THE OSTEOARTHRITIS INITIATIVE

PROTOCOL FOR THE COHORT STUDY

AUTHORS

Michael C. Nevitt, PhD

University of California, San Francisco

David T. Felson, MD

Boston University

Gayle Lester, PhD

National Institute of Arthritis, Musculoskeletal and Skin Diseases

TABLE OF CONTENTS

1.0 EXECUTIVE SUMMARY

Osteoarthritis (OA) is the most common form of arthritis and the major cause of activity limitation and physical disability in older people. Today, 35 million people (13 percent of the U.S. population) are 65 and older, and more than half of them have radiological evidence of osteoarthritis in at least one joint. By 2030, 20 percent of Americans (about 70 million people) will have passed their 65th birthday and will be at risk for OA.

At present, therapies available to treat osteoarthritis are limited. Most current treatments are designed only to relieve pain and reduce or prevent the disability caused by bone and cartilage degeneration. Drug therapies target the symptoms but not the cause of this disease; no treatment inhibits the degenerative structural changes that are responsible for its progression. Furthermore, clinical testing of new therapies is complicated by highly variable way that OA is manifested in individual patients.

Four clinical centers and a data coordinating center will conduct the Osteoarthritis Initiative (OAI), a public-private partnership that will bring together new resources and commitment to help find biochemical, genetic and imaging biomarkers for development and progression of OA. The OAI will establish and maintain a natural history database for osteoarthritis that will include clinical evaluation data and radiological (x-ray and magnetic resonance) images, and a biospecimen repository from nearly 4800 men and women ages 45-79 enrolled from February, 2004 to May 2006. Four 3.0 Tesla MRI scanners, one at each clinical center, are dedicated to imaging the knees of OAI participants annually over four years of follow-up. The seven-year project will recruit participants who have, and those who are at high risk for developing, symptomatic knee osteoarthritis. All data and images collected will be available to researchers worldwide to help quicken the pace of biomarker identification, scientific investigation and OA drug development.

The OAI will rely on the following recruitment centers and their principal investigators:

- *The Ohio State University, Columbus*; Rebecca Jackson, M.D.
- *University of Maryland School of Medicine, Baltimore*; Marc Hochberg, M.D., M.P.H., and *Johns Hopkins University School of Medicine,* Joan Bathon, MD
- *University of Pittsburgh School of Medicine*; C. Kent Kwoh, M.D.
- *Brown University School of Medicine and Memorial Hospital of Rhode Island, Pawtucket*; Charles Eaton, M.D.
- *University of California, San Francisco School of Medicine* (data coordinating center); Michael Nevitt, Ph.D.

The OAI consortium includes public funding from the National Institutes of Health (NIH) and private funding from several pharmaceutical company partners managed by the Foundation for the National Institutes of Health.

When complete, the OAI should provide an unparalleled state-of-the-art database showing both the natural progression of the disease and information on imaging and biochemical biomarkers and outcome measures.

2.0 BACKGROUND

2.1 Burden of Osteoarthritis

Osteoarthritis (OA), or degenerative joint disease, is the most common form of arthritis. It is a slowly progressing disease characterized clinically by pain, enlargement and deformity of the joints, and limitation of motion. OA is the most common form of arthritis and a leading cause of disability and work limitation among adults resulting in enormous costs to society.(1, 2) The disease usually occurs late in life and most commonly affects the hand and large weight bearing joints, most notably the knee and the hip. Approximately 21 million American adults have physician-diagnosed OA,(3) a diagnosis usually based on the combination of joint symptoms and radiographic changes. However, many more have undiagnosed or sub-clinical disease. The prevalence of OA in the population is difficult to determine because the degree of radiological change in symptomatic individuals varies greatly, and many individuals with radiographic evidence of OA have no symptoms. By age 60 nearly half of the population has radiographic evidence of OA in one or more joints, and by age 80 these findings are nearly universal.(4, 5) However, radiographs are an insensitive measure of OA pathology and reflect mainly more advanced disease.(6) One of the important goals of OAI is to support development and validation of imaging and biochemical markers that indicate the presence of OA, or an increased risk of OA, even when radiograph changes are minimal are absent, and which accurately predict the subsequent course of disease.

The hands are one of the most commonly affected sites in OA, but the knee is the major source of reported disability and loss of function. About 40% of the adult population age 55 and older has frequent knee pain or definite x-ray evidence of knee OA.(7-9) Only 1 in 6 of those with frequent knee pain consult a doctor for it.(8) Knee OA is associated with a progressive reduction in function, including difficulty in changing from the sitting to the standing position and decrease in mobility and in the ability to carry out activities of daily living.(2) Advanced OA accounts for the majority (85 percent) of knee replacement surgeries among Medicare recipients. Well over 200,000 knee replacement procedures for OA are performed every year the United States.

No proven disease-modifying therapies exist for knee OA and current treatment regimens are predominantly designed to relieve pain.(10) Approaches to prevent knee OA development, progression, or related disability are also very limited, in large part due to incomplete knowledge of potentially modifiable factors responsible for these outcomes.

2.2 Need for a Longitudinal Cohort Study of Biomarkers for OA

OA is a significant contributor to disability and loss of independence among the elderly and therefore presents a clear and growing public health need.(11, 12) Because of the chronic nature of OA and its variable clinical outcomes, studies of risk and prognostic factors and clinical trials that test interventions to prevent the disease or slow its progression using clinical endpoints are lengthy, require large numbers of patients and are very expensive. Although developing new drugs for OA treatment is a high national priority,(10) it is hampered by the lack of robust biomarkers of disease activity. However, there are new technologies that may improve the assessment of disease, its early development and its progression and that would greatly facilitate clinical and epidemiological research

in OA. Potential OA biomarkers include pathoanatomic characteristics assessed by imaging technologies (i.e. magnetic resonance), biochemical markers of bone and cartilage metabolism to assess disease presence, activity and progression, and genetic markers associated with the risk of OA.

Among the primary motivations for the OAI is the anticipation that these biomarkers for OA will provide the not-for-profit and for-profit scientific enterprise with new opportunities to develop preventive and disease-modifying therapies and streamline clinical trials assessing the safety and efficacy of these therapies. For these purposes, it is important to establish whether biomarkers can act as surrogates for OA status such as predicting onset of disease, predicting the pace of progression, or indicating response to therapy.(13) As valid indicators of disease onset, progression or regression, biomarkers may even serve as candidate surrogate endpoints in clinical trials of novel interventions. Valid biomarkers could be used to expedite OA clinical trials enabling more efficient identification of appropriate research subjects and more rapid and less costly evaluation of novel, disease modifying treatments. This will streamline the clinical trial process and provide incentives for private sector research and development of new osteoarthritis interventions.

An essential step to achieving all of these goals is the assessment of biomarkers in longitudinal studies, over a period of time in which clinical change can be clearly defined, in large, well-characterized populations of persons with OA or who are developing OA. Such data and materials do not currently exist. Existing cohorts provide valuable information on OA onset and progression. However, data from these cohorts are insufficient (too small, too short or lacking the appropriate measurements) for the comprehensive development and validation of biomarkers.

3.0 OBJECTIVES OF THE STUDY

The ultimate purpose of the Osteoarthritis Initiative (OAI) is to improve public health through the prevention or alleviation of pain and disability from OA. To achieve this, the OAI will develop a research resource available to a broad spectrum of scientists and clinicians for use in the scientific evaluation of biomarkers for OA. This public database will also support investigation of the natural history of, and risk factors for, knee OA onset and progression using both traditional measures of disease as well as data on novel biomarkers developed from the study. A multi-center, longitudinal, prospective observational cohort study, focusing primarily on knee OA, is being undertaken in order to provide these resources. The main focus of the OAI will be on knee OA because this is the site where OA symptoms most frequently cause significant loss of function and disability.

The principal scientific objectives guiding the design of the OAI cohort study are:

- To develop an ethnically diverse cohort of women and men ages 45 to 79 suitable for studying the natural history of, and risk factors for, the onset and progression of knee osteoarthritis.

- To determine the validity of radiographic, magnetic resonance imaging, biochemical and genetic measurements as biomarkers and potential surrogate endpoints for knee OA.

The OAI cohort study will recruit up to 5000 participants with clinically significant knee OA or at high risk for developing new clinically significant knee OA and obtain the appropriate images and bio-specimens needed for the investigation and validation of OA biomarkers.

4.0 COHORT STUDY DESIGN

4.1 Overview

The OAI cohort study is a multi-center, longitudinal, observational study focusing primarily on knee osteoarthritis (OA). The study will create a public archive of data, biological samples, and joint images collected over time from a very well clinically characterized population of individuals comprised of two subgroups, 1) those with clinically significant knee OA who are at risk of disease progression and 2) individuals who are at high risk of initiation of clinically significant knee OA.

As originally designed, up to 5,000 age-eligible women and men will be recruited and enrolled at four recruitment centers (the University of Maryland and John's Hopkins comprise a single recruitment center). The baseline assessments consist of an initial eligibility assessment by telephone, a screening clinic visit and an enrollment clinic visit. There will be four annual follow-up visits at which many of the baseline measures will be repeated.

Materials for the identification of joint imaging biomarkers (magnetic resonance imaging and radiography) and biochemical and genetic markers (blood and urine) are collected at baseline and at all follow-up visits. Study clinical centers are equipped with a dedicated Siemens Trio 3.0 Tesla magnetic resonance (MRI) scanner for imaging the knee and also have nearby radiology facilities to obtain joint x-rays. Data on the clinical and joint status of subjects and on risk factors for the progression and development of knee OA are collected by questionnaire and examination at baseline and at the yearly follow-up clinic visits. Clinical assessments of subjects include questionnaires assessing knee pain, aching and stiffness, an examination for knee swelling, tenderness and limited motion, assessments of pain and arthritis in other joints, questions about use of medications for joint pain and arthritis, and questionnaires assessing physical disability due to knee pain and arthritis. Knee pain and function questionnaires include the Western Ontario and McMasters Osteoarthritis Index (WOMAC), the Knee Outcomes in Osteoarthritis Survey (KOOS) and the Medical Outcomes Study Short Form 12 (SF 12). Examination assessments include upper leg muscle strength and walking endurance. Risk factors for the initiation and progression of knee OA include examinations and questions evaluating OA in other joints, history of knee injury and knee surgery, abnormal biomechanical stresses on the knees due to knee alignment abnormality, obesity and heavy physical activities, nutritional factors and use of certain medications, such as bone antiresorptive agents. Additional detail on data to be collected at each clinic visit can be found in Section 5.3.

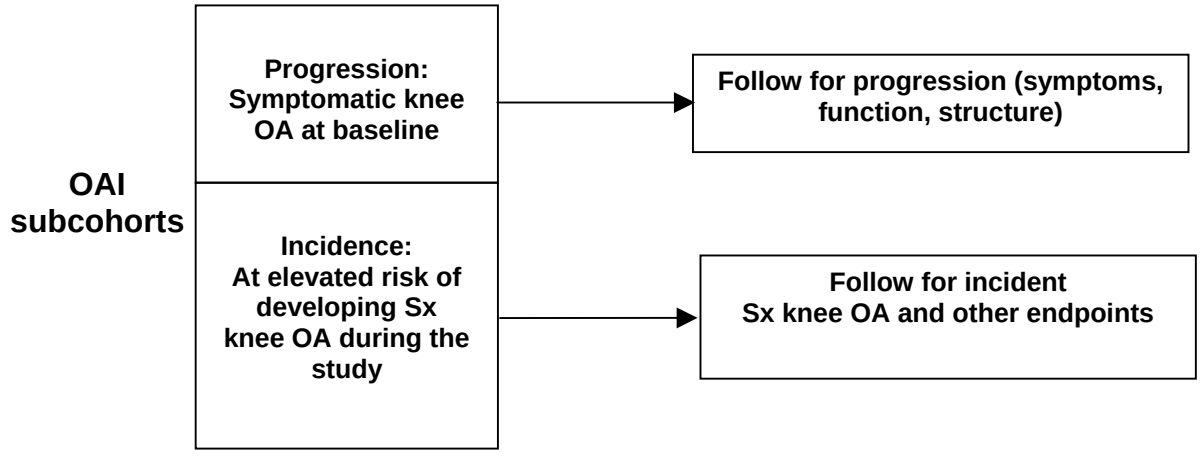
Participants will be followed for four years for changes in the clinical status of the knee and other joints, including worsening and onset of symptoms and disabilities, worsening and onset of knee structural abnormalities, and changes in other imaging and biochemical markers of knee OA.

4.2 Study Population

4.2.1 Overview

The concepts of onset and progression in the OAI's overall objectives connote two different populations of subjects, one with disease at baseline and the other at risk of developing disease. In addition, the emphasis in the OAI will be on progression and incidence of "clinically overt/significant osteoarthritis" using standard definitions. Consistent with these priorities, OAI will recruit two primary subcohorts, one with symptomatic knee OA at baseline followed for worsening of disease (the Progression subcohort), and another without symptomatic knee OA, but selected on the basis of having specific characteristics which give them an increased risk of developing incident symptomatic knee OA during the study (the Incidence subcohort).

Figure 4.1. Overview of OAI cohort design



The definition of prevalent symptomatic knee OA to be used in OAI (Section 4.2.2.2) corresponds to a clinical diagnosis of knee osteoarthritis with implications for prevention, requiring both the presence of frequent knee symptoms and radiographic findings reflecting the pathology of osteoarthritis, and is similar to the definition used in the published ACR criteria for clinical knee OA.(14)

The development of knee OA occurs over many years, and there is a continuum of pathology between newly developing and progressive disease. Therefore, the division into new onset and progressive worsening of disease during the study may be somewhat artificial. For example, there will be many knees in subjects in the Incidence subcohort that will have evidence of early, emergent or subclinical disease and these abnormalities may "progress" as part of the trajectory leading to the onset of clinically significant disease. In the Progression subcohort, prevalent disease may be present in only one knee and so the contralateral knee will be at risk for the onset of new disease.

The study sample will also include a small number (100-200) of participants in a "reference" or "nonexposed" control group who at baseline do not have any of the eligibility risk factors, do not have knee symptoms and do not have radiographic findings of knee OA. The purpose of this group is to provide normal reference data on biomarkers in subjects recruited and evaluated using the same methods as the rest of the OAI cohort.

This cohort design will position the OAI to evaluate biomarkers across the spectrum of disease, including initial onset of structural abnormalities and symptoms, progression of subclinical to clinically overt disease and worsening of clinically overt disease. Implicit in this approach is the notion that factors affecting the course of disease may differ by stage of disease. Indeed, several studies have suggested that risk factors for incident OA may be different from risk factors for progression.(15-18) If risk factors for OA differ at different stages of disease, then this suggests aspects of disease biology that differ by stage, and that optimal biomarkers may be different for different stages of disease. Valid biomarkers for specific pathologic processes and stages in OA will be useful to early-phase testing of treatments designed to slow the progression of specific processes.

4.2.2 Inclusion and Eligibility Criteria

4.2.2.1 Entire cohort

- Male or female. The recruitment goal is for approximately equal numbers of men and women overall and in each subcohort.
- Ages 45-79. Enrollment goals will be specified for each decade of age within each gender and subcohort. (Appendix A)
- All ethnic groups are eligible for the study. The recruitment goal is for approximately 23% of the cohort from ethnic minority groups.

4.2.2.2 Progression subcohort

Subjects with symptomatic tibiofemoral knee OA at baseline are eligible for the Progression subcohort if they have both of the following in at least one native knee at baseline:

- Frequent knee symptoms in the past 12 months defined as "pain, aching or stiffness in or around the knee on most days" for at least one month during the past 12 months;

- Radiographic tibiofemoral knee OA, defined as definite tibiofemoral osteophytes (OARSI atlas grades 1-3(19), equivalent to Kellgren and Lawrence (K-L) grade ≥ 2) on the fixed flexion radiograph.

4.2.2.3 Incidence subcohort

Participants in the Incidence subcohort will not have symptomatic knee OA, as defined above, in either knee at baseline. However, they will have characteristics that place them at increased risk for developing symptomatic knee OA during the study. Incident symptomatic knee OA will be defined as

the first occurrence during the study of frequent knee symptoms and definite tibiofemoral osteophytes in the same knee.

The eligibility criteria used to define "increased risk" represent established or putative risk factors for incident knee OA that can be assessed over the telephone. Analyses of existing data sets focusing on symptomatic knee OA as the outcome identified combinations of characteristics in each age and gender subgroup that will sufficiently enrich the cohort for risk of incident symptomatic knee OA. The details of the modeling analyses using various definitions of "increased risk" are contained in Appendix B.

The following age-specific eligibility criteria will allow a reasonable balance between effectiveness in enriching each stratum with incident events and the feasibility of recruitment, i.e. a high percent of age-eligible persons screened will be classified as "high risk." and therefore eligible:

- For those age 45-49, eligible participants will have frequent knee symptoms (defined above), or frequent use of medications for treatment of knee symptoms (defined below), or infrequent knee symptoms (defined below); AND will have one or more other eligibility risk factor (defined below).

- For those age 50-69, eligible participants will have any of the following: frequent knee symptoms, or frequent use of medications for treatment of knee symptoms, or be overweight, or have <u>two or more</u> other eligibility risk factors.

- For those age 70-79, eligible participants will have any of the following: frequent knee symptoms, or frequent use of medications for treatment of knee symptoms, or <u>one or more</u> other eligibility risk factor.

The specific eligibility risk factor criteria for the Incidence subcohort will be:

- <u>Knee symptoms in a native knee in the past 12 months</u>. Three definitions of knee symptoms during the past 12 months will be used as risk factors for eligibility purposes: 1) frequent knee symptoms (as defined above for symptomatic knee OA); 2) frequent use of medication to treat knee symptoms, defined as use of medications (all types) on most days of a month in the past 12 months (knee symptoms may be masked by the use of pain medications) and 3) infrequent knee symptoms, defined as "pain, aching or stiffness in or around the knee" at any time in the past 12 months but <u>not</u> on most days for at least one month.

  Symptomatic knees without definite osteophytes have an increased risk of developing radiographic OA compared to knees without symptoms.(15) In the Framingham OA study, subjects with knee pain and no definite osteophytes developed radiographic OA at a rate of 5% per year (40% in subjects followed 8 years) (unpublished data) compared to 1-2% per year in all subjects.(20)

- Overweight, defined using gender and age-specific cut-points for weight. Weight is one of the most potent risk factors for knee OA.(9, 15, 21) Weight rather than BMI will be used to facilitate eligibility determination by phone screen, since the relationship to risk of knee OA is similar for both variables. Weight cut-points will be defined using percentiles of self-reported weights based on the 2001 National Health Interview Survey (NHIS). Percentile cutpoints were selected based on analysis of enrichment of the subcohort for risk of incident knee OA using different weight cut-points (Appendix B). NHIS weight percentiles and cut-points will be as follows:

	Men		Women	
Age	Cumulative %	Weight (lbs)	Cumulative %	Weight (lbs)
45-69	70.8%	>205	70.3%	>170
70-79	85.1%	>215	85.8%	>180

- Knee injury, defined as a history of knee injury causing difficulty walking for at least a week. Serious knee injury is among the strongest known risk factors for knee OA.(15, 22, 23) There will be no limits on the time since the injury or age at which it occurred as there is no conclusive evidence at this time that subjects with older injuries will be more or less likely to develop knee OA during the study than those with recent injuries.(23-25)

- Knee surgery, defined as history of any knee surgery, including meniscal and ligamentous repairs and unilateral total knee replacement for OA.[i] Previous knee surgery is a strong risk factor for ipsilateral knee OA.(9, 24, 26) Persons who have progressed to end-stage OA in one knee have a high risk of developing progressive OA in the contralateral knee.(27) The likelihood that an existing total knee replacement (TKR) will cause serious artifacts in the MR image of the contralateral knee is small, so persons with a unilateral TKR for knee OA will be eligible..

- Family history, defined as a total knee replacement for OA in a biological parent or sibling. Twin studies show that knee OA has a significant heritability component.(28) A family history of end-stage knee OA, as indicated by TKR, is associated with a substantially increased risk of knee OA in probands.(29)

- Heberden's nodes, defined as self-report of bony enlargement ("knobby fingers") of 1+ DIP joint in both hands. Individuals with Heberden's nodes or hand OA have an increased risk of OA in other joints, including the knee.(15, 30, 31)[ii]

[i] While there is a slight potential for metal particles left after ligament repair to degrade ipsilateral MR image quality, this was monitored during early enrollment and found not to cause significant artifacts.

[ii] In a pilot study performed by OAI investigators, it was found that individuals similar to those to be recruited for OAI were able to self-report the presence of "hard bumps on the joints nearest the fingertips" with a low rate (10%) of false positives compared to a trained physician examiner. During the baseline clinic visit, a trained nurse will examine each participant for Heberden's nodes. The accuracy of self-report of Heberden's nodes was monitored during the early enrollment to confirm the pilot study results. Telephone interview self-report and clinic nurse examiner assessment of bilateral Heberden's nodes were compared for the first 1,945 women and 985 men screened. The false positive rate for self-report using the clinic

- Repetitive knee bending, defined as current daily activities at work or outside work requiring frequent climbing, stooping, bending, lifting, squatting or kneeling. Occupational knee bending and carrying are associated with an increased risk of knee OA.(32-34)[iii]

- Age 70-79 will be equivalent to a risk factor for eligibility purposes since in this age stratum only one other risk factor will be required for eligibility. The risk of knee OA increases sharply with age(9, 15, 30) and the incidence of clinical diagnoses of knee OA peaks in men and women at ages 70-79.(35)

Limits on prevalence of eligibility risk factors. The prevalence of eligibility risk factors in the Incidence subcohort at baseline will be monitored during enrollment. The goal in the Incidence subcohort will be for all eligibility risk factors to have a prevalence between 7% and 50% in each gender and age stratum to prevent overrepresentation of the most common risk factors (e.g. knee symptoms and overweight) and too few subjects with the less common risk factors (e.g. family history of TKR) to have adequate power for risk factor analyses. Disease characteristics, including the proportion of knees with definite osteophytes, the severity of structural findings of knee OA and the proportion with unilateral TKR will also be monitored during recruitment and may also be subject to stratum-specific goals or limits.

4.2.2.4 Reference ("Nonexposed") control subcohort

In order to distinguish biomarkers that are specific for OA and characterize biomarker distributions in normal subjects, a reference, or "nonexposed" control subcohort of 100 to 200 individuals will be recruited and undergo selected measurement at baseline and follow-up. Inclusion criteria for the "non-exposed" control subjects are:

- No pain, aching or stiffness in either knee in the past year;
- No radiographic findings of OA (OARSI osteophyte grade = 0 and joint space narrowing grade = 0) in the tibiofemoral joint of either knee using the clinic reading of the baseline bilateral fixed flexion radiograph;
- No eligibility risk factors, as defined above, present, with the exception of age $\geq$ 70.

A standing lateral patellofemoral view of the knees will be obtained for participants in the reference control group. This will not be used to determine eligibility, but is provided for use in analytical stratification.

---

examination as a gold standard was 12% for women and 17% for men. 63% of false positives by self-report had unilateral nodes based on the nurse exam.

[iii] The prevalence of repetitive knee bending, as defined in OAI, exceeded 50% in the Incidence subcohort and was therefore no longer used as an eligibility risk factor for the Incidence and Reference control subcohorts after February, 2005.

4.2.3 Exclusion Criteria

The following exclusion criteria will apply to the entire cohort:

- Rheumatoid Arthritis (RA) or inflammatory arthritis, defined as self-report of a physician diagnosis and ever use of any RA-specific prescription medications. Participants who report that a doctor has told them they have RA, SLE, psoriatic arthritis, ankylosing spondylitis or another inflammatory arthritis will be asked about use of specific medications that are used primarily for RA and other forms of inflammatory arthritis: e.g. gold, methotrexate, etanercept, infliximab, leflunamide, plaquenil, etc. If the person has ever used any of these medications, they will be excluded. If the participant reports having RA or inflammatory arthritis but none of these medications have been used, they will be asked about symptoms of RA and excluded if the responses are suggestive of RA. RA symptoms will be assessed with the connective tissue disease screening questionnaire from the Nurses' Health Study, a questionnaire that has been shown to have high sensitivity and specificity for RA.(36) In addition, participants will be considered to have possible inflammatory arthritis and will be excluded if their baseline fixed flexion knee radiograph shows severe joint space narrowing or bone on bone in both the medial and lateral compartments of either knee without the presence of a definite tibiofemoral osteophyte in that knee.
- Unlikely to demonstrate measurable loss of joint space during the study, defined as severe joint space narrowing (OARSI joint space narrowing grade 3 or bone-on-bone) in both knees on the baseline fixed flexion knee radiograph, or unilateral TKR and severe joint space narrowing in the other knee
- Bilateral total knee joint replacement or plans to have bilateral knee replacement in the next 3 years
- Unable to undergo a 3.0 Tesla MRI exam of the knee because of contraindications or inability to fit in the scanner or in the knee coil. Self-report weight limits at the Initial Eligibility Interview will be used to reduce number of persons attending the screening visit who fail to pass the MRI knee coil and bore size screens. Men over 285lbs and women over 250lbs will be excluded (see also section 6.1.1).
- Positive pregnancy test
- Unable to provide a blood sample for any reason, including having had a bilateral radical masectomy, bilateral graft or shunt for kidney dialysis, etc. or refusal to provide a blood sample.
- Use of ambulatory aids other than a single straight cane - for more than 50% of the time in ambulation
- Co-morbid conditions that might interfere with the ability to participate in a 4-year study
- Unlikely to reside in the clinic area for at least 3 years
- Current participation in a double-blind randomized controlled trial
- Unwilling to sign informed consent

4.3 Primary Outcome Assessments

The OAI will make available a public archive of data and images from the cohort study for use by investigators in developing biomarkers for knee OA, understanding the natural history of the disease, and identifying risk and prognostic factors for knee OA. To achieve this, a core set of knee OA status and knee OA outcome measurements (clinical and imaging) will be collected at baseline and at each follow-up visit. (Additional detail on data to be collected can be found in Section 5.3) Selection of primary outcome measures will be guided by the recommendations of the OMERACT III task force of the Osteoarthritis Research Society on core measures for OA clinical trials.(37, 38) Pain, physical function, patient global assessment and joint imaging comprise the four domains of the core set of recommended outcome measures. The outcome measurements made in the different subcohorts of the study will generally be the same, with a few exceptions as noted below.

4.3.1 Clinical Variables Assessed at Baseline and Follow-up

Frequent knee symptoms. Frequent knee symptoms will be defined as "pain, aching or stiffness in or around the knee on most days" for at least one month during the past 12 months. The OAI will use this definition of frequent knee symptoms in the definition of symptomatic knee OA (along with radiographic findings of OA) and as an inclusion criterion for individuals without radiographic knee OA. This definition of frequent knee symptoms is similar to that used in the published ACR criteria for clinical knee OA.(14) Nearly identical questions have been used extensively in previous population surveys of knee OA, including the NHANES series of studies, the Framingham OA study(39, 40) and other prominent epidemiological studies of knee OA. While frequent symptoms will be used to define clinically overt disease, use of the WOMAC, KOOS and other questions will allow investigation of knee symptoms regardless of whether they meet the above definition of frequent symptoms.

Knee pain severity scale. Global knee pain severity (not activity-specific) during the past 30 days and past 7 days will be assessed using an 11-point (0-10) numerical rating scale. The validity of numerical rating scales has been well documented, they are easy to administer and score and can be used with a greater variety of subjects than can a visual analog scale. (41, 42) Numerical rating scales can also be administered over the telephone to participants who become unable to visit the clinic.

Participant global assessment. A patient global assessment focusing on the overall impact of knee problems on their sense of well-being during the past 30 days will be collected. For the reasons noted above, the patient global assessment will also use an 11-point numerical rating scale.

WOMAC Osteoarthritis Index TM (hereafter called WOMAC). Knee pain, stiffness and knee-related physical function will be assessed using the WOMAC version LK 3.1. To characterize subjects' knee symptoms the OAI will use the WOMAC pain with activity and stiffness scales, and to evaluate knee-related disability will use the WOMAC disability scale. Of instruments used to assess change in persons with OA, the WOMAC, a survey based on self-report, has been the most extensively validated and is both recommended for (by the Osteoarthritis Research Society) and widely used in OA trials.(37,

38) Responsiveness has been tested in NSAID trials and each aggregated subscale score (e.g. pain) has been found to detect the effect of NSAID's, and to detect a clinically important statistically significant difference in efficacy between two NSAIDs.(43) In terms of sensitivity to change, WOMAC has been compared to other measures of patient status in OA including HAQ, AIMS, the Doyle index, the Lequesne index and walk time and range of motion(44-47) and has generally been found to be more sensitive to change (relative efficiency compared to other instruments $\geq$1). The 5-point Likert scale version of the WOMAC questions will be used, modified from the original format to ask about the right and left knee separately during the past 7 days. It can be utilized in a knee-specific fashion and has been shown to discriminate between outcomes in opposite knees and hips in the same patients.(9, 15, 21, 48)

Knee Outcomes in Osteoarthritis Survey (KOOS). The nonWOMAC components of the KOOS will be administered separately to assess knee symptoms and function under somewhat different activity conditions (e.g. during sport and recreation) than are evaluated by the WOMAC. The KOOS was designed specifically to extend the target population of the WOMAC to younger and middle age subjects with knee injuries or post-injury arthritis.(49) A history of knee injury and knee surgery are risk characteristics that will qualify some participants for the OAI. Several recent reports indicate that some of the outcome domains unique to KOOS (i.e. quality of life) are sensitive to change in intervention studies involving subjects with knee OA.(50-52) The 5-point Likert scale version of the KOOS questions will be used, modified from the original format to ask about the right and left knee separately during past 7 days.

Limitation in activity due to knee pain. The number of days in which activities are limited by health is a widely used measure of disability(53) that is responsive to the occurrence of a variety of medical conditions and injury(54, 55) and to treatments that prevent injury.(56) Questions about limitation of activity due to knee pain in the past 30 days will be adapted for use in OAI.

General health and functional status. The Medical Outcomes Study Short Form 12 (SF-12) will be used to assess general health status and function. The SF-12, an abbreviated version of the SF-36, is a self-administered, generic health-related quality of life instrument that takes approximately 2 minutes to complete.(57, 58) It consists of twelve questions covering eight health domains (physical functioning, social functioning, role-physical, role-emotional, mental health, energy/vitality, pain, and general health perception). It also generates a Physical Component Summary Scale Score (PCS-12) and a Mental Health Component Summary Scale Score (MCS-12). The SF-12 is one of the most extensively validated and versatile general health status measures, and will facilitate comparison between OAI participants and other studied populations.

Walking ability and endurance. 20-meter and 400-meter walks will be used as measures of walking ability and endurance. The timed 20-meter walk is a standard outcome measure for osteoarthritis.(37) The 400-meter walk, a modification of the validated and widely used 6-minute walk, is a self-paced endurance test that includes standardized encouragement and modifications that increase tolerability in elders and those with physical impairment.(59, 60) Walking endurance is a secondary outcome measure recommended by ORS(37, 38) and has been used successfully as an outcome in several trials of knee OA treatment.(61)

Upper leg strength. Bilateral isometric knee extensor and flexor strength will be measured using the Good Strength isometric strength chair (Metitur, Jyvaskyla, Finland).(62, 63) The maximal force produced during isometric contraction and the speed of force production and relaxation will be measured during isometric contractions of the right and left quadriceps and hamstring muscles at a knee angle of 60° from full extension . There are two warm-up trials and three measurement trials for each muscle group. The coefficient of variation between two consecutive measurements performed two weeks apart was 6.3% (SD 5.7) for knee extension strength.

The association between quadriceps muscle strength and knee OA has been well established. Knee extensor strength is reduced by up to one-third in knee OA patients compared with age-matched controls,(64-66) and knee flexor strength is also reduced.(67, 68) As the primary stabilizer of the knee, the quadriceps muscle provides shock absorption, assists with proprioception, and protects the articular structures from stresses that lead to knee pain and cartilage degradation.(69) Quadriceps muscle strengthening has been shown to decrease knee pain and disability in individuals with knee OA.(70) Upper leg strength will be both a risk factor and an outcome in OAI. Weakness may develop as the result of disuse atrophy secondary to knee pain, but weakness is also present in asymptomatic women who subsequently develop radiographic knee OA.(71) However, greater quadriceps strength may not provide consistent protection from the risk of structural progression. (17)

The chair stand test will be used as a direct assessment of integrated physical performance involving leg strength and knee function. Chair stands are a widely used performance measure of lower extremity function(72) and decline in chair stand performance has been associated with factors that predict structural progression of knee OA in observational studies.(73)

4.3.2 Knee Imaging for Structural Outcome Measures

The core knee imaging acquisition methods are described briefly below. A large variety of measurements of structural OA pathology can be derived from these images. The OAI Steering Committee will define a core set of measurements that will be obtained from the images and made available as part of the public data release (See Section 8.2.2). Raw images will also be available to the research community for additional measurements (See Section 8.1). In addition, the baseline radiographs will be assessed for the presence of tibiofemoral osteophytes and joint space narrowing by trained readers located at each clinical site in order to classify subjects by the presence of symptomatic knee OA (frequent knee symptoms and tibiofemoral osteophytes in the same knee) and assign them to the appropriate subcohort (See Section 4.3.2.3).

4.3.2.1 Knee MRI

One of the primary goals of the OAI is to develop and validate imaging structural biomarkers of knee OA using state of the art MR imaging modalities. Dedicated 3.0 Tesla Siemens Trio MR scanners will be in place at all recruitment centers (the two Baltimore clinical sites will share a scanner located at the University of Maryland). Scanner acceptance testing and ongoing QA testing are described in Appendices C and D.

Table 4.1. Knee imaging schedule

Knee Imaging Protocol	Screening Visit	Enrollment Visit	Follow-up Visit			
			12 month	24 month	36 month	48 month
Bilateral MRI exam of the knees using 3.0 Tesla Siemens Trio scanners [1]		All	All	All	All	All
Unilateral MRI exam of the knees, at either 18 month or 30 month follow-up visit			Pr[2]		Pr[2]	
Bilateral standing PA "fixed flexion" knee radiographs (both knees on 1 image)	All		All	All	All	All
Bilateral standing fluoroscopically positioned knee radiographs (1 knee per image) [2]		Pr[3]	Pr[3]	Pr[3]		

All = all of cohort (includes Reference – Nonexposed – controls)
Pr = Progression subcohort
[1] Includes bilateral thigh scan for muscle and fat distribution at baseline, year 2 and year 4.
[2] Approximately one-third of the Progression subcohort will have a single interim MRI exam 6 months after the 12-month follow-up visit and another one-third will have this six months after the 24-month follow-up visit.
[3] Fluoro-guided knee radiographs will be obtained in selected Progression subcohort participants in two clinics, each clinic using a different protocol (Semi-Flexed and Fixed Flexion with fluoroscopic selection of beam angle, also known as Lyon schuss)

The goals of the MRI protocol will be to allow a thorough clinical and research evaluation of the femoral-tibial and patellar-trochlear joints of both knees, to include as many articular structures and features believed to be relevant to knee OA as possible, and to support as broad a range of existing and anticipated measurement methods for each structure and feature as possible, while keeping the total scan time within a range tolerated by the participants and allowing adequate throughput for the large sample size and annual MRI examinations. The OAI opted to use dedicated 3 T MR systems rather than 1.5T systems because of the potential advantages 3T offers in terms of signal-to-noise ratio (SNR) which can potentially be traded off for spatial resolution and/or imaging speed. Because of the relative lack of data and experience with 3T systems at the time the imaging sequences were selected, pilot testing of candidate sequences was undertaken (Appendix E).

The knee MRI protocol will require less than 60 minutes of acquisition time and is optimized for assessment of both quantitative (e.g. cartilage volume) and qualitative measures of OA pathology (e.g. cartilage lesion scores). Acquisitions for the right and left knee differ in order to keep total scan time under 60 minutes. The knee acquisition sequences and times are listed in table 4.2. Appendix F and the

OAI MRI Procedure Manual (http://www.oai.ucsf.edu/datarelease/OperationsManuals.asp) contain additional MRI protocol acquisition details.

Table 4.2. Knee MRI sequences and scan times (min)

No.	Scan	R knee	L knee	Total
1	**Localizer (3-plane)**	0.5	0.5	**1.0**
2	**SAG 3D DESS WE**	10.6	10.6	**21.2**
3	*COR MPR 3D DESS WE*	*0.0*	*0.0*	*0.0*
4	*AXIAL MPR 3D DESS WE*	*0.0*	*0.0*	*0.0*
5	**COR IW TSE FS 3200 29**	3.4	3.4	**6.8**
6	**SAG IW TSE FS 3200 30**	4.7	4.7	**9.4**
7	**COR T1 3D FLASH WE**	8.6	-	**8.6**
8	**SAG T2 MAP 120mm FOV**	10.6	-	**10.6**
	Total	38.4	19.2	**57.6**

Thigh MRI. An additional 10 minutes of MRI scan time per participant at selected visits will be used to obtain measures of skeletal muscle and fat distribution in the mid thigh designed to complement the measures of muscle strength. Components of the protocol are optimized for segmentation of subcutaneous and intermuscular fat depots, skeletal muscle, and specific muscle groups. The thigh MR will consist of a 15 slice contiguous axial T1-weighted acquisition (Appendix F) of the quadriceps region centered at 100mm above the medial femoral epiphysis.

4.3.2.2 Knee joint radiography

Knee radiographs will focus on assessing OA of the tibiofemoral joint (T-F). It is recognized that patellofemoral joint (P-F) involvement is common in knee OA and contributes to symptoms and disability.(74-76) The P-F joint will be comprehensively imaged with the MRI protocol, which will provide ample opportunity for the investigation of biomarkers focusing on OA in this compartment. T-F joint space loss is the primary radiographic standard against which other biomarkers of progression will be evaluated. Much progress has recently been made in improving T-F joint radiography,(77) while precise and validated radiographic measures of P-F joint space loss are lacking. Subjects with isolated P-F radiographic involvement will not be included in the Progression subcohort; their disease may behave differently from those with T-F or mixed P-F/T-F OA and the likelihood of joint space loss in the T-F compartments is uncertain.

Radiography of the T-F joint will provide material for a variety of uses, including characterization of structural disease at baseline, assessment of incident disease and assessment of structural progression (e.g. qualitative and quantitative measurement of medial T-F joint space width). The “fixed flexion” knee radiography protocol(78) will be the primary protocol for T-F joint radiography. Using this protocol, all participants at baseline and all annual follow-up visits will have bilateral, standing knee films obtained in PA projection with knees flexed to 20-30 degrees and feet internally rotated 10

degrees. Right and left knees will be imaged together on 14 x 17 inch film using a focus-to-film distance of 72 inches. The degree of knee flexion and foot rotation will be fixed for each subject using a plexiglass positioning frame (SynaFlexer TM). The OAI Radiographic Procedures Manual contains additional detail on radiograph acquisition procedures (http://www.oai.ucsf.edu/datarelease/OperationsManuals.asp).

The fixed flexion protocol was selected based on several considerations. Weight-bearing with knees in a flexed position is necessary for the interbone distance, or joint space width, to be a valid indirect measure of cartilage thickness.(79-81) Weight-bearing is essential to displace intervening joint fluid and bring the opposing cartilage surfaces into contact. Flexion of the knee is required to bring into contact cartilage surfaces that are loaded during normal walking and to avoid artifactual increases in apparent cartilage thickness that can occur when the knee is fully extended.(82) Reproducible measurement of joint space width also requires a method for standardizing the degree of knee flexion and the position of the knee relative to the x-ray beam and x-ray film across serial examinations.(83, 84) The ability to reproducibly position the knee immediately adjacent to the x-ray film is required to avoid or minimize the need for correction of differential magnification that occurs when the knee-to-film distance varies between exams.(77, 78, 85) The fixed flexion protocol meets all of these conditions and has demonstrated short-term test-retest precision for measurement of joint space width(78, 86) comparable to that obtained with alternative fluoroscopically-guided(78, 83, 87, 88) and nonfluoroscopic(84, 89, 90) protocols.

Knee radiography protocols using fluoroscopic guidance to align the x-ray beam with the posterior and anterior rims of the tibial plateau have demonstrated sensitivity for detection of joint space loss over periods of 16 to 30 months.(91) There is also evidence that parallel alignment of the tibial plateau rims, which can be achieved consistently using fluoroscopy, may increase sensitivity to loss of joint space.(85, 92, 93) Fluoroscopic knee radiography was judged impractical, too costly and not appropriate for use in the overall OAI study population, and was not built into the original design of the study. Nevertheless, supplementary fluoroscopic radiographs will be obtained, but only in a sample of Progression subcohort participants. Since study sites were not selected based on the intention to use fluoroscopic radiography, radiology resources at only two of the five clinical sites allow the successful implementation of fluoroscopic protocols. The available equipment dictates the use of a different protocol at each of these sites; one will use a modification of fixed flexion using fluoroscopy to vary the angle of the x-ray beam(78) (also known as the Lyon schuss protocol(85)) and the other will use the semi-flexed protocol.(88) Progression subcohort participants at these two sites who have fluoroscopic knee radiographs at baseline will have these repeated at the 12 and 24 months follow-up visits, along with the standard fixed flexion protocol, which will allow a direct comparison of the methods.

In the Reference (Non-exposed) control cohort a standing lateral view of each knee will be obtained to allow assessment of isolated patellofemoral joint OA and evaluate its effect on values of biochemical markers.

4.3.2.3 Assessment of baseline fixed flexion knee radiographs for OA and cohort assignment

Readers at each clinical center will be trained to assess the baseline fixed flexion knee x-rays for osteophytes and joint space narrowing, using a classification based on the OARSI atlas grades(19) (Table 4.3). These assessments will be used in eligibility determination and subcohort assignment. Readers will be trained using a combination of didactic and interactive sessions including a web-based training program that requires scoring a training set of knee x-rays. Certification will have two stages: 1) Readers will score a set of validation knees that have been given a gold standard

Table 4.3 Baseline knee OA grading scheme

Osteophytes
0 = normal (OARSI grade 0)
1 = possible, minute (equivalent to K&L grade 1)
2 = definite (OARSI grades 1-3)
Joint space narrowing (medial and lateral each graded)
0 = normal
1 = mild to moderate narrowing (OARSI grade 1-2)
2 = severe narrowing (OARSI grade 3 or bone on bone)

score and must achieve acceptable agreement with the gold standard. 2) A consecutive sample of readings from each clinical center reader will be centrally reviewed and discrepancies with a central reading reported back to the clinical center reader. Readers must achieve acceptable agreement with the central reading. After certification is complete, a random sample of readings will be reviewed centrally, with feedback provided on discrepancies.

4.4 Biological Specimens for Biochemical Marker Development

One of the primary objectives of the OAI is to develop an archive of biological specimens that will be available to investigators, through a formal application and review process (See Section 9.7), for testing and validation of biochemical markers of OA. For this purpose, blood and urine specimens will be collected at the baseline and all follow-up visits.

Overnight fasting morning blood and second morning void urine specimens will be collected. Urine specimens will be obtained by providing participants with a collection cup and instructions for collecting a second morning void on the day of their clinic visit and bringing the specimen to the clinic.

In order to fully utilize the available scanning time on the dedicated MR scanners installed at each site, a small number of baseline clinic visits will take place in the afternoon. Morning blood draws after an overnight fast will be encouraged, whenever feasible, even for participants coming in for an afternoon visit. If this is not possible, afternoon blood may be drawn without an overnight fast but at least 2 hours after the intake of food or beverage (other than water). Participants with afternoon visits will still be asked to collect a fasting, second-morning-void urine specimen due to diurnal variation in urine bone turnover markers.

Diurnal variation is important for bone turnover markers, particularly markers of bone resorption, and food intake is known to affect serum markers of bone resorption.(94) For cartilage markers there are fewer data both with respect to diurnal variation and the effects of diet, but existing studies indicate substantially less diurnal variation than seen for bone markers.(95, 96) However, as is already documented for serum hyaluronic acid, levels of several serum markers of cartilage (COMP, KS5D4, CPII and others) have been found to increase significantly after 1-4 hours of morning activity, suggesting that blood for cartilage markers should be collected at least 1 hour after arising in the morning.

Blood will be processed for serum and plasma. The majority of blood will be saved and aliquoted as serum. Most of the currently available/reported biomarker assays for cartilage and bone turnover are performed with serum or urine.(97-102) Serum is also useful for proteomic studies.(103) A smaller amount of blood will be collected and saved as plasma. This will allow flexibility for specific assays that are currently available, or that may be developed in the future, that require plasma.(104)

Buffy coat from the plasma samples will be saved for later DNA extraction. At selected visits, PAXgene tubes will be used to collect blood for later RNA extraction. Additional blood specimens intended as a source of cryopreserved lymphocytes for use in developing immortalized cell lines may be added at a follow-up visit.

The target for the number of days allowed between blood and urine collection and the MRI examination and medication use assessment will be +/-7 days.

The goal for timing of follow-up visit blood draws will be for this to occur within +/-1 hour of the time of the baseline blood draw.

Processed blood products and urine specimens will be divided into aliquots and sent to a commercial specimen repository, where they will be bar-coded, entered into a computerized inventory system and stored at –70°C.

The blood and urine specimen collection and aliquoting scheme for each visit can be found in Appendix G. Details on specimen collection and processing methods can be found in the respective OAI operations manuals (http://www.oai.ucsf.edu/datarelease/OperationsManuals.asp).

4.5 Sample Size and Enrollment Goals

The goal will be to enroll 5,000 women and men ages 45 to 79; 4,000 in the Incidence subcohort, 800 in the Progression subcohort and 200 in the Reference (Nonexposed) control group over a period of 18 months (see Appendix A for original study enrollment goals). The goal will be for equal numbers of men and women in each age/gender group. Enrollment goals will be similar by age strata in the Progression subcohort, while in the Incidence subcohort, the goals for age strata will be selected to yield similar numbers of incident symptomatic knee OA cases by 10-year age strata.

Recruitment centers will each have the same enrollment goals for gender and age strata (45-49, 50-59, 60-69, 70-79) in the primary subcohorts (Progression, Incidence).

REVISED ENROLLMENT GOALS: Based on evaluation of progress midway through recruitment, enrollment limits in the Progression subcohort will be increased by 50% in response to the relatively large number of interested individuals who were eligible for this subcohort in combination with below goal recruitment to the Incidence subcohort. In addition, general enrollment will be extended to late 2005. One site will continue to recruit minority participants and two sites will continue to recruit Reference (Non-exposed) control participants during the first half of 2006.

Recruitment of ethnic minorities. The study-wide goal for minority recruitment in the OAI will be 23% of participants in both subcohorts. Due to large difference in the size of minority populations among the clinic catchment areas, minority recruitment goals will differ by clinic. It is anticipated that African Americans will constitute the largest single minority group.

Monitoring recruitment. The coordinating center will collect data on recruitment activity a (number of mailings and recruitment events, the number of potential participants contacting each site, the yield of different strategies, etc), post recruitment activity summaries on the OAI study website and submit them to the Recruitment and Retention Committee. The coordinating center will also post real time reports on eligible screenees and completed enrollment visits, focusing on each clinic's goals for age and gender groups within a subcohort and for minorities. The Recruitment and Retention Committee will work with the recruitment staff at each site to review recruitment goals and yields, quantify shortfalls, and fine tune each site's recruitment plan.

4.5.1 Participants enrolled

The number of participants enrolled (as of 4/14/06, based on meeting minimum data requirements – Appendix H) by subcohort, age-stratum and gender is shown in Tables 4.4 through 4.6. Enrollment in the Progression subcohort will exceed the revised goal of 1200 men and women. Enrollment in the

Table 4.4. Progression subcohort: number of enrollees at baseline 4/14/06

Age stratum	Women	Men	Total N
Age 45-49	87	70	157 (12%)
Age 50-59	224	211	435 (32%)
Age 60-69	276	154	430 (32%)
Age 70-79	167	141	308 (24%)
Age 45-79	754 (57%)	576 (43%)	1,330 (100%)

Incidence subcohort will be about 90% of the revised goal. Enrollment will be about 92% of the original goal for all cohorts combined. Sample sizes in both the Incidence and Progression subcohorts are expected to provide adequate numbers of knees with incident and worsening OA-related structural and clinical changes to achieve the primary aims of the study (see Section 8.0).

Table 4.5. Incidence subcohort: number of enrollees at baseline 4/14/06

Age stratum	Women	Men	Total N (%)
Age 45-49	186	173	359 (11%)
Age 50-59	626	493	1,119 (35%)
Age 60-69	648	326	974 (30%)
Age 70-79	434	329	763 (24%)
Age 45-79	1,894 (59%)	1,321 (41%)	3,215 (100%)

Overall, approximately 19% of the study sample will be minorities and 59% will be women, above original study goals for women but reflecting their greater prevalence of knee OA. The gender distribution is similar by subcohort and age strata. Nearly two-thirds of participants are 50-69 years old.

Table 4.6. Total number of enrollees (all 3 subcohorts) at baseline 4/14/06

Age stratum	Women	Men	Total N (%)
Age 45-49	289	248	537 (12%)
Age 50-59	870	740	1,584 (34%)
Age 60-69	927	482	1,409 (31%)
Age 70-79	601	476	1,077 (23%)
Age 45-79	2,687 (58%)	1,920 (42%)	4,607 (100%)

5.0 STUDY PLAN

5.1 Recruitment and Enrollment

The OAI recruitment centers are located at Brown University in Rhode Island, Ohio State University in Columbus, Ohio, University of Maryland/Johns Hopkins University joint center (2 separate clinic sites) in Baltimore, Maryland, and at the University of Pittsburgh in Pennsylvania. The original study design calls for each of the four recruitment centers to enroll one fourth of the participants. (Actual enrollment numbers per center differ by about 22% from highest to lowest.)

Recruitment and enrollment of participants at baseline will involve four stages:

1) an initial contact designed to reach persons in the intended target population through focused mailings, including to identified clinical populations with OA, advertisement in local newspapers, presentations at church, community, or civic meetings, and a website about knee pain and knee osteoarthritis;

2) an Initial Eligibility Interview by telephone to determine if interested individuals qualify for the study (as age/gender/subcohort cells are filled, participants will be prescreened so that those in cells that are full do not undergo and Initial Eligibility Interview);

3) for those who qualify on the telephone evaluation, a Screening Clinic Visit at which additional eligibility assessments are performed; and

4) for those who still qualify after the Screening Clinic Visit , an Enrollment Clinic Visit at which the majority of the baseline data are collected and the MRI exams performed. Enrollment may require more than one visit to the site to complete all of the baseline imaging.

Time windows between visits. The goal for the maximum time elapsed between the Initial Eligibility Interview and the Screening Clinic Visit and between the Screening Clinic Visit and the Enrollment Visit will be 6 weeks. Knee MRI examinations should occur within +/- 7 days of the collection of biospecimens, medication assessment and the knee examination, which are all part of the enrollment visit.

Informed Consent. Informed Consent procedures will follow all pertinent federal guidelines. Each component of the study will be explained thoroughly to potential participants, and informed consent obtained prior to participation in any screening or enrollment procedures. Verbal consent to participate in the initial phone eligibility interview and to maintain these responses in the study database will be obtained by specific questions at the start of the interview. Written consent will be obtained prior to each clinic visit. A copy of written consent materials will be provided for review before the scheduled visit. During the visit, a trained staff member will thoroughly describe the study component, review all of the consent materials, and answer any questions that the participant may have.

Model study-wide consent forms for clinic visits will be provided to assist the clinical centers with their IRB application; however, each clinical center will be able to modify the consent form templates to comply with the requirements of their local IRB. In compliance with HIPAA regulations, consent forms will incorporate language pertaining to the acquisition, use and disclosure of protected health information. Authorization for inclusion of the participant's study data in public release datasets will be part of the consent form. The consent forms will also include language concerning the storage ("banking") of biologic specimens, including DNA, for future analyses, and the availability of specimens to both OAI investigators and researchers who are not part of the Osteoarthritis Initiative.

Copies of each site's IRB approved Informed Consent documents and IRB approval letters will be kept on file at the UCSF data coordinating center.

5.1.1 Initial Contact

Participants will be recruited primarily by distribution to targeted groups, in person and by mail, of a centrally designed recruitment brochure. The brochure will briefly describes the purpose of the study, who would be eligible and who would not be eligible because of safety and other reasons, and what will be expected of study participants. It will include a self-addressed, postage-paid postcard that potential participants who believe they meet the qualifications for study entry can complete and mail back to their local OAI clinic expressing their interest and giving permission to be contacted with additional information about the study. Toll free numbers will be provided for interested individuals to call.

5.1.2 Initial Eligibility Interview by Telephone

Potential participants who self-identify as eligible and interested will be encouraged to contact the study clinic by mail or phone to request an initial phone eligibility assessment. During the telephone eligibility assessment, the interviewer will describe the goals and content of the study, and then review the eligibility and exclusion criteria by means of a structured interview. Persons who are deemed not eligible for the study will be thanked for their interest and no identifying data will be retained. Persons who are deemed eligible for the study based on the results of this interview will be scheduled for a screening clinic visit. The primary purpose of the initial eligibility interview is to insure that the majority of individuals who come to the screening clinic visit will be eligible to be enrolled in the study, and to avoid making an unnecessary trip to the OAI clinical center.

The initial eligibility assessment telephone interview will include the following components (http://www.oai.ucsf.edu/datarelease/forms.asp):

- contact information
- demographics (age, gender, ethnicity)
- frequent knee symptoms and frequent medications for knee symptoms
- additional screening risk factors (weight, history of knee injury and surgery, knobby fingers, frequent knee bending; total knee replacement (TKR) in parent or sibling)
- assessment of exclusions (bilateral TKR, plans to have bilateral TKR, rheumatoid and inflammatory arthritis, contraindications to 3.0 Tesla MRI, nonambulatory status, serious comorbid conditions likely to interfere with participation, plans to relocate, clinical trial participation)

5.1.3 Prescreening Interview

Recruitment goals for each clinic will include enrollment limits for age and gender cells within each of the two primary subcohorts (Appendix A). Therefore, as age-gender cells are filled clinics will be required to close off recruitment for these cells. A prescreening interview will be used to allow Initial Eligibility Interviews to be targeted to cells that are still open for enrollment. The prescreening interview will assess gender, age, knee pain status (to determine likely cohort assignment) and race/ethnicity. No cells will be closed to potential minority enrollees.

5.1.4 Screening Clinic Visit

Information about the Screening visit will be mailed to potential participants in advance. At the screening visit, participants will be asked for informed consent, and then interviewed and examined to confirm eligibility. MRI contraindications will be reviewed. A bilateral fixed flexion knee radiograph will be obtained and evaluated on site to determine eligibility and subcohort membership. The estimated mean duration of the screening visit is 80 minutes, including the x-ray.

The screening visit interview will include the following components (http://www.oai.ucsf.edu/datarelease/forms.asp):

- consent process
- reassessment of MRI contraindications
- history of arthritis diagnoses
- complete family history of total knee and hip replacement
- knee symptoms in past 12 months and past 30 days
- knee pain severity in past 30 days
- limitation of activity due to knee symptoms in past 30 days
- detailed history of knee injury and knee surgery
- hip symptoms in past 12 months
- back, shoulder, elbow, wrist, hand, ankle, foot symptoms in past 30 days
- temporomandibular symptoms
- menopausal status and pregnancy
- final eligibility assessment
- instructions for enrollment visit

The screening clinic visit examination will include the following components (http://www.oai.ucsf.edu/datarelease/forms.asp):

- standing height
- weight
- body size and knee size assessment for MRI eligibility
- bony enlargement of DIP joints
- standing, PA fixed flexion radiograph of both knees

At the end of the visit, eligible participants will be invited to attend the enrollment visit. In preparation, they will be given a container and instructions for providing a second morning void urine sample at the next visit. They will also be given a self-administered questionnaire to complete at home and bring with them to the enrollment visit.

5.1.5 Enrollment Clinic Visit

Based on the results of the screening clinic visit, participants will be invited to attend the enrollment clinic visit. Guidelines for the Enrollment visit, including what participants can eat and how they should dress, will be mailed prior to their visit. Participants will be given a self-administered questionnaire at the screening visit to complete at home and bring with them to the enrollment visit, where it will be reviewed for completeness. The self-administered questionnaire includes the following components (http://www.oai.ucsf.edu/datarelease/forms.asp):

- additional contact information
- marital status and household occupancy
- education
- health care access and health insurance
- Medical Outcomes Study Short-Form 12 (SF-12)
- co-morbidity index
- fracture history
- weight history
- smoking history
- current alcohol consumption
- CES-D for depressive symptoms
- income
- Block Brief 2000 Food Frequency Questionnaire

The remaining baseline data will be collected at the enrollment clinic visit, including knee MRI scans, additional radiographs and biological specimens. The estimated mean duration of the enrollment visit is 150 minutes, not including radiographs or MRI . The visit will include a physical examination of the knees, measurement of blood pressure, tests of strength and physical function, and an interview for the remaining assessments of joint symptoms, medical history and risk factors. The estimated mean duration of the enrollment visit is two and a half hours, not including the MRI and radiographs.

The enrollment visit interview will include the following components (http://www.oai.ucsf.edu/datarelease/forms.asp):

- review self-administered questionnaire
- WOMAC pain, stiffness and disability for each knee
- KOOS (nonWOMAC questions only) for each knee
- participant global assessment of knee symptoms impact
- current knee bending activities
- Physical Activity Scale for the Elderly (PASE)
- inventory of all prescription medications used in the past 30 days
- current use of prescription and over the counter medications, supplements and neutraceuticals for joint symptoms

- past use of medications that may have a lasting effect on bone or cartilage metabolism (e.g. bisphosphonates)
- knee injections for arthritis (hyaluronic acid and steroids)
- use of complementary and alternative medicine (CAM) for joint symptoms

The enrollment visit examination and laboratory will include the following components (http://www.oai.ucsf.edu/datarelease/forms.asp):

- MRI scan of both knees and thighs using a Siemens Trio 3.0 Tesla scanner
- (for a subset of subjects in the Progression subcohort) a radiograph of each knee with knee positioning determined under fluoroscopic guidance
- PA radiograph of right hand
- standing, bilateral AP radiograph of the pelvis
- biological specimens
  i. a second morning void urine specimen obtained at home and brought to the clinic
  ii. a fasting blood specimen
- abdominal circumference
- sitting blood pressure and resting heart rate
- bilateral examination of the knees (anserine bursitis, joint line tenderness, patellar tenderness, crepitus, effusion/swelling, flexion contracture, knee alignment)
- bilateral isometric quadriceps and hamstring strength
- physical performance measures (20 meter walk, 400 meter walk, rapid chair stands)

5.1.6 Eligibility determination and assignment to subcohort

For purposes of study and subcohort eligibility, the presence or absence of eligibility factors will be based on data collected at the initial eligibility interview. The one exception to this will be knee symptom status, which will be based on data collected at the screening clinic visit and thus closer in time to the acquisition of other baseline data, images and biospecimens.

Minimum requirements for imaging and biospecimens (Appendix H) must be met for a participant to be considered officially enrolled in the study.

Eligibility, subcohort assignment and minimum data requirements will be confirmed by the Data coordinating center using the central study database.

Prior to the enrollment clinic visit, eligible participants will be assigned to one of the three subcohorts (Progression, Incidence, Reference Controls) based on the subcohort eligibility criteria listed in Section 4.2.2 so that the knee radiographs appropriate for cohort will be obtained at the Enrollment visit.

Progression subcohort. Participants with frequent knee symptoms, defined as “pain, aching or stiffness in or around the knee on most days” for at least one month” during the previous 12 months, in one or

both knees at the screening clinic visit and who in the symptomatic knee(s) have a definite tibiofemoral osteophyte (defined as OARSI grade 1 or greater)(19) on the baseline fixed flexion radiograph will be considered to have symptomatic tibiofemoral knee OA at baseline. These participants will be assigned to the Progression subcohort.

Incidence subcohort. Participants who do not have symptomatic tibiofemoral knee OA at the screening clinic visit in at least one knee, but who do meet the risk factor eligibility criteria for their age group, will be assigned to the Incidence subcohort.

Reference (Non-exposed) controls. Participants without any knee symptoms in either knee, who do not have any of the eligibility risk factors and who have OARSI grade 0 in both tibiofemoral compartments for osteophytes and joint space narrowing in both native knees will be assigned to the Reference control group.

The radiograph reading for subcohort assignment will generally be the reading done by the local clinic reader. However, before the clinic reader has completed all stages of certification when there is a discrepancy between the clinic reader and the central reader, then assignment will be based on the central reading. For the Reference controls, a central reading will always be required to confirm the clinic reader's assessment of OARSI grade 0 for both osteophtyes and joint space narrowing.

5.1.5.1 Special cases and eligibility exceptions

Participants who do not meet all of the minimum baseline data requirements or subcohort eligibility requirements may be granted an enrollment exception at the discretion of the Steering Committee. For example, participants who had an Enrollment visit, imaging and biospecimens collected but whose eligibility status changed due to a central reading over-ride of a clinic reading may remain enrolled. Special consideration will be given to minorities and those in difficulty to recruit subgroups.

Participants who are granted an enrollment exception but who do not fit one of the subcohort definitions will be assigned to the Incidence subcohort.

5.2 Follow-up and Retention

5.2.1 Follow-up visit schedule

There will be four annual follow-up clinic visits for all participants, which will include MRI and radiograph examinations of the knees. Data will also be collected on other core outcome measures and information on selected risk factor and clinical measures will be updated. (See Section 5.3 for the detailed schedule of measurements.)

Interim 6 month examination. Approximately two-thirds of Progression subcohort participants will have a follow-up visit at the midway point between two annual follow-up visits. Knee MRIs and biosepecimens will be obtained and core outcome measures will be assessed. These visits will occur at

approximately the 18 month and 30 month follow-up time-points, with one half of the visits to occur at each of these two time-points.

5.2.2 Retention

The OAI will make every effort to encourage participants to return for all follow-up visits and to maintain contact with participants who do not attend follow-up visits or who become inactive. The baseline questionnaire asks for information on several contacts, who can help locate a participant that changes residence without notifying the clinic. This information remains in a locked file for use only by the clinical center and is not be entered into the study database. A twice yearly study-wide participant newsletter will help build a sense of identification with the study. Each clinic will develop additional positive reinforcement tools to maintain the good will of participants, such as inexpensive gifts given at the clinic visits and annual birthday cards. Potential barriers to participant retention, such as parking, transportation and clinic hours, will be identified and addressed. Inactive participants who do not return for clinic visits will be followed whenever possible by telephone and mail for vital status and key outcome measures.

Providing participants with results from their clinic visit is a proven retention tool. Height, weight, blood pressure and other general health information collected at the visits will be given to participants. Participants will be told whether they have definite findings (osteophytes) of OA on the baseline screening x-ray, a finding used both clinically and in research studies to define the presence of knee OA. Copies of knee MRI exams on CD will be made available to participants who request them. All the participants will be given patient education materials about OA and its treatment and prevention, including weight loss. General information about the progress of the study and news on health-related topics of interest to the study population will be shared with participants through the newsletters and other communications.

Monitoring retention. The data system will automatically provide the clinic staff with lists of participants who are due for follow-up contacts. The coordinating center will closely monitor adherence to the visit schedule and subject retention, providing real time reports that detail the frequency of late and missed visits. These reports will be reviewed by the Recruitment and Retention committee at their regular teleconference meetings. The committee will help formulate clinic-specific responses to emerging retention issues.

5.3 Data to be Collected and Frequency

Data for the study are collected when subjects visit one of the four designated OAI clinical research centers. Study clinical centers are each equipped with a dedicated 3.0 Tesla magnetic resonance (MRI) scanner (Siemens Trio) for MR imaging the knee and also have nearby radiology facilities to obtain radiographs. Materials for the identification of joint imaging biomarkers (MRI and radiography) and biochemical and genetic markers (blood and urine) are collected at the baseline and additional specimens will be collected at each of the four annual follow-up visits. Data on the clinical and joint status of subjects and on risk factors for the progression and development of knee OA are obtained by questionnaire and examination at baseline and will be selectively updated at the yearly follow-up clinic visits. The schedule of study measurements is shown in Table 5.1 (examinations) and in Table 5.2

(questionnaires and interviews). Examinations and selected questionnaire instruments are described briefly below. Questionnaires and interview instruments and operations manuals for examinations are available from the OAI public website.
(http://www.oai.ucsf.edu/datarelease/DataAndDocumentation.asp)

Weight: Body weight will be measured in kilograms using calibrated standard balance beam scales. Participants will be weighed twice in light-weight clothing without shoes, heavy jewelry or wallets.

Height: Height will be measured in millimeters using a calibrated wall-mounted stadiometer. Height is measured twice in light clothing without shoes during held inspiration.

Abdominal Circumference**:** Abdominal circumference, a measure of central adiposity, will be assessed using a tape measure over bare skin, with the participant standing. Abdominal circumference has been shown to be the best anthropometric measure of central body fat distribution, and has now been incorporated into guidelines for obesity treatment and is used to define metabolic syndrome, a pre-diabetic state of insulin resistance with dyslipidemia and hypertension.(105) Metabolic factors associated with central adiposity, such as C-reactive protein levels, may increase the risk of knee OA independently of body mass index.(106-108)

Body size for MRI eligibility: A simulated knee coil with the dimensions of the extremity coil used in OAI will be fitted on participants knees to ensure that the knee can be scanned. Similarly, maximum trunk size will be assessed with a wooden cutout having the same dimensions as the scanner bore to ensure that the participant will fit far enough into the bore to obtain high quality knee images.

Knee Examination: A standardized physical examination of the knee will be performed on all participants. The examination will be done on both knees and will include some or all (depending on the visit year) of the following components: visual assessment of knee alignment, anserine bursa tenderness, patellar quadriceps tendonitis/tenderness, crepitus, knee flexion pain, presence of flexion contracture, knee effusions, tibiofemoral joint line tenderness, and patellar tenderness. A manual assessment of medial/lateral laxity in all participants will be performed at a follow-up visit. The objectives of the knee exam are to characterize possible sources of knee pain, assess the severity of selected OA-related knee impairments, identify findings that may correlate with abnormalities detected by MRI (such as knee effusions with synovial enlargement), and evaluate the prognostic value of standard exam findings (i.e. effusion, malalignment and crepitus). Knee exam components were selected based on recent data demonstrating the potential for reproducibility across examiners.(109) Clinic examiners will participate in central training and will perform the knee examinations under the supervision of physician examiners at each site. Since pressure on palpation can affect the reproducibility of these measures, examiners will routinely calibrate manual pressure using a Chatillon dolorimeter.

Hand examination: Both hands will be evaluated for palpable bony swelling of the DIP joints (Heberden's nodes) by trained clinic examiners.

Table 5.1 Examination Measures and Frequency							
Measurement	**Screening Visit**	**Enrollment Visit**	**Follow-up Visit**				
			12-mo	**Interim 6-mo**	**24-mo**	**36-mo**	**48-mo**
Blood collection, fasting[1]							
- Blood draw for serum		X	X	X	X	X	X
- Blood draw for plasma and buffy coat		X	X	X	X	X	X
- Blood draw for RNA			X				
Urine collection							
- Fasting second AM void		X	X	X	X	X	X
- Pregnancy test for premenopausal women	X	X	X	X	X	X	X
Height, standing	X				X		X
Weight	X		X		X	X	X
Knee size screen for MRI knee coil	X		X[2]	X[2]	X[2]	X[2]	X[2]
Body size screen for MRI bore	X						
Abdominal circumference		X			X		X
Hand examination (DIP bony enlargements)	X						
Knee examination							
- Alignment (by goniometer)		X	X		X	X	
- Anserine bursa tenderness		X	X			X	X
- Effusion		X			X		X
- Flexion contracture and hyperextension		X					
- Tiobiofemoral joint line tenderness		X	X		X	X	X
- Knee flexion pain/tenderness		X					
- Patellar tenderness		X	X		X	X	X
- Patellar quadriceps tenderness/tendinitis		X					
- Patello-femoral crepitus		X	X		X	X	X
- Medial-lateral laxity					X		
- Knee pain location					X		
Blood pressure, seated		X	X		X	X	X
Resting heart rate		X			X		X
Performance Measures							
- 20-meter timed walk		X	X		X	X	X
- 400-meter timed walk		X			X		X
- Chair stands timed		X	X		X	X	X
- Isometric quadriceps and hamstring strength		X	X[3]		X		X

Table 5.1 Examination Measures and Frequency -- Continued							
Measurement	**Screening Visit**	**Enrollment Visit**	**Follow-up Visit**				
			12-mo	**Interim 6-mo**	**24-mo**	**36-mo**	**48-mo**
MRI							
- Right and left knee		X	X	X[4] (Unilat)	X	X	X
- Right and left thigh		X	X[3]		X		X
X-ray							
- Knee: bilateral PA fixed flexion view	X		X		X	X	X
- Knee: unilateral fluoroscopic-guided view (one or both knees)		X[5]	X[5]		X[5]		
- Knee: unilateral lateral view (both knees)		X[6]	X[3,6]			X[6]	
- Hip: AP pelvis view		X	X[3]			X[7]	
- Hand: dominant PA hand		X	X[3]			X[7]	
- Bilateral full limb for mechanical alignment			X[8]		X[3]		

[1] Most participants will have AM blood draws after an overnight fast; a small percent will have PM blood draws after a minimum 2 hour fast. AM vs PM blood draws will be consistent for the same participant across visits.

[2] Optional

[3] Obtained in those participants eligible for this measurement at the previous visit but for whom a valid measurement was not obtained.

[4] Obtained in the knee that had the extended set of sequences at baseline, usually the right knee.

[5] Obtained in a subset of Progression subcohort participants at 2 clinical centers.

[6] Obtained in Reference (Non-exposed) controls.

[7] To be obtained at either the 36-month or 48-month follow-up visit , to be determined

[8] Obtained in Progression subcohort participants.

Table 5.2 Questionnaire Measures and Frequency								
Questionnaire/ Interview Measures	**Initial Eligibil-ity**	**Screen-ing Visit**	**Enroll-ment Visit**	**Follow-up Visit**				
				12-mo	**Interim 6-mo**	**24-mo**	**36-mo**	**48-mo**
Contact information	X		X	X		X	X	X
Demographics (age, gender, ethnicity, educat, marital status, residency, income)	X		X				X	
Employment, current and past			X	X		X	X	X
Health care and health insurance			X	X		X	X	X
MRI contraindications	X	X	X	X	X	X	X	X
Knee Symptoms								
- Frequency of knee symptoms & medication use for knee symptoms, past 12 mos, 30 days	X	X		X		X	X	X
- Knee pain 0-10 rating scale, past 7, 30 days		X	X	X	X	X	X	X
- WOMAC knee pain and stiffness, past 7 days			X	X	X	X	X	X
- KOOS knee pain and symptoms, past 7 days			X	X	X	X	X	X
Knee-related function and QOL								
- WOMAC physical function, past 7 days			X	X	X	X	X	X
- KOOS sport, recreation, past 7 days			X	X	X	X	X	X
- KOOS Quality of life, past 7 days			X	X	X	X	X	X
- Participant global assessment of knee impact			X	X	X	X	X	X
- Limitation of activity due to knee Sx, past 30 days		X		X		X	X	X
- Work disability due to health problems			X	X		X	X	X
Other Joint Symptoms								
- Hip symptoms, past 12 months		X		X		X	X	X
- Frequency of symptoms in other joints (shoulder, elbow, wrist, hand/finger, ankle, foot/toe), past 30 days		X		X		X	X	X
- Back pain and function, past 30 days		X		X		X	X	X
- TMJ Pain, past 6 months		X				X		X
- History of inflammatory arthritis/other arthritis	X	X		X		X	X	X
- History of total hip replacement		X		X		X	X	X
General Health/ Functional Status								
- SF12			X	X		X	X	X
- CES-D (depressive symptoms)			X	X		X	X	X
- Comorbidity Index			X			X		X

Table 5.2 Questionnaire Measures and Frequency -- Continued								
Questionnaire/ Interview Measures	**Initial Eligibil-ity**	**Screen-ing Visit**	**Enroll-ment Visit**	**Follow-up Visit**				
				12-mo	**Interim 6-mo**	**24-mo**	**36-mo**	**48-mo**
Medication								
- Prescription medication inventory, past 30 days			X	X	X	X	X	X
- Current medications/supplements for joint symptoms			X	X	X	X	X	X
- Knee injections for arthritis			X	X	X	X	X	X
- Past use of selected medications			X	X	X	X	X	X
- CAM treatments for joint Sx, past 12 months			X			X		X
Health Behaviors and OA Risk Factors								
- History of knee injury	X	X		X		X	X	X
- History of knee surgery (incl TKR)	X	X		X		X	X	X
- Family history of total knee and hip replacement	X	X				X		X
- Fracture history			X	X		X	X	X
- Height and weight history			X					
- Tobacco and alcohol use			X					X
- Physical activity (PASE), past 7 days			X	X		X	X	X
- Frequent knee bending activities, past 30 days	X		X	X		X	X	X
- Dietary nutrient intake (Block Brief 2000), past 12 mo			X					
- Female history – menopausal, pregnancy status	X	X		X	X	X	X	X

Seated blood pressure and heart rate: Seated blood pressure and resting heart rate will be collected as a safety measure in conjunction with the 400 meter walk. Blood pressure will be measured using a standard sphygmomanometer. Participants with very high levels of blood pressure or high or low radial pulse will be excluded from the 400-meter walk test.

Knee MRI: (see Section 4.3.2.1)

Thigh MRI: (see Section 4.3.2.1)

Knee Radiographs: (see Section 4.3.2.2)

Pelvis and hand radiographs: To assess concomitant radiographic OA of the hip and hand, a standing, bilateral AP radiograph of the pelvis and a PA radiograph of the dominant hand or both hands (depending on clinic) will be collected at baseline and at one follow-up visit (to be determined).

Full limb radiograph for knee alignment: In the Progression subcohort, a single, weight-bearing AP radiograph of the full lower extremities will be obtained at the first follow-up visit using a 51 by 14 inch graduated grid cassette.(110) This will be used to assess knee mechanical alignment, the hip-knee-ankle angle, a major determinant of medial and lateral compartment load distribution. Malalignment is a potent risk factor for OA progression (73, 111) and may modify the effect of other prognostic factors.(112)

Blood and urine specimens: (see Section 4.4)

Physical activity: General physical activity will be assessed using the Physical Activity in the Elderly Scale (PASE), an instrument assessing multiple domains of activity in older adults that has been validated for use in persons with knee OA.(113) The PASE includes questions about household chores. For those who are employed, the PASE asks about the general level of physical activity on the job. Knee OA has been associated with specific occupational activities that require a combination of knee bending and lifting.(32-34, 114) Questions will evaluate both occupational and nonoccupational knee bending, squatting and stair climbing, adapted from a widely used instrument that has shown associations of these activities with knee OA in multiple studies.(34)

Medications, arthritis treatments and supplements: All currently used (past 30 days) prescription medications will be captured using the medication inventory method, in which the participant brings in all medications they are currently taking and the brand name, generic name or active ingredients are recorded and matched to an entry (and its seven digit code) in an online medication dictionary.(115) The seven digit code maps the medication to the Iowa Drug Information System (IDIS) pharmaceutical product ingredient database.

Additional targeted questions will ask about recent use of medications and health supplements taken and knee injections received for the treatment of joint pain and arthritis that may affect the course of OA and biochemical marker levels during the study and that can be used to characterize the OA treatment status of subjects at baseline. Past use of medications or supplements (prior to the most recent 30 day period) will be assessed only for those specific items (e.g. bisphosphonates) with a known effect on cartilage or bone metabolism that persists for more than a month after discontinuation. Nutritional and health supplements that influence the intake of nutrients of potential importance for the course of OA or that may affect biochemical markers during the study will be assessed with the Block Brief 2000 Food Frequency Questionnaire as well as by targeted questions. A questionnaire assessing complementary and alternative treatments for knee OA, provided for use in OAI by scientists at the National Center for Complementary and Alternative Medicine, will be administered.

Comorbid conditions: The presence of comorbid conditions will be assessed using a validated self-administered questionnaire modeled on the Charlson index.(116)

Food Frequency Questionnaire: Dietary intake data will be collected at baseline using a self-administered reduced length food frequency questionnaire, the Brief Block Questionnaire 2000. The Brief 2000 was developed from the NHANES III dietary intake data using the same methodology as an earlier reduced length FFQ developed from the NHANES II dietary data.(117-119) (http://www.nutritionquest.com/validation.html) Research on the role of nutritional factors in OA is at an early stage and few definitive conclusions can be reached. Nevertheless, there are many plausible mechanisms through which nutritional factors might influence the occurrence and course of OA, including obesity/metabolic syndrome, antioxidant effects and nutritional influences on bone.(120-122) Inclusion of a dietary and nutritional evaluation at the baseline of OAI will facilitate and help target in-depth investigations of nutritional factors.

5.4 Data Management System

The OAI data management system will combine decentralized data submission, centralized and remote data editing, and a centralized database structure designed to collect, transfer, and store data for large-scale multi-center clinical studies. Data will be collected on hard copy forms filled out by clinic staff, and in some cases directly by the participant. Data forms will be designed to be machine-readable using Cardiff Teleform Software, making each form electronically submittable via fax or scanner, or screen enterable via the web. The data coordinating center will not receive paper forms in the process of data submission. Participant files containing the original data collection forms will be maintained at the clinical sites.

After the data are received (electronically) by the data coordinating center, they will be assessed via automated and manual editing processes and then written to the study database. Data editing and reporting will be implemented via a secure study web site housed on a UCSF CC web-server. Every 24 hours, queries will be generated that identify potential errors in the study data. These queries will be immediately accessible via the web site so that clinic staff can resolve them in a timely manner. Data modifications will be made on screen and any changes saved to the database and to a separate audit table. The audit table generated during the editing process contains a complete record of the changes and automatically generates an audit trail. Query resolution that requires a change in how the data form is completed will be recorded on the paper form, dated and initialed at the clinical site.

Non-UCSF collected data, such as imaging quality assurance center data, reading center data and core lab data, are sent to the coordinating center via customized electronic data transfer protocols and the data integrated into the system as appropriate for study use. After data collection and real-time query resolution, data are further evaluated for quality and cleanliness using SAS prior to periodic database lock (see Appendix I for further description of the data management system).

Data management procedures and activities will be described in documentation maintained by the data coordinating center.

5.5 Quality Assurance

The overall goal of quality assurance in the OAI will be to provide complete and accurate data to address the study specific aims. The activities designed to achieve this goal will encompass all aspects of the study, including: clear, pretested data collection forms; measurements that are clearly described in operations manuals; central and local training and certification of clinic staff; site visits; monitoring of recruitment and retention; and surveillance and evaluation of data quality as it is collected. Oversight of quality control will rest with the appropriate OAI committees, utilizing data and reports provided by the coordinating center.

Staff training and certification requirements and performance standards for each study task will be detailed in the operations manuals. Central training will be provided for data management, examinations, interviews, imaging and laboratory. MRI technicians will receive extensive training in the use of the Trio MRI scanner that is provided by Siemens at its U.S. training facility, and will also attend a study-specific central training organized by the imaging QA center to be held at one of the clinical centers. Site-specific radiography training will be provided by the imaging QA center at each radiography facility involved in the study. Periodic site visits will be performed by the coordinating center and the imaging QA center to identify problems and ensure uniform adherence to study procedures. A quality assurance officer from each clinical site will participate in regular study-wide quality assurance conference calls.

The OAI Siemens MR scanners will undergo rigorous acceptance testing at the time of installation, according to system performance specifications required by the manufacturer as well as those required by the OAI (Appendix C). MR system performance will be continuously monitored during the study using several different phantoms and regular performance tests (Appendix D). A sample of images acquired during the study (MRIs and radiographs) will be reviewed centrally for quality and protocol adherence at the imaging QA center. The proportion of images centrally reviewed will vary by image type and stage of the study. Equally important, imaging technologists at each site will be trained to perform image quality and protocol adherence evaluations as images are acquired.

5.6 Website for Study Management

The OAI internal study web site will have several distinct components dedicated to study management and coordination: administrative, data system support, forms tracking, querying and editing, and reporting. The administrative component of the web site will include the following features:

- study directory
- meeting and conference call calendar, dial-in information
- searchable memo archive
- announcements and news
- document archive: operations manuals, data collection forms and policy documents
- Q & A submission and searchable protocol Q & A archive
- staff certification tracking log
- ancillary studies and publications tracking log

Data editing will be performed using the website as described in Section 5.4. Reports will be generated and posted on the website to provide an accurate picture of study progress, including recruitment tables, within visit window completion rates, retention rates, forms submission, incomplete data entry and remaining edits reports, and other QA reports as needed. Multi-tiered support will be provided for web site users, including written user manuals, searchable question and answer archives, and technical support via e-mail. All documents (manuals, forms, reports, etc.) will be downloadable in the portable document format (.pdf).

6.0 PARTICIPANT SAFETY

The OAI undertakes a variety of activities to minimize risks to participants and to ensure their safety, including screening evaluations of potential volunteers to determine whether it is safe for them to participate, monitoring safety during examinations, and providing selected results from study assessments when there are health and safety implications.

6.1 Risks to Participants

The primary risk of the study to participants is the possibility of injury from the MRI examination, from exposure to ionizing radiation from the x-rays and from the physical examinations. Trained and certified clinic technicians will administer all of the examinations with the exception of the following:

- MRI scans and x-rays will be obtained by appropriately licensed radiology technologists;
- baseline fixed flexion knee radiographs will be read by radiologists or rheumatologists using standardized protocols;
- phlebotomy will be performed by trained phlebotomists;
- the knee examination will be performed by trained clinic examiners.

Exclusion criteria for safety will be applied for each component of the study. If a participant appears too frail or at risk of injury from an examination, they will be excluded from that examination.

All pre-menopausal women (have not had a hysterectomy or tubal ligation and have had a menstrual period within the past 12 months) will be given a urine pregnancy test prior to radiographs and MRI scans. A positive pregnancy test at baseline will exclude the participation from the study, and at follow-up visits will exclude the participant from MRI and radiograph examinations.

6.1.1 MRI Safety

MR imaging uses non-ionizing radiation and is safe when used on subjects who are appropriately screened for contraindications. The FDA recently classified MRI as a class II risk, down from a prior class III risk.

MR imaging is a common clinical diagnostic and prognostic tool, with over 18 million MR exams performed in the United States in 2001, and a 16% annual growth rate from 1988 to 2001.(123) Such exams are typically performed using main magnetic field strengths of 1.5 Tesla (approximately 30,000 times larger than the earth's magnetic field) or less. However to increase the sensitivity of the exam, higher strength main magnetic fields can be utilized. For maximum sensitivity and spatial resolution, the OAI will use a Siemens whole body 3.0 Tesla MRI (Trio) system. The Siemens Trio has been Food and Drug Administration (FDA) 510(k) approved and all OAI imaging protocols will conform with FDA guidelines for non-significant risk. To be a non-significant risk, the FDA has specified (FDA Guidance Document 793, 14July2003) that a Magnetic Resonance system must achieve all of the following: a) main static magnetic field $\leq$ 4.0 Tesla; b) specific absorption rate $\leq$ 4 Watts/kg over the whole body for 15 minutes, $\leq$ 3 Watts/kg over the head for 10 minutes, $\leq$ 8 Watts/kg in any gram of tissue in the head or torso for 15 minutes, or $\leq$ 12 Watts/kg in any gram of tissue in the extremities for 15 minutes; c) change in gradient magnetic field (dB/dt) which does not cause severe discomfort or painful stimulation; and, d) peak acoustic power $\leq$ 140 dB or average (rms) sound level $\leq$ 99 dBA with hearing protection in place. As of early 2004, there were approximately 100 operational 3 Tesla MR systems in the United States and at least ten human whole body 4 Tesla units having safeguards that allow compliance with the non-significant risk specifications.

Despite the widespread use of MR imaging exams, very few adverse events occur.(124, 125) The majority of adverse event are caused by inadequate screening for metallic objects or by radiofrequency (RF) burns. Screening eliminates subjects with metallic objects, such as prostheses or aneurysm clips, which may move when in a magnetic field or which might heat when exposed to the RF fields. Ferromagnetic objects not contained within the subject, such as paper clips, hairpins, keys or equipment such as screw drivers or hammers, might become projectiles if not removed prior to entering the magnet proximity. Screening also eliminates subjects with biostimulation devices, such as pace makers, which may have altered performance or may even fail when exposed to either the magnetic or RF fields associated with an MR system. RF burns can result from damaged or improperly placed cables, such as from ECG leads or from an RF coil (used to detect the MR signal). In addition, the RF fields used to excite the MR signal might produce warming if not properly regulated. To ensure compliance with FDA guidelines and to reduce the risk of patient heating, all 3 Tesla and 4 Tesla MR systems have special RF power monitoring equipment built and installed by the manufacturer. Although acoustic noise levels are more an issue of the gradient magnetic field pulse sequence parameters, it is known to increase with increasing main magnetic field strength.

As a result of the low risk of injury, when used within FDA guidelines, MR is considered a 'non-significant risk' device and suitable for use on patients of all ages (neonates to geriatrics) who pass safety screening. However, the effects of an MR exam on a developing fetus are not fully understood and, as a result, women who are or might be pregnant will be excluded from this protocol. To minimize the risk of hearing loss all patients and subjects will be provided ear plugs, even if the examination utilizes 'quiet' gradient parameters.

MRI safety screening at baseline. Potential participants with any contraindications for an MRI exam of the knee will be excluded from the study at baseline. Individuals with contraindications to an MRI exam which utilizes the body RF coil, but not a local knee transmit / receive coil, will be eligible for the OAI but will only receive an MRI exam of the knee utilizing a transmit / receive knee coil. Such

subjects will not be eligible for the thigh MRI exam. All categories of implants and devices that include any specific type of implant/device listed as either "unsafe" or "conditional" in current MRI safety references will be classified as contraindications for participation in the OAI.(126-128) The MRI eligibility and safety assessments used in the OAI will be reviewed for completeness by recognized experts on MRI safety. Contraindications for the MRI exam will first be assessed on the Initial Eligibility Interview telephone screen. They will be reassessed at the screening clinic visit, and at this time additional information about MRI exclusions that are difficult to assess over the telephone will be covered. On the day of the MRI scan, contraindications will again be reviewed with the participant. The MRI technologist will review all MRI safety questions and the MRI technologist, participant, and witness will sign and date the form verifying the information. (See Appendix J for MRI safety screening instruments).

The risks of MRI also include discomfort associated with lying on the MRI table. The risk of claustrophobia is low with a knee MRI exam since the head usually is outside the magnet opening. However during the thigh MRI exam, the participants head may enter the magnet bore. During the baseline screening visit, the MRI 'bore sizer' will be used to screen out participants who will not fit into the magnet for the knee and thigh MRI exams. During this screening process, participants who are not comfortable with how far in the scanner they will go (or who do not fit) or who do not think they will be able to lie on their back on the table for 1.5 hours in the magnet will be excluded from the study at.

MRI safety screening at follow-up visits. Contraindications to the MRI will be reassessed at each follow-up clinic visit. The general approach to baseline screening for MRI contraindications will be to apply blanket exclusions for entire categories of implants and devices. Once subjects are enrolled, however, however, an effort will be made to determine if a specific implant or device acquired by a participant since baseline has been demonstrated to be MRI safe at 3T.

The MRI safety screening procedures for follow-up will be implemented as a 2-step approach Participants will first be assessed for MRI contraindications over the telephone and before they come to the clinic for a follow-up visit. This will identify those participants for whom an MRI is considered definitely no longer safe by OAI standards. This will also identify those participants for whom documentation is needed to confirm that it is safe for them to have a 3T MRI scan. Every effort will be made to obtain the safety documentation for those participants who report an implant or device that requires documentation. A letter spelling out the specific information needed to determine MRI safety and will be sent to the participant. An MRI safety expert will be identified at each clinic who will be responsible for reviewing the documentation according to the MRI safety protocol and making a decision about whether the documentation confirms that it is safe for a participant to be scanned at 3T.

As at baseline, a thorough MRI Safety Screener will be administered the day of the MRI exam to reassess contraindications and confirm safety, and if applicable, review the device safety documentation provided by the participant. The MRI Technologist will review the safety screening information once again with the subject prior to allowing the subject to enter the magnet room.

Each clinical site will have copies of The Reference Manual for Magnetic Resonance Safety: 2003 Edition(126) for reference.

6.1.2 Radiation Exposure

The x-ray examinations will involve exposure to ionizing radiation. Knee and pelvis radiographs are indicated and commonly used in the routine care of patients with pain or OA in the large joints of the lower extremities. Knee and hand radiographs involve a modest skin dose of radiation, but because vital anatomy is shielded and not irradiated, the effective organ dose for these exams is very small.

Skin dose for the OAI knee and hand radiographs is as follows:

- Unilateral PA knee x-ray — Skin dose is approximately 1,000 microGray
- Unilateral PA/AP knee x-ray with fluoroscopy — Skin dose is approximately 2,000 microGray
- PA single hand x-ray — Skin dose is approximately 300 microGray

Effective dose, rather than skin dose, is the most appropriate quantity for the assessment of the risk of radiation injury. The effective (i.e. whole body equivalent) dose from the extremity radiographs is very small with proper beam collimation and shielding of gonads and visceral organs, as will be done in this study, and since only a small portion of the total body bone marrow is exposed. For example, exposure to the testes or ovaries from a bilateral knee radiograph is less than 0.1 microSieverts (Handbook of Radiation Doses in Nuclear Medicine and Diagnostic X-ray, CRC Press, 1980.) The overall effective dose for each PA knee x-ray is under 2 microSieverts without fluoroscopy and under 4 microSieverts with fluoroscopy. 4 microSieverts is the equivalent of less than one day of natural background radiation. The effective dose for the hand x-ray is even less.

The effective dose for the pelvis x-ray is 1,100 – 1,700 microSieverts, reflecting the larger area of vital anatomy exposed.

A person who agrees to be in the study will receive a total effective dose of between 1,100 and 1,700 microSieverts from the full set of radiography examinations at the baseline visit. This is less than the amount of radiation received during one year as a result of natural background radiation on the east coast of the U.S. (2,000 – 4,000 microSieverts, depending on location). This amount of radiation is small and the risks from exposure are so small that they are difficult to measure. In most follow-up years, subjects will have only the knee x-rays.

The effective dose for the full limb radiograph of the pelvis and the entire lower extremity is 3,400 to 4,500 microSieverts, due in part to energy levels needed for effective x-ray penetration of the pelvis area and the large area of anatomy exposed even with appropriate shielding of gonads. The full limb and the pelvis radiographs are not planned for the same visit.

Knee radiographs will be repeated at each follow-up visit. The hand and the pelvis radiographs will be repeated at one follow-up visit. The complete set of exams will fall within typical guidelines for

annual and total radiation dosage to research subjects.[iv]

6.1.3 Phlebotomy

About 79 ml of blood will be drawn from each participant at the baseline enrollment visit. Somewhat lesser amounts will be drawn at each follow-up visit. This is consistent with the amount of blood drawn in other large population studies, including the National Health and Nutrition Examination Survey III, the Framingham Heart Study and the National Institute on Aging's Health, Aging and Body Composition study. The major risk to participants are bleeding and bruising at the site of the blood draw.

6.1.4 Walking Endurance

The 400-meter walk is a walking endurance test in which participants pace themselves and will be allowed to take as many breaks as they need to take within a maximum 15-minute period. A heart rate monitor will be worn during the test. To ensure participant safety there will be a number of exclusions:

- cannot perform the 20-meter walk test
- heart rate greater than 110 or less than 40 bpm
- systolic blood pressure greater than 180 mmHg or diastolic greater than 100 mmHg
- participant uses a three or four-prong cane or a walker
- participant uses supplemental oxygen
- participant feels it would be unsafe to walk up and down hallway

[iv] The above information was derived from a number of sources including:

Huda W, NA Gkanatsios, "Radiation dosimetry for extremity radiographs," Health Phys 1998; 75(5):492-499;

Okkalides D, Fotakis M, "Patient effective dose resulting from radiographic examinations," Br J Radiol 1994; 67:564-572;

Kereiakes JG, Rosenstein M. Handbook of Radiation Doses in Nuclear Medicine and Diagnostic X-ray. Boca Raton, FL: CRC Press, 1980;

Wall BF, Hart D. Revised radiation doses for typical x-ray examinations. Brit Med J Radiol 1997; 5: 437-39;

The Australian NHMRC website (http://www.nhmrc.gov.au/publications/hrecbook/02_ethics/35.htm); The CDRH website (http://www.fda.gov/cdrh/ohip/organdose.html);

and other web-based sources,
(http://www.ehs.umaryland.edu/Rad/pdf/A%20Summary%20of%20Radiation%20Dose%20Guidelines%20and%20Limits%20Applicable%20to%20Human%20Subjects%20in%20Research%20Studies.pdf);

(http://www.bcm.tmc.edu/envirosafety/rad_handbook_06.html);

(http://www.hps.org/publicinformation).

- participant had any of the following in the past 3 months:
    - saw or called doctor for worsening of angina or shortness of breath
    - hospitalized for heart attack or myocardial infarction
    - hospitalized for 3 or more days
    - angioplasty or heart surgery
    - major thoracic, abdominal or joint surgery

If there is a borderline or unclear answer to an exclusion question, the final decision to test or not to test will be made by the medical supervisor at each clinic.

Once the test begins it will be stopped for any of the following reasons:

- heart rate falls below 40 bpm
- heart rate rises above 135 bpm and participant is not feeling well after slowing down
- participant reports a significant degree of any of the following:
    - chest pain, tightness, or pressure
    - trouble breathing or shortness of breath
    - feeling faint, lightheaded or dizzy
    - calf pain
    - needs to sit down

If the participant is not feeling well during the test, the medical supervisor will be contacted immediately.

6.2 Notifications and Referrals

6.2.1 Routine Reports to Participants

Participants will be informed during the consent process that the measurements done as part of the OAI are for purposes of research only and are not a substitute for clinical care and that they should continue seeing their regular health care providers as usual. Results from selected assessments will be given to participants (e.g. height, weight and blood pressure) and they are encouraged to share these with their health care providers or to authorize the clinical center to send such reports to their physician. Participants will be told that they will not be receiving the results of many of the tests that are done, such as muscle strength and walking tests, since it is not known what results are considered "normal" for these tests. General information generated by the study will be shared with participants on a twice-yearly basis through the study newsletter.

Knee OA. Prior to the Enrollment Visit, a centrally trained radiologist or rheumatologist at the clinical centers will evaluate the fixed flexion knee radiograph for the presence of definite tibiofemoral osteophytes and joint space narrowing using standardized reading procedures and a radiograph atlas.(19) A finding of osteophytes is used both clinically and in research studies to define the presence of radiographic knee OA. Participants who have knee osteophytes on their baseline radiograph will be informed that they have radiograph findings consistent with knee OA and that these

findings may be related to their knee symptoms. Participants with possible but not definite osteophytes or joint space narrowing without definite osteophytes will be told they have radiographic findings of possible OA. All participants will be given information about OA and its treatment and prevention available from the Arthritis Foundation, NIAMS and NIA.

Generally, no diagnostic information from the knee MRI scans or the hand, pelvis and full limb radiographs will be provided to the participants, since these will not undergo a clinical reading as part of the study. These images will undergo selected research readings and measurements at various times throughout the duration of the study. In general, these research measurements will not be provided to participants. However, if there are suspicious findings the Reading Center will write a letter to the Clinic Coordinator and PI that describes the problem found on the x-ray or MRI. This letter will also be emailed to the coordinating center. It will be up to the clinical center investigators acting in accordance with local IRB guidelines to decide what to do with this information. Copies of joint images may be provided upon written request from a participant's health care provider. For the knee MRI, a limited subset of sequences with potential clinical utility will be provided to interested participants as a retention measure.

Overweight. Participants will be provided with information about their degree of overweight, based on body mass index.

Hypertension. Individuals with high blood pressure will be informed of this finding and encouraged to report this to their health care provider.

- If the participant's blood pressure is normal, i.e., <120 systolic, and <80 diastolic, or prehypertension, 120-139 systolic, or 80-89 diastolic, they are told to see their primary care provider to have their blood pressure checked again within 12 months.
- If the participant's blood pressure indicates hypertension, 140-159 systolic, or 90-99 diastolic, they are told to see their primary care provider to have their blood pressure checked again within two months.
- If the participant's systolic blood pressure is 160 to 179 mmHg, or their diastolic blood pressure is 100-109 mmHg, they are told to see their primary care provider to have their blood pressure checked within one month.
- If the participant's systolic blood pressure is 180 to 209 mmHg, or their diastolic blood pressure is 110-119 mmHg, they are told to see their primary care provider to have their blood pressure checked within 1 week.
- If the participant's systolic blood pressure is ≥ 210 mmHg, or their diastolic blood pressure is ≥ 120 mmHg, they are told to see their primary care provider immediately. With the participant permission, the clinic will contact their primary care provider immediately.

Participants are instructed to talk with their primary care provider about any specific questions that they may have about their blood pressure.

Pregnancy test. Premenopausal women will be informed of the results of their pregnancy test.

Lab tests. No biochemical assays or genetic studies will be carried out as part of the NIH-funded core protocol. Therefore, no lab results will be provided to the participants. These specimens are stored for later use in analyses that will require approval by the biospecimen resource allocation committee administered by NIAMS.

Other. At the discretion of the individual clinic center principle investigator, other observations during the clinic examinations may be reported to the participant, and if authorized by the participant, to their health care provider. These may include: unexplained weight loss, cognitive decline, new or uncontrolled angina, shortness of breath, etc.

6.2.2 Urgent Notifications

If anomalous findings requiring immediate medical attention are made during the course of a clinic visit, or during quality assurance review and research evaluation of study materials, these will be reported to the participant, and if authorized by the participant, to their health care provider. Urgent notification should occur while the participant is at the clinical center or immediately upon receipt of the information at the clinic from the central reading center or laboratory. Authorized notification of the participant's health care provider should be sent within one week of receipt of the authorization or request by the participant.

Findings requiring urgent notification include:

- If the participant's systolic blood pressure is ≥ 210 mmHg, or their diastolic blood pressure is ≥ 120 mmHg, they are told to see their doctor immediately. With the participant permission, the clinic will contact their health care provider immediately.
- Severe depression
- Serious safety concerns noted on MRI scans or radiographs, such as suspicious masses, tumors, lytic or blastic lesions, during QA review or research readings, or during review by a local radiologist in instances where the clinic is required by their IRB to provide this.

7.0 PARTICIPANT CONFIDENTIALITY

The OAI will develop a public domain research resource to facilitate the scientific evaluation of biomarkers for osteoarthritis as potential surrogate endpoints for disease onset and progression and to understand the factors that shape the natural history of the disease. The disclosure of individual health information to the general public or researchers not affiliated with the OAI will comply 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 confidentiality will be protected thorough a multi-tiered approach.

Participant consent. First and foremost, only participants who sign an IRB-approved consent form at the clinical center will have their data included in the publicly accessible dataset and their biologic specimens available to researchers not directly affiliated with the OAI. Prior to the public release of a participant's data, the clinical centers will also have the participants sign all necessary HIPAA authorizations. The release of stored biological specimens will be subject to review by the NIAMS-administered Biospecimen Resource Allocation Committee to assess the consistency of the proposed use with the original intent of the study and consent.

Participant identifiers. OAI participant data, including x-ray and MRI images and biologic specimens that are submitted to the UCSF coordinating center and reading centers will be identified by a study ID number and a four letter check code. Only the clinical centers will have the key that maps the ID # and four letter check code to the participant's name and contact information for those participants at their site only. All participant data will be maintained in locked file cabinets and on secured password protected computers at each clinical center and the coordinating center with limited access by OAI researchers and staff.

Data submission. The bulk of the data will be electronically transferred from the clinical sites to the coordinating center by a scanner using a secure connection to the coordinating center network. The clinics will be able to view, update and edit only the data that they have submitted using the internal OAI website, which is secured with a 128-bit SSL. Imaging QA center and other reading center data will be transferred to the coordinating center via a secure-FTP transmission.

Public access datasets. A limited data set, containing most of the examination measurements and questionnaire data, with all direct identifiers removed, will be created and made available to the public, via a publicly accessible website call OAI OnLine. The limited data set will exclude the following direct identifiers of the study participants and their relatives, employers or household members: names; postal address; telephone and fax numbers; e-mail addresses and URLs; internet protocol (IP) address numbers; social security numbers; medical record numbers; health plan beneficiary numbers; account numbers; certificate/license numbers; vehicle identifiers/serial numbers, including license plate numbers; device identifiers and serial numbers; biometric identifiers including finger or voice prints; and full face photographic images. In order to access and download the datasets and corresponding documentation from the OAI OnLine website, the user will have to complete the registration process and review and agree to the terms of a Data Use Agreement.

MRI and X-ray images will be available upon request via hard drives. Similar to accessing data from the OAI OnLine website, requestors interested in OAI images will need to review, sign, and fax in a completed Data User Agreement, along with a Request for Image Data Set(s) form, to the UCSF coordinating center in order to obtain the images on a hard drive.

The public access data sets will use the unique ID # for each participant that is assigned during the initial screening process. The four-letter check code is used for quality control purposes only and will not be released. Data values that have the potential for unmasking participant identity, such as clinic location and rare medical conditions, will not be available in the public use data set or will be made available only as calculated variables that cannot be mapped back to raw values. Extreme outliers and

uncommon combinations of demographic characteristics (e.g. small numbers in a particular race category, marital status and education categories) will be collapsed.

8.0 DATA ANALYSIS

The data coordinating center will provide access to data and resources to facilitate analysis of OAI data by the scientific community.

8.1 Public Website for Access to OAI Data and Images

Potential users will obtain access to data and images through a public website (http://www.oai.ucsf.edu/datarelease/) developed and maintained by the data coordinating center. This site will provide general information about the OAI and its design, describe the study data, procedures and materials, provide online access to forms, operations manuals and data documentation, and enable limited online data exploration. Clinical data sets will be made available for download to registered users through the web site. Joint images will be distributed on various electronic media. Access to biological specimens will be by application to the NIAMS-administered Biospecimen Resource Allocation Committee (See Section 9.7.) The planned major features of the website are listed below.

Study information.

- Description of OAI - information about the study, investigators and participating organizations;
- Links - links to participating organizations and arthritis-related web sites and required plug-ins for interacting with the web site;
- Q&A - a form for submitting a question about the study, and a searchable archive of previously asked questions and their posted answers;
- Help - instructions for using the Web site and experiencing full functionality.

Data description.

- description of available public use OAI data sets;
- data documentation (downloadable) – variable distributions, data documentation and metadata, forms, operations manuals;
- data documentation (online) – search on keywords or browse through categories of related variable content;
- custom datasets (downloadable) – small datasets based on subsetting criteria set by the user will be programatically created and made available to download from the website.
- data exploration - an online query and reporting tool (SAS) for generating simple reports and tables of OAI data in real-time.
- requests for images – a section of the website will detail the procedures for requesting joint images.

Study data and materials access.

- user registration and user agreements;
- guidelines for data and image distribution;
- automated submission of data and image requests;
- analysis user's guide - documentation on known data-related issues pertinent to statistical analysis;
- biospecimen access guidelines and link to Biospecimen Resource Allocation Review Committee;
- clearing house for publications and analysis plans using OAI data;
- bulletin board - a forum for facilitating discussion and collaboration in the use of OAI data and materials.

The coordinating center will also host OAI data users meetings during the study.

Public data releases will generally occur within 6 to 12 months after the end of clinic visits for each of the first half of cohort and for the entire cohort. Hence there will be at least two data releases for each visit cycle.

8.2 Analytical and Statistical Issues

8.2.1 Key Research Questions Driving the Study Design

The design of the OAI and the data being collected will allow users to develop and evaluate OA biomarkers and to describe the natural history of OA and investigate factors that shape it. It is not practical to anticipate all of the potential uses of the data, nor all the types of analysis that will be performed to address user defined questions. However, the following are examples of the types of research questions that data users will be able to address:

- In knees with symptomatic OA at baseline, determine the relationship of:
  - baseline imaging structural markers, biochemical markers and risk factors with progression of symptoms and disability;
  - baseline imaging structural markers, biochemical markers and risk factors with progression of joint space loss assessed by x-ray and with loss of cartilage assessed by MRI;
  - changes in imaging structural markers and biochemical markers during the study with progression of symptoms and disability;
  - changes in imaging structural markers and biochemical markers during the study with progression of joint space loss assessed by x-ray and with loss of cartilage assessed by MRI.

- In knees without symptomatic OA (including those with subclinical disease) at baseline, determine the relationship of:

- baseline imaging structural markers, biochemical markers and risk factors with the onset of knee OA, defined in various ways (e.g. symptomatic OA, specific structural abnormalities, symptom onset, etc.);
- changes in imaging structural markers and biochemical markers during the study with the onset of knee OA defined in various ways (e.g. symptomatic OA, specific structural abnormalities, symptom onset, etc.);
- baseline imaging structural markers, biochemical markers and risk factors with progression of joint space loss assessed by x-ray and with loss of cartilage assessed by MRI.

8.2.2 Assessment of Images Needed for Key Research Questions

The OAI will obtain selected readings and measurements from the joint images acquired during the study and make these available to investigators. However, given the very large number of images that will be acquired over the course of the study (Tables 4,1 and 5.1, e.g. over 40,000 separate knee MRI exams and over 40,000 separate knee radiograph exams) only a fraction of the images will be included in these assessments, and the measurements will only be a subset of all the types of measurements desired by investigators. Instead, the OAI will make available in the public use data sets a limited number of image assessments in subjects selected to enable investigators to address the broad types of questions posed above. In addition, all joint images will be available for user-defined assessments and measurements.

8.2.2.1 Clinic reader assessment of baseline knee radiographs in the entire cohort

In order to assign participants to the appropriate subcohort and to exclude individuals with bilateral severe joint space narrowing, the following evaluations will be performed for each knee by readers at the clinical sites using the baseline fixed flexion knee radiograph:

- the presence of definite tibiofemoral osteophytes (OARSI atlas grade 1-3,); and
- mild to moderate (OARSI grade 1-2) or severe (OARSI atlas grade 3 or 'bone on bone') joint space narrowing in the medial and lateral tibiofemoral compartments of each knee.

8.2.2.2 Central assessment of joint images in the Progression subcohort

Progressive disease in those with symptomatic knee OA at baseline will be common,(73, 129) and the OAI will undertake longitudinal evaluation of knee images in those with baseline prevalent symptomatic disease, the group most likely to be a target of treatment interventions. Potential assessments for Progression subcohort knees include:

- Knee radiographs: quantitative measurement of the medial and lateral tibiofemoral joint space and qualitative assessment of structural features of OA at baseline and follow-up;
- Knee MRIs: quantitative measurement of cartilage volume and thickness at baseline and follow-up; qualitative assessment of structural features of OA at baseline;
- Hand radiographs: presence and severity of baseline hand OA;
- Pelvis radiographs: presence and severity of baseline hip OA.

8.2.2.3 Central assessment of joint images in the Incidence subcohort, nested case-cohort design

Since the rate of onset of knee OA, even in those at high risk, will be relatively low, efficiencies can be gained and little information lost by targeting those subjects who develop new disease and comparing them to selected subjects at risk who don't (instead of intensively studying all of those without disease). As with other measurements that can be prohibitively expensive in large cohorts, such as biochemical marker assays, a nested case-cohort or case-control approach to assessing joint images is an efficient alternative to the evaluation of predictor-outcome relationships in longitudinal data sets.(130) Studies suggest that one approximates the statistical power of evaluating the entire cohort by studying cases and a large number of controls (usually 4) per case. This approach requires articulating specific research questions, as in Section 8.2.1, in order to define the predictors and endpoints and to estimate the sample size needed for measurements.

To identify cases of incident radiographic and symptomatic knee OA, a central reading of the follow-up fixed flexion knee radiographs will be performed in order to identify new tibiofemoral osteophytes, a component of the study definitions of incident radiographic and incident symptomatic knee OA (the first occurrence during the study of frequent knee symptoms and definite tibiofemoral osteophytes in the same knee).

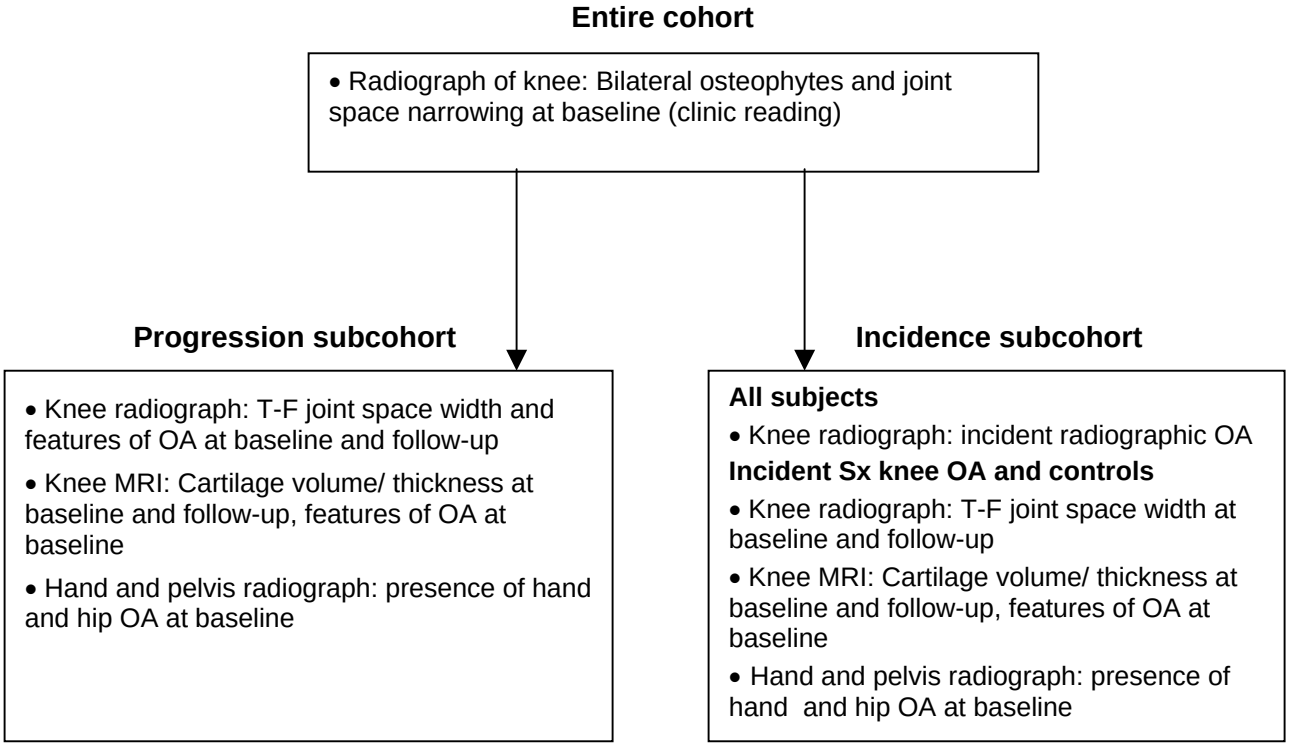
A commitment to specific definitions of incident disease is also a potential disadvantage of the case-cohort design. While alternative definitions of endpoints can be studied within a planned sample of cases, power will be limited for smaller subsets of endpoints and there is a potential for bias in the subsamples of cases. However, since alternative endpoint definitions are likely to be highly correlated with a primary endpoint (e.g. symptomatic OA), the definition of incident endpoints can be expanded to yield additional and different cases with modest increases in numbers and cost.

Potential central assessments for incident OA knees and control knees include:

- Knee radiographs: quantitative measurement of the medial and lateral-tibiofemoral joint space at baseline and follow-up.
- Knee MRIs: quantitative measurement of cartilage volume and thickness at baseline and follow-up; qualitative assessment of structural features of OA at baseline;

- Hand radiographs: presence and severity of baseline hand OA.
- Pelvis radiographs: presence and severity of hip OA.

Figure 8.1. Potential central assessment of images



8.2.2.4 Methods for central image assessments

Specific assessments, measurement methods and protocols will be recommended by the Steering Committee.

The data coordinating center will contract with vendors to make measurements on joint images. All centrally funded and acquired measurements will be made available as part of the OAI public release databases.

Importantly, all of the study images will be archived and available for investigations of user-defined endpoints and to extract alternative and novel structural markers.

8.2.3 Biomarker and Surrogate Validation: Statistical Issues

The usually accepted definition of a surrogate marker is a measure which can substitute for a more difficult, distant, or expensive-to-measure endpoint in predicting the effect of a treatment or therapy in a clinical trial.(131) Greatly complicating the issue is the fact that all the definitions of surrogacy revolve around the elucidation of the joint and conditional distributions of the desired endpoint, putative surrogate and their dependence on a specified therapy.(131-135) Therefore, what may work adequately for a given endpoint and one type of therapy may not be adequate for the same endpoint and a different type of therapy.(135) The OAI is an observational study, not a clinical trial, and it will be impossible to anticipate all the potential therapies for which a surrogate marker might be desired.

Nevertheless, as measurements are developed that capture more and more accurately the structure, functioning and tissue metabolism of the joints, it will become more likely that proposed biomarkers are on the causal pathway to OA and its clinical outcomes and can function as surrogate markers for at least one element of disease. Furthermore, the longitudinal nature of the OAI allows correlation of changes within a person over time between different elements of disease including different measures of structural change, such as radiographic and MRI findings, and disability and pain. So that the OAI will support analyses that researchers may want to perform to evaluate putative biomarkers and assess their potential for surrogacy, it is designed to have adequate precision for estimating the joint relationship between proposed biomarkers and desired endpoints. At the very least, investigators will be able to identify a number of promising biomarkers for use in early development of treatments and that can be tested – or 'validated' – in trials as surrogates for treatment effects. These initial objectives for surrogacy may require somewhat different validation standards in comparison to use of surrogates by regulatory authorities in registering a new drug treatment.

Surrogacy means more than a demonstrable or even a strong association between the desired endpoint and the proposed surrogate(135) and original definitions have been criticized as being limited in scope and having fundamental shortcomings.(132, 133, 135) Recent proposals in the context of meta-analysis get more to the heart of surrogacy.(134) By correlating changes in the surrogate with changes in a primary endpoint, these approaches more directly address the surrogacy question. These analytic techniques are equally applicable in a longitudinal setting, such as the OAI.

The techniques for doing so are most easily described in the context of a continuous surrogate (e.g. change in cartilage volume) and a continuous outcome (e.g. changes in WOMAC score or joint space width). Linear mixed models (136)with random slopes (or, more generally, random functions) and intercepts through time are built for both the surrogate marker and the endpoint. That is, the joint distribution of the surrogate marker and the endpoint are modeled using the same techniques as used for each variable individually. The degree to which the random slopes for the surrogate and the endpoint are correlated give a direct measure of how well changes in the surrogate correlate with changes in the endpoint.(134) The ability of the surrogate to extinguish the influence of potent risk factors, such as obesity or being female, in a multivariate model, further strengthens its use as a surrogate marker.

A typical analysis of candidate surrogate biomarkers using OAI data will fully utilize repeated measurements of an outcome variable, such as WOMAC score, and/or correlated measurements

assessed in two knees, while accounting for the correlation of measurements within an individual. In a typical knee-based analysis, clustered data techniques will be used (i.e., mixed effects models, frailty models - the primary methods for clustered survival analysis - or GEE methods(136)) to adjust for the within person correlation between the two knees.

Continuous outcome measurements, such as WOMAC disability score or joint space width, might be analyzed with mixed linear models with terms for time, interactions with time, predictors such as change in cartilage volume, and confounders such as gender. The time effect captures the rate of decline and a time interaction with a biomarker or risk factor describes how these predictors modify the rate of decline in the continuous outcome.

Similarly, dichotomous outcomes might be modeled using a logistic function with random slopes and intercepts and fit using a nonlinear mixed model program such as SAS Proc NLMIXED (SAS, Version 8). Time-to-event variables, such as incident symptomatic OA, could be analyzed using the discrete-time Cox proportional hazards model with time-varying covariates (a GEE version of this model would be used for knee-based analyses). Predictors of interest might include terms like cartilage volume and possible confounders, or effect modifiers, such as gender. The assumption of proportional hazards can be assessed by including interactions with time and functions of time.

In practice, it is likely there will often be competing candidate surrogate markers each correlated to a different degree with the endpoint. The preferred surrogate is one that is biologically defensible and most highly correlated with the endpoint. The statistical significance of the differences between correlations can be evaluated using a parametric bootstrap.(137)

8.2.4 Expected Rates of Knee OA Incidence and Power for Analyses of Incident Disease

Table 8.1 shows the number of subjects and knees that are expected to develop incident symptomatic knee OA during four years of follow-up in the Incidence subcohort. For the purpose of these estimates, incident symptomatic knee OA is defined as the first occurrence in a knee of frequent knee symptoms (pain, aching or stiffness on most days of at least one month during the past 12 months) and definite tibiofemoral osteophytes in the same knee. Expected incidence is estimated by applying age and gender-specific incidence rates, derived from analyses modeling enrichment of the cohort using risk factors (See Appendix B for details), to the original goals for enrolled subjects in each gender and age stratum (Appendix A). The base age- and gender-specific incidence rates used in the cohort enrichment modeling are taken from published estimates from the Fallon Community Health Plan(35) and the Framingham study.(20, 22) Cumulative loss to follow-up is assumed to be 28% by the end of year 4; 10% dropout at the first follow-up visit and 7% additional dropout in each year after that. Similar calculations are used to estimate the expected number of incident knees, taking into account the ratio of bilateral to unilateral incidence from the Framingham study (unpublished).

The overall incidence of symptomatic knee OA expected among subjects selected for the OAI Incidence subcohort is 1.8/100 person-years in men and women combined. Adjusted age-specific risks range from about 1.0/100 p-y at age 45-49 to about 2.0/100 p-y in those age 60 and over and are similar by gender. This compares with an observed range in age-specific risks of about 0.2/100 p-y to

0.8/100 p-y in the general population in the same age strata.(35) Cumulative incidence after 4 years is expected to be about 5.5%.

It is likely that these are conservative estimates. The increased risk in the overweight groups derived from the cohort enrichment modeling suggest a smaller effect of weight than is seen in the existing incidence studies. In the Fallon Health Plan, women (mean age 60) who weighed 175 lbs or more had a 5 to 6 fold increased risk of incident clinical knee OA compared to those who weighed less.(138) In the Bristol cohort, men and women in the highest third of BMI ($\geq$ 25.4 kg/m2) had at least a 9-fold higher risk of developing knee OA than those in the lower third.(15) This compares to a risk ratio of 2.0 for prevalent symptomatic knee OA in the upper third of weight in Framingham women and 1.6 for the upper third of weight in men (Appendix B).

Most participants in this subcohort will have two knees at risk for incident disease, and consistent with this the number of knees with incident symptomatic OA (Table 8.1) is projected to be greater than the number of incident case subjects.(20) (and unpublished data) In addition, contralateral knees in the Progression subcohort that are free of prevalent disease at baseline have a high risk of developing OA(139) and may be pooled with cases from the Incidence subcohort for some analyses.

Table 8.1 Expected number of cases of incident symptomatic knee OA based on enrollment goals in the Incidence subcohort

Gender/ Age stratum	Subjects with Incident Sx OA N	Knees with Incident Sx OA N (%)
Men age 45-69	73	121 (32%)
Men age 70-79	37	62 (17%)
Men age 45-79	110	183 (49%)
Women age 45-69	76	127 (34%)
Women age 70-79	37	61 (17%)
Women age 45-79	113	188 (51%)
All subjects	223	371 (100%)

Incident radiographic OA (the first occurrence of tibiofemoral osteophytes in knees free of this finding at baseline) is another potential endpoint of interest in this subcohort. The age- and gender-specific incidence of radiographic knee OA, without taking knee symptoms into account, is expected to be about 2.3 to 2.6 times greater than the incidence of symptomatic knee OA.(20) Assuming that one-third of subjects in the Incidence subcohort will already have radiographic knee OA at baseline in at least one knee, over 550 knees are expected develop incident radiographic OA during follow-up.

Occurrence of incident symptomatic OA for knees in the same subject is correlated, so the equivalent number of independent incident knees is smaller. To reflect this, the projected number of incident knees is divided by 1 plus the interclass correlation coefficient to obtain the equivalent number of independent knees.(140) Using the 0.4 interclass correlation for prevalent symptomatic knee OA in the Framingham cohorts, the equivalent of 265 independent knees with incident symptomatic OA is expected by the end of the fourth year of follow-up.

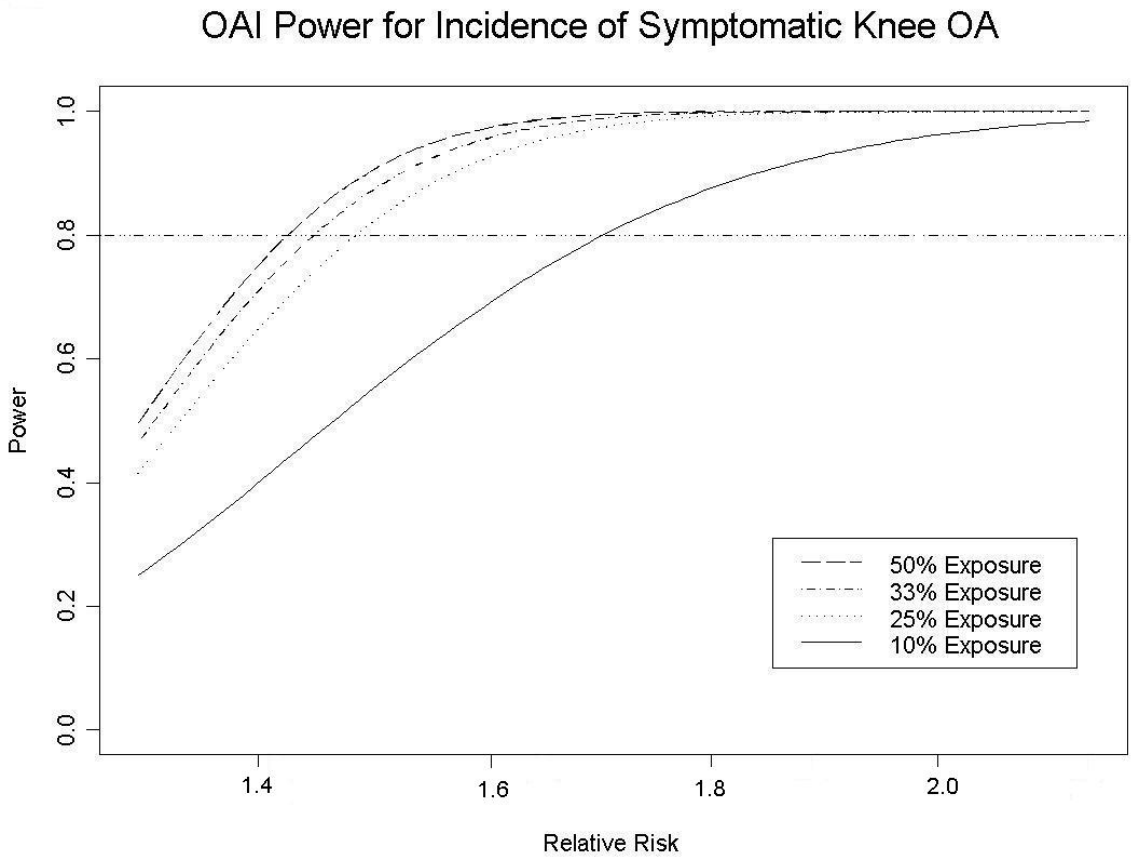
Table 8.2. Power for dichotomous predictors of incident Sx OA obtained in <u>all subject</u>

Exposure Prevalence (%)	*Relative Risk detectable with 80% power*
50	1.43
33	1.45
25	1.49
10	1.70

Based on expected numbers of endpoints using the original study design assumptions, the power to detect relative risks (RR) between exposed and nonexposed subjects <u>in the Incidence subcohort</u> is displayed in table 8.2. The smallest detectable RR by Cox regression of time to incident OA using a two-sided 0.05 hypothesis test with 80% power is given for dichotomous exposures of 10%, 25%, 33% and 50% prevalence in the table. (In reality, incident cases will accrue on an annual basis and would be analyzed using a grouped failure time model.)

Figure 8.2 shows the power curves by smallest detectable RR value for each of these exposure prevalence values. Detectable relative risks will be smaller for more common endpoints, such as incident radiographic OA.

Figure 8.2



Analyses of structural biomarkers for incident OA will use only the knees from the nested case-control sample, which will have full marker information. (A similar approach will likely be applied to analysis of biochemical markers and incident OA.) Table 8.3 shows relative risks that could be detected in a nested case-control analysis using an MRI-derived risk factor or a biochemical marker as a predictor of time to incident OA. For this it is conservatively assumed that image or biochemical marker data would be available from about 300 case knees and 1200 control knees. Because the number of cases and controls is reduced in the case-control analysis, the detectable relative risks are larger. Even for exposures with 10% prevalence, there is 80% power to detect a relative risk of 1.62 in all subjects, and 1.91 in the case-control analyses.

Table 8.3 Power for dichotomous predictors of incident Sx OA in case-cohort analyses

Exposure Prevalence (%)	*Relative Risk detectable with 80% power*
50	1.56
33	1.57
25	1.62
10	1.91

Analysis of the association of biomarkers with incident OA to evaluate surrogacy, in the case-cohort sample with full biomarker data, might consider the correlation between the time trend in the biomarker with time trend in log odds of incident OA from a logistic regression model having a random slope (fit using the SAS NLMIXED procedure). These trends are estimated with some error, due to instrument-specific measurement error, making the observed correlation values have some bias toward 0. The accuracy calculations below take this attenuation toward 0 into account.

To select the most promising biomarkers, 95% confidence intervals could be used, and Table 8.4 displays results for the attenuated correlation values. Confidence intervals for the correlations are found using Fisher's Z-transformation.(141) The table uses the MRI cartilage volume, which has an interclass correlation of 0.92 at the medial tibia,(142) as an example biomarker. Table 8.4 shows various correlation values between time trends in the first column, the attenuated correlation (allowing for measurement error) in the second column, and the 95% confidence interval (CI) for the attenuated correlation in the third column. These results show that correlations with incident OA will be estimated with good precision, having confidence interval widths close to 0.1 for moderate correlation values.

Table 8.4 Precision of attenuated correlations between time trend for cartilage volume change and the time trend in log odds of incident symptomatic OA

True Correlation	Attenuated Correlation	95% CI for Attenuated Correlation
0.20	0.196	(0.136, 0.254)
0.40	0.393	(0.340, 0.444)
0.60	0.589	(0.548, 0.628)
0.80	0.786	(0.761, 0.808)
0.90	0.884	(0.870, 0.897)

8.2.4.1 Impact of a reduced number of participants in the Incidence subcohort

These statistical power estimates are sensitive to key assumptions, including the number and age distribution of actual enrollment in the subcohort, selection of base incidence rates, how well the adjusted incidence rate reflects the success of risk enrichment of the cohort using eligibility risk factors, etc. Enrollment numbers that are less than original goals may be offset, to some degree, by conservative estimates used for base incidence rates, the effectiveness of risk enrichment strategies or the correlation between knee-specific incidence within individuals and the addition of incident knees from those with unilateral symptomatic knee OA at baseline. Table 8.5 gives an approximation of the effect that reduced numbers of incident cases will have on power estimates in tables 8.2 and 8.3 for detection of relative risks for incident symptomatic knee OA. All other things equal, a reduction in the size of the incidence cohort of 20% will result in a proportional drop in the number of incident cases from this cohort.

Table 8.5 Effect of reduced number of endpoints on power for detecting relative risks for incident symptomatic knee OA [v]

	For revised detectable effect ratios with a reduced sample size, raise the original effect ratio to power indicated							
		If detectable effect ratio based on original number of endpoints						
If number of cases drops by	Detectable risk ratio is raised to power	1.3	1.4	1.5	1.6	1.7	1.8	1.9
		Then the detectable effect ratio with reduced sample size is:						
10%	1.05	1.32	1.42	1.53	1.64	1.75	1.85	1.96
20%	1.11	1.34	1.45	1.57	1.68	1.80	1.92	2.04
30%	1.18	1.36	1.49	1.61	1.74	1.87	2.00	2.13

8.2.5 Power for Analyses of Progression Biomarkers

Rates of change in key measures of progression such as WOMAC and especially rates of joint space loss could be speculated, but since it is not known whether the rates of change in OAI subjects will more closely resemble those in a community sample with a mixture of symptomatic and radiographic OA(143) or the higher rates observed in clinical samples,(144, 145) projecting such rates would be speculative. A community sample with symptomatic knee OA will probably be somewhere in between. Moreover, power analysis for progression biomarkers will focus not on detecting loss of joint space or decline in WOMAC scores, but rather on testing correlations between changes in these

[v] These calculations utilize the fact when the effects are ratios, and from a statistical point of view handled on the log scale, then the loss in detectable effect size for a change in the effective sample size can be estimated by raising the effect size to a power calculated based on the fact that the detectable effect size is proportional to the square root of the effective sample size.

and other variables. Therefore, power for these analyses are not substantially dependent on the rates of change.

An analysis of predictors of progression of knee OA (called OA progression below) might test the effect of risk factors (dichotomous predictors) on outcome (e.g. change in disability and joint space) in knees with prevalent OA at baseline over the follow-up period using random effects models. Based on the original study goals, there will be an expected 480 subjects with bilateral prevalent knee OA and 320 subjects with prevalent unilateral OA. Allowing for withdrawal from the study and the correlation between knees in the same person, the equivalent of about 620 independent knees with symptomatic OA at baseline will have four years of follow-up and these are used to determine the power for OA progression.

The WOMAC disability scale and WOMAC pain scale are potential outcomes in this analysis. For the WOMAC disability scale (Likert version, range 0-68) a standard deviation of 16.29 is expected for a single administration(146) with an expected correlation of 0.70 between yearly WOMAC assessments for a subject. Using the 5 assessments, it is possible to obtain yearly change with a standard deviation of 2.82 units. The WOMAC pain scale (Likert version, range 0-20) has a standard deviation of 4.32 units for a single measure. Using 5 measures per subject, a standard deviation of 0.75 will hold for yearly change in WOMAC pain scale.

Table 8.6. Yearly change in WOMAC scores detectable with 80% power for predictors of various prevalence in knees with symptomatic OA at baseline

Exposure Prevalence (%)	*Detectable WOMAC Disability Yearly Change Difference*	*Detectable WOMAC Pain Yearly Change Difference*
50	0.636	0.169
33	0.676	0.180
25	0.734	0.195
10	1.059	0.282

Table 8.6 gives the differences in yearly change in the two WOMAC scores that can be detected with 80% power using two-sided 0.05 significance tests for predictors of varying prevalence. For example, a difference of 0.676 units in yearly WOMAC disability change, which would account for a 2.7 unit difference at the end of 4 years of follow-up, could be detected for a risk factor affecting one third of subjects.

Candidate biomarkers for OA progression can be evaluated through the correlation of their time trend (slope over time in the random effects model) with the time trend of the WOMAC disability and pain scales. These correlations are attenuated by measurement error in both the WOMAC scales and in the biomarker. While there will be many candidate biomarkers, Table 8.7 shows results using cartilage volume as an example.

Table 8.7. Precision of attenuated correlations between time trend for cartilage volume change and the time trend in WOMAC pain and disability

WOMAC Scale	True Correlation	Attenuated Correlation	95% CI for Attenuated Correlation
Pain	0.20	0.169	(0.091, 0.244)
Pain	0.40	0.338	(0.266, 0.406)
Pain	0.60	0.507	(0.446, 0.563)
Pain	0.80	0.676	(0.631, 0.717)
Pain	0.90	0.761	(0.725, 0.792)
Disability	0.20	0.176	(0.098, 0.251)
Disability	0.40	0.351	(0.280, 0.419)
Disability	0.60	0.527	(0.468, 0.582)
Disability	0.80	0.703	(0.661, 0.741)
Disability	0.90	0.791	(0.759, 0.819)

Published test-retest reliabilities (ICC values) for the WOMAC pain scale are 0.65, 0.74, and 0.90, and values of 0.71, 0.80 and 0.92 for the disability scale. For calculating the attenuated correlation between cartilage volume change and WOMAC change, the moderate ICC values of 0.74 and 0.80 for pain and disability,(43) respectively, as well as the ICC for cartilage volume were used. Table 8.3 shows various true correlation values, the corresponding attenuated correlation, and the 95% confidence interval for the attenuated correlation. For example, if the true correlation between the time trend in WOMAC pain and the time trend in cartilage volume were 0.6, we would expect an attenuated correlation of 0.507 with a 95% confidence interval extending from 0.446 to 0.563. This should allow good discrimination between candidate biomarkers for progression with reasonable levels of correlation with WOMAC scales.

9.0 STUDY ORGANIZATION

9.1 Overview

The Study organization of OAI will include 4 clinical centers, the data coordinating center and its subcontractors (including the imaging quality assurance center, core laboratory and scientific advisory and analysis center), the Project Office at the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), and several standing and ad hoc study committees. The OAI committees will draw their members from the investigators and staff of the participating centers, from the NIH and the

pharmaceutical partners of OAI. An external Observational Study Monitoring Board (OSMB) and an external Biospecimen Resource Allocation Committee (BRAC) will report directly to the NIAMS

9.2 Federal Sponsors

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS - http://www.niams.nih.gov/) and the National Institute on Aging (NIA - http://www.nia.nih.gov/) will lead the OAI at the National Institutes of Health (NIH - http://www.nih.gov/). Other public partners in the Osteoarthritis Initiative at the NIH will include the Office of Research on Women's Health, National Institute of Dental and Craniofacial Research, National Center on Minority Health and Health Disparities, National Institute Of Biomedical Imaging and Bioengineering, and the National Center for Complementary and Alternative Medicine. The National Center for Research Resources, the Office of Technology Transfer, the Office of the General Counsel, and the Office of Science Policy have also played pivotal roles in the establishment of this initiative. Another Department of Health and Human Services component the will be involved is the Center for Drug Evaluation and Research of the Food and Drug Administration.

NIAMS is the lead institute of the consortium of NIH institutes, centers and offices sponsoring the study. The study will be administered through contracts from NIAMS. The contracts office and the project office at NIAMS are responsible for the overall administration and fiscal management of the study. Representatives from this office will participate in all phases of the study and be active on OAI committees. The NIAMS project office will organize the OSMB and the BRAC and coordinate their activities. NIAMS reserves the right to terminate the study in the event of unforeseen circumstances.

Funds from NIH institutes and centers and a group of pharmaceutical company sponsors will be combined with a 7-year commitment to fund the OAI.

9.3 Industry Sponsors

A group of pharmaceutical companies will co-fund the OAI. Private-sector funding for the OAI will be managed by the Foundation for the National Institutes of Health (http://www.fnih.org/). Representatives of the sponsoring companies will participate in all phases of the study and be active on OAI committees. The sponsors are Novartis Pharmaceuticals, Merck and Co, Inc, Pfizer, Inc. and GlaxoSmithKline.

9.4 Clinical Centers

Each clinical center will consist of an interdisciplinary team of clinical investigators who provide the areas of expertise necessary for the successful completion of the OAI protocol. Clinical center responsibilities will include:

- collaborate in the design and monitoring of the study, including regular attendance at Steering Committee meetings;
- recruit participants for the study according to inclusion and exclusion criteria and in numbers and strata specified in the protocol;

- purchase, install and operate a Siemens Trio 3.0 Tesla MR scanner and acquire scans according to study protocols;
- arrange for bone and joint radiography to be performed according to study protocols;
- perform all study procedures according protocol and collect and manage data in a standardized fashion;
- make provisions to ensure the safety, confidentiality and ethical treatment of study participants;
- collaborate in the analysis and dissemination of study results.

9.5 Data Coordinating Center

The OAI coordinating center at UCSF, under the direction of Dr. Michael Nevitt, will have operational responsibility for the design, implementation, coordination and monitoring of all aspects of the study. Specific responsibilities of the coordinating center will include:

- develop the study protocol under the guidance of the steering committee;
- prepare the data collection forms, manuals, recruitment and other study materials;
- develop and implement the study data management and communication systems;
- perform central training of study personnel and monitor clinic performance;
- perform data management and quality assurance of study data;
- prepare data files and documentation for use by OAI investigators and the larger community of scientists;
- develop and maintain the study and public web sites for OAI;
- distribute data files, documentation and images to users;
- coordinate the activities of subcontractors, reading centers and core labs;
- monitor study progress and report on progress to the steering committee and OSMB;
- arrange and coordinate study teleconferences and meetings;
- provide biostatistical expertise to OAI investigators and other users of OAI data;
- hold public meetings for data and image users to provide information on use of the dataset;
- prepare, in collaboration with the clinical center and other OAI investigators, manuscripts of the study results.

The central imaging Quality Assurance Center will be Synarc, Inc, of San Francisco, Ca., under the direction of Dr. Charles Peterfy. The imaging QA center will be the scientific and operational hub for imaging related activities within the OAI. Synarc, Inc, will function as a subcontractor to the coordinating center. The Biospecimen repository for the study will be located at Fisher Bioservices, Inc, in Rockville, MD, under a subcontract to the coordinating center. The Boston University Multidisciplinary Clinical Research Center, under the direction of Dr. Felson, will provide expertise to the OAI in methodological, analytical and biostatistical areas of direct relevance to osteoarthritis. Boston University is a subcontractor to the coordinating center.

9.6 Steering Committee

The Steering Committee will be the primary governing body of the study and provides its scientific leadership. It will have responsibility for the overall study design, policy decisions and operations of the OAI. Voting members of the Steering Committee will include 2 representatives (the principal investigators and coinvestigators) from each of the clinical centers and the coordinating center, the NIAMS project officer and a representative from NIA, and 2 representatives from the pharmaceutical sponsors. Nonvoting participants will include an FDA-appointed representative to serves as a liaison between FDA and the OAI, outside consultants as needed, and others as decided by the Steering Committee. Major scientific and protocol decisions will be determined by majority of the voting members of the Steering Committee. The Steering Committee will elect a chair from among its members. The Steering Committee will form subcommittees of investigators and staff as needed throughout the study. These will include Imaging, Measurements, Recruitment and Retention, Quality Assurance, and Ancillary Studies and Publications. Subcommittees will be chaired by a member of the Steering Committee, who will report its activities to the Steering Committee.

9.6.1 Protocol amendments and changes in study procedures

Changes in the protocol and procedures will be adopted by a majority vote of the Steering Committee. A record of changes in study procedures and conduct will be maintained by the coordinating center. Changes that alter the written study protocol will be summarized in an appendix to the current version of the protocol (Appendix K).

9.7 Biospecimen Resource Allocation Committee

The NIH will select, with recommendations from the Steering Committee, a Biospecimen Resource Allocation Committee (BRAC) that will oversee the allocation and distribution of biological specimens generated from the OA Initiative. The BRAC will be made up of individuals not directly involved in the OA Initiative or cartilage-related research and without conflict of interest. Membership on this committee will rotate multi-year terms. Meetings of the BRAC will be widely advertised. The BRAC will review applications to use the biological specimens. The format of the application and criteria for the use of repository biological specimens will be developed by the BRAC with advice from the Steering Committee and made available to potential users.

9.8 Observational Study Monitoring Board

The NlH will establish and appoint members of an Observational Study Monitoring Board (OSMB) to monitor regularly the data from the observational study, review and assess the study performance, and to make recommendations, as appropriate, to the NIH with respect to 1) the performance of individual centers; 2) issues related to participant safety and informed consent, including notification of and referral for abnormal findings; 3) adequacy of study progress in terms of recruitment, quality control, data analysis, and publications; 4) issues pertaining to participant burden; 5) impact of proposed ancillary studies and sub-studies on participant burden and overall achievement of the main study goals; and 6) overall scientific directions of the study. The NIH will be responsible for organization

and scheduling of these meetings. The coordinating center will provide to the OSMB materials needed to carry out the evaluations described above.

10.0 ANCILLARY STUDIES

An ancillary study will be a study that requires access to OAI participants, whether from a single clinical center or from the entire cohort, to collect measurements or data that are not part of the core protocol or routine OAI database or that enrolls additional participants needed to address a specific research question. The Steering Committee and/or the Ancillary Studies subcommittee will review and approve proposals and protocols for ancillary studies. Ancillary studies must be approved by the institutional review boards of the participating centers and may require separate consent.

The following will not be considered ancillary studies for the purposes of these guidelines:

- studies that generate new data that are not part of the routine OAI database from existing measurements (such as measurements from joint images);
- studies that generate new data from stored core biospecimens (Such studies will be reviewed and require approval by the Biospecimen Resource Allocation Committee.);
- substudies funded by the OAI, such as modifications or additions to the existing contract.

Ancillary study guidelines will be developed by the Steering Committee (Appendix L).

11.0 REFERENCES CITED

1. Dunlop DD, Manheim LM, Yelin EH, Song J, Chang RW. The costs of arthritis. Arthritis Rheum 2003;49(1):101-13.
2. Guccione AA, Felson DT, Anderson JJ, et al. The effects of specific medical conditions on the functional limitations of elders in the Framingham Study. Am J Public Health 1994;84:351-8.
3. Lawrence RC, Helmick CG, Arnett FC, Deyo RA, Felson DT, Giannini EH. Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. Arthritis Rheum 1998;41:778-99.
4. Bagge E, Bjelle A, Valkenburg HA, Svanborg A. Prevalence of radiographic osteoarthritis in two elderly European populations. Rheumatol Int 1992;12:33-8.
5. Van Saase JLCM, Van Romunde LKJ, Cats A, Vandenbroucke JP, Valkenburg HA. Epidemiology of osteoarthritis: Zoetermeer survey. Comparison of radiological osteoarthritis in a Dutch population with that in 10 other populations. Ann Rheum Dis 1989;48:271-80.
6. Brandt KD, Fife RS, Braunstein EM, Katz B. Radiographic grading of the severity of knee osteoarthritis: relation of the Kellgren and Lawrence grade to a grade based on joint space narrowing, and correlation with arthroscopic evidence of articular cartilage degeneration. Arthritis Rheum 1991;34(11):1381-6.
7. Urwin M, Symmons DPM, Allison T, et al. Estimating the burden of muskuloskeletal disorders in the community: the comparative prevalence of symptoms at different anatomical sites and the relation to social deprivation. Annals of Rheumatic Diseases 1998;57:649-55.
8. Peat G, McCarney R, Croft P. Knee pain and osteoarthritis in older adults: a review of community burden and current use of primary health care. Annals of Rheumatic Diseases 2001;60:91-7.
9. Felson DT, Zhang Y. An update on the epidemiology of knee and hip osteoarthritis with a view to prevention. Arthritis Rheum 1998;41(8):1343-55.
10. Felson DT, Lawrence RC, Hochberg MC, et al. Osteoarthritis: new insights. Part 2: treatment approaches. Ann Intern Med 2000;133(9):726-37.
11. National Arthritis Action Plan: A Public Health Strategy. Atlanta: Arthritis Foundation, 1999. (Accessed 2002, at
12. Felson DT, Lawrence RC, Dieppe PA, et al. Osteoarthritis: new insights. Part 1: the disease and its risk factors. Ann Intern Med 2000;133(8):635-46.
13. Lohmander LS, Felson DT. Defining the role of molecular markers to monitor disease, intervention, and cartilage breakdown in osteoarthritis. J Rheumatol 1997;4:782-5.
14. Altman R, Asch E, Bloch D, et al. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. Arthritis Rheum 1986;29(8):1039-49.
15. Cooper C, Snow S, McAlindon TE, et al. Risk factors for the incidence and progression of radiographic knee osteoarthritis. Arthritis Rheum 2000;43(5):995-1000.
16. Zhang Y, Hannan MT, Chaisson CE, et al. Bone mineral density and risk of incident and progressive radiographic knee osteoarthritis in women: the Framingham Study. J Rheumatol 2000;27(4):1032-7.

17. Brandt KD, Heilman DK, Slemenda C, et al. Quadriceps strength in women with radiographically progressive osteoarthritis of the knee and those with stable radiographic changes. J Rheumatol 1999;26(11):2431-7.
18. McAlindon TE, Felson DT, Zhang Y, et al. Relation of dietary intake and serum levels of vitamin D to progression of osteoarthritis of the knee among participants in the Framingham Study. Ann Intern Med 1996;125(5):353-9.
19. Altman R, Hochberg M, Murphy W, Wolfe F, Lequesne M. Atlas of individual radiographic features in osteoarthritis. Osteoarthritis and Cartilage 1995;3(A):3-70.
20. Felson DT, Zhang Y, Hannan MT, et al. The incidence and natural history of knee osteoarthritis in the elderly. The Framingham Osteoarthritis Study. Arthritis Rheum 1995;38(10):1500-5.
21. Manninen P, Riihimaki H, Heliovaara M, Makela P. Overweight, gender and knee osteoarthritis. Int J Obes Relat Metab Disord 1996;20(6):595-7.
22. Felson DT, Zhang Y, Hannan M, et al. Risk Factors For Incident Radiographic Knee Osteoarthritis In The Elderly. Arthritis & Rheumatism 1997;40(4 April 1997):728-33.
23. Roos H, Adalberth T, Dahlberg L, Lohmander LS. Osteoarthritis of the knee after injury to the anterior cruciate ligament or meniscus: the influence of time and age. Osteoarthritis Cartilage 1995;3(4):261-7.
24. Roos H, Lauren M, Adalberth T, Roos EM, Jonsson K, Lohmander LS. Knee osteoarthritis after meniscectomy: prevalence of radiographic changes after twenty-one years, compared with matched controls. Arthritis Rheum 1998;41(4):687-93.
25. Gelber AC, Hochberg MC, Mead LA, Wang NY, Wigley FM, Klag MJ. Joint injury in young adults and risk for subsequent knee and hip osteoarthritis. Ann Intern Med 2000;133(5):321-8.
26. Neyret P, Donell ST, Dejour H. Results of partial meniscectomy related to the state of the anterior cruciate ligament. Review at 20 to 35 years. J Bone Joint Surg Br 1993;75(1):36-40.
27. McMahon M, Block JA. The risk of contralateral total knee arthroplasty after knee replacement for osteoarthritis. J Rheumatol 2003;30(8):1822-4.
28. Spector TD, Cicuttini F, Baker J, Loughlin J, Hart D. Genetic influences on osteoarthritis in women: a twin study. Bmj 1996;312(7036):940-3.
29. Chitnavis J, Sinsheimer JS, Clipsham K, et al. Genetic influences in end-stage osteoarthritis. Sibling risks of hip and knee replacement for idiopathic osteoarthritis. J Bone Joint Surg Br 1997;79(4):660-4.
30. Hart D, Doyle D, Spector T. Incidence and risk factors for radiographic knee osteoarthritis in middle-aged women: the Chingford Study. Arthritis Rheum 1999;42(1):17-24.
31. Dahaghin S, Bierma-Zeinstra SM, Reijman M, Pols HA, Hazes JM, Koes BW. Does hand osteoarthritis predict future hip or knee osteoarthritis? Arthritis Rheum 2005;52(11):3520-7.
32. Felson DT, Hannan MT, Naimark A, et al. Occupational physical demands, knee bending and knee osteoarthritis: results from the Framinham Study. J Rheumatol 1991;18:1587-92.
33. Cooper C, McAlindon T, Coggon D, Egger P, Dieppe P. Occupational activity and osteoarthritis of the knee. Ann Rheum Dis 1994;53:90-3.
34. Coggon D, Croft P, Kellingray S, Barrett D, McLaren M, Cooper C. Occupational physical activities and osteoarthritis of the knee. Arthritis Rheum 2000;43(7):1443-9.
35. Oliveria SA, Felson DT, Reed JI, Cirillo PA, Walker AM. Incidence of symptomatic hand, hip, and knee osteoarthritis among paiteints in a health maintenance organization. Arthritis Rheum 1995;38:1134-41.

36. Karlson EW, Sanchez-Guerrero J, Wright EA, Lew RA, Katz JN, Liang MH. A connective tissue disease screening questionnaire (CSQ) for population studies. Ann Epidemiol 1995;In Press.
37. ORS, Osteoarthritis Research Society. Design and conduct of clinical trials of patients with osteoarthritis: Recommendations from a task force of the Osteoarthritis Research Society. Osteoarthritis Cartilage 1996;4.
38. Bellamy N, Kirwan JR, Boers M, et al. Recommendations for a core set of outcome measures for future phase III clinical trials in knee, hip, and hand osteoarthritis. Concensus development at OMERACT III. J Rheum 1997;24:799-802.
39. Felson DT, Naimark A, Anderson J, Kazis L, Castelli W, Meenan RF. The prevalence of knee osteoarthritis in the elderly. Arthritis Rheum 1987;30(8):914-8.
40. LaValley M, McAlindon TE, Evans S, Chaisson CE, Felson DT. Problems in the development and validation of questionnaire-based screening instruments for ascertaining cases with symptomatic knee osteoarthritis: the Framingham Study. Arthritis Rheum 2001;44(5):1105-13.
41. Bellamy N. Musculoskeltal Clinical Metrology. London: Kluwer Academic Publishers; 1993.
42. Turk DC, Melzack R. Handbook of pain assessment. 2nd ed. New York: Guilford Press; 2001.
43. McConnell S, Kolopack P, Davis AM. The Western Ontario and McMaster University Osteoarthritis Index (WOMAC): a review of utility and measurement properties. Arthritis Care Res 2001;45:453-61.
44. Bellamy N, Buchanan Ww, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol 1988;15:1833-40.
45. Bellamy N, Kean WF, Buchanan WW, Gerecz-Simon E, Campbell J. Double blind randomized controlled trial of sodium meclofenamate (Meclomen) and diclofenac sodium (Voltaren): post validation reapplication of the WOMAC Osteoarthritis Index. J Rheumatol 1992;19(1):153-9.
46. Griffiths G, Bellamy, N., Bailey, W.H., Bailey, S.I., McLaren, A.C., Campbell, J. A comparative study of the relative efficiency of the WOMAC, AIMS and HAQ instruments in evaluating the outcome of total knee arthroplasty. Inflam 1994.
47. Stucki G, Sangha O, Stucki S, et al. Comparison of the WOMAC (Western Ontario and McMaster Universities) osteoarthritis index and a self-report format of the self-administered Lequesne-Algofunctional index in patients with knee and hip osteoarthritis. Osteoarthritis Cartilage 1998;6(2):79-86.
48. McGrory BJ, Harris WH. Can the western Ontario and McMaster Universities (WOMAC) osteoarthritis index be used to evaluate different hip joints in the same patient? J Arthroplasty 1996;11(7):841-4.
49. Roos EM, Roos HP, Lohmander LS. WOMAC Osteoarthritis Index--additional dimensions for use in subjects with post-traumatic osteoarthritis of the knee. Western Ontario and MacMaster Universities. Osteoarthritis Cartilage 1999;7(2):216-21.
50. Nau T, Lavoie P, Duval N. A new generation of artificial ligaments in reconstruction of the anterior cruciate ligament. Two-year follow-up of a randomised trial. J Bone Joint Surg Br 2002;84(3):356-60.
51. Colker CM, Swain M, Lynch L, Gingerich DA. Effects of a milk-based bioactive micronutrient beverage on pain symptoms and activity of adults with osteoarthritis: a double-blind, placebo-controlled clinical evaluation. Nutrition 2002;18(5):388-92.

52. Braham R, Dawson B, Goodman C. The effect of glucosamine supplementation on people experiencing regular knee pain. Br J Sports Med 2003;37(1):45-9; discussion 9.
53. Scholes D, LaCroix AZ, Wagner EH, Grothaus LC, Hecht JA. Tracking progress toward national health objectives in the elderly: what do restricted activity days signify? Am J Public Health 1991;81(4):485-8.
54. Wagner EH, LaCroix AZ, Grothaus LC, Hecht JA. Responsiveness of health status measures to change among older adults. J Am Geriatr Soc 1993;41(3):241-8.
55. Nevitt MC, Ettinger, B., Black, D. M., Stone, K., Jamal, S. A., Ensrud, K., Segal, M., Genant, H. K., Cummings, S. R. The association of radiographically detected vertebral fractures with back pain and function: a prospective study. Ann Intern Med 1998;128(10):793-800.
56. Nevitt MC, Thompson DE, Black DM, et al. Effect of alendronate on limited-activity days and bed-disability days caused by back pain in postmenopausal women with existing vertebral fractures. Fracture Intervention Trial Research Group. Arch Intern Med 2000;160(1):77-85.
57. Jenkinson C, Layte R, Jenkinson D, et al. A shorter form health survey: can the SF-12 replicate results from the SF-36 in longitudinal studies? J Public Health Med 1997;19(2):179-86.
58. Ware J, Jr., Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Med Care 1996;34(3):220-33.
59. Simonsick EM, Montgomery PS, Newman AB, Bauer DC, Harris T. Measuring fitness in healthy older adults: the Health ABC Long Distance Corridor Walk. J Am Geriatr Soc 2001;49(11):1544-8.
60. Newman AB, Haggerty CL, Kritchevsky SB, Nevitt MC, Simonsick EM. Walking Performance and Cardiovascular Response: Associations With Age and Morbidity-The Health, Aging and Body Composition Study. J Gerontol A Biol Sci Med Sci 2003;58(8):M715-M20.
61. Ettinger WH, Jr., Burns R, Messier SP, et al. A randomized trial comparing aerobic exercise and resistance exercise with a health education program in older adults with knee osteoarthritis. The Fitness Arthritis and Seniors Trial (FAST). Jama 1997;277(1):25-31.
62. Rantanen T, Era P, Heikkinen E. Maximal isometric strength and mobility among 75-year-old men and women. Age Ageing 1994;23(2):132-7.
63. Rantanen T, Era P, Heikkinen E. Physical activity and the changes in maximal isometric strength in men and women from the age of 75 to 80 years. J Am Geriatr Soc 1997;45(12):1439-45.
64. OReilly SC, Jones A, Muir KR, Doherty M. Quadriceps weakness in knee osteoarthritis: the effect on pain and disability. Ann Rheum Dis 1998;57(10):588-94.
65. Slemenda C, Brandt KD, Heilman DK, et al. Quadriceps Weakness and Osteoarthritis of the Knee. Annals of Internal Medicine 1997;127 number 2(15 July 1997):97-104.
66. Fisher NM, Pendergast DR. Reduced muscle function in patients with osteoarthritis. Scand J Rehabil Med 1997;29(4):213-21.
67. Hall KD, Hayes KW, Falconer J. Differential strength decline in patients with osteoarthritis of the knee: revision of a hypothesis. Arthritis Care Res 1993;6(2):89-96.
68. Fransen M, Crosbie J, Edmonds J. Isometric muscle force measurement for clinicians treating patients with osteoarthritis of the knee. Arthritis Rheum 2003;49(1):29-35.
69. Hurley MV. The role of muscle weakness in the pathogenesis of osteoarthritis. Rheum Dis Clin North Am 1999;25(2):283-98, vi.
70. Baker K, McAlindon T. Exercise for knee osteoarthritis. Curr Opin Rheumatol 2000;12(5):456-63.

71. Slemenda C, Heilman DK, Brandt KD, et al. Reduced quadriceps strength relative to body weight: a risk factor for knee osteoarthritis in women? Arthritis Rheum 1998;41(11):1951-9.
72. Studenski S, Perera S, Wallace D, et al. Physical performance measures in the clinical setting. J Am Geriatr Soc 2003;51(3):314-22.
73. Sharma L, Song J, Felson DT, Cahue S, Shamiyeh E, Dunlop DD. The role of knee alignment in disease progression and functional decline in knee osteoarthritis. Jama 2001;286(2):188-95.
74. McAlindon TE, Snow S, Cooper C, Dieppe PA. Radiographic patterns of osteoarthritis of the knee joint in the community: the importance of the patellofemoral joint. Ann Rheum Dis 1992;51:844-9.
75. Cicuttini FM, Baker JR, Spector TD. The association of obesity with osteoarthritis of the hand and knee in women: a twin study. J Rheumatol 1996;23(7):1221-6.
76. Felson DT, McAlindon TE, Anderson JJ, et al. Defining radiographic osteoarthritis for the whole knee. Osteoarthritis Cartilage 1997;5:241-50.
77. Brandt K, Mazzuca S, Conrozier T, et al. Which is the best radiographic protocol for a clinical trial of a structure modifying drug in patients with knee osteoarthritis? J Rheumatol 29(6):1308-20 2002;29(6):1308-20.
78. Peterfy C, Li J, Zaim S, et al. Comparison of Fixed-Flexion Positioning with Fluoroscopic Semi-Flexed Positioning for Quantifying Radiographic Joint-Space Width in the Knee: Test-Retest Reproducibility. Skeletal Radiology 2003;32(3):128-32.
79. Buckland-Wright JC, Macfarlane DG, Lynch JA, Jasani MK, Bradshaw CR. Joint space width measures cartilage thickness in osteoarthritis of the knee: high resolution plain film and double contrast macroradiographic investigation. Ann Rhem Dis 1995;54:263-8.
80. Alexander EJ, Rinderknecht D, Andriacchi TP. Regional variations in femoral cartilage thickness relative to functional load. In: Orthopedic Research Society; 2002; 2002.
81. Bennett L, Buckland-Wright C. Meniscal and articular cartilage changes in knee osteoarthritis: a cross-sectional double-contrast macroradiographic study. Rheumatology 2002;41:917-23.
82. Buckland-Wright C. Which radiographic techniques should we use for research and clinical practice? Best Pract Res Clin Rheumatol 2006;20(1):39-55.
83. Buckland-Wright C. Protocols for precise radioanatomical positioning of the tibiofemoral and patellofemoral compartments of the knee. Osteoarthritis Cartilage 1995;3(A):71-80.
84. Buckland-Wright JC, Wolfe F, Ward RJ, Flowers N, Hayne C. Substantial superiority of semiflexed (MTP) views in knee osteoarthritis: a comparative radiographic study, without fluoroscopy, of standing extended, semiflexed (MTP), and schuss views. J Rheumatol 1999;26(12):2664-74.
85. Vignon E, Piperno M, Le Graverand MP, et al. Measurement of radiographic joint space width in the tibiofemoral compartment of the osteoarthritic knee: comparison of standing anteroposterior and Lyon schuss views. Arthritis Rheum 2003;48(2):378-84.
86. Kothari M, Guermazi A, von Ingersleben G, et al. Fixed-flexion radiography of the knee provides reproducible joint space width measurements in osteoarthritis. European Radiology 2004;14:1568-73.
87. Mazzuca SA, Brandt KD, Buckland-Wright JC, et al. Field test of the reproducibility of automated measurements of medial tibiofemoral joint space width derived from standardized knee radiographs. J Rheumatol 1999;26(6):1359-65.

88. Buckland-Wright JC, Bird CF, Ritter-Hrncirik CA, et al. X-ray technologisits' reproducibility from automated measurements of the medial tibiofemoral joint space width in knee osteoarthritis for a multicenter, multinational clinical trial. J Rheum 2003;30(2):329-38.
89. Mazzuca SA, Brandt KD, Buckwalter KA, Lane KA, Katz BP. Field test of the reproducibility of the semiflexed metatarsophalangeal view in repeated radiographic examinations of subjects with osteoarthritis of the knee. Arthritis Rheum 2002;46(1):109-13.
90. Buckland-Wright JC, Ward RJ, Peterfy C, Mojcik F, Leff RL. Reproducibility of the semiflexed (Metatarsaophalangeal) radiographic knee position and automated measurements of tibiofemoral joint space width in a multicenter clinical trial of knee osteoarthritis. J Rheum 2004;31:1588-97.
91. Brandt KD, Mazzuca SA, Katz BP, et al. Effects of doxycycline on progression of osteoarthritis: results of a randomized, placebo-controlled, double-blind trial. Arthritis Rheum 2005;52(7):2015-25.
92. Buckland-Wright JC, Macfarlane DG, Williams SA, Ward RJ. Accuracy and precision of joint space width measurements in standard and macroradiographs of osteoarthritic knees. Ann Rheum Dis 1995;54(11):872-80.
93. Mazzuca S, Brandt K, Buckwalter KA. Detection of radiographic joint space narrowing in subjects with knee osteoarthritis: longitudinal comparison of of the metatarsalphalangeal and semiflexed anteroposterior view. Arthritis and Rheumatism 2003;48(2):385-90.
94. Garnero P, Delmas PD. In: Hochberg MC, Silman AJ, Smolen JS, eds. Investigation of Bone: Bone Turnover in Rheumatology. 3rd ed. London, UK: Harcourt Health Sciences; 2004.
95. Criscione LG, Elliott AL, Stabler TV, Jordan JM, Pieper CF, Kraus VB. Variation of serum hyaluronan with activity in individuals with knee osteoarthritis. Osteoarthritis Cartilage 2005;13(9):837-40.
96. Kong SY, Stabler TV, Crisione LG, Elliott AL, Jordan JM, Kraus VB. Diurnal variation of biomarkers in patients with radiographic knee osteoarthritis. Osteoarthritis Cartilage 2005;13((Suppl A)):15.
97. Garnero P, Ayral X, Rousseau J-C, et al. Uncoupling of type II collagen synthesis and degradation predicts progression of joint damage in patients with knee osteoarthritis. Arthritis Rheum 2002;46:2613-24.
98. Poole AR. Can serum biomarker assays measure the progression of cartilage degeneration in osteoarthritis? Arthritis Rheum 2002;46(10):2549-52.
99. Garnero P, Delmas PD. Biomarkers in osteoarthritis. Curr Opin Rheumatol 2003;15(5):641-6.
100. Sowers M, Jannausch M, Stein E, Jamadar D, Hochberg M, Lachance L. C-reactive protein as a biomarker of emergent osteoarthritis. Osteoarthritis Cartilage 2002;10(8):595-601.
101. Clark AG, Jordan JM, Vilim V, et al. Serum cartilage oligomeric matrix protein reflects osteoarthritis presence and severity: the Johnston County Osteoarthritis Project. Arthritis Rheum 1999;42(11):2356-64.
102. Garnero P, Piperno M, Gineyts E, Christgau S, Delmas PD, Vignon E. Cross sectional evaluation of biochemical markers of bone, cartilage, and synovial tissue metabolism in patients with knee osteoarthritis: relations with disease activity and joint damage. Ann Rheum Dis 2001;60(6):619-26.
103. Pusch W, Flocco MT, Leung SM, Thiele H, Kostrzewa M. Mass spectrometry-based clinical proteomics. Pharmacogenomics 2003;4(4):463-76.

104. Beekman B, Drijfhout JW, Ronday HK, TeKoppele JM. Fluorogenic MMP activity assay for plasma including MMPs complexed to alpha 2-macroglobulin. Ann N Y Acad Sci 1999;878:150-8.
105. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. Jama 2002;287(3):356-9.
106. Spector TD, Hart, D.J., Nandra, D., et al. Low-level increases in serum creative protein are present in early osteoarthritis of the knee and predict progressive disease. Arthritis Rheum 1997;40:723-27.
107. Hart DJ, Doyle DV, Spector TD. Association between metabolic factors and knee osteoarthritis in women: the Chingford Study. J Rheum 1995;22:1118-23.
108. Meulenbelt I, Bijkerk C, Miedema HS, et al. A genetic association study of the IGF-1 gene and radiological osteoarthritis in a population-based cohort study (the Rotterdam Study). Ann Rheum Dis 1998;57(6):371-4.
109. Cibere J, Bellamy N, Thorn A, et al. Reliability and standardization of the knee examination in osteoarthritis. Osteoarthritis Cartilage 2002;10A:S62-3.
110. Moreland JR, Bassett LW, Hanker GJ. Radiographic analysis of the axial alignment of the lower extremity. J Bone Joint Surg Am 1987;69(5):745-9.
111. Felson DT, McLaughlin S, Goggins J, et al. Bone marrow edema and its relation to progression of knee osteoarthritis. Ann Intern Med 2003;139(5 Pt 1):330-6.
112. Sharma L, Dunlop DD, Cahue S, Song J, Hayes KW. Quadriceps strength and osteoarthritis progression in malaligned and lax knees. Ann Intern Med 2003;138(8):613-9.
113. Martin KA, Rejeski WJ, Miller ME, James MK, Ettinger WH, Jr., Messier SP. Validation of the PASE in older adults with knee pain and physical disability. Medicine & Science in Sports & Exercise 1999:627-33.
114. Croft P, Cooper C, Wichham C, Coggon D. Osteoarthritis of the hip and occupational activity. Scand J Work Environ Health 1992;18:59-63.
115. Pahor M, Chrischelles E, Guralnik JM, et a. Drug data coding and analysis in epidemiologic studies. Eur J Epidemiol 1994;10:405-11.
116. Katz JN, Chang LC, Sangha O, Fossel AH, Bates DW. Can Comorbidity be measured by questionnaire rather than by medical record? Medical Care 1996;34:73-84.
117. Block G, Hartman AM, Naughton D. A reduced dietary questionnaire: development and validation. Epidemiology 1990;1(1):58-64.
118. Block G, Hartman AM, Dresser CM, Carroll MD, Gannon J, Gardner L. A data-based approach to diet questionnaire design and testing. Am J Epidemiol 1986;124(3):453-69.
119. Block G, Norkus E, Hudes M, Mandel S, Helzlsouer K. Which plasma antioxidants are most related to fruit and vegetable consumption? Am J Epidemiol 2001;154(12):1113-8.
120. Schwartz ER, Leveille C, Oh WH. Experimentally-induced osteoarthritis in guinea pigs: effect of surgical procedure and dietary intake of vitamin C. Lab Anim Sci 1981;31(6):683-7.
121. Meacock SC, Bodmer JL, Billingham ME. Experimental osteoarthritis in guinea-pigs. J Exp Pathol (Oxford) 1990;71(2):279-93.
122. McAlindon TE, Jacques P, Zhang Y, et al. Do antioxidant micronutrients protect against the development and progression of knee osteoarthritis? Arthritis Rheum 1996;39(4):648-56.
123. Bhargavan M, Sunshine JH. Utilization of radiology services in the United States: levels and trends in modalities, regions, and populations. Radiology 2005;234(3):824-32.

124. Zhou J, Gullapalli RP. AAPM/RSNA physics tutorial for residents: MR artifacts, safety, and quality control. Radiographics 2006;26(1):275-97.
125. Kanal E, Borgstede JP, Barkovich AJ, et al. American College of Radiology White Paper on MR Safety: 2004 update and revisions. AJR Am J Roentgenol 2004;182(5):1111-4.
126. Shellock F. Reference Manual for Magnetic Resonance Safety: 2003 Edition. Salt Lake City: Amirsys; 2003.
127. The List. MRISafety.com, 2003. (Accessed 2003, at
128. Kanal E, Borgstede JP, Barkovich AJ, et al. American College of Radiology White Paper on MR Safety. AJR Am J Roentgenol 2002;178(6):1335-47.
129. Dougados M, Gueguen A, Nguyen M, et al. Longitudinal radiologic evaluation of osteoarthritis of the knee. J Rheumatol 1992;19:378-84.
130. Wacholder S. Practical considerations in choosing between the case-cohort and nested case-control design. Epidemiology 1991;2:155-8.
131. Prentice RL. Surrogate endpoints in clinical trials: Definition and operational criteria. Statistics in Medicine 1989;8:431-40.
132. Buyse M, Molenberghs G, Burzykowski T, Renard D, Geys H. Statistical validation of surrogate endpoints: problems and proposals. Drug Information Journal 2000;34:447-54.
133. Freedman LS, Graubard BI, Schatzkin A. Statistical validation of intermediate endpoints for chronic diseases. Statistics in Medicine 1992;11:167-78.
134. Buyse M, Molenberghs G, Burzykowski T, Geys H, Renard D. The validation of surrogate endpoints in meta-analyses of randomized experiments. Biostatistics 2000;1:1-19.
135. Fleming TR, DeMets DL. Surrogate endpoints in clinical trials: are we being mislead? Annals Int Med 1996;125:605-13.
136. McCulloch CE, Searle SR. Generalized, Linear and Mixed Models. New York: Wiley; 2000.
137. Davison AC, Hinkley DV. Bootstrap methods and their application. Cambridge: Cambridge University Press; 1997.
138. Oliveria SA, Felson DT, Cirillo PA, Reed JI, Walker AM. Body weight, body mass index, and incident symptomatic osteoarthritis of the hand, hip, and knee. Epidemiology 1999;10(2):161-6.
139. Spector TD, Hart DJ, Doyle DV. Incidence and progression of osteoarthritis in women with unilateral knee disease in the general population: the effect of obesity. Ann Rheum Dis 1994;53:565-8.
140. Rosner B, Milton RC. Significance testing for correlated binary outcome data. Biometrics 1988;44(2):505-12.
141. Arnold SF. Mathematical Studies. Englewood Cliffs, NJ: Prentice-Hall; 1990.
142. Stammberger T, Eckstein F, Englmeier K-H, Reiser M. Determination of 3D cartilage thickness data from MR imaging: computational method and reproducibility in the living. Magnetic Resonance in Medicine 1999;41:529-36.
143. Lethbridge-Cejku M, Scott SS, Reichle R, al. e. Association of radiographic features of osteoarthritis of the knee with knee pain: data from the Baltimore Longitudinal Study of Aging. Arthritis Care Res 1995;8(3):181-8.
144. Kirwan JR, Cushnaghan J, Dacre J, et al. Abstract: The progression of joint space narrowing in knee osteoarthritis. Arthritis Rheum 1992;17:232.

145. Mazzuca SA, Brandt KD, Katz BP. Is conventional radiography suitable for evaluation of a disease-modifying drug in patients with knee osteoarthritis? Osteoarthritis Cartilage 1997;5(4):217-26.
146. Bellamy N, Buchanan WW, Chalmers A, et al. A multicenter study of tenoxicam and diclofenac in patients with osteoarthritis of the knee. J Rheumatol 1993;20(6):999-1004.