

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



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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.



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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



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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.



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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.



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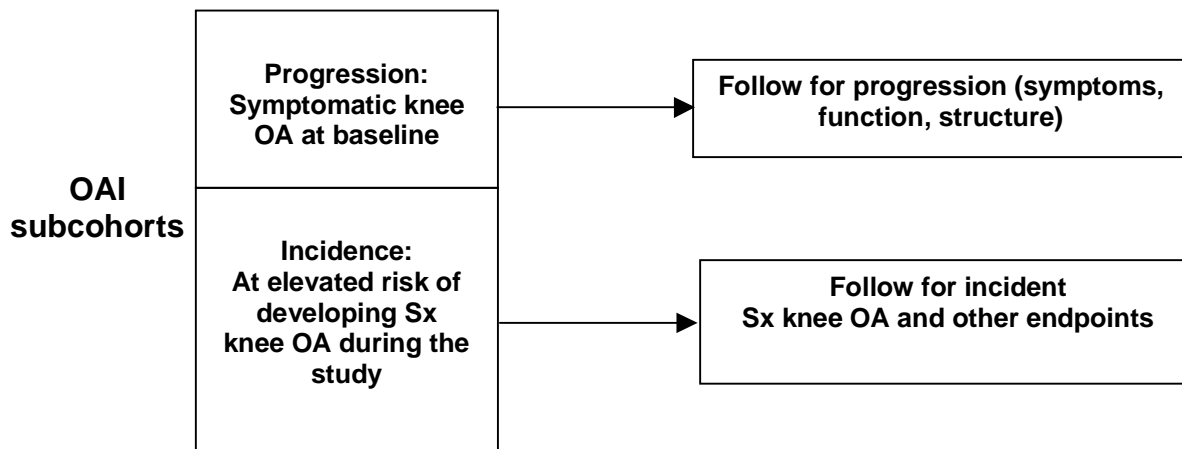
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4.2 Study Population

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.



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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



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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 two or more 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 one or more other eligibility risk factor.

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

- Knee symptoms in a native knee in the past 12 months. 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 not 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)



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- 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:

| <u>Age</u> | <u>Men</u> | | <u>Women</u> | |
|------------|---------------------|---------------------|---------------------|---------------------|
| | <u>Cumulative %</u> | <u>Weight (lbs)</u> | <u>Cumulative %</u> | <u>Weight (lbs)</u> |
| 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



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- 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 ≥ 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.



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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 mastectomy, 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



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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,



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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 ≥ 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)



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Upper leg strength. Bilateral isometric knee extensor and flexor strength will be measured using the Good Strength isometric strength chair (Metitur, Jyväskylä, 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.



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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



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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 | <i>COR MPR 3D DESS WE</i> | <i>0.0</i> | <i>0.0</i> | <i>0.0</i> |
| 4 | <i>AXIAL MPR 3D DESS WE</i> | <i>0.0</i> | <i>0.0</i> | <i>0.0</i> |
| 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



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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.



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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) |
| <u>Joint space narrowing (medial and lateral each graded)</u> |
| 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.



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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).



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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;



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- 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.



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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.



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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.



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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 nutraceuticals for joint symptoms



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- 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



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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 osteophytes 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 biospecimens will be obtained and core outcome measures will be assessed. These visits will occur at



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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



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(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.



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Table 5.1 Examination Measures and Frequency

| Measurement | Screen- ing Visit | Enroll- ment Visit | Follow-up Visit | | | | |
|---|-------------------------|--------------------------|-----------------|-----------------|----------------|----------------|----------------|
| | | | 12-mo | Interim 6-mo | 24-mo | 36- mo | 48- mo |
| Blood collection, fasting¹ | | | | | | | |
| - 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 |



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Table 5.1 Examination Measures and Frequency -- Continued

| Measurement | Screen- ing Visit | Enroll- ment 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.

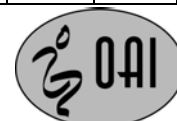


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Table 5.2 Questionnaire Measures and Frequency

| Questionnaire/ Interview Measures | Initial Eligibility | Screening Visit | Enrollment 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, education, 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 |



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Table 5.2 Questionnaire Measures and Frequency -- Continued

| Questionnaire/ Interview Measures | Initial Eligibility | Screening Visit | Enrollment 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)



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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)



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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.



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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



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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.



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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 ≤ 4.0 Tesla; b) specific absorption rate ≤ 4 Watts/kg over the whole body for 15 minutes, ≤ 3 Watts/kg over the head for 10 minutes, ≤ 8 Watts/kg in any gram of tissue in the head or torso for 15 minutes, or ≤ 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 ≤ 140 dB or average (rms) sound level ≤ 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



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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.



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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



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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>).



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- 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



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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.



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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.



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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



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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.



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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:



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- 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:



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- 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;

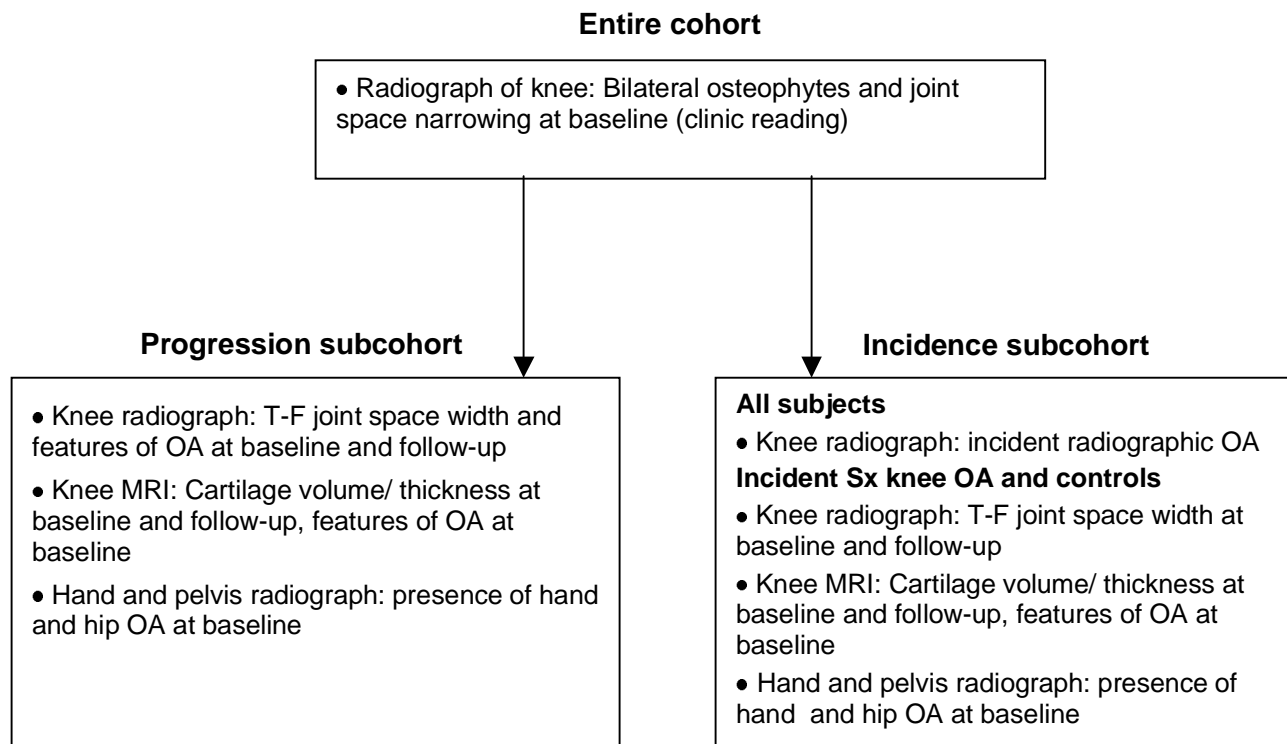


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- Hand radiographs: presence and severity of baseline hand OA.
- Pelvis radiographs: presence and severity of hip OA.

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



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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



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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 (≥ 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.



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Table 8.2. Power for dichotomous predictors of incident Sx OA obtained in all subject

| <i>Exposure Prevalence (%)</i> | <i>Relative Risk detectable with 80% power</i> |
|--------------------------------|--|
| 50 | 1.43 |
| 33 | 1.45 |
| 25 | 1.49 |
| 10 | 1.70 |

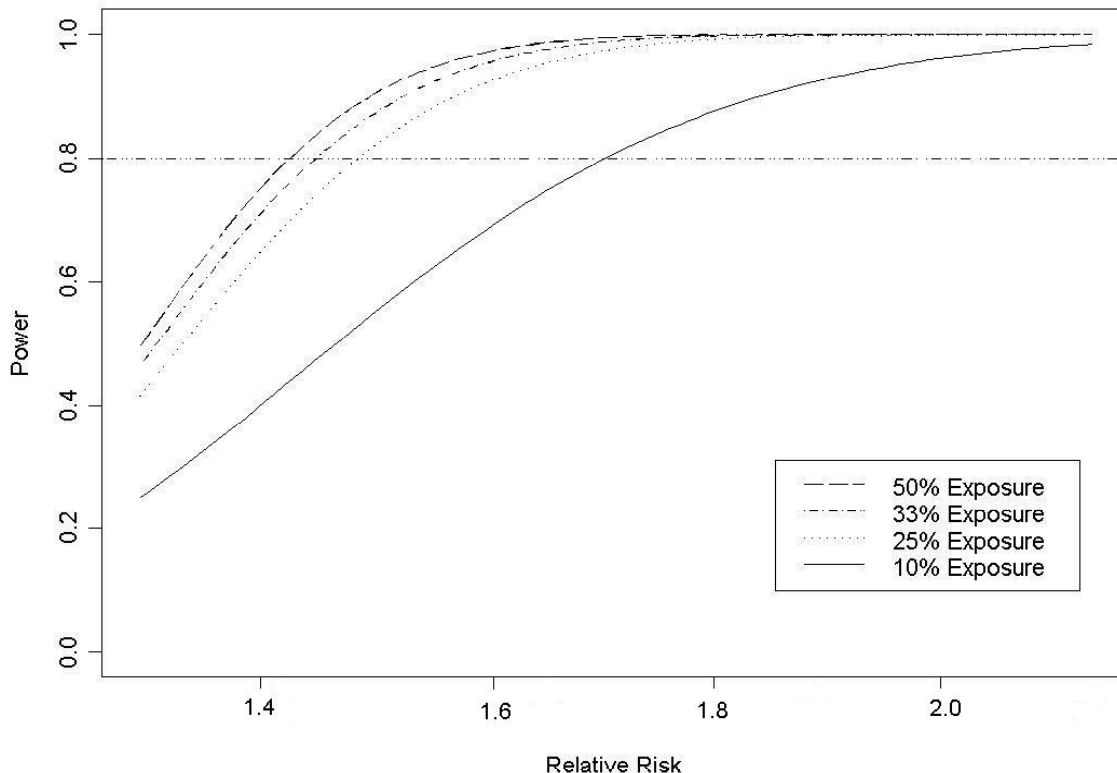
Based on expected numbers of endpoints using the original study design assumptions, the power to detect relative risks (RR) between exposed and nonexposed subjects in the Incidence subcohort is displayed in table 8.2. The smallest detectable RR by Cox regression of time to incident OA using a two-sided 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

OAI Power for Incidence of Symptomatic Knee OA



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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

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

| <i>Exposure Prevalence (%)</i> | <i>Relative Risk detectable with 80% power</i> |
|--|--|
| 50 | 1.56 |
| 33 | 1.57 |
| 25 | 1.62 |
| 10 | 1.91 |

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.

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,

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

| <i>True Correlation</i> | <i>Attenuated Correlation</i> | <i>95% CI for Attenuated Correlation</i> |
|-----------------------------|-----------------------------------|--|
| 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) |

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.



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.



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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

| <i>Exposure Prevalence (%)</i> | <i>Detectable WOMAC Disability Yearly Change Difference</i> | <i>Detectable WOMAC Pain Yearly Change Difference</i> |
|--|---|---|
| 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.



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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 n | 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



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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 that 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;



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- 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.



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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 serve 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 NIH 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



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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).



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Appendix A.
Original Study Enrollment Goals for Progression and Incidence Subcohorts,
by Age and Gender

The OAI plans to enroll 5,000 women and men ages 45 to 79, 800 in the Progression subcohort, 4,000 in the Incidence subcohort, and 200 in the reference (“nonexposed”) control group. Sample sizes in the Progression and Incidence subcohorts are expected to provide adequate numbers of knees with worsening and incident OA-related structural and clinical changes to achieve the primary aims of the study.

Table 1. Progression subcohort: number of enrollees at baseline

| Age stratum | Women | Men | Total N (%) |
|--------------------|--------------|------------|--------------------|
| Age 45-49 | 80 | 80 | 160 (20%) |
| Age 50-59 | 104 | 104 | 208 (26%) |
| Age 60-69 | 112 | 112 | 224 (28%) |
| Age 70-79 | 104 | 104 | 208 (26%) |
| Age 45-79 | 400 | 400 | 800 (100%) |

The target number of enrollees by age-stratum and gender is shown in Tables 1 and 2. The target number of enrollees will be equal by gender in all age strata of the cohorts. In the Progression subcohort (Table 1), enrollment goals will be similar for each of four age-strata. For the reference control group, goals will also be similar by age strata. In the Incidence subcohort (Table 2), the number of enrollees per age stratum will yield roughly equal numbers of cases of incident knee OA by gender and roughly equal numbers of incident cases by 10-year age strata.

Table 2. Incidence subcohort: number of enrollees at baseline

| Age stratum | Women | Men | Total N (%) |
|--------------------|--------------|------------|--------------------|
| Age 45-49 | 140 | 140 | 280 (7%) |
| Age 50-59 | 472 | 472 | 944 (24%) |
| Age 60-69 | 780 | 780 | 1560 (39%) |
| Age 70-79 | 608 | 608 | 1216 (30%) |
| Age 45-79 | 2000 | 2000 | 4000 (100%) |

Appendix B. Modeling OAI Incidence Subcohort Enrichment Using Risk Factors

Michael LaValley, PhD, Boston University
Michael Nevitt, PhD, UCSF
Updated 4/15/03

I. SUMMARY

We estimated the effect of using risk factors to enrich the Incidence subcohort for the endpoint of incident symptomatic knee OA. For this we pooled subjects from both the original Framingham Cohort¹, most of whom were over age 70, and the second-generation Framingham Offspring Cohort², most of whom were under age 70, to derive the level of risk associated with various combinations of most of the risk factors listed in Section I.3. Men and women aged 45 to 79 years old are included in these analyses. Symptomatic knee OA is defined as the presence of both knee pain on most days of the month and Kellgren and Lawrence grade of 2 or more on the AP radiograph in the same knee. All data are cross-sectional, and prevalence rather than incidence was analyzed.

The Framingham study subjects were separated into 6 strata by sex and age. All analyses were performed stratified by these 6 groups:

1. Men ages 45-49
2. Men ages 50-69
3. Men ages 70-79
4. Women ages 45-49
5. Women ages 50-69
6. Women ages 70-79

Within each stratum, “high risk” subgroups were defined using risk factors. The prevalence ratios for the high risk subgroups were determined by dividing the prevalence of symptomatic knee OA among high risk subjects in a sex and age stratum back to the prevalence in all subjects in that stratum. The resulting prevalence ratios were used as multipliers applied to the gender and age-specific incidence of clinical symptomatic knee OA from the Fallon Community Health Plan^{i, 3}.

The following items were analyzed as risk factors for symptomatic knee osteoarthritis:

- Pain in knee on most days of the preceding month

ⁱ The estimates for incident symptomatic knee OA from Framingham (1) are consistent with the rates from the Fallon study. In the Framingham study, subjects were mostly age 70 or older and were followed for eight years. For women, the per person incidence of symptomatic knee OA was 1% per year; for radiographic knee OA it was 2%/year and for progressive radiographic disease, it was 4%/year. Rates are slightly lower for men in Framingham. High BMI increased the risk of incident and progressive OA in women, but not among all men.

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- Previous knee injury
- Previous knee operation
- Weight
- Presence of Heberden's nodes in the DIP joints of both hands (this is only available currently in members of the original Framingham cohort, who are mainly in strata 3 and 6).

Some risk factors that will be used in OAI screening could not be evaluated in this fashion due to lack of data in the Framingham cohorts, including total knee replacement in a parent or sibling and current frequent knee bending.

To help determine which weight cut-points were most useful, we considered three stratum-specific cut-points in conjunction with the other risk factors: top 15th percentile of weight, top 30th percentile of weight, and top 50th percentile of weight. Similar results were found using BMI percentile cut-points instead of weight.

We also considered an alternative definition for Heberden's nodes, which was bilateral nodes plus total number of nodes above the median for the stratum. This had a small effect on both the percent at risk and the prevalence ratio, and was not considered further.

The following definitions of "high risk" were selected based on a reasonable balance between effectiveness in enriching the cohort (high prevalence ratio) and feasibility of recruitment (high percent who would be classified as "high risk").

Age 45-49 high riskⁱⁱ

- Subject has knee pain and one or more non-pain risk factor (using 30th percentile weight cut-point)

Age 50-69 high riskⁱⁱⁱ

- Subject has knee pain or 2 or more non-pain risk factors (using 30th percentile weight cut-point)

Age 70-79 high risk

- Subject has knee pain or 1 or more non-pain risk factor (using 15th percentile weight cut-point)

ⁱⁱ As it was anticipated that men and women aged 45 to 49 years will need additional risk factors to make their inclusion 'power-neutral', we consider a different risk factor threshold for these strata. Due to the small numbers of cases of symptomatic knee OA in this group, more restrictive thresholds (i.e. requiring pain plus 2 or more risk factors) lead to having no cases in the at risk group

ⁱⁱⁱ For the 50-69 and 70-79 age groups, two alternative definitions of high risk were evaluated, 1 or more risk factors and 2 or more risk factors.

Table 1. Results of modeling incidence subcohort enrichment for above definitions of “high risk”

| Stratum | N of subjects | Knee pain (%) | X-ray knee OA (%) | Sx knee OA (%) | % of stratum in high risk | Prevalence ratio in high risk |
|-----------------|---------------|---------------|-------------------|-------------------|---------------------------|-------------------------------|
| 1. Men, 45-49 | 130 | 17.7 | 8.5 | 3.1% | 7.7% | 9.7 |
| 2. Men, 50-69 | 614 | 19.1 | 20.0 | 5.5% | 26.1% | 3.9 |
| 3. Men, 70-79 | 382 | 12.5 | 29.8 | 6.3% | 47.6% | 2.1 |
| 4. Women, 45-49 | 138 | 26.1 | 5.1 | 0.7% ³ | 9.4% | ND* |
| 5. Women, 50-69 | 729 | 24.1 | 19.1 | 6.9% | 31.4% | 3.2 |
| 6. Women, 70-79 | 553 | 20.5 | 38.2 | 11.8% | 60.9% | 1.6 |

* There is only 1 case of symptomatic OA in this group, and it lies in the upper 15% of weight.

For the 50-69 year age strata, using the 50% instead of the 30% weight cut-point would slightly increase the proportion of the stratum at high risk but also decrease the prevalence ratio. For men, these estimates were 29.2% of the age group at high risk and with a prevalence ratio of 3.5, while for women the results were 36.5% and 2.7, respectively.

Table 2. Rates for symptomatic knee OA used in endpoint calculations, for each gender and age group

| Gender and age groups | Base annual risk of clinical knee OA * | Adjusted annual risk or clinical knee OA ** | Adjusted annual risk of Sx knee OA *** |
|-----------------------|--|---|--|
| Men, 45-49 | 0.15 | 0.98 | 1.07 |
| Men, 50-59 | 0.25 | 0.98 | 1.07 |
| Men, 60-69 | 0.49 | 1.91 | 2.10 |
| Men, 70-79 | 0.84 | 1.76 ^{&} | 1.94 |
| Women, 45-49 | 0.15 | 0.91 | 1.01 |
| Women, 50-59 | 0.28 | 0.90 | 0.99 |
| Women, 60-69 | 0.66 | 2.11 | 2.32 |
| Women, 70-79 | 1.08 | 1.73 | 1.90 |

* Annual incidence of clinical knee OA per 100 p-yrs from Oliveria, et al 1995 ³

** Adjusted incidence per 100 p-yrs equals the base annual risk times the prevalence ratios from Table 1. For ages 45-49, we used a multiplier that made the adjusted incidence rate in this group equal to the adjusted incidence rate in the 50-59 age group, 6.5 for men and 6.1 for women. Within each gender, the multiplier estimated for the 50-69 stratum was used with the 50-59 and 60-69 year old incidence from Fallon.

*** Annual incidence of symptomatic knee OA per 100 p-yrs assumed to be 10% higher than clinical knee OA.

& Because the risk multiplier is so much higher in the 60-69 compared to the 70-79 year age group, the adjusted annual risk ends up being a little higher in the younger subjects.

We multiplied the prevalence ratios from Table 1 times the annual risk of clinical knee OA observed in the Fallon HMO population to obtain an estimate of the annual risk of clinical knee in the high risk groups (adjusted annual risk) (Table 2). Because of the small numbers of men in the 45-49 year age group in the sample, estimates of prevalence ratios in this group may be unstable. Further, there was only one woman with symptomatic knee OA in this age group. Therefore, we did not use empirically

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derived prevalence ratios for this age group. Instead, we calculated the multiplier that would be needed to make the adjusted annual risk in the 45-49 year olds equal to the adjusted annual risk in the 50-69 year olds. For men this was 6.5 and for women this was 6.1, which is less than the prevalence ratio actually observed for men this age.

For the annual incidence of symptomatic knee OA in each age and gender group (Table 2), we assumed (based on data from Framingham) that the incidence of symptomatic knee OA (defined as the first co-occurrence of knee pain on most days of a month and Kellgren-Lawrence grade 2 or higher radiographic knee OA) is 10% greater than the incidence of clinical knee OA. The adjusted annual risk per 100 person-years for symptomatic knee OA in Table 2 and the age and gender specific recruitment goals for the Incidence subcohort (Appendix A) were used to estimate the number of endpoints expected in Table 3.

Table 3. Expected number of cases of incident symptomatic knee OA in the Incidence subcohort

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

The number of incident knees is expected to be about 60-70% greater than the number of incident case subjects since most subjects will have two knees at risk.¹ (and unpublished data from Framingham)

Limitations of the enrichment modeling

There are several limitations and uncertainties of these analyses. First, we were not able to model incidence directly as the existing data sets contain only a small number of cases of incident symptomatic knee OA. Risk multipliers drawn from cross-sectional analyses of risk factors and symptomatic OA may not apply to risk factors for true incidence. It is also uncertain whether analysis using incident radiographic OA, a more common endpoint that has been used in several existing cohort studies, would provide more valid inference since it is not known whether risk factors for incident radiographic OA differ from those for symptomatic OA. In addition, there were no data available for modeling on incidence of symptomatic knee OA as specifically defined in the present analyses, which is the first co-occurrence of knee pain on most days of a month and Kellgren and Lawrence grade 2 or greater radiographic OA.

Consistency of results with previous studies of risk factors for incident knee OA

However, our results are concordant with the small number of studies that have directly assessed risk factors for incident radiographic OA. In a cohort of 2,101 men and women ages 55 and older living in Bristol, England, high BMI, knee pain at baseline, Heberden's nodes, previous knee injury and regular sports participation each independently increased the risk of incident radiographic OA⁴. In a cohort of over 1000 women ages 45 to 60 residing in Chingford, England, those with incident knee OA were

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heavier, had more hand OA and more often had knee symptoms than those who did not develop OA ⁵. In analyses of incident radiographic knee OA in the original (older) Framingham cohort, higher BMIs and high levels of physical activity increased the risk of incident knee OA in both genders ⁶. In addition, there were nonsignificant trends for an increased risk in Framingham men with hand OA and previous knee injury and for women with a knee injury during follow-up. Women in Framingham had a 1.8 to 2.0 fold higher risk than men for both incident radiographic and incident symptomatic knee OA in these older Framingham subjects ¹. This last finding supports the higher base rates for incident clinical knee OA that we are using for women, based on the Fallon Health Plan data ³. Finally, in the only study of risk factors for incident clinical knee OA, heavier women in the Fallon Health Plan had a greatly increased risk of new knee OA ⁷.

II. DETAILED TABLES OF RESULTS

1. Number of subjects and prevalence of Sx knee OA for sex and age strata

Weight cut-points were based on percentile distributions in the Framingham cohort. Weight values for percentile cut-points used in OAI are taken from the weight distributions of the 2001 National Health Interview Survey, which are higher than those corresponding weights in Framingham.

| Stratum | Number of Subjects | Subjects with Knee OA | Knee OA Prevalence (%) |
|-----------------|--------------------|-----------------------|------------------------|
| 1. Men, 45-49 | 130 | 4 | 3.1 |
| 2. Men, 50-69 | 614 | 34 | 5.5 |
| 3. Men, 70-79 | 382 | 24 | 6.3 |
| 4. Women, 45-49 | 138 | 1 | 0.7 |
| 5. Women, 50-69 | 729 | 50 | 6.9 |
| 6. Women, 70-79 | 553 | 65 | 11.8 |

2. Weight Cutoffs by Strata

Table entry is weight in pounds

| Stratum | Upper 50% Cutoff | Upper 30% Cutoff | Upper 15% Cutoff |
|-----------------|------------------|------------------|------------------|
| 1. Men, 45-49 | 184 | 202 | 222 |
| 2. Men, 50-69 | 185 | 199 | 213 |
| 3. Men, 70-79 | 167 | 180 | 193 |
| 4. Women, 45-49 | 146 | 169 | 191 |
| 5. Women, 50-69 | 145 | 159 | 173 |
| 6. Women, 70-79 | 139 | 151 | 167 |

3. Results for men 45-49 years of age (Stratum 1)

Tables show the prevalence ratio (PR) vs. prevalence in all subjects in that stratum for “at risk” defined by knee pain and 1+ risk factors

3A. Endpoint is symptomatic OA.

| At risk group for different weight cut-points | PPV: % with Sx knee OA | PR: At Risk (pain and 1+ risk factors) | % (n) at Risk |
|---|------------------------|--|---------------|
| A. 15% wt | 28.8 | 9.28 | 5.4 (7) |
| B. 30% wt | 30.1 | 9.74 | 7.7 (10) |
| C. 50% wt | 23.3 | 7.49 | 10.0 (13) |

3B. Endpoint is X-ray OA (Because of the small numbers of cases of Sx knee OA in this age group, we also examined the effect of risk stratification on the prevalence of X-ray OA)

| At risk group for different weight cut-points | PPV: % with Radiographic knee OA | PR: At Risk (pain and 1+ risk factors) | % (n) at Risk |
|---|----------------------------------|--|---------------|
| A. 15% wt | 28.6 | 3.38 | 5.4 (7) |
| B. 30% wt | 30.0 | 3.55 | 7.7 (10) |
| C. 50% wt | 23.1 | 2.73 | 10.0 (13) |

4. Results for men 50-69 years of age (Stratum 2)

Tables show the prevalence ratio (PR) vs. prevalence in all subjects in that stratum for:

4A. “at risk” defined by knee pain or 2+ risk factors

| At risk group for different weight cut-points | PPV: % with Sx knee OA | PR: At Risk (pain or 2+ risk factors) | % (n) at Risk |
|---|------------------------|---------------------------------------|---------------|
| A. 15% wt | 23.1 | 4.20 | 23.9 (147) |
| B. 30% wt | 21.2 | 3.85 | 26.1 (160) |
| C. 50% wt | 19.0 | 3.45 | 29.2 (179) |

4B. “at risk” defined by knee pain or 1+ risk factors

| At risk group for different weight cut-points | PPV: % with Sx knee OA | PR: At Risk (pain or 2+ risk factors) | % (n) at Risk |
|---|------------------------|---------------------------------------|---------------|
| A. 15% wt | 12.1 | 2.20 | 45.8 (281) |
| B. 30% wt | 9.8 | 1.78 | 56.4 (346) |
| C. 50% wt | 8.1 | 1.47 | 68.6 (421) |

5. Results for men 70-79 years of age (Stratum 3)

Tables show the prevalence ratio (PR) vs. prevalence in all subjects in that stratum for:

5A. “at risk” defined by pain or 2+ risk factors

| At risk group for different weight cut-points | PPV: % with Sx knee OA | PR: At Risk (pain or 2+ risk factors) | % (n) at Risk |
|---|------------------------|---------------------------------------|---------------|
| A. 15% wt | 28.8 | 4.57 | 13.6 (52) |
| B. 30% wt | 26.4 | 4.19 | 17.8 (68) |
| C. 50% wt | 23.0 | 3.65 | 23.8 (91) |

5B. “at risk” defined by pain or 1+ risk factors

| At risk group for different weight cut-points | PPV: % with Sx knee OA | PR: At Risk (pain or 2+ risk factors) | % (n) at Risk |
|---|------------------------|---------------------------------------|---------------|
| A. 15% wt | 13.2 | 2.10 | 47.6 (182) |
| B. 30% wt | 11.1 | 1.76 | 56.5 (216) |
| C. 50% wt | 9.2 | 1.46 | 68.3 (261) |

6. Results for women 45-49 years of age (Stratum 4)

Tables show the prevalence ratio (PR) vs. prevalence in all subjects in that stratum for “at risk” defined by pain and 1+ risk factors

6A. Endpoint is symptomatic OA.

| At risk group for different weight cut-points | PPV: % with Sx knee OA | PR: At Risk (pain and 1+ risk factors) | % (n) at Risk |
|---|------------------------|--|---------------|
| A. 15% wt | 12.50 | 17.36 | 5.8 (8) |
| B. 30% wt | 7.69 | 10.68 | 9.4 (13) |
| C. 50% wt | 4.55 | 6.32 | 15.9 (22) |

*Note that there is only 1 case in this group, and it lies in the upper 15% of weight.

6B. Endpoint is X-ray OA (Because of the small numbers of cases of Sx knee OA in this age group, we also examined the effect of risk stratification on the prevalence of X-ray OA)

| At risk group for different weight cut-points | PPV: % with Sx knee OA | PR: At Risk (pain and 1+ risk factors) | % (n) at Risk |
|---|------------------------|--|---------------|
| A. 15% wt | 12.50 | 2.47 | 5.8 (8) |
| B. 30% wt | 7.69 | 1.52 | 9.4 (13) |
| C. 50% wt | 4.55 | 0.90 | 15.9 (22) |

7. Results for women 50-69 years of age (Stratum 5)

Tables show the prevalence ratio (PR) vs. prevalence in all subjects in that stratum for:

7A. “at risk” defined by pain or 2+ risk factors

| At risk group for different weight cut-points | PPV: % with Sx knee OA | PR: At Risk (pain or 2+ risk factors) | % (n) at Risk |
|---|------------------------|---------------------------------------|---------------|
| A. 15% wt | 24.2 | 3.51 | 28.4 (207) |
| B. 30% wt | 21.8 | 3.16 | 31.4 (229) |
| C. 50% wt | 18.8 | 2.72 | 36.5 (266) |

7B. “at risk” defined by pain or 1+ risk factors

| At risk group for different weight cut-points | PPV: % with Sx knee OA | PR: At Risk (pain or 2+ risk factors) | % (n) at Risk |
|---|------------------------|---------------------------------------|---------------|
| A. 15% wt | 12.6 | 1.83 | 54.3 (396) |
| B. 30% wt | 11.0 | 1.59 | 62.3 (434) |
| C. 50% wt | 9.4 | 1.36 | 73.0 (532) |

8. Results for women 70-79 years of age (Stratum 6)

Tables show the prevalence ratio (PR) vs. prevalence in all subjects in that stratum for:

8A. “at risk” defined by pain or 2+ risk factors

| At risk group for different weight cut-points | PPV: % with Sx knee OA | PR: At Risk (pain or 2+ risk factors) | % (n) at Risk |
|---|------------------------|---------------------------------------|---------------|
| A. 15% wt | 42.6 | 3.61 | 22.1 (122) |
| B. 30% wt | 36.6 | 3.10 | 27.2 (153) |
| C. 50% wt | 29.7 | 2.52 | 36.5 (202) |

8B. “at risk” defined by pain or 1+ risk factors

| At risk group for different weight cut-points | PPV: % with Sx knee OA | PR: At Risk (pain or 2+ risk factors) | % (n) at Risk |
|---|------------------------|---------------------------------------|---------------|
| A. 15% wt | 19.3 | 1.64 | 60.9 (337) |
| B. 30% wt | 17.9 | 1.52 | 65.8 (364) |
| C. 50% wt | 15.4 | 1.31 | 76.1 (421) |

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Appendix C. Acceptance Testing Requirements for OAI Siemens Trio 3 Tesla Magnetic Resonance Systems

Acceptance testing for the Osteoarthritis Initiative's four 3.0 Tesla MR systems should meet or exceed the following standards:

American College of Radiology (ACR) Standard for Diagnostic Medical Physics Performance Monitoring of Magnetic Resonance Imaging (MRI) Equipment (1999). (See the American College of Radiology) MRI Accreditation web site for details: http://www.acr.org/s_acr/sec.asp?CID=675&DID=14339)

Measurements and calculations will conform to, but not be limited to, ACR acceptance testing standards including:

- ACR Phantom Measurement in the head RF coil (3T specifications have not yet been set; however only RF coil uniformity is expected to decrease to 85%);
- Right and Left knee MR exam in the extremity RF coil;
- The C- and L-spine imaging requirement of the ACR standard are excluded;
- Siemens Trio performance specifications. (Unpublished. Contact Siemens for details.);
- Stability of Head and Knee imaging (ACR, OAI QA, SNR) performance over 6 weeks.

OAI Quality Assurance Phantoms:

- OAI Daily QA phantom (cylindrical, diameter 125mm, length 140mm) with positioning marks and holder suitable for reproducible use in knee coil
- ACR phantom (cylindrical, diameter 204mm, length 165mm) with positioning marks and holder suitable for reproducible use in head coil

Magnetic Resonance (MR) system acceptance testing will be conducted prior to the start of the OAI study. Several testing time frames are specified (daily, weekly).

Calibration of the 3T Magnetic Resonance systems should be performed in a manner in which the system will be able to exceed the manufacturer's performance specifications.

Items of particular concern are:

- Magnetic field homogeneity.
- Room temperature *in vivo* shimming using off isocenter imaging field-of-views (R60+/-70mm and L60+/-70mm) as well as at magnet isocenter.
- Gradient field eddy currents
- Geometric distortion arising from the combination of gradient field non-uniformity and magnetic field homogeneity over a 300mm diameter spherical volume centered at magnet isocenter.
- RF Coil Stability (signal-to-noise, uniformity, R/L performance).

Appendix D. OAI 3T Magnetic Resonance Quality Control Testing Methods

Magnetic Resonance (MR) system quality control (QC) testing is performed systematically over the course of the OAI. Several testing time frames are specified (daily, weekly, monthly). Several of the evaluations are performed manually by the MR technologists, others are performed using an automated analysis program at a central location (Simply Physics). (See OAI MRI procedure manual for additional details (<http://www.oai.ucsf.edu/datarelease/OperationsManuals.asp>).

The OAI QC procedures are designed to:

- Provide uniformly high quality artifact-free images from all sites.
- Provide longitudinal consistency across all sites of key image characteristics such as signal-to-noise, contrast-to-noise, signal homogeneity, local and global distortion.
- Provide a means to compare MR data acquired from each of the four 3T systems.
- Minimize need to repeat imaging by correcting slowly developing problems before image quality is affected.

The results of the automated analysis of the American College of Radiology (ACR) MR phantom exam (conducted monthly and annually using OAI specific acquisitions and performance criteria) are reported in the attached Summary. The Simply Physics automated analyses program for evaluation of the ACR Phantom images are performed in compliance with ACR guidelines ("Phantom Test Guidance for the ACR MRI Accreditation Program").

There are two study specific phantoms (OAI measured in the knee coil and ACR measured in the head coil) as well as three coil specific phantoms (knee, head, body) for checking signal-to-noise (SNR). The schedule of QC measurements is shown in Table 1.

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Table 1. Schedule of MR QC phantom measurements

| Time Period | Phantom | Coil | Measurement | Evaluation |
|--------------------|--------------------------|--------------------------------|---|-------------------|
| Daily | Knee SNR | Knee (isocenter) | SNR | Technologist |
| Daily | OAI | Knee (MWF at R60; TThS at L60) | Geometry, Signal Uniformity, Ghosting | Technologist |
| Weekly | None | None | Physical inspection of all coils, phantom, magnet bore, screen room door. | Technologist |
| Weekly | Head SNR | Head | SNR | Technologist |
| Weekly | Knee SNR | Backup Knee (isocenter) | SNR | Technologist |
| Monthly (week 1) | OAI | Knee (Odd at R60; Even at L60) | Geometry, SNR, Signal Uniformity, Ghosting, T2, Volume | SimplyPhysics |
| Monthly (week 2) | Body SNR | Body | SNR | Technologist |
| Monthly (week 3) | ACR, modified | Head | Geometry, SNR, Signal Uniformity, Ghosting | SimplyPhysics |
| Monthly (week 4) | All | All | Preventative Maintenance | Siemens |
| Annually | ACR, standard + modified | Head | Geometry, SNR, Signal Uniformity, Ghosting | SimplyPhysics |

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I. Monthly and Annual Testing using the ACR Phantom and Head Coil

Quality Control using the American College of Radiology (ACR) MR phantom is conducted monthly using OAI specific acquisitions and annually using both OAI and ACR specific acquisitions and performance criteria. The Simply Physics automated analyses program for evaluation of the ACR Phantom images was created and applied in compliance with ACR guidelines ("Phantom Test Guidance for the ACR MRI Accreditation Program") and is used for analysis of both Monthly and Annual QC images of the ACR phantom.

Monthly ACR Phantom QC:

- Monthly Quality Control using the cylindrical ACR Accreditation Phantom (inner length 148mm, inner diameter 190mm) with positioning marks and holder suitable for reproducible use in head coil.
- Phantom Description (from Geoffrey D. Clarke, "MRI Phantoms and QA Testing," Ch. Overview of the ACR MRI Accreditation Phantom.):
 - The ACR MRI accreditation phantom is constructed of acrylate plastic, glass, and silicone rubber. Ferromagnetic materials have been excluded. The unit is a cylinder with outer dimensions 20.4cm in diameter by 16.5cm in length. There is a reference line down one side of the phantom.
 - The phantom is filled with 10 millimolar (mmol) nickel chloride solution containing sodium chloride (45 mmol) to simulate biological conductivity.
 - The resolution insert on one end of the phantom consists of three matrices of holes in an 11mm thick bar. Hole diameters are 1.1mm, 1.00mm, and 0.9mm. The spaces between the holes are equal to the respective hole diameters. This insert is used to test limiting in-plane spatial resolution.
 - Two counter-descending wedges are found at this end of the phantom. They each contain a 1 cm slit. The wedges form two ramps of test solution which descend at a 1:10 ratio to permit accurate measurement of slice thickness.
 - The grid insert toward the center of the phantom is a 10 by 10 array of squares 144 mm on a side and 10 mm thick. It is used for placing the diagonal lines in the geometric distortion tests. The nominal interior diameter of the phantom is 190 mm.
 - Four low-density contrast disks are located on the far end of the phantom. They consist of thin sheets of polycarbonate plastic 0.002, 0.004, 0.006, and 0.008 inch in thickness. Holes of different diameters have been cut into the disks. Partial volume contributions of both the fill solution and these membranes produce slight variations in signal strength which may be used to visually assess the scanner's ability to distinguish low contrast objects.
 - Two sets of paired 45° wedges are located on the top and bottom of the phantom. Each pair is 2 cm in length with the center of intersections at 1 cm from either end. The distance between the intersection points of the paired wedges is 100mm. The wedges are used to precisely measure physical and electronic slice offsets. The paired wedges can also be used to evaluate small interslice gaps.
- The MR acquisitions consist of a 3 plane localizer, a single sagittal T1-weighted (T1W) spin echo (SE) slice and eleven axial intermediate-weighted (IW) turbo spin echo (TSE) slices. The IW TSE acquisition simulates the contrast and spatial resolution of the 2D

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TSE (coronal and sagittal) OAI acquisitions and uses TE 30ms, TR 1750ms, 2 averages, 5 echo train length, 355 Hz/pixel bandwidth, 3mm slice thickness, a 250mm field of view (FOV), and in plane spatial resolution of 0.36mm X 0.45mm (matrix 555 X 704).

- Quantitative evaluations and performance thresholds:
 - Geometric Accuracy – inner phantom dimension
 - Inside end-to-end length (sagittal) 148 ± 1.0 mm
 - Inside sagittal lengths vary in absolute value from site to site due to phantom manufacturing tolerances. The longitudinal variation was measured to be within specifications, except when the phantom was mis-positioned.
 - Inside diameter (axial measured top to bottom, right to left and along both diagonals) 190 ± 1.0 mm
 - Inner phantom diameters are generally within ± 0.5 mm. However the inner phantom length is consistently shorter than the nominal value, with specific values varying on a site-by-site basis.
 - Slice thickness accuracy (axial) $3 \text{ mm} \pm 1.0 \text{ mm}$
 - Slice thickness is consistently larger than requested on the Trio MR systems. Because slice thickness adjustment is not independent of other measures, we have chosen to have longitudinally stable slice thickness. 3.0mm is approximately 3.6mm on all four systems. Variations outside a narrow range result from errors in phantom alignment and / or slice placement.
 - Slice position error (axial) $\leq 2 \text{ mm}$
 - This measure is routinely achieved.
 - Percent Signal Ghosting (axial) $\leq 1.0 \%$
 - Typical MR system characteristics which affect the ghost level are vibration and eddy currents. A service call is made anytime they are $> 0.5\%$.
 - Measured ghosting is typically $\leq 0.2\%$.
 - Wedge difference (axial) -- combination of z-gradient amplitude calibration and of z-gradient non-uniformity $\pm 5.0\text{mm}$
 - This measure is routinely achieved $< \pm 2.0\text{mm}$.
- Analyses of limited insight into MR system performance include:
 - Low Contrast object visibility
 - At 3T, this measure is systematically above 30 spokes if the phantom is aligned properly and if the scan prescription allows the slices to fall through the test objects. This measurement is not particularly insightful about 3T MR system performance as it would at lower magnetic field strengths because of the good contrast-to-noise at 3T.

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- High contrast spatial resolution (axial) ≤ 0.9 mm
 - This measure is routinely achieved due to the high contrast of the 3T field strength and the high spatial resolution of the acquisition.
- Image Uniformity is measured on the head coil and does not reflect overall MR system performance. Clear decreases in head coil signal uniformity are observed as the head coils age. Dramatic changes can be visible when the coil is replaced.
- Signal-to-Noise Ratio (SNR) is measured on the head coil and reflects in part the overall MR system performance as well as the stability of the magnet room temperature. Small fluctuations in head SNR are usually related to room temperature. Clear decreases in head coil signal uniformity are observed as the head coils age. Dramatic SNR changes can be visible when the coil is replaced. The head coil SNR increased by about 44% around December 2005 because the number of averages in the MR acquisition doubled. This change was made to decrease the influence of the noise when measuring phantom diameter.
- Landmark assesses how precisely the phantom is aligned and how accurately the spatial landmark is chosen rather than true MR system performance.

Annual ACR Phantom QC:

- Annual Quality Control using the cylindrical ACR Accreditation Phantom (inner length 148mm, inner diameter 190mm) with positioning marks and holder suitable for reproducible use in head coil.
- The MR acquisitions consist of a 3 plane localizer, a single sagittal T1W SE slice, eleven axial T1W SE slices, eleven axial proton density (PD) SE slices, eleven axial T2-weighted (T2W) slices, and eleven axial intermediate-weighted (IW) turbo spin echo (TSE) slices. The axial T1W, PD, T2W and sagittal T1W series are performed as specified by the ACR with the PD and T2W contrasts measured in a dual echo acquisition. The IW TSE acquisition simulates the contrast and spatial resolution of the 2D TSE (coronal and sagittal) OAI acquisitions and uses TE 30ms, TR 1750ms, 2 averages, 5 echo train length, 355 Hz/pixel bandwidth, 3mm slice thickness, a 250mm FOV, and in plane spatial resolution of 0.36mm X 0.45mm (matrix 555 X 704).
- The same quantitative evaluations are performed as for the monthly QC using the ACR phantom with the following performance thresholds:
 - Geometric Accuracy
 - Inside end-to-end length 148 ± 1.0 mm;
 - Inside diameter 190 ± 1.0 mm.
 - High contrast spatial resolution ≤ 0.9 mm
 - Slice thickness accuracy 5 mm ± 0.7 mm for SE sequences; 3mm ± 1.0 mm for TSE sequences
 - Slice position error ≤ 2 mm
 - Percent Signal Ghosting ≤ 2.5 % for SE sequences; $< 1.0\%$ for TSE sequences

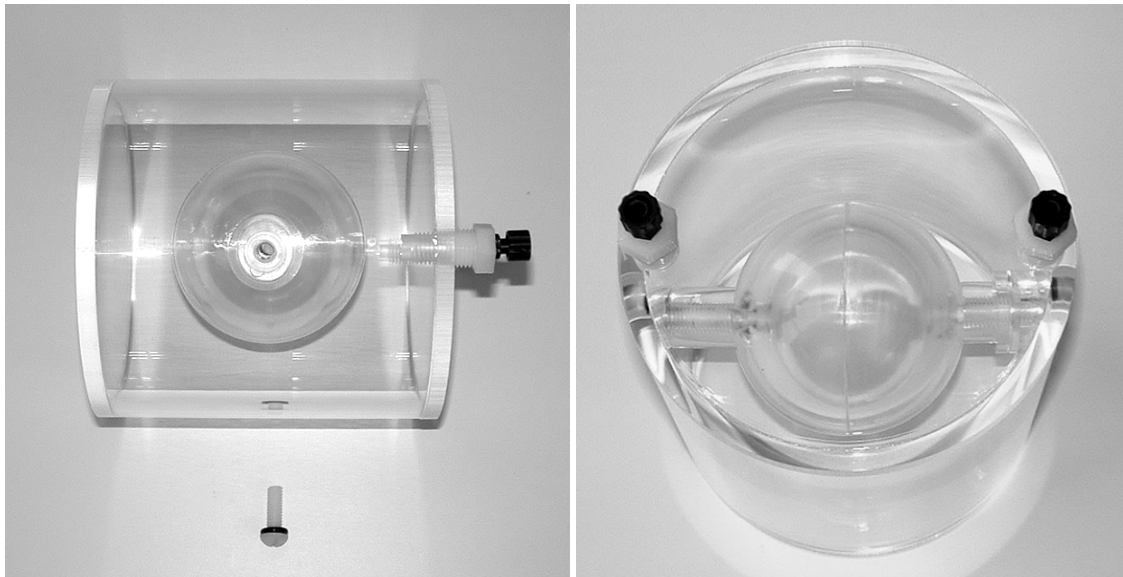
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II. Daily and Monthly Testing using the OAI Phantom and Knee Coil

OAI specific acquisitions are performed both daily and monthly using the knee coil and a custom built, two compartment phantom (OAI phantom). Manual analysis of the Daily OAI phantom images are conducted on site by the MR technologist as a quick check of system performance. Automated analysis by Simply Physics is performed on the monthly OAI MR phantom exam.

Daily OAI Phantom QC:

- Daily OAI Quality Control utilizes a custom phantom. The OAI phantom is a 12.5cm outer diameter cylinder with outer length 12.8cm (approximate inside diameter 114mm, approximate inside length 114 mm). The OAI phantom contains a hollow sphere of 57 mm inside diameter and was designed to fit inside a standard knee coil. Each compartment contains a different MR-visible Gd-DTPA solution (inner sphere 10mM Gd-DTPA; outer volume 3.33mM Gd-DTPA). Photos are below.



- The knee coil is positioned at the R60 (Monday, Wednesday, Friday) or L60 (Tuesday, Thursday, Saturday) location for the daily QC exam.
- The daily MR QC protocol consists of a 3 plane localizer, a seven slice sagittal intermediate-weighted (IW) TSE acquisition and a seven slice axial IW TSE acquisition. The IW TSE acquisition simulates the contrast and spatial resolution of the 2D TSE (coronal and sagittal) OAI acquisitions and uses TE 29ms, TR 1750ms, 1 average, 5 echo train length, 352 Hz/pixel bandwidth, 3mm slice thickness, a 140mm FOV, and in plane spatial resolution of 0.365mm X 0.456mm (matrix 384 X 307).
- Quantitative evaluations and performance thresholds:
 - Signal Intensity
 - Inner sphere (sagittal, axial) < 5% day-to-day variation

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- Signal Standard Deviation
 - Inner sphere (sagittal, axial) < 10% day-to-day variation
- Noise
 - Outside phantom, frequency encode axis (axial) < 10% day-to-day variation
- Ghost
 - Outside phantom, phase encode axis (axial) < 10% day-to-day variation
- Geometric Accuracy – inner phantom dimension
 - Inside end-to-end length (sagittal) 114 ± 1.0 mm
 - Inside diameter (axial) 114 ± 1.0 mm
- Decision Tree for Daily QA Exam:
 - If the MR system fails any test, the coil connections (including top/bottom latch), the coil and phantom positions are checked and the test is repeated.
 - If the MR system fails a second time, the test is repeated with the alternate knee coil.
 - If the MR system fails with the alternate knee coil, the system is rebooted with the head coil and SNR phantom in place. The Head Coil SNR measurement is then performed, if Head SNR does not pass, the measurement is repeated. If Head SNR passes, the knee coil SNR test is performed. If Knee SNR does not pass, the measurement is repeated. If Knee SNR passes, the daily QA exam is repeated with the knee coil.
 - If the system fails the two Head S/N tests, the two Knee S/N tests (with both coils), or the Daily QA exam, the MR technologist will call Siemens Service and will not scan study subjects until the performance issue is resolved.

Monthly OAI Phantom QC:

- Monthly OAI Quality Control uses the cylindrical OAI Phantom (inside diameter 114mm, inside length 114 mm) with the knee coil.
- The OAI QC phantom is a 12.5cm outer diameter cylinder with outer length 12.8cm (approximate inside diameter 114mm, approximate inside length 114 mm). The OAI phantom contains a hollow sphere of 57 mm inside diameter and was designed to fit inside a standard knee coil. Each compartment contains a different MR-visible Gd-DTPA solution (inner sphere 10mM Gd-DTPA; outer volume 3.33mM Gd-DTPA).
- The knee coil is positioned at the R60 (even months) or L60 (odd months) location for the monthly OAI phantom QC exam.
- The monthly MR QC protocol consist of a 3 plane localizer, a seven slice sagittal intermediate-weighted (IW) turbo spin echo (TSE) acquisition, a seven slice axial IW TSE acquisition, a 27 slice multi-slice, multi-echo (MSME) spin echo (SE) sequence, and a 160 slice 3D DESS acquisition. The IW TSE acquisition simulates the contrast and spatial resolution of the 2D TSE (coronal and sagittal) OAI acquisitions and uses

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TE 29ms, TR 1750ms, 1 average, 5 echo train length, 352 Hz/pixel bandwidth, 3mm slice thickness, a 140mm FOV, and in plane spatial resolution of 0.365mm X 0.456mm (matrix 384 X 307). The MSME acquisition is identical to the T2 map OAI acquisition with 7 echoes at TE 10ms, 20ms, 30ms, 40ms, 50ms, 60ms, and 70ms. TR 2700ms, 1 average, 250 Hz/pixel bandwidth, 3mm slice thickness, a 120mm field of view and in plane spatial resolution of 0.313mm X 0.446mm (matrix 384 X 269) is used. The 3D DESS acquisition is identical to the 3D DESS OAI acquisition, except water excitation is not used. The 3D acquisition has 25 degree flip angle, TE 4.6ms, TR 16.4ms, 1 average, 183 Hz/pixel bandwidth, 0.7mm slice thickness, and in plane spatial resolution of 0.365mm X 0.456mm (matrix 384 X 307).

- Similar quantitative evaluations are performed as for the monthly QC using the ACR phantom with the following performance thresholds. Because of the differences in analysis methods between the automated monthly and the manual daily QC procedures using the same phantom, the absolute values of the results differ.
- Results for 2D and 3D SNR, image uniformity, geometric accuracy and ghosting are listed separately. Historic performance is listed for each measurement, rather than target specifications. Correction of any deficits in the MR system has been made using measurements on the ACR phantom to date. 3D measurements and T2 values are not reported at this time:
 - 2D Geometric Accuracy – inner phantom dimension
 - Inside end-to-end length (sagittal) 114.75 ± 0.5 mm
 - Inside sagittal lengths vary in absolute value from site to site due to phantom manufacturing tolerances.
 - Typical sagittal inner lengths measured at R60 and L60 are indistinguishable when measured up to 1 month apart.
 - Sagittal inner lengths are found not to vary by more than ± 0.25 mm over multiple years, indicating that this is not a sensitive measure of system change.
 - Inside diameter (axial) 114.75 ± 0.5 mm
 - Typical axial diameters measured at R60 and L60 are highly correlated do not vary by more than 0.25mm, a value well below typical annual variations.
 - Typical axial diameters measured over time vary by less than 0.5mm, with the largest changes along the Right – Left axis (expected). Multiple year tracking of these values indicates up to 0.75mm range can be observed, more typically variations are within ± 0.5 mm.
 - Axial diameter measurements are systematically largest along the Right – Left axis and smallest along the Anterior – Posterior Axis. Diagonal measurements fall closer to the Anterior – Posterior values and have less variation. Since the frequency encode axis is Right – Left, these axial diameter measurements combine the effects of gradient field non-linearity and magnetic susceptibility and therefore represent an over-estimation of the variations in gradient magnetic field calibration.

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- 2D Signal-to-Noise Ratio (SNR)
 - Outer region (axial) 90 +/- 10 (11%)
 - Outer region (sagittal) 85 +/- 5 (6%)
 - Inner region (sagittal, axial) 35 +/- 3 (9%)
 - SNR for both the outer and inner regions is systematically and substantially lower for L60 than R60 by 10-15% for the majority of the quadrature transmit/receive knee coils manufactured by USA Instruments (USAI).
 - SNR generally trends downwards overtime until the coil is exchanged when it no longer is within performance range. Coil exchange results in a dramatic increase in SNR which once again trends downwards.
 - The UPMC MR system is the exception to these prior two general trends; the Right – Left SNR difference is very small and SNR has been stable (sagittal) or increasing (axial) over time.
 - Outer region SNR is more sensitive to coil performance and coil position inside the magnet due both the larger field-of-view as well as the higher overall SNR values (caused by the lower Gd-DTPA concentration).
- 2D Image Uniformity
 - Inner region (sagittal) 97 +/- 2
 - Inner region (axial) 95 +/- 3
 - Outer region (sagittal) 75 +/- 3
 - Outer region (axial) 85 +/- 5
 - Sagittal inner region image uniformity is consistent at R60 and L60 and is well behaved over time. These results indicate that superior-inferior and anterior-posterior signal shading and chemical shift saturation artifacts should not be problematic over the immediate knee joint (emulated by the 57mm diameter inner sphere).
 - Sagittal outer region image uniformity is much lower and less well behaved than inner region uniformity. This is expected. R60 has consistently lower uniformity than L60. Both R60 and L60 show substantial time varying uniformity. These results indicate that superior-inferior and anterior-posterior signal shading and chemical shift saturation artifacts will likely be observed in the imaging FOV outside the immediate knee joint.
 - Axial inner region image uniformity is consistently higher than axial outer region image uniformity, and is more variable over time than sagittal inner region image uniformity (more on the order of sagittal outer region uniformity). Axial image uniformity may be related to phantom positioning inside the knee coil as well as knee coil positioning in the magnet as well as overall knee coil performance. Axial inner image uniformity is consistently and substantially lower at L60 than R60, and

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probably is the source of the consistently lower L60 SNR. Axial image uniformity is variable over time, and the variability echoes the variability in the axial inner SNR measurement. These results indicate that right-left shading and chemical shift saturation shading artifacts are likely to be observed over the immediate knee joint (emulated by the 57mm diameter inner sphere).

- Axial outer image uniformity is consistently lower than axial inner image uniformity as well as lower at L60 than R60. Axial image uniformity is more variable over time, with only a remote correspondence, than the variability in the axial outer SNR measurement. These results indicate that coil position inside the magnet contributes to amount of shading and is probably the source of the consistently lower L60 SNR. Right-left shading and chemical shift saturation shading artifacts are likely to be observed over the entire imaging FOV.
- The UPMC MR system is again the exception. The axial R60 signal uniformity decreased over time, as expected, whereas the L60 increased dramatically. Sagittal signal uniformity was fairly constant.
- Outer region image uniformity should be more sensitive to coil performance due to the larger imaging FOV monitored.
- 2D Percent Signal Ghosting (axial) $\leq 1.0\%$
 - Typical MR system characteristics which affect the ghost level are vibration and eddy currents. A service call is made anytime they are $> 0.5\%$.
 - Measured ghosting typically $\leq 0.2\%$; spurious automated analysis measurements have been made when the phantom fill ports contain fluid. Upon manual reassessment of images, no ghosting problems have been identified.

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III. Knee, Head and Body Coil SNR Checks

Quality Control of the radiofrequency (RF) coils used to excite and receive the MR signal is performed as an integral part of the Monthly and Annual ACR phantom QC as well as part of the Daily and Monthly OAI phantom QC procedures. In addition to these integrated tests, SNR checks of the transmit / receive knee, head and body coils are also performed periodically using Siemens provided phantoms and test procedures.

Weekly Knee Coil SNR Check:

There are three USA Instruments transmit – receive quadrature knee coils at each OAI MR facility. There are two backup coils because of the frequent failure rate of the coils in the early part of the study. The primary coil is used for OAI subject scanning and for the Daily and Monthly QC using the OAI phantom.

- The phantom used for the knee coil SNR tests is the Siemens knee phantom in a 125mm outer diameter, 140mm length cylindrical Nalgene container. Phantom volume is 2000ml and composition is (1.25g NiSO₄*6H₂O + 5g NaCL) per liter filled with distilled, dionized water.
- The knee coil SNR Check is performed using the Siemens S/N test (Options, Customer QA Menu) with the knee phantom and phantom holder.
- At least once per week, the SNR check is run on all three knee coils.
- The S/N value computed by the Siemens S/N test is recorded for each knee coil, along with the coil serial number, on the Knee QA log sheet.

Weekly Head Coil SNR Check:

There is one USA Instruments transmit – receive quadrature head coil at each OAI MR facility. The head coil is only used by the OAI for the Monthly and Annual ACR Phantom QC measurements of overall MR system performance.

- The phantom used for the head coil SNR tests is the Siemens head phantom in a 160mm outer diameter, 200mm length cylindrical Nalgene container. Phantom volume is 7300ml and composition is (1.24g NiSO₄*6H₂O + 2.62g NaCL) per liter filled with distilled, dionized water.
- The head coil SNR Check is performed using the Siemens S/N test (Options, Customer QA Menu) with the head phantom and phantom holder.
- At least once per week, the SNR check is run on the head coil.
- The S/N value computed by the Siemens S/N test is recorded for the head coil, along with the coil serial number, on the Head QA log sheet.

Monthly Body Coil SNR and Artifacts Check:

The transmit – receive quadrature body coil is integrated in the Trio magnet / gradient coil / body coil ensemble, it cannot be removed/replaced or adjusted by the MR technologist. The body coil is only used by the OAI for the thigh MR exam as well as for Monthly QC and Siemens Service Tuneup measurements of the MR system. However, body coil performance

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can impact overall MR system performance as well as knee and head coil SNR, shading, artifacts *etc.*

- The phantom used for the body coil SNR and Artifacts check is the Siemens Body Loader, the spherical non-conducting phantom (D240) and phantom holder. The D240 phantom has a 240mm outer diameter and contains 7300ml Bayol-oil + 0.011g macrolex blue. The Body Loader is cylindrical and contains 11000mls of (2.6 g MnCl₂*4 H₂O + 2.0g NaCL + 0.11g SICOVIT blue) per liter.
- The body coil SNR and Artifacts Check is performed using the Siemens S/N test (Options, Customer QA Menu) with the D240 phantom and phantom holder contained inside the Body Loader phantom.
- At least once per month, the SNR and Artifacts check is run on the body coil.
- The S/N value computed by the Siemens S/N test is recorded for the body coil, as is the (Pass / Fail) results for the artifact test, on the Body QA log sheet.

Decision Tree for SNR and Artifacts Checks:

- If the MR system fails any one of the tests, check the positions of the phantoms (refer to Customer QA menu instructions) and repeat the exam.
- If the system fails a second time, reboot the system with the head coil and SNR phantom in position, let the phantom settle for 3-5 minutes, run Head Coil S/N DIP (Customer QA Menu), and record on the SNR log sheet. If the Head S/N passes, then re-run the body coil tests. If the system fails the Head S/N test, try once again. If the Head S/N continues to fail, Siemens Service is contacted.
- If the system continues to fail Knee, Head or Body S/N or Body Calc Artifacts after two attempts and after passing the Head S/N, Siemens Service is contacted.

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MRI QA Protocol Details

| | Daily / Monthly QA Knee Coil Localizer | Daily QA 2D TSE | Daily QA 2D TSE | Monthly QA 2D TSE | Monthly QA 2D TSE | Monthly QA 2D TSE | Monthly QA 3D DESS | Monthly QA 2D MSME | Head Coil Localizer | ACR Localizer | ACR Localizer with Large FOV Filter | Monthly OAI IW ACR | Annual T1W ACR | Annual PD / T2W ACR |
|--------------------------------|--|-----------------|-----------------|-------------------|-------------------|-------------------|--------------------|----------------------------|---------------------|---------------|-------------------------------------|--------------------|----------------|---------------------|
| Pulse Sequence | fl2d1 | tse2d1_5 | tse2d1_5 | tse2d1_5 | tse2d1_5 | tse2d1_5 | de3d1 | se | fl2d1 | se2d1 | se2d1 | tse2d1_5 | se2d1 | se2d2 |
| Plane | 3-plane | Sagittal | Axial | Sagittal | Sagittal | Axial | Sagittal | Sagittal | 3-plane | Sagittal | Sagittal | Axial | Axial | Axial |
| Fat Sat | No | No | No | No | No | No | WE | No | No | No | No | No | No | No |
| Matrix (phase) | 128 | 307 | 307 | 307 | 307 | 307 | 307 | 269 | 128 | 256 | 256 | 555 | 256 | 256 |
| Matrix (freq) | 256 | 384 | 384 | 384 | 384 | 384 | 384 | 384 | 256 | 256 | 256 | 704 | 256 | 256 |
| No. of slices | 21 | 7 | 7 | 7 | 7 | 7 | 160 | 21 | 13 | 1 | 1 | 11 | 11 | 11 |
| FOV (mm) | 200 | 140 | 140 | 140 | 140 | 140 | 140 | 120 | 300 | 250 | 250 | 250 | 250 | 250 |
| Slice thickness (mm) | 5 | 3 | 3 | 3 | 3 | 3 | 0.7 | 3 | 5 | 20 | 20 | 3 | 5 | 5 |
| Skip (mm) | 2.5 | 6 | 6 | 6 | 6 | 6 | 0 | 0.5 | 2.5 | 10 | 10 | 7 | 5 | 5 |
| Flip Angle (deg) | 40 | 180 | 180 | 180 | 180 | 180 | 25 | 90 | 40 | 90 | 90 | 180 | 90 | 90 |
| TE/TI (ms) | 5 | 29 | 29 | 29 | 29 | 29 | 4.7 | 10, 20, 30, 40, 50, 60, 70 | 5 | 20 | 20 | 29 | 20 | 20 / 80 |
| TR (ms) | 10 | 1750 | 1750 | 1750 | 1750 | 1750 | 16.3 | 2700 | 10 | 200 | 200 | 1750 | 500 | 2000 |
| BW (Hz/pixel) | 180 | 352 | 352 | 352 | 352 | 352 | 183 | 250 | 280 | 300 | 300 | 355 | 300 | 300 |
| Chemical Shift | 2.4 | 1.3 | 1.3 | 1.3 | 1.3 | 1.3 | 0 | 1.8 | 1.6 | 1.5 | 1.5 | 1.2 | 1.5 | 1.5 |
| NAV (NEX) | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 1 | 1 |
| Echo train length | 1 | 5 | 5 | 5 | 5 | 5 | 1 | 1 | 1 | 1 | 1 | 5 | 2 | 1 |
| Phase Encode Axis | A/P, R/L | A/P | A/P | A/P | A/P | A/P | A/P | A/P | A/P, R/L | A/P | A/P | A/P | A/P | A/P |
| Phase Partial Fourier | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Readout Partial Fourier | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Slice Partial Fourier | 1 | 1 | 1 | 1 | 1 | 1 | 0.75 | 0.75 | 1 | 1 | 1 | 1 | 1 | 1 |
| Distance Factor (%) | 50 | 0 | 0 | 0 | 0 | 0 | 20 | 16 | 50 | 50 | 50 | 333 | 100 | 100 |
| Phase Oversampling | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Slice Oversampling | 0 | 0 | 0 | 0 | 0 | 0 | 10 | 0 | 0 | 0 | 0 | 0 | 0 | 10 |

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| | Daily / Monthly QA Knee Coil Localizer | Daily QA 2D TSE | Daily QA 2D TSE | Monthly QA 2D TSE | Monthly QA 2D TSE | Monthly QA 3D DESS | Monthly QA 2D MSME | Head Coil Localizer | ACR Localizer | ACR Localizer with Large FOV Filter | Monthly OAI IW ACR | Annual T1W ACR | Annual PD / T2W ACR |
|--------------------------|---|--------------------|--------------------|-------------------------|-------------------------|--------------------------|--------------------------|------------------------|------------------|---|--------------------------|----------------------|---------------------------|
| Phase Resolution | 50 | 80 | 80 | 80 | 80 | 80 | 70 | 50 | 100 | 100 | 80 | 100 | 100 |
| X-Resolution (mm) | 0.781 | 0.365 | 0.365 | 0.365 | 0.365 | 0.365 | 0.313 | 1.172 | 0.977 | 0.977 | 0.355 | 0.977 | 0.977 |
| Y-Resolution (mm) | 1.563 | 0.456 | 0.456 | 0.456 | 0.456 | 0.456 | 0.446 | 2.344 | 0.977 | 0.977 | 0.450 | 0.977 | 0.977 |
| Scan time (min) | 0.5 | 1.8 | 1.8 | 1.8 | 1.8 | 10.5 | 10.6 | 0.4 | 0.8 | 0.8 | 3.3 | 2.8 | 8.5 |

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Appendix E. Knee MRI Protocol Development

In the planning stages of the OAI, it was decided that MR scanners dedicated solely to use in the study would be needed to minimize technical and acquisition variability and to accommodate the large number of subjects. The OAI opted to use 3 Tesla (T) MR systems rather than 1.5T systems because of the advantages 3T offered in terms of signal-to-noise ratio (SNR) which could be potentially traded off for spatial resolution and imaging speed. The SNR advantage was felt to be particularly useful for T2 mapping of the cartilage. The disadvantage of using 3T MR systems in 2003 was the relative lack of clinical and research experience compared to 1.5T. In addition, it was understood that the clinical and research 1.5T knee MR protocols would not translate directly to 3T without adjusting for the variable increases in tissue spin-lattice (T1) relaxation times as well as the doubling of the chemical shift artifact on non-fat suppressed acquisitions.

The broad requirements of the OAI MR exam were decided by the Steering Committee - to support a thorough clinical and research evaluation of the femoral-tibial and patellar-femoral joints of both knees with less than 1 hour of scan time. The primary emphasis was to be on quantitative and secondarily qualitative cartilage measurements (morphology and T2 mapping) and to also include a thorough assessment of all the relevant tissues in the knee. The goals of the OAI MR exam thus required anatomical coverage of the entire patellar-femoral and femoral-tibial joints. An additional requirement was that only commercially available, FDA-approved, pulse sequences, radiofrequency (RF) coils, and MR systems could be utilized.

Prioritization of the MR acquisitions to achieve the quantitative cartilage and whole knee assessments were made by the Imaging Working Group with regards to acquisition planes, spatial resolution, image contrast, and relative acquisition time consideration. The Imaging Working Group included scientists and musculoskeletal imaging experts from academia and the industry with expertise MR of OA.

The MR acquisitions that met these goals were optimized (e.g. 'tuned up') for coverage, acquisition time, signal-to-noise ratio (SNR) and artifacts as well as contrast-to-noise ratio (CNR) of the knee anatomy. Optimization of the MR acquisitions were performed with IRB approval at Cincinnati Children's Hospital Medical Center using an identical Siemens Trio (Siemens Medical Solutions, Erlangen, Germany) whole body MR system and transmit-receive USA Instruments quadrature knee coils as the OAI would eventually use.

Images from 23 'optimized' MR acquisitions on both normal and OA knees were presented to the Imaging Working Group for review. Based on an informal subjective review, the Working Group selected the most promising candidate MR acquisitions for further evaluation in a pilot study. In addition to a three-plane localizer, 15 separate acquisitions and four multi-planar reconstructions (MPRs) of 3D acquisitions number 13 and 14 were selected (Table 1). To accomplish the measurement goals of the OAI MR exam on both knees within the allotted time period, it was clear that the SNR advantages of the 3T magnet could not be completely utilized to obtain increased spatial resolution compared to a 1.5T exam. Also, anatomic coverage could be optimized only for the regions of interest. Never-the-less, the increase in SNR and spatial resolution of the 3T knee acquisitions was found to produce striking improvements in image quality.

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A total of 12 knees (four right and eight left) of 10 healthy adult volunteers (5 men, 5 women) underwent MR exams of the knee in a Pilot Study at Ohio State University. All knees were scanned on the dedicated OAI 3T whole-body MR system (Trio, Siemens Medical Solutions, Erlangen, Germany) and a quadrature transmit-receive extremity RF coil (USA Instruments, Aurora, OH). Informed consent was obtained from all subjects and the study protocol underwent institutional board review.

All MR images were reviewed at OSU by the MR technologist for image quality and were immediately reacquired if the scans were unacceptable (orientation, incomplete anatomical coverage, motion artifact, *etc.*). Images were subsequently and independently reviewed by 8 experts. Two separate reviews were undertaken. The first review, by cartilage quantification experts, visually assessed the ability of each 3D acquisition and MPR to undergo image segmentation for morphological cartilage assessment. Part of this review was also a visual and quantitative evaluation by of the multi-slice, multi-echo sequences to undergo spin-spin relaxation (T2) time quantification. The second review, a visual assessment of each scan on each knee by musculoskeletal imaging experts, focused on the ability of each acquisition and MPR to provide the basis for semi-quantitative and qualitative assessments of all the relevant tissues in the knee. Each MR acquisition was scored in terms of homogeneity and structural discrimination of articular cartilage at the cartilage-fluid, cartilage-fat, cartilage-capsule/muscle, cartilage meniscus and cartilage-cartilage interfaces. The results are presented in Table 2.

Assembly of the MR exam protocol was based on the review results as well as the goal of the OAI to examine both knees in a 60-minute total exam time. The final OAI MR exam protocol is presented in Appendix F.

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Table 1: Measurement Objectives for each acquisitions in the OAI Pilot MR Study for Protocol Selection

| Weighting | #1 TSE T2W | #2 TSE Int | #3 TSE T1W | #4 TSE Int | #5 TSE T1W | #6 TSE PD | #7 IR-TSE PD | #8 TSE PD |
|----------------------|--|--|--|--|---|--|--|--|
| | Effusion volume (suprapatellar bursa / popliteal cysts), bone marrow edema | Cartilage morphology and T2 (semi-quantitative; patella); osteophytes, cysts, attrition (patella M/L), bone marrow edema (patella) | Osteophytes, cysts, attrition and sclerosis (femur central, tibial central), meniscus (body), collateral ligaments (reduced sensitivity) | Cartilage morphology and T2 (semi-quantitative; entire knee); osteophytes, cysts, attrition and sclerosis (patella S/I, femur AS / PS), meniscus (A/P horns), cruciate ligaments | Osteophytes, attrition and sclerosis (patella S/I, femur AS / PS), meniscus (A/P horns), cruciate ligaments | Cartilage morphology and T2 (semi-quantitative; femur central, tibia central); osteophytes, cysts, attrition and sclerosis (femur central, tibial central), meniscus (body), collateral ligaments, bone marrow edema | Cartilage morphology and T2 (semi-quantitative; femur central, tibia central); osteophytes, cysts, attrition and sclerosis (femur central, tibial central), meniscus (body), collateral ligaments, bone marrow edema | Cartilage morphology and T2 (semi-quantitative; femur central, tibia central); osteophytes, cysts, attrition and sclerosis (femur central, tibial central), meniscus (body), collateral ligaments, bone marrow edema |
| Plane | Sagittal | Axial | Coronal | Sagittal | Sagittal | Sagittal | Coronal | Coronal |
| Fat Sat | Yes | Yes | No | Yes | Yes | YES | STIR | CHES |
| Matrix (phase) | 260 | 286 | 340 | 320 | 320 | 320 | 256 | 320 |
| Matrix (freq) | 320 | 384 | 384 | 384 | 384 | 384 | 320 | 384 |
| FOV (mm) | 200 | 120 | 140 | 140 | 140 | 140 | 140 | 140 |
| Slice thickness (mm) | 4 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Skip (mm) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Flip Angle (deg) | 180 | 180 | 180 | 180 | 180 | 180 | 180 | 180 |
| ETL | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Bandwidth (Hz/pixel) | 210 | 205 | 350 | 195 | 230 | 230 | 205 | 200 |
| TE/TI (ms) | 60 | 26 | 9 | 27 | 10 | 9 | 9 | 9 |
| TR (ms) | 4500 | 3000 | 800 | 3000 | 800 | 3000 | 4500 | 4500 |

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| | # 9 2D MSME | # 10 2D MSME | # 11 3D FLASH VIBE | # 12 3D FLASH VIBE New* | # 13 3D FLASH VIBE New* | MPR of #13 | # 15 3D DESS | # 16 3D DESS | # 17 3D DESS (isotropic) | MPR of #17 |
|----------------------------|--|---|---|--|--|---------------|---|--|--|---------------|
| Weighting | T2 Map | T2 Map | FS-T1W | FS-T1W | FS-T1W | | FS-T2W | FS-T2W | FS-T2W | |
| Measure | Cartilage T2 (quantitative and semi- quantitative; patella); cartilage morphology (semi- quantitative patella); osteophytes, cysts, attrition and sclerosis (patella M/L, femur A/M/L, P/M/L) | Cartilage T2 (quantitative and semi- quantitative; entire knee); cartilage morphology (semi- quantitative entire knee); osteophytes, cysts, attrition and sclerosis (patella S/L, femur AS / PS), meniscus (A/P horns), cruciate ligaments | Cartilage morphology (femur central, tibia central); osteophytes, cysts, attrition (femur central, tibia central) | Cartilage morphology (femur central, tibia central); osteophytes, cysts, attrition (femur central, tibia central) | Cartilage morphology (entire knee); osteophytes (patellar S/L, femur AS / PS, tibia A/P) | | Cartilage morphology (femur central, tibia central); osteophytes, cysts, attrition (femur central, tibia central); cartilage T2 (semi- quantitative); meniscus (body); collateral ligaments | Cartilage morphology (entire knee); osteophytes, cysts, attrition (patellar S/L, femur AS / PS, tibia A/P); cartilage T2 (semi- quantitative); meniscus (A/P horns); collateral ligaments | Cartilage morphology (entire knee); osteophytes, cysts, attrition (patellar S/L, femur AS / PS, tibia A/P); cartilage T2 (semi- quantitative); meniscus (A/P horns); collateral ligaments | |
| Plane | Axial | Sagittal | Cor | Cor | Sag | Cor | Cor | Sag | Sag | Cor |
| Fat Sat | No | No | Yes | Yes | Yes | | WE | WE | WE | |
| Matrix (phase) | 240 | 240 | 512 | 384 | 384 | 384 | 320 | 320 | 320 | 320 |
| Matrix (freq) | 320 | 320 | 512 | 384 | 384 | | 384 | 384 | 320 | |
| FOV (mm) | 120 | 100 | 160 | 140 | 140 | 140 | 140 | 140 | 140 | 140 |
| Slice thickness (mm) | 3 | 3 | 1.5 | 0.7 | 0.7 | 1.5 | 0.7 | 0.7 | 0.5 | 1.5 |
| Skip (mm) | 3 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Flip Angle (deg) | 180 | 180 | 12 | 12 | 12 | | 25 | 25 | 25 | |
| ETL | 1 | 1 | 1 | 1 | 1 | | 1 | 1 | 1 | |
| Bandwidth (Hz/pixel) | 250 | 250 | 130 | 130 | 130 | | 185 | 185 | 210 | |
| TE/TI (ms) | 10, 20, 30, 40, 50, 60, 70, 80, 90 | 9, 18, 27, 36, 45, 54, 63, 72, 81 | 5.8 | 4.0 | 4.0 | | 4.7 | 4.7 | 4.2 | |
| TR (ms) | 1500 | 3000 | 11.6 | 10.3 | 9.7 | | 16.3 | 16.3 | 14.7 | |

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Table 2: Results of subjective expert review for cartilage quantitation and visual semi-quantitative and qualitative scoring for MR acquisitions detailed in Table 1.

| Scan | Anatomic coverage | Artifacts | | | | | Homogeneity | Results Artifacts | |
|--|-------------------|-----------|--------------------|-----------------|----------------|------|-------------|-------------------|------|
| | | Metallic | Vascular pulsation | Fat Suppression | Chemical Shift | Wrap | | SUM | Mean |
| SAG T2 FS | 2 | 0 | 2 | 1 | 1 | 0 | 1 | 4 | 1 |
| SAG T1W 3D VIBE FS | 2 | 0 | 0 | 0 | 0 | 0 | 2 | 1 | 0 |
| COR T1W 3D FLASH FS | 2 | 0 | 0 | 0 | 0 | 0 | 2 | 1 | 0 |
| SAG T2 MAP | 2 | 0 | 1 | 0 | 1 | 1 | 2 | 3 | 1 |
| AXIAL T2 MAP | 1 | 0 | 0 | 0 | 1 | 0 | 2 | 1 | 0 |
| COR MPR Sag DESS | 2 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 |
| SAG IW TSE FS 3000-30 | 2 | 0 | 1 | 0 | 0 | 0 | 2 | 2 | 0 |
| SAG TSE T1W FS 800 10 | 2 | 0 | 1 | 0 | 1 | 0 | 2 | 2 | 0 |
| COR T1W 800 9.5 | 2 | 0 | 1 | 0 | 1 | 0 | 2 | 2 | 0 |
| COR PD FS 3000 10 | 2 | 0 | 1 | 0 | 0 | 0 | 2 | 1 | 0 |
| STIR COR PD | 2 | 0 | 1 | 0 | 0 | 0 | 2 | 1 | 0 |
| AXIAL IW TSE FS 3000-30 | 2 | 0 | 1 | 0 | 0 | 0 | 2 | 1 | 0 |
| SAG 3D DESS WE | 2 | 0 | 0 | 1 | 0 | 1 | 2 | 1 | 0 |
| COR 3D DESS WE | 2 | 0 | 0 | 1 | 0 | 1 | 2 | 1 | 0 |
| COR T1W 3D VIBE FS | 2 | 0 | 0 | 0 | 0 | 1 | 2 | 1 | 0 |
| COR T1W 3D FLASH FS | 2 | 0 | 0 | 0 | 0 | 1 | 2 | 1 | 0 |
| SAG 3D DESS WE ISOTROPIC | 2 | 0 | 0 | 0 | 0 | 1 | 2 | 1 | 0 |
| Anatomical Coverage | | | | | | | | | |
| Homogeneity | | | | | | | | | |
| Artifacts | | | | | | | | | |
| 0 = not acceptable, 1 = acceptable, 2 = excellent | | | | | | | | | |
| 0 = not acceptable, 1 = acceptable, 2 = excellent | | | | | | | | | |
| 0 = none, 1 = present but insignificant, 2 = 1 structure obscured, 3 = >1 but not all structures obscured, | | | | | | | | | |
| 4 = all structures obscured | | | | | | | | | |
| | N/A | | | | | | | | |
| | Inadequate | | | | | | | | |
| | Borderline | | | | | | | | |
| | Adequate | | | | | | | | |
| | Excellent | | | | | | | | |

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| Scan | Structural Discrimination | | | | | | | | | | Results |
|--------------------------------|--|---------------|--------------------------|--------------------|---------------------|-------------|--------------|------------|------|-----------|---------|
| | Cartilage-Fluid | Cartilage-Fat | Cartilage-Capsule/Muscle | Cartilage-Meniscus | Cartilage-Cartilage | Osteophytes | Marrow Edema | Bone Cysts | Mean | Cartilage | Media n |
| SAG T2 FS | 8 | 6 | 7 | 8 | 6 | 5 | **** | **** | 7 | 7 | 7 |
| SAG T1W 3D VIBE FS | 5 | 9 | 4 | 5 | 4 | 9 | **** | **** | 5 | 5 | 5 |
| COR T1W 3D FLASH FS | 7 | 9 | 6 | 7 | 5 | 9 | **** | **** | 7 | 7 | 7 |
| SAG T2 MAP | 8 | 10 | 8 | 10 | 6 | **** | n/a | n/a | 9 | 9 | 8 |
| AXIAL T2 MAP | 9 | 10 | 9 | n/a | 6 | **** | n/a | n/a | 8 | 8 | 9 |
| COR MPR Sag DESS | 6 | 9 | 5 | 5 | 3 | **** | **** | **** | 6 | 5 | 5 |
| SAG IW TSE FS 3000-30 | 9 | 8 | 8 | 10 | 7 | 7 | **** | **** | 8 | 8 | 8 |
| SAG TSE T1W FS 800 10 | 3 | 9 | 7 | 9 | 4 | 8 | **** | **** | 6 | 7 | 7 |
| COR T1W 800 9.5 | 2 | 9 | 5 | 9 | 4 | 7 | n/a | n/a | 6 | 5 | 5 |
| COR PD FS 3000 10 | 8 | 8 | 7 | 9 | 8 | 7 | **** | **** | 8 | 8 | 8 |
| STIR COR PD | 8 | 5 | 5 | 7 | 7 | 5 | **** | **** | 6 | 7 | 7 |
| AXIAL IW TSE FS 3000-30 | 10 | 8 | 7 | n/a | 7 | 6 | **** | **** | 8 | 7 | 7 |
| SAG 3D DESS WE | 9 | 9 | 8 | 9 | 8 | 10 | **** | **** | 9 | 9 | 9 |
| COR 3D DESS WE | 9 | 9 | 7 | 9 | 7 | 10 | **** | **** | 8 | 9 | 9 |
| COR T1W 3D VIBE FS | 6 | 9 | 6 | 5 | 3 | 10 | **** | **** | 6 | 6 | 6 |
| COR T1W 3D FLASH FS | 7 | 9 | 5 | 7 | 4 | 10 | **** | **** | 6 | 7 | 7 |
| SAG 3D DESS WE ISOTROPIC | 8 | 9 | 8 | 8 | 7 | 10 | **** | **** | 8 | 8 | 8 |
| Coronal MPR SAG DESS ISOTROPIC | 9 | 10 | 8 | 8 | 7 | **** | **** | **** | 8 | 8 | 8 |
| Anatomical Coverage | 0 = not acceptable, 1 = acceptable, 2 = excellent | | | | | | | | | | |
| Homogeneity | 0 = not acceptable, 1 = acceptable, 2 = excellent | | | | | | | | | | |
| Artifacts | 0 = none, 1 = present but insignificant, 2 = 1 structure obscured, 3 = >1 but nor all structures obscured, 4 = all structures obscured | | | | | | | | | | |
| Structural Discrimination | 0-2 = inadequate, 3-5 = borderline, 6-8 = adequate, 9-10 = excellent; N/A (feature not present) | | | | | | | | | | |
| N/A | | | | | | | | | | | |
| Inadequate | | | | | | | | | | | |
| Borderline | | | | | | | | | | | |
| Adequate | | | | | | | | | | | |
| Excellent | | | | | | | | | | | |
| **** | Features not present in subject image series. | | | | | | | | | | |

Appendix F. Knee MRI Sequence Parameters

| | | 2D TSE | 3D DESS | 2D TSE | 3D FLASH | 2D MSME | Thigh Axial |
|-----------------------------------|--|--|--|--|---|--|--|
| Weighting | | Int | T2* | Int | T1W | T2 Map | Int |
| Plane | | Coronal | Sag | Sagittal | Cor | Sagittal | Axial |
| Fat Sat | | No | WE | Yes | WE | No | No |
| Matrix (phase) | | 307 | 307 | 313 | 512 | 269 | 512 |
| Matrix (freq) | | 384 | 384 | 448 | 512 | 384 | 512 |
| No. of slices | | 41 | 160 | 37 | 80 | 21 | 15 |
| FOV (mm) | | 140 | 140 | 160 | 160 | 120 | 500 |
| Phase FOV (%) | | 100 | 100 | 100 | 100 | 100 | 50 |
| Slice thickness (mm) | | 3 | 0.7 | 3 | 1.5 | 3 | 5 |
| Skip (mm) | | 0 | 0 | 0 | 0 | 0.5 | 0 |
| Flip Angle (deg) | | 180 | 25 | 180 | 12 | n/a | 90 |
| TE/T1 (ms) | | 29 | 4.7 | 30 | 7.57 | 10, 20, 30, 40, 50, 60, 70 | 10 |
| TR (ms) | | 3850 | 16.3 | 3200 | 20 | 2700 | 500 |
| BW (Hz/pixel) | | 352 | 185 | 248 | 130 | 250 | 199 |
| Chemical Shift (pixels) | | 1.3 | 0 | 0 | 0 | 1.8 | 2.2 |
| NAV (NEX) | | 1 | 1 | 1 | 1 | 1 | 1 |
| Echo train length | | 7 | 1 | 5 | 1 | 1 | 1 |
| Phase Encode Axis | | R/L | A/P | S/I | R/L | A/P | A/P |
| Phase Partial Fourier (8/8 = 1) | | 1 | 1 | 1 | 1 | 1 | 1 |
| Readout Partial Fourier (8/8 = 1) | | 1 | 1 | 1 | 1 | 1 | 1 |
| Slice Partial Fourier (8/8 = 1) | | 1 | 0.75 | 1 | 0.75 | 0.75 | 1 |
| Options: | | elliptical k-space filter and large FOV filter | elliptical k-space filter, elliptical sampling, large FOV filter | elliptical k-space filter and large FOV filter | elliptical scanning, elliptical k-space filter, larger FOV filter | elliptical k-space filter and large FOV filter | elliptical k-space filter and large FOV filter |
| Distance Factor (%) | | 0 | 0 | 0 | 0 | 16 | 0 |
| Phase Oversampling | | 20 | 0 | 40 | 0 | 0 | 0 |
| Slice Oversampling | | 0 | 10 | 0 | 0 | 0 | 0 |
| Phase Resolution | | 80 | 80 | 70 | 100 | 70 | 50 |
| Gradient Rise Time | | Fast | Fast | Fast | Fast | Fast | Normal |
| RF Amplitude | | Normal | Fast | Normal | Fast | Normal | Normal |
| X-Resolution (mm) | | 0.365 | 0.365 | 0.357 | 0.313 | 0.313 | 0.977 |
| Y-Resolution (mm) | | 0.456 | 0.456 | 0.511 | 0.313 | 0.446 | 0.977 |
| Scan time (min) | | 3.4 | 10.6 | 4.7 | 8.6 | 10.6 | 4.8 |

OAI Protocol Appendix F

Examples of assessments which can be performed using the OAI MR exam are:

1. Sagittal IW TSE with fat suppression enables identification of subarticular marrow edema and cysts as well as quantitation of the joint effusion. The large (20cm) imaging FOV covers the suprapatellar bursae as well as dissecting popliteal cysts. Additional assessments enabled by this acquisition include cartilage quality (signal heterogeneity / T2 lesion), marrow edema and cysts, anterior cruciate ligament (ACL), posterior cruciate ligament (PCL) as well as osteophytes (superior – inferior patella, anterior – posterior femur and tibia).
2. Sagittal 3D DESS with water excitation enables quantitation of cartilage volume over the entire knee (patellofemoral and femorotibial joints). Another primary use of the 3D DESS acquisition is to identify osteophytes in both the original sagittal (superior-inferior patella, anterior-posterior femur and tibia) as well as in the coronal (medial / lateral femur and tibia) and axial (medial-lateral patella) MPR. Secondly, it also potentially provides assessment of subarticular marrow edema and cysts both in the original sagittal plane as well as in the coronal (central femur and tibia) and axial (patella) MPR. This latter marrow assessment does not have proven sensitivity and specificity, but is presumed to be less sensitive than a fat suppressed IW or T2W.
3. Coronal T1W 3D FLASH with water excitation enables quantitation of cartilage volume over the central load bearing compartment of the knee (femorotibial joint). Another primary use of the 3D FL acquisition is to identify medial / lateral osteophytes on the femur and tibia in the original coronal plane. Secondly, it also potentially provides assessment of subarticular marrow edema and cysts in the coronal plane (central femur and tibia). This latter marrow assessment does not have proven sensitivity and specificity, but is presumed to be less sensitive than a fat suppressed IW or T2W.
4. Sagittal T2 map is a 7 echo sequence (every 10msec) acquired using a 12cm imaging FOV. The resulting image contrasts include PD, IW and T2W. These images enable assessment of subchondral bone (PD, T2W) for sclerosis, cysts and edema, the meniscal horns (PD), and for cartilage morphology and quality (PD, IW and T2W).
5. Coronal IW TSE enables assessment of the medial collateral ligament (MCL), lateral collateral ligament (LCL), osteophytes and cysts (medial - lateral central femur and central tibia), sclerosis (central femur and tibia), and the meniscal body.

Appendix G. Biological Specimen Collection and Aliquoting Scheme

The amount of each type of specimen to be collected and the aliquoting schemes, by visit, are detailed below.

Table 1. Baseline blood and urine collection and aliquoting

| | Matrix/ Cells | Volume/ Tubes | Yield | Aliquots (2 mL) | Aliquots (0.5 mL) | Total Cryovials |
|---|--------------------------|---|-------------------------------------|----------------------------|------------------------------|----------------------------|
| 78 mL blood drawn (through 7/04) | Serum | 52 mL blood (no anticoag.) 4 x 13 mL | 25 mL serum | 10 x 2 mL aliquots | 10 x 0.5 mL aliquots | 20 cryovials |
| 79.5 mL blood drawn (after 7/04) | Serum | 53.5 mL blood (no anticoag.) 5 x 9.5 mL + 1 x 6 mL | 25 mL serum | 10 x 2 mL aliquots | 10 x 0.5 mL aliquots | 20 cryovials |
| | Plasma | 17 mL blood (EDTA) 1 x 10 mL + 1 x 7 mL | 8 mL EDTA plasma | | 16 x 0.5 mL aliquots | 16 cryovials |
| | Buffy coat | Buffy coat from EDTA plasma tubes | 0.5-1.0 mL buffy coat (PBMCs) | 1 x 2 mL aliquot | | 1 cryovial |
| | Citrated Plasma | 9 mL blood (CPT tube) 2 x 4.5 mL | 4.5 mL citrated plasma | | 9 x 0.5 mL aliquots | 9 cryovials |
| | Buffy coat | Buffy coat from CPT tubes | 0.5-1.0 mL buffy coat (PBMCs) | 1 x 2 mL aliquot | | 1 cryovials |
| 26 mL urine obtained | Urine | 26 mL | 26 mL | 13 x 2 mL aliquots | | 13 cryovials |
| Grand Total | | 8 (through 7/04), 10 (after 7/04) | | | | 60 cryovials |

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Table 2. Interim 6 Month follow-up visit blood and urine collection and aliquoting

| | Matrix/ Cells | Volume/ Tubes | Yield | Aliquots (2 mL) | Aliquots (0.5 mL) | Total Cryovials |
|-------------------------------------|--------------------------|---|-------------------------------------|----------------------------|------------------------------|----------------------------|
| 33.5 mL blood drawn | Serum | 19 mL blood (no anticoag.) 2 x 9.5 mL | 9 mL serum | 2 x 2 mL aliquots | 10 x 0.5 mL aliquots | 12 cryovials |
| | Plasma | 10 mL blood (EDTA) 1 x 10 mL | 4.5 mL EDTA plasma | | 9 x 0.5 mL aliquots | 9 cryovials |
| | Buffy coat | Buffy coat from EDTA plasma tube | 0.5-1.0 mL buffy coat (PBMCs) | 1 x 2 mL aliquot | | 1 cryovial |
| | Citrated Plasma | 4.5 mL blood (CPT tube) 1 x 4.5 mL | 2.5 mL citrated plasma | | 5 x 0.5 mL aliquots | 5 cryovials |
| | Buffy coat | Buffy coat from CPT tube | 0.5-1.0 mL buffy coat (PBMCs) | 1 x 2 mL aliquot | | 1 cryovials |
| 26 mL urine obtained | Urine | 26 mL | 26 mL | 13 x 2 mL aliquots | | 13 cryovials |
| Grand Total | | 4 draw tubes | | | | 41 cryovials |

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Table 3. 12 Month follow-up blood and urine collection and aliquoting

| | Matrix/ Cells | Volume/ Tubes | Yield | Aliquots (2 mL) | Aliquots (0.5 mL) | Total Cryovials |
|-------------------------------------|--------------------------|--|-------------------------------------|----------------------------|------------------------------|----------------------------|
| 56 mL blood drawn | Serum | 34.5 mL blood (no anticoag.) 3 x 9.5 mL + 1 x 6mL | 15 mL serum | 5 x 2 mL aliquots | 10 x 0.5 mL aliquots | 15 cryovials |
| | Plasma | 10 mL blood (EDTA) 1 x 10 mL | 4.5 mL EDTA plasma | | 9 x 0.5 mL aliquots | 9 cryovials |
| | Buffy coat | Buffy coat from EDTA plasma tube | 0.5-1.0 mL buffy coat (PBMCS) | 1 x 2 mL aliquot | | 1 cryovial |
| | Citrated Plasma | 9 mL blood (CPT tube) 2 x 4.5 mL | 4.5 mL citrated plasma | | 9 x 0.5 mL aliquots | 9 cryovials |
| | Buffy coat | Buffy coat from CPT tubes | 0.5-1.0 mL buffy coat (PBMCS) | 1 x 2 mL aliquot | | 1 cryovials |
| | PAXgene | 2.5 mL 1 x 9.5 mL (~ 7 mL reagent) | RNA to be extracted | NA | NA | Tube archived |
| 26 mL urine obtained | Urine | 26 mL | 26 mL | 13 x 2 mL aliquots | | 13 cryovials |
| Grand Total | | 8 draw tubes | | | | 48 cryovials |

OAI Protocol Appendix G

Table 4. 24 Month follow-up blood and urine collection and aliquoting

| | Matrix/ Cells | Volume/ Tubes | Yield | Aliquots (2 mL) | Aliquots (0.5 mL) | Total Cryovials |
|-------------------------------------|--------------------------|--|-------------------------------------|----------------------------|------------------------------|----------------------------|
| 53.5 mL blood drawn | Serum | 34.5 mL blood (no anticoag.) 3 x 9.5 mL + 1 x 6mL | 15 mL serum | 5 x 2 mL aliquots | 10 x 0.5 mL aliquots | 15 cryovials |
| | Plasma | 10 mL blood (EDTA) 1 x 10 mL | 4.5 mL EDTA plasma | | 9 x 0.5 mL aliquots | 9 cryovials |
| | Buffy coat | Buffy coat from EDTA plasma tube | 0.5-1.0 mL buffy coat (PBMCS) | 1 x 2 mL aliquot | | 1 cryovial |
| | Citrated Plasma | 9 mL blood (CPT tube) 2 x 4.5 mL | 4.5 mL citrated plasma | | 9 x 0.5 mL aliquots | 9 cryovials |
| | Buffy coat | Buffy coat from CPT tubes | 0.5-1.0 mL buffy coat (PBMCS) | 1 x 2 mL aliquot | | 1 cryovials |
| 26 mL urine obtained | Urine | 26 mL | 26 mL | 13 x 2 mL aliquots | | 13 cryovials |
| Grand Total | | 7 draw tubes | | | | 48 cryovials |

Appendix H. Minimum Baseline Data Requirements

1. Biospecimens

The minimum blood requirements for enrollment in the study are:

- one full draw tube and at least partial filling of the second draw tube of serum, and
- one full draw tube of the other blood specimen types (EDTA, citrated plasma).

Operationally, this will be determined based on the number of cryovials filled. For citrated plasma: 5 cryovials (21-24 filled and 25 at least partially filled); EDTA plasma: 9 cryovials (31-38 filled and 39 at least partially filled); serum: 11 cryovials (01-10 filled and 11 at least partially filled).

One half of the complete urine collection is enough for the participant to be enrolled. Operationally, this would be 7 cryovials (48-53 filled and 54 at least partially filled). The minimum biospecimen requirements must be obtained within **3 months** of the Enrollment Visit (EV). If possible, it is recommended that participants return within the window of 7-10 days to complete the biospecimen collection.

2. Baseline screening knee x-ray

The minimum requirement is for an acceptable quality baseline fixed flexion knee x-ray. An acceptable quality fixed flexion knee x-ray must be obtained within **6 months** of the EV.

If a participant does not meet this requirement within the time limitation, an exception can only be made if both native knees can be adequately assessed, as determined by a central reader, for osteophytes and joint space narrowing for determination of cohort assignment and exclusions.

3. Baseline knee MRI

The minimum requirements are:

- All participants must have an acceptable quality SAG 3D DESS WE in at least one knee.
- Progression cohort participants must also have an acceptable COR IW TSE and SAG IW TSE sequence in the same knee as an acceptable SAG 3D DESS WE.

An acceptable minimum set of MRI sequences must be obtained within **3 months** of the EV.

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Even if a participant meets the minimum MRI requirements, a site PI may decide that a participant should no longer be eligible based on the advice of the site MRI be obtained within **6 months** of the EV.

If a participant does not meet this requirement within the time limitation, an exception can only be made if both native knees can be adequately assessed, as determined by a central reader, for osteophytes and joint space narrowing for determination of cohort assignment and exclusions.

4. Criteria for unacceptable baseline imaging

Fixed flexion knee x-ray:

- Missing part of the joint (anatomical coverage)
- Beads of SynaFlexer not included
- Incorrect beam angle (i.e. not 10 degrees)
- Image quality makes either joint space or osteophytes unreadable (i.e. due to excessive motion, under/over exposure, grossly incorrect beam centering, etc)

SAG 3D DESS sequence for cartilage volume:

- Cartilage cannot be measured (due to incomplete anatomical coverage, severe motion, severe heterogeneity of fat suppression)
- Sequence is missing

COR IW TSE and SAG IW TSE FS:

- Severe motion
- Incomplete anatomic coverage
- Severe heterogeneity of fat suppression (on SAG IW TSE FS)
- Sequence is missing

Appendix I

Research Data Management System

For the Osteoarthritis Initiative

Overview

The UCSF (Coordinating Center) CC will implement its standardized Research Data Management System (RDS) 4.0 for multi-center studies, a customized hybrid of off-the shelf software that combines decentralized data submission, centralized and remote data editing, and a centralized database structure designed to collect, transfer, and store data for multi-center clinical research.

In this system, data will be collected and transmitted to the CC by remote clinical sites. After the data are received (electronically) by the Coordinating Center, they will be assessed via automated and manual processes and then written to the study database. Every hour during business hours, queries (data discrepancies) will be generated to identify potential errors in the study data. These query results will be immediately accessible via a secure study web site so that clinic staff can resolve them in a timely manner. When appropriate, sites will audit data in real-time via the web site, which automatically generates a full audit trail. Non-UCSF collected data, such as reading center or core lab data, will be integrated into the system as appropriate for study use. After data collection and real-time query resolution, data will be further reviewed for quality and cleanliness using SAS prior to periodic database lock. Study data will be maintained in concordance with FDA regulations after study completion as outlined by UCSF CC Standard Operating Procedures (SOP's).

Data system design

The UCSF CC standardized research data management system (RDS) will provide flexible and easy entry of data from a variety of data forms (CRFs) and ensure timely data discrepancy identification and resolution to facilitate easy transformation of data to appropriate formats for data viewing, reporting, and analysis.

Study data for OAI will reside on a dedicated SQL Server, within a defined OAI database. In this database, forms data (CRFs) will be stored using WYSIWYG (What You See Is What You Get) tables. These tables mimic the format of each CRF, with no restructuring of data required. Specifically, each database table will be a mirror of the structure of a corresponding CRF, with each data point laid out in successive rows and columns. Thus, each table will correspond to a CRF, each row to a unique CRF, and each column in the table to a particular field on the CRF.

The OAI database will also house data describing the forms data ("metadata") in supporting database tables. Separate metadata tables will include information about the study clinics and identifier ranges, study visits and required forms at each visit, database users, and variable information. The variable information table (also called a data dictionary) will contain information on every data field collected in the study, including variable type, question description, location within the CRF, and discrepancy identification parameters (query creation criteria). The database will also include tables related to the process of data discrepancy resolution, such as a listing of all discrepancies generated by the CC, and a comprehensive audit trail. Each record in the audit trail will contain information corresponding to one unique change made to study data. Using this audit trail, the CC will be able to automate the rollback process to produce a study database corresponding to a particular point in time.

OAI PROTOCOL APPENDIX I

Reporting and analysis database In order to facilitate data reporting, analysis and incorporation of outside data streams, the CC will employ an "entry/reporting" database model. OAI data will be extracted for release from the source SQL database and processed thorough a series of validated SAS programs to a second locked database which is used for reporting and analysis. During this process, datasets will be merged and transposed, and new variables created (e.g. calculated variables), to provide data more usable for analysis and reporting. This will be a one way automated process, so that the SQL source data will remain pristine irrespective of the nature of the transformation process. Non-UCSF data streams will enter the UCSF system in a similar manner, transformed from their native format to SAS datasets via validated SAS programs. Consequently, the resulting analysis and reporting database will be a complete repository of OAI study data appropriate for access via the OAI study web site. Use of this approach will allow the end user to access the data without having to deal with the complexity or delay associated with the merging of WYSIWYG tables or creation of new variables.

Coordinating Center hardware and software

The UCSF CC system currently runs on a Microsoft NT network with the following software installed: Microsoft SQL Server 2000, Microsoft web server (IIS5), Cardiff Teleform Enterprise Edition, and SAS v9.

System validation and SOP's

The core OAI data systems at the CC are in the process of becoming 021 CFR Part 11 (Electronic Records and Electronic Signatures Regulation) compliant.

The UCSF CC Data Management Group will follow Standard Operating Procedures approved by the Coordinating Center Executive Committee. These SOPs cover all aspects of the data management system, including System Setup and Installation, Data Collection and Handling, System Maintenance, System Backup, Recovery and Contingency Plans, Computer System Security, and Change Control. In following our validation procedures, we provide assurance that the system will meet the CC's own requirements for completeness, accuracy, confidentiality, and reliability of data within the system, as well as the applicable regulatory requirements.

Data input and editing

In the OAI study data management system, data input and cleaning (editing) will consist of three components. Each component will either read or write to the Microsoft SQL Server OAI database:

- The **data collection, input and verification component** will consist of data forms (CRFs) developed using Cardiff Software's Teleform product, electronic data submission and verification with Cardiff Software's Verifier product.
- The **data querying component** will consist of a custom program that uses appropriate metadata tables in the OAI study database to identify potential discrepancies (as queries) in study data. The queries will be written to a query output table in the database.
- The **edit reporting/data access component** will consist of a number of custom-written active server pages (ASP) that:
 - use the World Wide Web to display the results of the data querying component
 - provide the user a means to access the database and make changes to the data.

OAI PROTOCOL APPENDIX I

Data collection, input and verification

All the data collection instruments will be machine-readable using Cardiff Teleform Software, making each form electronically submittable via a scanner, or screen enterable via the web. All data forms and questionnaires (including coding and data entry) will be validated prior to implementation to ensure clarity, efficiency and reliability of the instruments.

Once forms have been tested and validated, they will be distributed to OAI study sites. There, scannable forms will be manually completed and then submitted to the CC via scan. Immediately after the appropriate CC server receives a scanned form, Teleform's Reader product will automatically "evaluate" it (the software identifies the form and attempts to read the data). The reader will automatically reject forms with corrupt images (e.g. partially scanned). The UCSF CC will not receive any paper forms in the process of data submission.

When "evaluation" is completed, the form is ready for "verification" for which a CC operator will run Teleform's Verifier product. During verification, the operator will have the opportunity to view all data interpreted by the software and correctly enter any data in fields that the software has had difficulty interpreting. Once a form has been verified, the system will write its data to a "holding" database table. A SQL trigger will then checks for duplicate forms, incorrect identifier information and other specified acceptance criteria prior to automatic insertion in the final form database table.

Data querying and editing

Every hour during the day, the UCSF CC query generator application will examine the OAI database looking for data discrepancies within-forms and across many forms.

Data Tracking, Cleaning, and Edit Reports (Web site)

All OAI data tracking, cleaning, and reporting will be done via a secure study website housed on a UCSF CC web-server running Internet Information Server 5.0. All users of the site, including UCSF CC personnel must have accounts on a specified Windows NT domain.

Forms Tracking Reports Once a data collection form is received by the system, study personnel are able to use several forms tracking reports to view submitted data, or locate missing data (forms). These reports will allow the user to find a form based on identifier, form, or time criteria. A listing of outstanding forms by visit will be generated in real-time, and a list of forms that have been rejected by the system displayed along with the reason for rejection.

Data Query Tables and Data Edits The contents of the data query table will be displayed on the web site via an active server page. This screen will serve as the gatekeeper for access to the database. If a user chooses to address a particular problem, he/she will click on the line that contains the problem of interest and then update the data. All changes will be saved to the database and to an additional audit table

Real Time Audit Trail The audit table generated during the editing process will contain a record of each change made, regardless of whether the change is made via the edits interface or directly to the backend table. Each record in the audit trail will contain the date of the change, username of person making the

OAI PROTOCOL APPENDIX I

change, date the change was made to the database, old and new value of data point changed, and the reason for the change.

Incorporation and management of Reading Center and Core Lab data

The design of the OAI data system will facilitate incorporation and cleaning of data from outside sources.

Data will be transmitted to the UCSF CC from each outside source as outlined in a transfer-specific Data Transmission Agreement (DTA).

Data quality control and verification

As described above, the UCSF CC will implement its standard multi-step approach for data verification and quality control, including:

- 100% visual verification at the CC of all data values as interpreted by Cardiff Teleform Reader optical character recognition (OCR) against scanned images of the completed source data collection forms
- Data form specific insertion criteria (via SQL triggers) to prevent duplicate or incorrectly identified form entry
- Missing forms reports based on temporal or logical relationships, generated by a batch Visual Basic application (These reports will be made available on the OAI study web site.);
- Comprehensive univariate and multivariate field discrepancy identification by a query generation application (These queries involve within-form and cross-form comparisons and will appear on the study web site for real-time resolution.);
- A complete audit trail of all changes made to the study database;
- Complex and resource intensive second-tier data cleaning in SAS.

SAS data cleaning, release datasets and documentation

The UCSF CC will utilize SAS for “second tier” data cleaning, data quality control, data management, and statistical analysis. With respect to data cleaning, SAS will be utilized to identify discrepancies which may be too complex for the batch query application, or too resource-intensive to run frequently. When appropriate, discrepancies identified in SAS data cleaning will result in editing on the SQL database.

The release datasets, which are appropriate for analysis, will be created in SAS v9. These files will differ from the source raw SQL data in that they will include additional variables, such as calculated or composite variables. These variables will be defined by UCSF CC and OAI study investigators during the planning and early implementation phases of the project. The analysis files will also differ from the source SQL data in that they are composite data sets, resulting from the complex merging of SQL data to provide data more appropriate for analysis (e.g. longitudinal results). In addition to the analysis files themselves, extensive documentation about each file will be provided. This includes a general description of the data, information on the source of each variable, information on the data set structure

OAI PROTOCOL APPENDIX I

and contents, data set index formulation and key variable mapping, and general strategies for manipulating and merging the data.

System Security

The Coordinating Center maintains and complies with SOPs for computer system security to ensure the confidentiality and validity of OAI data. These SOPs are designed to prevent unauthorized access and limit authorized access to our computer systems, and are in compliance with established standards for Information Technology Security. Physical and logical security of the computer system at all levels are covered by the UCSF Security SOPs.

Security at UCSF

All study data will be housed at the UCSF CC in a secure server room. The building will be locked outside of normal business hours. All system servers are located in a limited access suite fitted with an Access Control System. Within the locked suite is a locked server room fitted with an additional secure door. Only critical Information Systems staff will possess the access code required to enter the room. All who enter the system server room will sign a server room access log in accordance with UCSF IT Security SOPs.

Study database access will be controlled via two-factor password security. Development workstation access will be controlled via Microsoft NT logon. Once a workstation is accessible, access to the study data on the SQL server via any development application will require appropriate logon-specific permission assigned in SQL Security Manager. Only two system administrators will have administrative access to system servers. Communication between study servers and client machines on the UCSF network will be encrypted at the 128-bit level using an SSL certificate issued by Verisign. All servers will be protected from viruses by Network Associates Virusscan 7.x. This software will automatically check for virus signature file updates from a Network Associates FTP site once an hour, and if necessary will directly update itself. All anti-virus software will be monitored and network personnel notified in the event that the software stops functioning on a given server.

Security Outside of UCSF

Data submission to UCSF CC

Data from the clinics will be transferred to the CC by means of a scanner (converts paper form to an image) and a secure connection to the CC network. Peer Sync software at the Clinic will track and move the scanned images into a directory on the CC network via a password protected secure web gateway. Secure remote access to this website will be provided by a Virtual Private Network (VPN) connection which sits behind the network firewall. All transmissions will be encrypted with SSL.

Web site access The OAI study web sites are protected by two hardware-based firewalls to shape incoming and outgoing traffic. Access to the study management web site is restricted to approved personnel only. Approved personnel gain access to the system using 2-factor authentication. These factors include a Windows domain account password and a username. A log of all personnel with level of access is kept and updated regularly as outlined by UCSF CC SOPs. Once a clinic site user accesses

OAI PROTOCOL APPENDIX I

the system they will only be permitted to view data received from their site, with the exception of official aggregate reports. Users will not be permitted to view or alter another clinic's data.

Data transmission from web server to client. The UCSF CC currently utilizes a VeriSign™ (the leading certificate authority) 128-bit Secure Socket Layer (SSL) which will protect all study data transmissions sent over the Internet between the CC IIS Web Server and every client machine which accesses our study web sites.

System Backup

The OAI study database will be backed up nightly, using the SQL Server 2000 “Database Maintenance Plan,” to a file server that is in turn backed up nightly by recovery software and then saved to tape every three days. This process is essentially Disk to Disk to Disk to Tape. Tapes will be taken off site twice a month.

Additionally, specific procedures to fully restore the system in the event of partial or complete system failure (e.g. building destroyed) are outlined in validation documentation as dictated by UCSF CC SOPs.

Appendix J.
MRI Safety Screening Forms

Baseline

MRI Safety Screening Interview
MRI Knee Coil Size Screen
MRI Bore Size Screen
Final MRI Eligibility Assessment

Follow-up

Prescreener for MRI Safety
MRI Safety Screener



36886



| OAI Participant ID # | Acrostic | Staff ID# |
|----------------------|----------------------|----------------------|
| <input type="text"/> | <input type="text"/> | <input type="text"/> |
| <input type="text"/> | <input type="text"/> | <input type="text"/> |
| <input type="text"/> | <input type="text"/> | <input type="text"/> |
| <input type="text"/> | <input type="text"/> | <input type="text"/> |
| <input type="text"/> | <input type="text"/> | <input type="text"/> |

MRI SCREENING INTERVIEW

1 Have you ever had an MRI before?

☐ Yes

☐ No

☐ Don't know

☐ Refused

STOP. NOT ELIGIBLE.
Go to Page 29, Question #13.

a. Did you have any problems related to the MRI scan?

☐ Yes

☐ No

☐ Don't know

Please describe: _____

(Examiner Note: Determine if the reason makes participant NOT eligible for an MRI scan. If NOT ELIGIBLE, go to Page 29, Question #13.)

b. Were you able to complete the MRI scan?

☐ Yes

☐ No

☐ Don't know

Are you willing to have another MRI scan?

☐ Yes

☐ No

STOP. NOT ELIGIBLE.
Go to Page 29, Question #13.

i. Why weren't you able to complete the MRI scan?

Please describe: _____

(Examiner Note: Determine if the reason makes participant NOT eligible for an MRI scan. If NOT ELIGIBLE, go to Page 29, Question #13.)

ii. Are you willing to have another MRI?

☐ Yes

☐ No

STOP. NOT ELIGIBLE.
Go to Page 29, Question #13.

2 Would you be able to lie on your back for 1 1/2 hours for an MRI scan?

(Examiner Note: If participant responds "Don't know," probe for additional information.)

☐ Yes

☐ No

☐ Don't know

☐ Refused

STOP. NOT ELIGIBLE.
Go to Page 29, Question #13.



| OAI Participant ID # | Acrostic |
|---|---|
| <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> | <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> |

MRI SCREENING INTERVIEW

- 3** Have you had any surgery in the past 3 months?
(**Examiner Note: Please ask participant the type of surgery they had in the past 3 months. Refer to the list of surgeries/procedures that do not require a 3-month wait. If the surgery or procedure does not require a 3-month wait, mark "No" and specify type of surgery below.**)

☐ Yes

☐ No

☐ Don't know

☐ Refused

a. When was the surgery?

| | | | | |
|---|---|---|---|---|
| <input type="text"/> <input type="text"/> | / | <input type="text"/> <input type="text"/> | / | <input type="text"/> <input type="text"/> |
| Month | | Day | | Year |

STOP. NOT ELIGIBLE.

Go to Page 29, Question #13.

Re-contact 3 months after surgery to reassess eligibility.

STOP. NOT ELIGIBLE.

Go to Page 29, Question #13.

Please specify type of surgery that does not require a 3-month wait: _____

- 4** Do you have claustrophobia?

(**Examiner Note: Only definite claustrophobia is a firm contraindication. True claustrophobia is relatively uncommon [2-3%]. Participants with claustrophobia will know who they are. Some may say they are uncomfortable in small spaces, but may tolerate MRI without difficulty. It is useful to make an attempt in persons who seem uncertain or who have mild concern.**)

☐ Yes

☐ No

☐ Don't know

☐ Refused

a. Are you willing to have an MRI?

☐ Yes

☐ No

STOP. NOT ELIGIBLE.

Go to Page 29, Question #13.

- 5** Please indicate if you currently have any of the following:

| | | | | |
|---|---------------------------|--------------------------|----------------------------------|-------------------------------|
| a. Hemostatic "Surgiclip" | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |
| b. Surgically implanted stent, filter, or coil | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |
| c. Shunt (spinal or intraventricular) | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |
| d. Vascular access port or catheter, such as a central venous catheter or PICC line | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |
| e. Electronic implant or device, such as a cochlear implant | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |
| f. Magnetically-activated implant or device, such as magnetically-activated dental implant or dentures, or magnetic eye implant | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |
| g. Heart pacemaker | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |
| h. Implanted heart defibrillator | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |



| OAI Participant ID # | Acrostic |
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MRI SCREENING INTERVIEW

Please indicate if you currently have any of the following:

| | | | | |
|---|---------------------------|--------------------------|----------------------------------|-------------------------------|
| i. Internal electrodes or wires, such as pacemaker wires or bone growth/bone fusion stimulator wires | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |
| j. Neurostimulation system, such as a spinal cord stimulator or gastric electrical stimulation system | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |
| k. Tissue expander, such as breast | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |
| l. Surgically implanted hearing device (not a regular hearing aid) or prosthesis in your ear | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |
| m. Surgically implanted insulin or drug pump | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |
| n. Eyelid spring, wire or weights | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |
| o. Inflatable breast implant with magnetic port <i>(women only)</i> | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |
| p. Penile implant or prosthesis <i>(men only)</i> | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |
| q. Tattoos on both knees | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |
| r. Severe breathing problem | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |
| s. Severe motion disorder, such as body tremor or Parkinsons | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |

6 Please indicate if you ever had any of the following:

| | | | | |
|---|---------------------------|--------------------------|----------------------------------|-------------------------------|
| a. Brain aneurysm surgery, aneurysm clip(s) or coil | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |
| b. Heart valve surgery | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |
| c. Injury in which metal fragments entered your eye and you had to seek medical attention | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |
| d. Injury by a metal object such as shrapnel or bullet | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |

(Examiner Note: Do not ask the following question.)

7 Are any of the above items in Question #5 (starting on Page 26) or Question #6 marked "Yes," "Don't know," or "Refused"?

☐ Yes

☐ No

STOP. NOT ELIGIBLE.

Go to Page 29, Question #13.



50602



| OAI Participant ID # | Acrostic |
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MRI SCREENING INTERVIEW

8 Please indicate if you have any of the following removable items:

| | | | | |
|--|---------------------------|--------------------------|----------------------------------|-------------------------------|
| a. Any type of artificial or prosthetic limb | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |
| b. Dentures or partial plates | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |
| c. Hearing aid | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |
| d. Diaphragm (women only) | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |
| e. Body piercing jewelry, such as earrings | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |
| f. Medication patch that your physician said is okay to remove, such as Nicotine, Nitroglycerine, Estrogen | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |

(Examiner Note: Do not ask the following question.)

9 Are any of the above items in Question #8 marked "Yes"?

☐ Yes

☐ No



(Examiner Note: Ask participant the following question.)

a. Are you able to remove the item for the MRI scan?

☐ Yes

☐ No



STOP. NOT ELIGIBLE.
Go to Page 29, Question #13.

Examiner Note: Please ask the participant to remove the item prior to MRI scan.

(Examiner Note: Do not ask the following question.)

10 Are any of the above items in Question #8 marked "Don't know" or "Refused"?

☐ Yes

☐ No



STOP. NOT ELIGIBLE.
Go to Page 29, Question #13.



27772



| OAI Participant ID # | Acrostic |
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MRI SCREENING INTERVIEW

11 Has a doctor ever told you that you should not have an MRI?

☐ Yes

☐ No

↓
STOP. NOT ELIGIBLE.

Please describe and then go to Question #13 below: _____

(Examiner Note: Do not ask the following question.)

12 Is there any other reason why this participant would not be eligible for an MRI?

☐ Yes

☐ No

↓
STOP. NOT ELIGIBLE.

Please describe and then go to Question #13 below: _____

(Examiner Note: Do not ask the following question.)

13 Based on this MRI Screening Interview, what is the participant's MRI eligibility status?

☐ Eligible for an MRI scan

☐ Not eligible for an MRI scan

↓
STOP. NOT ELIGIBLE.

Go to Page 38,
Question #4.





58681



| OAI Participant ID # | Acrostic | Staff ID# |
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MRI KNEE COIL SIZE SCREEN

1 Has participant had knee replacement surgery?

(Examiner Note: Do not ask the question. Please refer to Page 12, Question #26 and Page 15, Question #33.)

☐ Yes, right knee only

☐ Yes, left knee only

☐ Yes, both knees

☐ No

a. Does participant's left knee fit comfortably inside the knee coil with the coil completely closed?

☐ Yes ☐ No ☐ Refused

**STOP.
NOT ELIGIBLE.**
Go to Page 38,
Question #5.

**STOP.
NOT ELIGIBLE.**
Go to Page 39,
Question #10.

b. Does participant's right knee fit comfortably inside the knee coil with the coil completely closed?

☐ Yes ☐ No ☐ Refused

**STOP.
NOT ELIGIBLE.**
Go to Page 38,
Question #5.

**STOP.
NOT ELIGIBLE.**
Go to Page 39,
Question #10.

STOP. NOT ELIGIBLE.
Go to Page 39,
Question #10.

c. Do participant's knees fit comfortably inside the knee coil with the coil completely closed?

☐ Yes, right knee only ☐ Yes, left knee only ☐ Yes, both knees ☐ No ☐ Refused

**STOP.
NOT ELIGIBLE.**
Go to Page 38,
Question #5.

**STOP.
NOT ELIGIBLE.**
Go to Page 39,
Question #10.

MRI BORE SIZE SCREEN

2 Could MRI bore sizer pass over participant without obstruction?

☐ Yes

☐ No

☐ Refused

STOP. NOT ELIGIBLE.
Go to Page 38,
Question #6.

STOP. NOT ELIGIBLE.
Go to Page 39,
Question #10.





| OAI Participant ID # | Acrostic | Date Form Completed | Staff ID# |
|---|---|---|---|
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Baseline MRI status: ☐ First MRI scan ☐ Repeat MRI scan

What is your...?

[illegible]

First Name

7

M.I.

| | | | | | | | | | | | | | | |
|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|
| | | | | | | | | | | | | | | |
|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|

Last Name

(Examiner Note: Please ask participant the type of surgery they had in the past 3 months. Refer to the list of surgeries/procedures that do not require a 3-month wait. If the surgery or procedure does not require a 3-month wait, mark "No" and specify type of surgery below.)

☐ Yes

☐ No

☐ Don't know

☐ Refused

a. When was the surgery? (Examiner note: If participant unsure, please probe.)

Month / Day / Year

Month

Day

Year

STOP. NOT ELIGIBLE.

Go to Page 4, Question #10.

Re-contact 3 months after surgery to reassess eligibility.

STOP. NOT ELIGIBLE.

Go to Page 4, Question #10.

Please specify type of surgery that does not require a 3-month wait:

2 Please indicate if you currently have any of the following:

| | | | | |
|---|---------------------------|--------------------------|----------------------------------|-------------------------------|
| a. Hemostatic "Surgiclip" | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |
| b. Surgically implanted stent, filter, or coil | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |
| c. Shunt (spinal or intraventricular) | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |
| d. Vascular access port or catheter, such as a central venous catheter or PICC line | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |
| e. Electronic implant or device, such as a cochlear implant | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |
| f. Magnetically-activated implant or device, such as magnetically-activated dental implant or dentures, or magnetic eye implant | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |
| g. Heart pacemaker | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |
| h. Implanted heart defibrillator | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |



| OAI Participant ID # | Acrostic | Visit |
|--|---|--|
| <div><div></div><div></div><div></div><div></div><div></div><div></div><div></div></div> | <div><div></div><div></div><div></div><div></div></div> | <div><input type="radio"/> First scan</div> <div><input type="radio"/> Repeat scan</div> |

FINAL MRI ELIGIBILITY ASSESSMENT

Please indicate if you currently have any of the following:

| | | | | |
|---|---------------------------|--------------------------|----------------------------------|-------------------------------|
| i. Internal electrodes or wires, such as pacemaker wires or bone growth/bone fusion stimulator wires | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |
| j. Neurostimulation system, such as a spinal cord stimulator or gastric electrical stimulation system | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |
| k. Tissue expander, such as breast | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |
| l. Surgically implanted hearing device (not a regular hearing aid) or prosthesis in your ear | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |
| m. Surgically implanted insulin or drug pump | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |
| n. Eyelid spring, wire or weights | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |
| o. Inflatable breast implant with magnetic port | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |
| p. Penile implant or prosthesis (<i>men only</i>) | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |
| q. Tattoos on both knees | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |
| r. Severe breathing problem | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |
| s. Severe motion disorder, such as body tremor or Parkinsons | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |

3 Please indicate if you ever had any of the following:

| | | | | |
|---|---------------------------|--------------------------|----------------------------------|-------------------------------|
| a. Brain aneurysm surgery, aneurysm clip(s) or coil | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |
| b. Heart valve surgery | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |
| c. Injury in which metal fragments entered your eye and you had to seek medical attention | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |
| d. Injury by a metal object such as shrapnel or bullet | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |

(Examiner Note: Do not ask the following question.)

4 Are any of the above items in Question #2 (starting on Page 1) or Question #3 marked "Yes," "Don't know," or "Refused"?

☐ Yes

☐ No

STOP. NOT ELIGIBLE.
Go to Page 4, Question #10.



| OAI Participant ID # | Acrostic | Visit |
|---|---|--|
| <div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div></div> | <div><div></div><div></div><div></div><div></div></div> | <div><input type="radio"/> First scan</div> <div><input type="radio"/> Repeat scan</div> |

FINAL MRI ELIGIBILITY ASSESSMENT

5 Please indicate if you have any of the following removable items:

| | | | | |
|--|---------------------------|--------------------------|----------------------------------|-------------------------------|
| a. Any type of artificial or prosthetic limb | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |
| b. Dentures or partial plates | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |
| c. Hearing aid | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |
| d. Diaphragm (women only) | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |
| e. Body piercing jewelry, such as earrings | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |
| f. Medication patch that your physician said is okay to remove, such as Nicotine, Nitroglycerine, Estrogen | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |

(Examiner Note: Do not ask the following question.)

6 Are any of the above items in Question #5 marked "Yes"?

☐ Yes

☐ No

(Examiner Note: Ask participant the following question.)

a. Are you able to remove the item for the MRI scan?

☐ Yes

☐ No

STOP. NOT ELIGIBLE.
Go to Page 4, Question #10.

Examiner Note: Please ask the participant to remove the item prior to MRI scan.

(Examiner Note: Do not ask the following question.)

7 Are any of the above items in Question #5 marked "Don't know" or "Refused"?

☐ Yes

☐ No

STOP. NOT ELIGIBLE.
Go to Page 4, Question #10.



1725



| OAI Participant ID # | Acrostic | Visit |
|---|---|---|
| <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> | <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> | <input type="radio"/> First scan <input type="radio"/> Repeat scan |

FINAL MRI ELIGIBILITY ASSESSMENT

Examiner Note: Complete Question #8 for women only. For men, go to Question #9.

8 Did participant have a positive pregnancy test?

(Examiner Note: Do not ask the question. Please refer to the Data from Prior Visits Report for the Enrollment Visit to determine who requires a pregnancy test. If pregnancy test is required, consult with clinic examiner for test results.)

☐ Yes (positive test)

☐ No (negative test)

☐ Pregnancy test not required

☐ Participant refused test

STOP. NOT ELIGIBLE.
Go to
Question #10 below.

STOP. NOT ELIGIBLE.
Go to
Question #10 below.

(Examiner Note: Do not ask the following question.)

9 Is there any other reason why this participant would not be eligible for an MRI?

☐ Yes

☐ No

STOP. NOT ELIGIBLE.

Please describe and then go to Question #10 below: _____

(Examiner Note: Do not ask the following question.)

10 Based on the Final MRI Eligibility Assessment, what is the participant's MRI eligibility status?

☐ Eligible for an MRI scan

☐ Not eligible for an MRI scan

STOP. NOT ELIGIBLE.
Do not perform MRI scan.



42443



| OAI Participant ID # | Acrostic | Visit |
|--|---|---|
| <div><div></div><div></div><div></div><div></div><div></div><div></div><div></div></div> | <div><div></div><div></div><div></div><div></div></div> | <input type="radio"/> First scan <input type="radio"/> Repeat scan |



FINAL MRI ELIGIBILITY ASSESSMENT

10 The information recorded on Pages 1-4 is correct to the best of my knowledge.

a. Participant Name: _____

Participant Signature: _____

Date: / /
Month Day Year

b. MRI Technologist Name: _____

MRI Technologist Signature: _____

Date: / /
Month Day Year

c. Witness Name: _____

Witness Signature: _____

Date: / /
Month Day Year





17492



PRESCREENER FOR FOLLOW-UP VISITS

| Type of Follow-up Visit | OAI Participant ID # | Acrostic | Date Form Completed | Staff ID# |
|---|---|---|---|---|
| <input type="radio"/> 12-month <input type="radio"/> 24-month <input type="radio"/> 36-month <input type="radio"/> 48-month <input type="radio"/> Interim 6-month | <div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div></div> | <div><div></div><div></div><div></div><div></div><div></div><div></div></div> | <div><div></div><div></div></div> / <div><div></div><div></div></div> / <div><div></div><div></div><div></div><div></div></div> Month Day Year | <div><div></div><div></div><div></div><div></div></div> |

1. What is your...?

First Name

M.I.

Last Name

1a. Does the participant have a permanent MRI exclusion (refer to Data from Prior Visits Report) or did the participant refuse the MRI for this visit?

(Interviewer Note: If documentation that was not previously available is now available to confirm 3T MRI safety, mark "No" below and administer the entire Prescreener for Follow-up Visits.)

☐ Yes☐ No☐ Don't know

Go to Page 1, Question #2.

1b. Have you had any surgery within the past 2 months? Please include arthroscopy, endoscopy, and laparoscopy.

☐ Yes☐ No☐ Don't know☐ Refused

i. What type of surgery did you have?

(Interviewer Note: If participant had more than one surgery, please list all types.)

ii. When was this done?

(Interviewer Note: If participant had more than one surgery, please record the date of the most recent surgery. If participant unsure, please have them make their best guess.)

 / /
Month Day Year

(Interviewer Note: Do NOT ask the following question. Refer to the list of surgeries/procedures that do not require a 2-month wait.)

iii. Does this surgery or procedure require a 2-month wait before the participant comes to the clinic for their biospecimen collection?

☐ Yes☐ No

Recontact 2-months post-surgery.
Go to Question #1d.





| Type of Follow-up Visit | OAI Participant ID # | Acrostic |
|---|--|--|
| <input type="radio"/> 12-month <input type="radio"/> 24-month <input type="radio"/> 36-month <input type="radio"/> 48-month <input type="radio"/> Interim 6-month | <div style="border: 1px solid black; width: 100px; height: 30px; display: flex; justify-content: space-between;"> </div> | <div style="border: 1px solid black; width: 100px; height: 30px; display: flex; justify-content: space-between;"> </div> |

PRESCREENER FOR FOLLOW-UP VISITS

1c. Are you planning to have surgery within the next 2 months? Please include arthroscopy, endoscopy, and laparoscopy.

☐ Yes ☐ No ☐ Don't know ☐ Refused



i. What type of surgery are you going to have? _____

ii. What is the date of your surgery?
(Interviewer note: If participant unsure, please have them make their best guess.)

//

Month
Day
Year

(Interviewer Note: Do NOT ask the following question. Refer to the list of surgeries/ procedures that do not require a 2-month wait.)

iii. Does this surgery or procedure require a 2-month wait before the participant comes to the clinic for their biospecimen collection?

☐ Yes ☐ No



If follow-up visit and biospecimen collection cannot be scheduled before surgery, then recontact 2-months post-surgery.
 If follow-up visit and biospecimen collection can be scheduled before surgery, then schedule follow-up visit.
 Go to Question #1d.

1d. Does participant's follow-up clinic visit and biospecimen collection need to be delayed because of a recent surgery or an upcoming surgery?

(Interviewer note: Refer to Questions #1b-iii and #1c-iii.)

☐ Yes ☐ No



Stop interview.
 Recontact 2-months post-surgery.
 Record date participant should be recontacted.

//

Month
Day
Year

Stop interview.
 Schedule participant for follow-up visit and biospecimen collection.
 Go to Page 6, Question #9





60609



| Type of Follow-up Visit | OAI Participant ID # | Acrostic |
|---|--|--|
| <input type="radio"/> 12-month <input type="radio"/> 24-month <input type="radio"/> 36-month <input type="radio"/> 48-month <input type="radio"/> Interim 6-month | <div style="border: 1px solid black; width: 100px; height: 20px; display: flex; justify-content: space-between;"> </div> | <div style="border: 1px solid black; width: 100px; height: 20px; display: flex; justify-content: space-between;"> </div> |

PRESCREENER FOR FOLLOW-UP VISITS

2. Are you planning to have surgery or an operation within the next 2 months? Please include arthroscopy, endoscopy, and laparoscopy.

☐ Yes

☐ No

☐ Don't know

☐ Refused

Go to Page 2, Question #3.

NOT eligible for MRI.
Please go to Page 5, Question #8 and mark
"No. NOT eligible for an MRI scan."

a. What type of surgery are you going to have? _____

b. What is the date of your surgery?

(Interviewer note: If participant unsure, please have them make their best guess.)

| | | | | | | | |
|-------|--|---|-----|--|---|------|--|
| | | / | | | / | | |
| Month | | | Day | | | Year | |

(Interviewer Note: Do NOT ask the following question. Refer to the list of surgeries/procedures that do not require a 2-month wait.)

c. Does this surgery or procedure require a 2-month wait before an MRI scan?

☐ Yes

☐ No

If follow-up visit and MRI scan cannot be scheduled before surgery, go to Page 5, Question #8 and mark "No. Recontact 2-months post-surgery."
If follow-up visit and MRI can be scheduled before surgery, go to Page 2, Question #3.

Go to Page 2, Question #3.



24268



| Type of Follow-up Visit | OAI Participant ID # | Acrostic |
|---|--|--|
| <input type="radio"/> 12-month <input type="radio"/> 24-month <input type="radio"/> 36-month <input type="radio"/> 48-month <input type="radio"/> Interim 6-month | <div style="border: 1px solid black; width: 100px; height: 20px; display: flex; justify-content: space-between;"> </div> | <div style="border: 1px solid black; width: 100px; height: 20px; display: flex; justify-content: space-between;"> </div> |

PRESCREENER FOR FOLLOW-UP VISITS

3. Since your last MRI scan at the OAI clinic about [12 months ago][6 months ago], have you had any surgery or anything implanted in your body? Please include arthroscopy, endoscopy, and laparoscopy.

☐ Yes

☐ No

☐ Don't know

☐ Refused

Go to Page 4,
Question #5.

Go to Page 3,
Question #4.

NOT eligible for MRI.
Please go to Page 5, Question #8 and mark
"No. NOT eligible for an MRI scan."

- a. What type of surgery or implant did you have?

(Interviewer Note: If participant had more than one surgery, please list all types.)

- b. When was this done?

(Interviewer Note: If participant had more than one surgery, please record the date of the most recent surgery. If participant unsure, please have them make their best guess.)

//

Month
Day
Year

(Interviewer Note: Do NOT ask the following question.)

- c. Was this surgery or procedure within the past 2-months?

☐ Yes

☐ No

Go to Page 3, Question #4.

(Interviewer Note: Refer to the list of surgeries/procedures that do not require a 2-month wait.)

- i. Does the surgery or procedure require a 2-month wait before an MRI scan?

☐ Yes

☐ No

Please go to Page 5, Question #8 and mark
"No. Recontact 2-months post-surgery."

Go to Page 3, Question #4.





| Type of Follow-up Visit | OAI Participant ID # | Acrostic |
|---|--|--|
| <input type="radio"/> 12-month <input type="radio"/> 24-month <input type="radio"/> 36-month <input type="radio"/> 48-month <input type="radio"/> Interim 6-month | <div style="border: 1px solid black; width: 100px; height: 20px; display: flex; justify-content: space-between;"> </div> | <div style="border: 1px solid black; width: 100px; height: 20px; display: flex; justify-content: space-between;"> </div> |



PRESCREENER FOR FOLLOW-UP VISITS

| 4. Please indicate if you <u>have</u> any of the following: | | | | |
|---|----------------------------|--------------------------|-----------------------------------|--------------------------------|
| a. Stent, filter, coil, or clips | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |
| b. Shunt (spinal or intraventricular) | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |
| c. Vascular access port or catheter, such as a central venous catheter or PICC line | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |
| d. Electronic implant or device, such as a cochlear implant* | <input type="radio"/> Yes* | <input type="radio"/> No | <input type="radio"/> Don't know* | <input type="radio"/> Refused* |
| e. Magnetically-activated implant or device, such as magnetically-activated dental implant or dentures, or magnetic eye implant * | <input type="radio"/> Yes* | <input type="radio"/> No | <input type="radio"/> Don't know* | <input type="radio"/> Refused* |
| f. Surgically implanted hearing device (not a regular hearing aid) or prosthesis in your ear | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |
| g. Surgically implanted insulin or drug pump * | <input type="radio"/> Yes* | <input type="radio"/> No | <input type="radio"/> Don't know* | <input type="radio"/> Refused* |
| h. Internal electrodes or wires, such as pacemaker wires or bone growth/bone fusion stimulator wires * | <input type="radio"/> Yes* | <input type="radio"/> No | <input type="radio"/> Don't know* | <input type="radio"/> Refused* |
| i. Neurostimulation system, such as a spinal cord stimulator or gastric electrical stimulation system * | <input type="radio"/> Yes* | <input type="radio"/> No | <input type="radio"/> Don't know* | <input type="radio"/> Refused* |
| j. Implanted heart defibrillator * | <input type="radio"/> Yes* | <input type="radio"/> No | <input type="radio"/> Don't know* | <input type="radio"/> Refused* |
| k. Heart pacemaker * | <input type="radio"/> Yes* | <input type="radio"/> No | <input type="radio"/> Don't know* | <input type="radio"/> Refused* |
| l. Heart valve surgery | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |
| m. Brain aneurysm surgery, brain aneurysm clip(s) or coil * | <input type="radio"/> Yes* | <input type="radio"/> No | <input type="radio"/> Don't know* | <input type="radio"/> Refused* |
| n. Knee replacement surgery in BOTH knees (if only one knee replaced participant is still eligible for MRI) * | <input type="radio"/> Yes* | <input type="radio"/> No | <input type="radio"/> Don't know* | <input type="radio"/> Refused* |
| o. Tissue expander with magnetic port (such as inflatable breast implant with magnetic port) * | <input type="radio"/> Yes* | <input type="radio"/> No | <input type="radio"/> Don't know* | <input type="radio"/> Refused* |
| p. Penile implant or prosthesis (men only) | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |
| q. Eyelid spring, wire or weights | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |
| r. Tattoos on both knees * | <input type="radio"/> Yes* | <input type="radio"/> No | <input type="radio"/> Don't know* | <input type="radio"/> Refused* |





| Type of Follow-up Visit | OAI Participant ID # | Acrostic |
|---|--|--|
| <input type="radio"/> 12-month <input type="radio"/> 24-month <input type="radio"/> 36-month <input type="radio"/> 48-month <input type="radio"/> Interim 6-month | <div style="border: 1px solid black; width: 100px; height: 20px; display: flex; justify-content: space-between;"> </div> | <div style="border: 1px solid black; width: 100px; height: 20px; display: flex; justify-content: space-between;"> </div> |

PRESCREENER FOR FOLLOW-UP VISITS

5. Since your last MRI scan at the OAI clinic about [12 months ago][6 months ago], have you had...

a. An injury in which metal fragments entered your eye and you had to seek medical attention?

☐ Yes

☐ No

☐ Don't know

☐ Refused

b. An injury in which metal fragments, such as shrapnel, BB, or bullet entered your body?

☐ Yes

☐ No

☐ Don't know

☐ Refused

(Interviewer Note: Do not ask the following question.)

6. Are any of the items in Question #4 or Question #5 marked "Yes", "Don't know" or "Refused"?

☐ Yes

☐ No

a. Are any asterisked (*) items in Question #4 marked "Yes", "Don't know" or "Refused"?

☐ Yes

☐ No

NOT eligible for MRI.
Please go to Page 5, Question #8 and mark
"No. NOT eligible for an MRI scan."

(Interviewer Note: Ask participant the following question.)

b. Would you be willing to ask your doctor and/or your surgeon for your medical records so that we could determine whether it would be safe for you to have an MRI scan?

(Interviewer Note: If participant reports that they have documentation, please mark "Yes".)

☐ Yes

☐ No

☐ Don't know

Ask participant to send
safety documentation to the
clinic prior to their visit.

NOT eligible for MRI.
Please go to Page 5, Question #8 and mark
"No. NOT eligible for an MRI scan."



40524



| Type of Follow-up Visit | OAI Participant ID # | Acrostic |
|---|--|--|
| <input type="radio"/> 12-month <input type="radio"/> 24-month <input type="radio"/> 36-month <input type="radio"/> 48-month <input type="radio"/> Interim 6-month | <div style="border: 1px solid black; width: 100px; height: 30px; display: flex; justify-content: space-between;"> </div> | <div style="border: 1px solid black; width: 100px; height: 30px; display: flex; justify-content: space-between;"> </div> |

PRESCREENER FOR FOLLOW-UP VISITS

(Interviewer Note: Do not ask Question #7 and #8 below.)

7. Is there any other reason why this participant would not be eligible for an MRI?

☐ Yes

☐ No

What is the reason? Please describe below.

NOT eligible for MRI.
Please go to Question #8 below and mark
"No. NOT eligible for an MRI scan."

8. Based on this Prescreener for Follow-up Visits, is the participant eligible for an MRI scan?

☐ Yes

Schedule participant for follow-up visit, x-rays (if appropriate) and MRI scan (MRI safety needs to be confirmed for those participants who require documentation).
Participant is not eligible for the Interim 6-month Visit if safety documentation is required.

☐ Decision pending. Documentation required to confirm safety

☐ No. Recontact 2-months post-surgery

Record date participant should be recontacted (2-months post-surgery).

Month
Day
Year

Participant is not eligible for the Interim 6-month Visit if they need to be recontacted 2-months post-surgery.

☐ No. NOT eligible for an MRI scan

Schedule participant for follow-up clinic visit and x-rays (if appropriate). Do NOT perform MRI scan.
Participant is not eligible for the Interim 6-month Visit if they are NOT eligible for an MRI.





20165



| Type of Follow-up Visit | OAI Participant ID # | Acrostic |
|---|--|--|
| <input type="radio"/> 12-month <input type="radio"/> 24-month <input type="radio"/> 36-month <input type="radio"/> 48-month <input type="radio"/> Interim 6-month | <div style="border: 1px solid black; width: 100px; height: 30px; display: flex; justify-content: space-between;"> </div> | <div style="border: 1px solid black; width: 100px; height: 30px; display: flex; justify-content: space-between;"> </div> |

PRESCREENER FOR FOLLOW-UP VISITS

9. We would like to update your contact information so that we can mail you information about your upcoming clinic visit. The address that we currently have for you is:

(Interviewer Note: Please review the participant's contact information and confirm that the address you have for the participant is correct.)

Is the address that we currently have correct?

☐ Yes

☐ No



Interviewer Note: Please update the street address, city, state and zip code for the participant in your local records.

10. The telephone number(s) that we currently have for you is (are):

(Interviewer Note: Please review the participant's contact information and confirm that the telephone number(s) you have for the participant are correct.)

Is/are the telephone number(s) that we currently have correct?

☐ Yes

☐ No



Interviewer Note: Please update the telephone number(s) for the participant in your local records.

11. The e-mail address that we currently have for you is:

(Interviewer Note: Please review the participant's contact information and confirm that the e-mail address you have for the participant is correct.)

Is the e-mail address that we currently have correct?

☐ Yes

☐ No

☐ NA (no e-mail)



Interviewer Note: Please update the e-mail address for the participant in your local records.





MRI SAFETY SCREENER

| Type of Follow-up Visit | OAI Participant ID # | Acrostic | Date Form Completed | Staff ID# |
|---|--|--|---|--|
| <input type="radio"/> 12-month <input type="radio"/> 24-month <input type="radio"/> 36-month <input type="radio"/> 48-month <input type="radio"/> Interim 6-month | <div style="border: 1px solid black; width: 100px; height: 20px;"></div> | <div style="border: 1px solid black; width: 100px; height: 20px;"></div> | <div style="border: 1px solid black; width: 100px; height: 20px;"></div> / <div style="border: 1px solid black; width: 100px; height: 20px;"></div> / <div style="border: 1px solid black; width: 100px; height: 20px;"></div> <div style="display: flex; justify-content: space-around; font-size: small;"> Month Day Year </div> | <div style="border: 1px solid black; width: 100px; height: 20px;"></div> |

MRI status: ☐ First MRI scan ☐ Repeat MRI scan

1. What is your...?

First Name

M.I.

Last Name

2. Have you had any surgery or anything implanted in your body in the past 2-months? Please include arthroscopy, endoscopy, and laparoscopy.

☐ Yes



☐ No



☐ Don't know



☐ Refused



Go to Page 2, Question #3.

NOT eligible for MRI.
Please go to Page 5, Question #10 and mark
"No. NOT eligible for an MRI scan."

a. What type of surgery or implant did you have?

(Examiner Note: If participant had more than one surgery, please list all types.)

b. When was this surgery or procedure?

(Examiner Note: If participant had more than one surgery, please record the date of the most recent surgery. If participant unsure, please have them make their best guess.)

/
 /

Month
Day
Year

c. **(Examiner Note: Do NOT ask the following question. Refer to the list of surgeries/procedures that do not require a 2-month wait.)**

Does this surgery or procedure require a 2-month wait before an MRI scan?

☐ Yes



Please go to Page 5, Question #10 and mark
"No. Recontact 2-months post-surgery."

☐ No



Go to Page 2, Question #3.



| Type of Follow-up Visit | OAI Participant ID # | Acrostic | MRI status |
|---|---|---|---|
| <input type="radio"/> 12-month <input type="radio"/> 24-month <input type="radio"/> 36-month <input type="radio"/> 48-month <input type="radio"/> Interim 6-month | <div style="border: 1px solid black; height: 30px; width: 100%;"></div> | <div style="border: 1px solid black; height: 30px; width: 100%;"></div> | <input type="radio"/> First MRI scan <input type="radio"/> Repeat MRI scan |

MRI SAFETY SCREENER

3. Please indicate if you have any of the following:

| | | | | |
|--|--|--------------------------|---|--|
| a. Stent, filter, coil, or clips | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |
| b. Shunt (spinal or intraventricular) | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |
| c. Vascular access port or catheter, such as a central venous catheter or PICC line | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |
| d. Electronic implant or device, such as a cochlear implant [*] | <input type="radio"/> Yes [*] | <input type="radio"/> No | <input type="radio"/> Don't know [*] | <input type="radio"/> Refused [*] |
| e. Magnetically-activated implant or device, such as magnetically-activated dental implant or dentures, or magnetic eye implant [*] | <input type="radio"/> Yes [*] | <input type="radio"/> No | <input type="radio"/> Don't know [*] | <input type="radio"/> Refused [*] |
| f. Surgically implanted hearing device (not a regular hearing aid) or prosthesis in your ear | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |
| g. Surgically implanted insulin or drug pump [*] | <input type="radio"/> Yes [*] | <input type="radio"/> No | <input type="radio"/> Don't know [*] | <input type="radio"/> Refused [*] |
| h. Internal electrodes or wires, such as pacemaker wires or bone growth/bone fusion stimulator wires [*] | <input type="radio"/> Yes [*] | <input type="radio"/> No | <input type="radio"/> Don't know [*] | <input type="radio"/> Refused [*] |
| i. Neurostimulation system, such as a spinal cord stimulator or gastric electrical stimulation system [*] | <input type="radio"/> Yes [*] | <input type="radio"/> No | <input type="radio"/> Don't know [*] | <input type="radio"/> Refused [*] |
| j. Implanted heart defibrillator [*] | <input type="radio"/> Yes [*] | <input type="radio"/> No | <input type="radio"/> Don't know [*] | <input type="radio"/> Refused [*] |
| k. Heart pacemaker [*] | <input type="radio"/> Yes [*] | <input type="radio"/> No | <input type="radio"/> Don't know [*] | <input type="radio"/> Refused [*] |
| l. Heart valve surgery | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |
| m. Brain aneurysm surgery, brain aneurysm clip(s) or coil [*] | <input type="radio"/> Yes [*] | <input type="radio"/> No | <input type="radio"/> Don't know [*] | <input type="radio"/> Refused [*] |
| n. Knee replacement surgery in BOTH knees (if only one knee replaced participant is still eligible for MRI) [*] | <input type="radio"/> Yes [*] | <input type="radio"/> No | <input type="radio"/> Don't know [*] | <input type="radio"/> Refused [*] |
| o. Tissue expander with magnetic port (such as inflatable breast implant with magnetic port) [*] | <input type="radio"/> Yes [*] | <input type="radio"/> No | <input type="radio"/> Don't know [*] | <input type="radio"/> Refused [*] |
| p. Penile implant or prosthesis (<i>men only</i>) | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |
| q. Eyelid spring, wire or weights | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |
| r. Tattoos on both knees [*] | <input type="radio"/> Yes [*] | <input type="radio"/> No | <input type="radio"/> Don't know [*] | <input type="radio"/> Refused [*] |
| s. Injury in which metal fragments entered your eye and you had to seek medical attention | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |
| t. Injury in which metal fragments, such as shrapnel, BB, or bullet entered your body | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |



44078



| Type of Follow-up Visit | OAI Participant ID # | Acrostic | MRI status |
|---|--|--|---|
| <input type="radio"/> 12-month <input type="radio"/> 24-month <input type="radio"/> 36-month <input type="radio"/> 48-month <input type="radio"/> Interim 6-month | <div style="border: 1px solid black; width: 100px; height: 20px; display: flex; justify-content: space-between;"> </div> | <div style="border: 1px solid black; width: 100px; height: 20px; display: flex; justify-content: space-between;"> </div> | <input type="radio"/> First MRI scan <input type="radio"/> Repeat MRI scan |

MRI SAFETY SCREENER

(Examiner Note: Do not ask the following question.)

4. Are any of the items in Question #3 marked "Yes", "Don't know" or "Refused"?

☐ Yes

☐ No

a. Are any asterisked (*) items in Question #3 marked "Yes", "Don't know" or "Refused"?

☐ Yes

☐ No

NOT eligible for MRI.

Please go to Page 5, Question #10 and mark "No. NOT eligible for an MRI scan."

b. Does the participant have medical documentation that confirms that it is safe to have an MRI scan?

☐ Yes,
Safety confirmed

☐ MRI safety unconfirmed;
Additional documentation
required

☐ No, MRI unsafe
and/or documentation
not available

☐ Don't know

Please go to Page 5, Question #10
and mark "Unsure. Additional
documentation required."

NOT eligible for MRI.
Please go to Page 5, Question #10 and
mark "No. NOT eligible for an MRI scan."

Name of staff authorized to review documentation and confirm MRI safety (Please print):

Authorized staff signature (signature confirms 3T MRI safety):

Date: ____/____/____
Month Day Year

Please file documentation in participant's chart.

(Examiner Note: A "Yes" response to Question #5a or #5b below does not make the participant ineligible for an MRI scan but could affect the quality of the MRI scan. The final decision whether or not to scan the participant should be determined by the MRI tech.)

5. Do you have a...

a. Severe breathing problem?

☐ Yes

☐ No

☐ Don't know

☐ Refused

b. Severe motion disorder, such as body tremor or Parkinsons?

☐ Yes

☐ No

☐ Don't know

☐ Refused





48874



| Type of Follow-up Visit | OAI Participant ID # | Acrostic | MRI status |
|---|--|--|---|
| <input type="radio"/> 12-month <input type="radio"/> 24-month <input type="radio"/> 36-month <input type="radio"/> 48-month <input type="radio"/> Interim 6-month | <div style="border: 1px solid black; width: 100px; height: 20px; display: flex; justify-content: space-between;"> </div> | <div style="border: 1px solid black; width: 100px; height: 20px; display: flex; justify-content: space-between;"> </div> | <input type="radio"/> First MRI scan <input type="radio"/> Repeat MRI scan |

MRI SAFETY SCREENER

6. Please indicate if you have any of the following removable items:

| | | | | |
|--|---------------------------|--------------------------|----------------------------------|-------------------------------|
| a. Any type of artificial or prosthetic limb | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |
| b. Dentures or partial plates | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |
| c. Hearing aid | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |
| d. Diaphragm (women only) | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |
| e. Body piercing jewelry, such as earrings | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |
| f. Medication patch that your physician said is okay to remove, such as Nicotine, Nitroglycerine, Estrogen | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't know | <input type="radio"/> Refused |

(Examiner Note: Do not ask the following question.)

7. Are any of the above items in Question #6 marked "Yes", "Don't know" or "Refused"?

☐ Yes

☐ No

(Examiner Note: Ask the participant the following question. If any of the items in Question #6 are marked "Don't know" or "Refused", mark "No" to the question below.)

a. Are you able to remove the item for the MRI scan?

☐ Yes

☐ No

NOT eligible for MRI.
Please go to Page 5, Question #10 and
mark "No. NOT eligible for an MRI scan."

Examiner Note: Please ask the participant to remove the item prior to MRI scan.



35216



| Type of Follow-up Visit | OAI Participant ID # | Acrostic | MRI status |
|---|--|--|---|
| <input type="radio"/> 12-month <input type="radio"/> 24-month <input type="radio"/> 36-month <input type="radio"/> 48-month <input type="radio"/> Interim 6-month | <div style="border: 1px solid black; width: 100px; height: 20px; display: flex; justify-content: space-between;"> </div> | <div style="border: 1px solid black; width: 100px; height: 20px; display: flex; justify-content: space-between;"> </div> | <input type="radio"/> First MRI scan <input type="radio"/> Repeat MRI scan |

MRI SAFETY SCREENER

(Examiner Note: Do not ask Question #8, #9, or #10 below. Complete Question #8 for women only. For men, go to Question #9.)

8. Did participant have a positive pregnancy test?

(Examiner Note: Please refer to the Data from Prior Visits Report for the Follow-up Visit to determine who may require a pregnancy test. Consult with clinic examiner for test results.)

- ☐ Yes (positive test)
 ☐ No (negative test)
 ☐ Pregnancy test not required
 ☐ Participant refused test

NOT eligible for MRI.
Please go to Question #10 below and mark "No. NOT eligible for an MRI scan."

NOT eligible for MRI.
Please go to Question #10 below and mark "No. NOT eligible for an MRI scan."

9. Is there any other reason why this participant would not be eligible for an MRI?

- ☐ Yes
 ☐ No

What is the reason? Please describe below.

NOT eligible for MRI.
Please go to Question #10 below and mark "No. NOT eligible for an MRI scan."

10. Based on this MRI Safety Screener, is the participant eligible for an MRI scan?

- ☐ Yes → Perform MRI scan.
- ☐ Unsure. Additional documentation required → Do NOT perform MRI scan. Recontact participant to schedule MRI scan after documentation received and safety confirmed. Re-administer MRI safety screener the day of MRI scan.
- ☐ No. Recontact 2-months post-surgery → Record date participant should be recontacted (2-months post-surgery).
 _____ / _____ / _____
 Month Day Year
- ☐ No. NOT eligible for an MRI scan → Conduct follow-up clinic visit and x-rays (if appropriate). Do NOT perform MRI scan.



| Type of Follow-up Visit | OAI Participant ID # | Acrostic | MRI status |
|---|---|---|---|
| <input type="radio"/> 12-month <input type="radio"/> 24-month <input type="radio"/> 36-month <input type="radio"/> 48-month <input type="radio"/> Interim 6-month | <div style="border: 1px solid black; width: 100px; height: 20px; margin-bottom: 5px;"></div> <div style="border: 1px solid black; width: 100px; height: 20px; margin-bottom: 5px;"></div> <div style="border: 1px solid black; width: 100px; height: 20px; margin-bottom: 5px;"></div> <div style="border: 1px solid black; width: 100px; height: 20px; margin-bottom: 5px;"></div> <div style="border: 1px solid black; width: 100px; height: 20px; margin-bottom: 5px;"></div> <div style="border: 1px solid black; width: 100px; height: 20px; margin-bottom: 5px;"></div> <div style="border: 1px solid black; width: 100px; height: 20px; margin-bottom: 5px;"></div> <div style="border: 1px solid black; width: 100px; height: 20px; margin-bottom: 5px;"></div> | <div style="border: 1px solid black; width: 100px; height: 20px; margin-bottom: 5px;"></div> <div style="border: 1px solid black; width: 100px; height: 20px; margin-bottom: 5px;"></div> <div style="border: 1px solid black; width: 100px; height: 20px; margin-bottom: 5px;"></div> <div style="border: 1px solid black; width: 100px; height: 20px; margin-bottom: 5px;"></div> | <input type="radio"/> First MRI scan <input type="radio"/> Repeat MRI scan |



MRI SAFETY SCREENER

11. The information recorded on Pages 1-5 is correct to the best of my knowledge.

a. Participant Name: _____

Participant Signature: _____

Date: ____/____/____
 Month Day Year

b. MRI Technologist Name: _____

MRI Technologist Signature: _____

Date: ____/____/____
 Month Day Year

c. Witness Name: _____

Witness Signature: _____

Date: ____/____/____
 Month Day Year

Appendix K.

Protocol Amendments Adopted after 9/30/03 (Date of Steering Committee Approval of Original Protocol)

| Changes to protocol section/page | Description of Amendment/Revision and Rationale | Steering Committee Approval |
|---|--|-----------------------------|
| 4.2.2.2 Inclusion and eligibility criteria, Progression subcohort / page 10 | <p>The definition of frequent knee symptoms required for classification of symptomatic knee OA and to qualify a participant for the Progression subcohort was changed. Use of medications for knee symptoms on most days of a month in the past year will <u>not</u> qualify for the definition of symptomatic knee OA and therefore for assignment of a participant to the Progression subcohort. Only a report of knee symptoms on most days for at least one month in the past year will qualify for the definition of symptomatic knee OA. Use of medications for knee symptoms on most days of a month in the past year will continue to count as an eligibility risk factor for the Incidence subcohort.</p> <p>The questions about use of medication for knee pain do not differentiate between right and left knees. The study definition of symptomatic knee OA requires knee-specific information about symptoms.</p> | 1/30/04 |
| 4.2.2.3 Inclusion and eligibility criteria, Incidence subcohort / page 10 | <p>Participant report of <u>infrequent</u> knee symptoms, i.e. knee pain, aching or stiffness in the past 12 months but <u>not on most days</u> of any month (current Question #9 on the IEL and Questions #15 and #18 of the SV workbook) was added as a knee symptom eligibility criterion for the Incidence subcohort in those ages 45-49 and as an eligibility risk factor for the Incidence subcohort in those ages 50-79. As a result of this change, those age 45-49 are eligible for the Incidence subcohort if they report frequent knee symptoms (on most days for at least one month in the past 12 months) or frequent use of medications to treat knee symptoms or <u>infrequent</u> knee symptoms AND in addition to symptoms have at least one other eligibility risk factor. Also as a result of this change, <u>infrequent</u> knee symptoms is counted as an Incidence subcohort eligibility risk factor for those age 50-79.</p> <p>This change will decrease the number of participants ages 45-49 who are found ineligible at the Screening visit because they no longer report frequent knee symptoms at this visit although they reported this on the IEL. The change will also increase the number of participants age 50-79 eligible for the Incidence subcohort based on having the required eligibility risk factors.</p> | 7/13/04 |

*Changes made since Steering Committee adoption of OAI Protocol Version 1.0, 9/24/2003

+ IEL = Initial Eligibility Interview; SV = Screening Visit; EV = Enrollment Visit; OM = Operations Manual

Updated 21 June 2006

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| Changes to protocol section/page | Description of Amendment/Revision and Rationale | Steering Committee Approval |
|--|--|-----------------------------|
| 4.2.2.3 Inclusion and eligibility criteria, Incidence subcohort / page 10 | Eligibility criteria for the Incidence subcohort were changed so that participants ages 50-69 whose only eligibility risk factor is overweight will be eligible. This change should increase the number of Incidence subcohort participants who are overweight. | 2/25/05 |
| 4.2.2.4 Inclusion and eligibility criteria, Reference ("Nonexposed") control subcohort / page 13 | The knee radiography protocol for the <u>Reference Control subcohort</u> was modified to include a standing lateral radiograph of each knee at baseline. This lateral knee will not be read or used for eligibility determination, but may be used for later stratification of the Reference Control subcohort for presence of PF OA. | 1/30/04 3/26/04 |
| 4.2.3 Exclusion criteria / page 14 | Possible inflammatory arthritis based on reading of the baseline fixed flexion knee radiograph was added as an exclusion criterion. Severe joint space narrowing (OARSI grade 3 or bone on bone) and no evidence of definite osteophytes in the same knee. This finding will be confirmed by central readers prior to exclusion. The radiographic definition of possible inflammatory arthritis was further revised to require severe joint space narrowing, or bone on bone, in both the medial and lateral compartments of a knee in which there is no definite osteophyte. Bicompartmental involvement of the knee is more typical of RA and inflammatory arthritis than is unicompartmental involvement. | 1/30/04 7/13/04 |
| 4.2.3 Exclusion criteria / page 14 | The upper limit for self-report weight by women at the IEI was decreased from 285 lbs to 250 lbs. Women greater than 250 lbs are not eligible for a Screening Visit. This change will reduce the number of women who have a screening visit and whose knees do not fit into the MRI knee coil. | 5/26/04 |

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| Changes to protocol section/page | Description of Amendment/Revision and Rationale | Steering Committee Approval |
|---|--|--------------------------------|
| <p>4.3.2 Knee Imaging for Structural Outcome Measures / page 17</p> <p>5.2.1 Follow-up visit schedule / page 30</p> <p>5.3 Data to be Collected and Frequency / page 31</p> | <p>The clinic visit schedule was modified to add a 6-month interim visit for participants in the Progression subcohort: one-half of the subcohort will have this additional visit at 18 months and one-half at 30 months. The visit will include complete knee MRI sequences, blood and urine collection, current prescription medications and treatments for joint pain, WOMAC and KOOS, patient global assessment, and knee pain rating.</p> <p>This change will provide data on the ability of MRI and biochemical measurements to detect clinically and statistically significant changes in OA biomarkers over 6 months, and whether these to predict long-term structural and clinical outcomes.</p> <p>The knee MRI protocol for the 6-month interim visit was further modified to scan the right knee only using the complete set of sequences (or the left knee if it had the complete set of sequences at baseline) and not to scan the other knee.</p> <p>This change will reduce the burden on the participants who volunteer for a 6 month interim visit and will reduce the impact of these additional visits on MRI scheduling.</p> | <p>7/14/04</p> <p>10/28/05</p> |
| 4.3.2.2 Knee joint radiography / page 19 | <p>The acquisition protocols for fluoroscopic radiographs in the Progression cohort were modified. Clinics with the appropriate equipment for the fixed flexion with fluoro (Lyon Schuss) protocol will continue to acquire images using this preferred method. The other sites will use the Buckland-Wright semi-flexed fluoro knee positioning protocol, with appropriate phantoms for magnification correction .</p> <p>This change was necessary due to site-specific equipment limitations and logistical constraints.</p> | 1/30/04 |

*Changes made since Steering Committee adoption of OAI Protocol Version 1.0. 9/24/2003

⁺ IIEI = Initial Eligibility Interview; SV = Screening Visit; EV = Enrollment Visit; OM = Operations Manual

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| Changes to protocol section/page | Description of Amendment/Revision and Rationale | Steering Committee Approval |
|---|---|-----------------------------|
| 4.3.2 Knee Imaging for Structural Outcome Measures / page 17 | Fluoro-guided knee radiography was discontinued at two clinical centers due to intractable problems with fluoro equipment, logistical barriers and image quality. All participants at <u>all sites</u> will get non-fluoro fixed-flexion radiographs at every annual visit. At two sites, fluoro-guided radiographs will continue to be acquired in addition to fixed flexion at the 12- and 24-month follow-up visits in knees that had a successful fluoro film at baseline. | 4/13/05 |
| 4.3.2.2 Knee joint radiography / page 19 | The acquisition of both fluoro-guided and nonfluoro knee radiographs at baseline, 12- and 24-month visits in a subset of participants will provide data for a head-to-head comparison between these two types protocol. | |
| 4.4 Biological Specimens for Biochemical Marker Development / page 21 | <p>The biospecimen collection procedures were modified to allow for a small number of afternoon baseline clinic visits with a 2-hour fast prior to an afternoon blood draw.</p> <p>Morning blood draws with an overnight fast will still be arranged whenever possible for participants coming for an afternoon baseline clinic visit. Second morning void urine specimens will continue to be collected at home and brought into the clinic. Blood draws at follow-up visits should be within +/- one hour of the time of the baseline blood draw.</p> <p>This change will allow more efficient use of all available MRI exam slots.</p> | 2/25/05 |
| 4.5 Sample Size and Enrollment Goals / page 22 | <p>The enrollment goals for the Progression subcohort were increased by 50% over the original study goals, to 1,200 studywide and 300 at each of the four recruitment centers. In addition, a limit of 200 was placed on the number of women enrolled in the Progression subcohort at an individual recruitment center. Enrollment goals for the Incidence subcohort were reduced by an equal number. Minority participants will continue to be enrolled regardless of limits on enrollment in a subcohort or age/gender subgroup.</p> <p>This change takes advantage of the large numbers of women with frequent knee symptoms (most of whom qualify for the Progression subcohort) who are interested in, and eligible for, the study. It will also allow overall enrollment numbers to be closer to the original study goals despite below goal enrollment in the Incidence subcohort.</p> | 4/13/05 |

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| | | |
|--|--|-------------------------|
| 4.5 Sample Size and Enrollment Goals / page 22 | The period for enrolling participants was extended through November 2005 at all recruitment centers. Enrollment of minorities at one recruitment center and of nonexposed controls at two centers was extended into the first half of calendar year 2006. | 7/22/05 10/28/05 |
| 5.1 Recruitment and Enrollment / page 24 5.1.3 Prescreening Interview / page 26 | A prescreening interview was adopted to exclude potential participants who would be in age/gender/subcohort cells that are full. Minority participants will continue to be enrolled regardless of limits on enrollment in a subcohort or age/gender subgroup. This change will decrease the number of participants who have IELs and Screening clinic visits who are in filled cells. | 7/13/04 |
| 5.1 Recruitment and Enrollment / page 24 | The goal for the maximum duration of time between baseline IEL and Screening Visit and Screening Visit and Enrollment Visit (Visit windows) was increased to 6 weeks for each of these intervals. Clinics will continue to set 3 weeks as the goal for the majority of participants. This change adapts the protocol to the logistical realities of the recruitment process and to limitations in the number of available MRI examination slots. | 3/26/04 5/26/04 |
| 5.1.6 Eligibility determination and assignment to subcohort / page 29 | Minimum biospecimen requirements were adopted, as recommended by the Biospecimen Working Group. | 7/13/04 |
| 5.1.6 Eligibility determination and assignment to subcohort / page 29 | Minimum baseline requirements for imaging and biospecimens, and time limitations for meeting requirements, were adopted. Participants must meet these requirements to be considered enrolled in the study, unless an enrollment exception is granted. Procedures were adopted for enrollment exceptions for selected participants who do not meet the minimum data requirements. Exceptions require approval by the local PI and by the Data Coordinating Center. | 2/25/05 5/24/05 |

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| | | |
|---|---|------------|
| 5.1.6 Eligibility determination and assignment to subcohort / page 29 | <p>Procedures were adopted for subcohort classification for those participants with radiographic severe joint space narrowing but without definite osteophytes (not bicompartamental). Such a participant with symptomatic OA in the other knee will be assigned to the Progression subcohort. The remainder of participants with knees that have severe joint space narrowing but no osteophytes will be assigned to the Incidence subcohort.</p> <p>While MRI may show osteophytes present in these knees, there is no standard way of using MRI information about osteophytes to define OA presence/absence. If these knees develop the combination of radiographic osteophytes and frequent symptoms during, they may be classified as incident symptomatic OA.</p> | 10/15/2004 |
| 5.3 Data to be collected and frequency, knee examination / page 31 | <p>The knee flexion range of motion component of the knee examination was dropped. Participants will still be asked to maximally flex their knees and asked if this results in knee pain.</p> <p>Less than one percent of participants are positive for limited range of knee flexion (<100 degrees).</p> | 11/24/2004 |
| 6.1.4 Participant safety, Walking endurance / page 44 | <p>The 400-meter walk eligibility assessment was revised to incorporate suggestions that were made by the OAI Observational Study Monitoring Board. The exclusion criterion for the resting heart rate was lowered from 135 to 110 bpm. The blood pressure was lowered from 199/109 to 180/100. The time period for exclusions for 1) hospitalizations of 3 or more days, 2) hospitalizations for heart attack or myocardial infarction and 3) having had other major surgeries (thoracic, abdominal or joint) was increased from the past 6 weeks to the past 3 months. Using supplemental oxygen, having had to see or call the doctor for worsening of angina or shortness of breath in past 3 months, and having angioplasty or heart surgery in past 3 months were added as exclusions for the 400-meter walk.</p> | 2/25/05 |
| | | |

*Changes made since Steering Committee adoption of OAI Protocol Version 1.0, 9/24/2003

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OAI ANCILLARY STUDIES GUIDELINES

A. Definition of an ancillary study

A.1 An ancillary study is a study that requires access to OAI participants, whether from a single clinical center or from the entire cohort, to collect measurements or data directly from OAI participants using procedures or instruments that are not included in the already funded core protocol and are not part of the routine OAI database.

Studies proposing to use OAI protocols in order to expand the subject population beyond the planned 5000 at 4 clinical centers will be treated as ancillary studies.

A.2 The following are not considered ancillary studies:

A.2.1. Studies that generate new data that are not part of the routine OAI database from existing measurements (such as reading of joint images) are not ancillary studies for the purposes of these guidelines;

A.2.2 Studies that generate new data from stored existing biospecimens are not ancillary studies for the purposes of these guidelines. Such studies will be reviewed, and require approval, by the Biospecimen Resource Allocation Committee.

A.2.3 Substudies funded by the OAI, such as modifications or additions to the existing contract.

B. Who may submit a proposal?

B.1 Investigators are encouraged to conduct ancillary studies with the stipulation that such studies be scientifically sound and have little or no adverse impacts on the main study or the participants of OAI.

B.2 Investigators affiliated with OAI and those without an affiliation with OAI may propose ancillary studies.

B.2.1 Proposals must have at least one OAI investigator as a sponsor and include an OAI investigator at each of the 4 OAI clinical centers undertaking the study. The Data Coordinating Center should be involved with every ancillary study proposal.

C. Proposal format

C.1 An investigator who wishes to conduct an ancillary study submits a written proposal to the Ancillary Studies Committee. The proposal, generally 4-5 pages in length, should include the following elements:

- 1) name of principal investigator and contact information;
- 2) OAI investigator sponsoring the proposal;
- 3) list of other participating investigators;
- 4) working title of proposal;
- 5) research question with clearly stated hypothesis;
- 6) background and rationale for the study;
- 7) a detailed description of the methods and procedures;
- 8) an estimate of the sample size required to test the primary hypothesis (including the assumptions underlying the estimate);
- 9) a detailed estimate of the impact of the study on the main study: cost (including data collection and administration, data coordination and data management; data analysis), staff and participant time, risks to participants;
- 10) a discussion of human subjects issues and risks related to the ancillary study measurements and procedures;
- 11) plans and timeline for submitting the ancillary study data to the OAI for inclusion in the public release data base;
- 12) plans for obtaining funds to pay for the study, including RFA or RFP identifier (where applicable) application submission dates, amount of funds available, or letters from funding agencies committing funds to the project.

D. Approval process

D.1 All proposals for ancillary studies are initially reviewed by and approved by the OAI Ancillary Studies committee.

D.2 The Committee will review each application, considering:

- 1) its scientific merit,
- 2) quality of the design and methods, and
- 3) the potential impact (both positive and negative, including participant burden) on the main study.

D.3 The Ancillary Studies Committee will pass its review on to the full Steering Committee for a decision about approval or disapproval. Either Committee may ask the investigator to revise and resubmit the proposal before voting.

D.4 All ancillary studies will be reviewed by the Steering Committee along with the recommendations of the Ancillary Studies Committee. Ancillary studies must be approved by a 2/3 majority of members who participate in the vote.

E. Priorities

E.1 Priority will be given to proposals that are scientifically important and consistent with the overall goals of the OAI.

E.2 In general, proposals that augment or complement the main scientific aims of the OAI will be favored over those that take advantage of OAI for more tangential purposes.

F. IRB approval

F.1 All ancillary studies must eventually be approved by the appropriate institutional review boards of the participating center before they are performed, but IRB approval is not required to submit a proposal to the Steering committees. Ancillary studies may have separate consent forms from the main study.

G. Funding

G.1 Proposals for funding ancillary studies must be approved by the Ancillary Studies Committee before they are submitted to the funding agencies. Proposers should allow at least 8 weeks between the submission of the ancillary study proposal to the committee and the funding application deadline.

G.2 Proposals for funding must include coverage of all relevant costs, including clinical center investigators, coordinators and staff for data collection, procedure-related costs, equipment and supplies needed at the clinic, data coordinating center and data management costs, training and quality assurance costs, etc.

H. Changes after approval

H.1 If substantial changes in the design of the protocol or in the potential impact of the protocol on the main study occur after Steering Committee approval, then the investigators must submit a revised protocol to the Ancillary Studies Committee for review. If the changes are substantial, the Ancillary Studies Committee may submit the proposal for approval by the Steering Committee.

H.2. The Steering Committee may, by majority vote, terminate an ancillary study if it judges that a study has become too burdensome or its scientific value has

diminished, or it has failed to make substantial progress toward the completion of its goals.

I. Disposition of ancillary study data

I.1 Investigators of approved ancillary studies are strongly encouraged to make the data available to other investigators as part of the OAI public use data set. A plan and timeline for making the data available should be included in the ancillary study proposal.

J. Publication of ancillary study data

The publications committee will perform prior review of ancillary study manuscripts, prior to submission to a peer-reviewed journal, with approval required for the authors to claim that the study represents the OAI.

All approved publications must include a standard set of acknowledgments and disclaimers, which will be specified by the Steering Committee.

Additional publications guidelines may apply to ancillary studies, as determined by the Steering Committee.