFR Part 160 and Part 164, hereinafter the “HIPAA Privacy Rule”): examinations, questionnaires and images, information derived from these sources, and information derived from blood and tissue samples.

As required by the HIPAA Privacy Rule (https://www.hhs.gov/hipaa/for-professionals/special-topics/research/index.html), to receive a Limited Data Set, a public user and his/her institutional officials are required to sign a Data Use Agreement. The Data Use Agreement includes statements that the user will not attempt to identify any individual participant, will secure the data using appropriate computer technology, will obtain any required local IRB approvals for the intended use of the data, and that permissions and access are not transferable.

The Limited Data Set excludes all of the following identifiers of the individual(s) who is (are) the subject(s) of the Protected Health Information, or of relatives, employers or household members of the individual(s).

a. Names
b. Geographic subdivisions smaller than a state (including addresses and zip codes)
c. Dates directly related to an individual
d. Telephone numbers
e. Fax numbers
f. Electronic mail addresses
g. Social Security numbers
h. Medical record numbers
i. Health plan beneficiary numbers
j. Account numbers

k. Certificate/license numbers
l. Vehicle identifiers and serial numbers, including license plate numbers
m. Device identifiers and serial numbers
n. Web Universal Resource Locators (URLs)
o. Internet Protocol (IP) address numbers
p. Biometric identifiers, including fingerprints and voiceprints
q. Full face photographic images and any comparable images

Datasets for public use undergo further de-identification, including replacing the MOST study ID with a randomly generated number (the key linking this to the study ID is kept on secure servers at the Coordinating Center). Indirect identifiers and other information that could lead to "deductive disclosure" are collapsed or replaced with a missing data code.

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Appendix A. MOST Publications

MULTICENTER OSTEOARTHRITIS STUDY

PUBLISHED ARTICLES

JANUARY 2020

Note: For more recent publications, the following are searches on https://app.dimensions.ai/ for publications associated with the MOST grant numbers:
U01 AG18820 (David Felson, Boston University)
U01 AG18947 (Cora E. Lewis, University of Alabama at Birmingham)
U01 AG18832 (James Torner, University of Iowa)
U01 AG19069 (Michael Nevitt, University of California, San Francisco)

2020

1. Hart HF, Gross KD, Crossley KM, Barton CJ, Felson DT, Guermazi A, Roemer F, Segal NA, Lewis CE, Nevitt MC, Stefanik JJ.
   Step Rate and Worsening of Patellofemoral and Tibiofemoral Joint Osteoarthritis in Women and Men: The Multicenter Osteoarthritis Studyf
   Arthritis Care Res (Hoboken). 2020 Jan;72(1):107-113. doi: 10.1002/acr.23864.
   PMCID: 6717684 [Available on 2021-01-01]
   https://www.ncbi.nlm.nih.gov/pubmed/?term=30821927

2019

2. Kothari MD, Rabe KG, Anderson DD, Nevitt MC, Lynch JA, Segal NA, Franz H; Multicenter Osteoarthritis Study Group.
   The relationship of three-dimensional joint space width on weight bearing CT with pain and physical function
   J Orthop Res. 2019 Dec 16. doi: 10.1002/jor.24566. Epub ahead of print.
   PMID: 31840831
   https://www.ncbi.nlm.nih.gov/pubmed/?term=31840831

3. Carlesso LC, Neogi T.
   Identifying pain susceptibility phenotypes in knee osteoarthritis.
   Clin Exp Rheumatol. 2019 Sep-Oct;37 Suppl 120(5):96-99. Epub 2019 Oct 15.
   https://www.ncbi.nlm.nih.gov/pubmed/?term=31621573
   [This is a supplement (commentary) article to L. Carlesso's Arthritis Rheumatology MOST article "Pain susceptibility phenotypes in those free of knee pain with or at risk of knee osteoarthritis: The Multicenter Osteoarthritis Study" (April 2019, PMCID #6442725)]

4. Voinier D, Neogi T, Stefanik JJ, Guermazi A, Roemer FW, Thoma LM, Master H, Nevitt MC, Lewis CE, Torner J, White DK.
   Using cumulative load to explain how body mass index and daily walking relate to worsening knee cartilage damage over two years: The MOST Study.
   Arthritis Rheumatol. 2019 Nov 29. doi: 10.1002/art.41181. Epub ahead of print.
   PMID: 31785075
   https://www.ncbi.nlm.nih.gov/pubmed/31785075

5. Dai Z, Neogi T, Brown C, Nevitt M, Lewis CE, Torner J, Felson DT.
Sleep quality is related to worsening knee pain in those with widespread pain: The Multicenter Osteoarthritis Study.
J Rheumatol. 2019 Nov 15. pii: jrheum.181365. doi: 10.3899/jrheum.181365. Epub ahead of print.
PMID: 31732550
https://www.ncbi.nlm.nih.gov/pubmed/31732550

6. Sisante JF, Wang N, Felson DT, Nevitt MC, Lewis CE, Frey-Law L, Segal NA, Multicenter Osteoarthritis Study (MOST) Group.
PM R. 2019 Oct 4. doi: 10.1002/pmrj.12253. Epub ahead of print.
Influence of antagonistic hamstring coactivation on measurement of quadriceps strength in older adults
PMID: 31585496
https://www.ncbi.nlm.nih.gov/pubmed/31585496

7. Macri EM, Neogi T, Tolstykh I, Widjajahakim R, Lewis CE, Torner JC, Nevitt MC, Roux M, Stefanik JJ.
Relation of patellofemoral joint alignment, morphology, and radiographic osteoarthritis to frequent anterior knee pain: The MOST Study.
Arthritis Care Res (Hoboken). 2019 Jun 14. doi: 10.1002/acr.24004. Epub ahead of print.
PMID: 31199605
https://www.ncbi.nlm.nih.gov/pubmed/31199605

8. Carlesso LC, Segal NA, Frey-Law L, Zhang Y, Na L, Nevitt M, Lewis CE, Neogi T.
Pain susceptibility phenotypes in those free of knee pain with or at risk of knee osteoarthritis: The Multicenter Osteoarthritis Study.
Arthritis Rheumatol. 2019 Apr;71(4):542-549. doi: 10.1002/art.40752. Epub 2019 Feb 7.
PMCID: 6442725 [Available on 4/1/20]
https://www.ncbi.nlm.nih.gov/pubmed/30307131

9. Hart HF, Gross KD, Crossley KM, Barton CJ, Felson DT, Guermazi A, Roemer F, Segal NA, Lewis CE, Nevitt MC, Stefanik JJ.
Is step rate associated with worsening of patellofemoral and tibiofemoral joint osteoarthritis in women and men? The Multicenter Osteoarthritis Study.
Arthritis Care Res (Hoboken). 2019 Mar 1. doi: 10.1002/acr.23864. Epub ahead of print.
PMID: 30821927
https://www.ncbi.nlm.nih.gov/pubmed/30821927

10. Macri EM, Felson DT, Ziegler ML, Cooke TDV, Guermazi A, Roemer FW, Neogi T, Torner J, Lewis CE, Nevitt MC, Stefanik JJ.
The association of frontal plane alignment to MRI-defined worsening of patellofemoral osteoarthritis: The MOST Study.
2019 Mar;27(3):459-467. doi: 10.1016/j.joca.2018.11.004. Epub 2018 Nov 28.
PMCID: 6391198 [Available on 3/1/20]
https://www.ncbi.nlm.nih.gov/pubmed/30500383

2018

11. Rogers-Soeder TS, Lane NE, Walimbe M, Schwartz AV, Tolstykh I, Felson DT, Lewis CE, Segal NA, Nevitt MC; Multicenter Osteoarthritis (MOST) Study Group.
Association of diabetes mellitus and biomarkers of abnormal glucose metabolism with incident radiographic knee osteoarthritis.
Arthritis Care Res (Hoboken). 2018 Nov 12. doi: 10.1002/acr.23809. Epub ahead of print.
PMCID: 6511494 [Available on 2020-05-12]
https://www.ncbi.nlm.nih.gov/pubmed/30418707

12. Culvenor AG, Segal NA, Guermazi A, Roemer F, Felson DT, Nevitt MC, Lewis CE, Stefanik JJ.
The sex-specific influence of quadriceps weakness on worsening patellofemoral and tibiofemoral cartilage damage: the MOST Study.
Arthritis Care Res (Hoboken). 2018 Oct 8. doi: 10.1002/acr.23773. Epub ahead of print.
PMCID: 6050106
https://www.ncbi.nlm.nih.gov/pubmed/30295439

13. Kim C, Nevitt M, Guermazi A, Niu J, Clancy M, Tolstykh I, Jungmann PM, Lane NE, Segal NA, Harvey WF, Lewis CE, Felson DT.
Brief report: Leg length inequality and hip osteoarthritis in the Multicenter Osteoarthritis Study and the Osteoarthritis Initiative.
Arthritis Rheumatol. 2018 Oct;70(10):1572-1576. doi: 10.1002/art.40537.
PMCID: 6160315 [Available on 10/1/19]
https://www.ncbi.nlm.nih.gov/pubmed/?term=29700988

14. Wink AE, Gross KD, Brown CA, Lewis CE, Torner J, Nevitt MC, Tolstykh I, Sharma L, Felson DT.
Association of varus knee thrust during walking with worsening WOMAC knee pain: A Prospective Cohort Study.
Arthritis Care Res (Hoboken). 2018 Sep 22. doi: 10.1002/acr.23766. Epub ahead of print.
PMCID: 6430708 [Available on 3/22/20]
https://www.ncbi.nlm.nih.gov/pubmed/30242985

15. Bacon KL, Segal NA, Oiestad, BE, Lewis CE, Nevitt MC, Brown C, Felson DT.
Concurrent change in quadriceps strength and physical function over 5 years in the Multicenter Osteoarthritis Study.
Arthritis Care Res (Hoboken). 2018 Sep 17. doi: 10.1002/acr.23754. Epub ahead of print.
PMCID: 6421097 [Available on 3/17/20]
https://www.ncbi.nlm.nih.gov/pubmed/30221484

16. Bacon K, Segal NA, Oiestad BE, Lewis CE, Nevitt MC, Brown C, LaValley MP, McCulloch CE, Felson DT.
Thresholds in the relationship of quadriceps strength with functional limitations in women with knee osteoarthritis.
Arthritis Care Res (Hoboken). 2018 Aug 29. doi: 10.1002/acr.23740. Epub ahead of print.
PMCID: 6395532 [Available 2/29/20]
https://www.ncbi.nlm.nih.gov/pubmed/30156759

17. Misra D, Fielding RA, Felson DT, Niu J, Brown C, Nevitt MC, Lewis CE, Torner J, Neogi; The Multicenter Osteoarthritis (MOST) Study.
Risk of knee osteoarthritis with obesity, sarcopenic obesity and sarcopenia.
Arthritis Rheumatol. 2018 Aug 14. doi: 10.1002/art.40692. Epub ahead of print.
PMCID: 6374038 [Available on 2/1/20]
https://www.ncbi.nlm.nih.gov/pubmed/30106249

18. Hart HF, Crossley KM, Felson D, Jarraya M, Guermazi A, Roemer F, Lewis B, Torner J, Nevitt M, Stefanik JJ.
Relation of meniscus pathology to prevalence and worsening of patellofemoral joint osteoarthritis: the Multicenter Osteoarthritis Study.
Osteoarthritis Cartilage. 2018 Jul;26(7):912-919. doi: 10.1016/j.joca.2017.11.017. Epub 2018 Feb 7.
PMCID: 6005722
https://www.ncbi.nlm.nih.gov/pubmed/29427724

19. Fenton SAM, Neogi T, Dunlop D, Nevitt M, Doherty M, Duda JL, Klocke R, Abhishek A, Rushton A, Zhang W, Lewis CE, Torner J, Kitas G, White DK; Multicenter Osteoarthritis Group.
Does the intensity of daily walking matter for protecting against the development of a slow gait speed in people with or at high risk of knee osteoarthritis? An observational study.
Osteoarthritis Cartilage. 2018 May 2. pii: S1063-4584(18)31227-5. doi: 10.1016/j.joca.2018. 04.015. Epub 2018 May 2..
PMCID: 6098720 [Available on 9/1/19]
https://www.ncbi.nlm.nih.gov/pubmed/29729332

20. Vaughan MW, LaValley MP, Felson DT, Orsmond GI, Niu J, Lewis CE, Segal NA, Nevitt MC, Keysor JJ.
Affect and Incident Participation Restriction in Adults with Knee Osteoarthritis: The MOST Study
Arthritis Care Res (Hoboken). 2018 Apr;70(4):542-549. doi: 10.1002/acr.23308. Epub 2018 Feb 18.
PMCID: 6492559
https://www.ncbi.nlm.nih.gov/pubmed/28686817

2017

21. Crema MD, Felson DT, Guermazi A, Nevitt MC, Niu J, Lynch JA, Marra MD, Torner J, Lewis CE, Roemer FW.
Is the atrophic phenotype of tibiofemoral osteoarthritis associated with faster progression of disease? The MOST study.
Osteoarthritis Cartilage. 2017 Oct;25(10):1647-1653. doi: 10.1016/j.joca.2017.05.019. Epub 2017 Jun 9.
PMCID: 5605441
https://www.ncbi.nlm.nih.gov/pubmed/28606556

22. Widjajahakim R, Roux M, Jarraya M, Roemer FW, Neogi T, Lynch JA, Lewis CE, Torner JC, Felson DT, Guermazi A, Stefanik JJ.
Relationship of trochlear morphology and patellofemoral joint alignment to superolateral hoffa fat pad edema on MR images in individuals with or at risk for osteoarthritis of the knee: The MOST study.
Radiology. 2017 Sep;284(3):806-814. doi: 10.1148/radiol.2017162342. Epub 2017 Apr 17.
PMCID: 5584646
https://www.ncbi.nlm.nih.gov/pubmed/28418810

23. Jarraya M, Guermazi A, Felson DT, Roemer FW, Nevitt MC, Torner J, Lewis CE, Stefanik JJ.
Is superolateral Hoffa's fat pad hyperintensity a marker of local patellofemoral joint disease? - The MOST study.
Osteoarthritis Cartilage. 2017 Sep;25(9):1459-1467. doi: 10.1016/j.joca.2017.05.020. Epub 2017 Jun 9.
PMCID: 5583732
https://www.ncbi.nlm.nih.gov/pubmed/28606557

24. Segal NA, Frick E, Duryea J, Nevitt MC, Niu J, Torner JC, Felson DT, Anderson DD.
Comparison of tibiofemoral joint space width measurements from standing CT and fixed flexion radiograph.
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Appendix B. MOST Bioassay Measurements

	Study Title (Dataset, Investigators)	Assays	N ppts	Visit Biospecimens from
1	Nutritional Risk Factors for Knee OA (MOSTV0NUTR)	Vit C	1067	Baseline
		Vit D	1389	Baseline
		Vit E, Vit A	1372	Baseline
		PHT	1383	Baseline
	Association of Vitamin K with MRI Features of Osteoarthritis: Cartilage and Osteophytes (MOSTV0NUTR; AS05-06; T Neogi)	Vit K	1179	Baseline
	Ethnic Differences in the Role of Vitamin D to Achieve & Maintain Musculoskeletal Health (MOSTV0NUTR; AS06-01; J Curtis)	Vit D, PTH	434	Baseline
2	Inflammation and Knee Osteoarthritis (MOSTAS0501_Bioassay; B Lewis; 2008; pilot)	TNFa, Adiponectin Total, CRP, Ox LDL, Leptin, MCP-1, PAI-1, MMP-3, TIMP-1, ICAM-1, COMP, IGF-1, IGFBP-3, TGFb, Estradiol, SHBG, DHEA-s	100	Baseline/30m
	(MOSTAS0501_Bioassay; B Lewis; 2010; main study)	TNFa, Adiponectin Total, CRP, Ox LDL, Leptin, MMP-3, TIMP-1, ICAM-1, COMP	1076	Baseline/30m
3	The Association of n-3 Fatty Acids with Symptoms and Synovial Thickening in Knee Osteoarthritis (MOSTAS0503_Bioassay; K Baker)	Phospholipid n-6 and n-3 PUFAs, arachidonic acid	500	30m
4	Nerve Growth Factor Serum Levels and Pain and Radiographic Severity of Knee Osteoarthritis (MOSTAS1002_Bioassay; B Wise)	NGF	337	Baseline/30m
5	Association of Central Sensitization with Pain Post-TKR: (MOSTAS1007_Bioassay; T Neogi)	Leptin, Adipoinectin, TNFa	1121	Baseline/ 30m/60m
6	Hyperglycemia and Osteoarthritis (MOSTAS1102_Bioassay; A Schwartz, N Lane)	Glucose, Insulin	999	Baseline
7	Obesity and Knee Osteoarthritis: Understanding the Link (MOSTAS1201_Bioassay; D Misra)	Leptin	691	Baseline/30m
8	The Predictive Values of Novel Plasma Metabolic Markers for Early Knee Osteoarthritis Changes (MOSTAS1403_Bioassay; G Zhai)	Metabolite assays: Amino acids, biogenic amines; acylcarnitines; glycerophospholipids; sphingolipids. Total of 156 metabolites	1246	Baseline
9	Fat, Fiber and Osteoarthritis (MOSTAS1406_Bioassay; D. Felson, D. Misra)	Magnesium, lipid profile, fatty acids, alkylresorcinol	994	Baseline
10	Magnesium and Chondrocalcinosis in Osteoarthritis: the Multicenter Osteoarthritis Study (MOSTAS1406mg_bioassay; D. Felson, D. Misra)	Magnesium	215	Baseline
11	Fat and Osteoarthritis – pilot study (MOSTAS1406pilot_bioassay; D. Felson, D. Misra)	Leptin, sLeptin Receptor, HMW Adiponectin, Visfatin, TNFa, IL-6, SAA	150	Baseline
12	Fat and Osteoarthritis – SxOA study (MOSTAS1406SX_bioassay; D. Felson, D. Misra)	Total Adiponectin & High Molecular Wt. Adiponectin	1456	Baseline