The MeTeOR Trial: Rationale and Design Features

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Overview:

This paper presents the rationale and design features of the MeTeOR Trial (Meniscal Tear in Osteoarthritis Research; Clinical Trials.gov NCT00597012). MeTeOR is an NIH-funded seven-center prospective randomized controlled trial (RCT) of the efficacy of arthroscopic partial meniscectomy combined with a standardized physical therapy program as compared with a standardized physical therapy program alone in middle-aged and older patients with a symptomatic meniscal tear in the setting of mild to moderate knee osteoarthritic change (OA). The design and execution of trials that compare surgery with nonoperative strategies present distinctive challenges. The goal of this paper is to provide the clinical rationale for MeTeOR and to highlight salient design features, with particular attention to those that present methodologic or clinical challenges.

Rationale:

Symptomatic, radiographic osteoarthritis affects over 27 million people in the US, including over 9 million with knee osteoarthritis.[1] Meniscal teas are also highly prevalent, as evidenced by community-based magnetic resonance imaging (MRI) studies which show that 35% of individuals greater than 50 years of age have evidence of a meniscal tear on MRI, even though two thirds of these subjects are asymptomatic.[2] Meniscal damage is especially prevalent among persons with osteoarthritis. In fact, 75% of persons with radiographically documented symptomatic knee OA have evidence of a meniscal tear on MRI.[3] Prior studies have shown that the coexistence of a meniscal tear in patients with symptomatic OA is not associated with an increase in the severity of pain as compared to patients with OA and no meniscal tear.[3] Thus,

although structural evidence of a meniscal tear is common, especially in patients with osteoarthritis, these tears are often asymptomatic.

The high prevalence of meniscal tear in patients with knee OA and the observation that these lesions are often asymptomatic create challenges in patient management and decision-making. In patients with both meniscal tears and osteoarthritis of the knee, it is often difficult to determine whether the patients' symptoms are due primarily to bone marrow lesions, synovitis, effusion, the meniscal tear, or a combination of these features. This differentiation is critical because if nonoperative measures fail to control symptoms, and if the clinical history, physical exam and imaging studies suggest a meniscal tear as the primary source of symptoms, clinicians often recommend surgery and perform an arthroscopic partial meniscectomy (APM).

The history of arthroscopic approaches in patients with knee osteoarthritis is noteworthy. Over the last decade, two pivotal trials have been published on the efficacy of arthroscopic surgical approaches in patients with advanced OA in whom there is no clinical suspicion of symptomatic meniscal tear. Moseley and colleagues[4] compared arthroscopic debridement and arthroscopic lavage to a sham surgical procedure. Kirkley and colleagues[5] compared debridement to a nonoperative regimen. In each of these trials, both the surgical intervention and the control intervention resulted in substantial improvement in pain and functional status over 24 months of follow-up, with no meaningful differences between arms. Thus, consistent evidence from two high-quality randomized controlled trials suggests that arthroscopic surgery is not effective for the treatment of severe knee osteoarthritis.

However, the most frequent indication for arthroscopic surgery in patients with knee OA is symptomatic meniscal tear. These tears are frequently addressed surgically with arthroscopic partial meniscectomy (APM), in which the surgeon trims the torn meniscus back to a stable rim. This procedure is performed on over 300,000 persons with concomitant OA and meniscal pathology annually in the US.[6] At over $5,000 per case, these procedures account for about $1.5 billion in direct medical costs in the US annually. Despite the frequency of APM, the efficacy of this procedure has not been evaluated rigorously among patients with concomitant mild or moderate OA. There is only one published randomized controlled trial of the efficacy of APM, involving 90 patients followed for six months at one Swedish center. This study found that APM plus an exercise regimen was no more effective than the exercise regimen alone.[7] Given the frequency and cost of APM and the lack of evidence supporting utilization of this procedure, this question requires further rigorous clinical evaluation in a multicenter randomized trial.

This rationale gives rise to the specific aims of the MeTeOR trial: 1) To evaluate the efficacy after six months of follow up of arthroscopic partial meniscectomy, as compared with a standardized nonoperative regimen in the management of symptomatic meniscal tear occurring in patients with concomitant osteoarthritic change; 2) to follow the randomized groups through 24 months of follow-up to evaluate longer term efficacy of APM; and, 3) to assess the cost-effectiveness of APM in this clinical setting.

Design justification and the importance of equipoise:

The RCT is the most rigorous test of efficacy and is often used to address significant public health problems. RCTs are often more resource–intensive than cohort studies, and they

also require that both patients and physicians must be comfortable with the element of randomization. This critical feature of impartiality between two (or more) alternative therapies is known as equipoise.[8, 9]

To assess physician equipoise, the trial design was presented to interested surgeons who were then asked if they would be willing to randomize. We chose not to include in the study those surgeons who had misgivings about randomization. At the time MeTeOR began, there were no prior published randomized trials of operative vs. nonoperative therapy for this condition. Thus, the literature did not identify patient subgroups in which one treatment or the other was superior. Discussions were held with surgeon investigators to identify the clinical circumstances in which they would or would not feel comfortable with both surgical and nonoperative options. We then codified these preferences in the entry and exclusion criteria. For example, the surgical team was uncomfortable with the idea of randomizing patients with advanced OA (Kellgren-Lawrence (KL) Grade 4) because they felt such patients would have poor outcomes following APM; consequently KL Grade 4 became an exclusion criterion for the study. These entry and exclusion criteria were further supported by our survey of orthopedic sports surgeons, among whom the most important factors prompting the decision to perform APM are the presence of a normal radiograph, failure of nonoperative therapy and physical examination findings suggestive of symptomatic meniscal tear, particularly the McMurray test.[10]

We assessed patient equipoise by field-testing pilot enrollment well before MeTeOR was launched. In this pilot study, we identified patients who met the eligibility criteria for MeTeOR and summarized the study design and protocol to them. We explained that we were planning a

study in which patients would be assigned randomly to receive either APM or nonoperative therapy. We then asked subjects if they would agree to participate in such a study. Of 88 patients in three centers included in this pilot study, 22% reported they would definitely agree to the trial and another 24% reported they would probably agree.[11] On the basis of these data, we anticipated that 20-25% of eligible patients would participate and planned sample size projections accordingly. These projections are consistent with the rate of enrollment into other surgical RCTs such as the randomized components of SPORT (Spine Outcomes Research Trial).[12-14]

Setting and sample:

We designed an efficacy study in which the interventions were administered under ideal circumstances. Accordingly, the MeTeOR trial was performed in academic referral centers and with participating surgeons considered to be leaders in their fields. The trial was originally set in five centers: Brigham and Women's Hospital, Boston; Hospital for Special Surgery, New York; Cleveland Clinic, Cleveland; Vanderbilt University, Nashville; and Mayo Clinic, Rochester. In order to accelerate the pace of enrollment, two additional centers were added in the second year of enrollment: Rush University Medical Center, Chicago, and Washington University, St. Louis.

The entry and exclusion criteria are provided in Table One. Our goal was to enroll patients with meniscal tear in the setting of mild to moderate OA who did not have conditions that might confound the effects of treatment on outcome. The definition of osteoarthritis posed a design issue: we did not wish to restrict the sample to patients with radiographically documented osteoarthritis (requiring a definite osteophyte, joint space narrowing, or both) because radiographic findings reflect intraarticular tissue damage only in advanced stages of joint

damage.[15] There is general recognition that osteoarthritis begins well before signs of radiographic osteoarthritis become apparent. In accordance with contemporary thinking about early OA, we considered cartilage defects on MRI to be a marker of early disease and therefore appropriate for trial eligibility.[16]

The definition of a *symptomatic meniscal tear* also posed methodological challenges.[17] There is general agreement among clinicians that the symptoms of isolated knee OA differ from those arising specifically from meniscal tear, which frequently have a more mechanical quality.[17] Presumably, these more mechanical symptoms reflect interference with smooth joint motion as a result of the torn meniscal fragment. However, there is no standard, valid definition of meniscal symptoms and there is a paucity of literature on the sensitivity and specificity of the symptoms typically regarded as consistent with torn meniscus such as locking, clicking, popping, pain with pivot, and pain localized to one spot. Acknowledging this limitation in our understanding of meniscal symptoms, we adopted a broad definition: patients must have one or more of the checklist of symptoms listed in the third "Entry Criteria" bullet point in Table One. In the analytic phase of this trial, we will be able to determine whether one or more of these symptoms is associated with response to surgery.

Enrollment and randomization:

Research coordinators in all centers screen the schedules of participating surgeons to identify patients who met screening criteria (see Figure). These includ age 45 or greater, knee pain and no prior surgery on the index knee, as well as a documented meniscal tear on MRI. The research coordinator flags these patients' charts when they are seen in clinic. The surgeon

completes an eligibility checklist that included the eligibility and exclusion criteria shown in Table One. If patients were eligible, the surgeon informs them of the trial and asks if they are potentially interested in participating. If so, the surgeon refers them to the research coordinator, who provides a detailed description of the study, using a script to ensure that these conversations are standardized across all centers. Patients who wish to participate complete an informed consent form and baseline questionnaire. The research coordinator received training from a study physical therapist in order to perform a standardized physical examination, which includes measures of knee range of motion, quadriceps and hamstring strength, leg length, varus and valgus knee deformity, pes planus deformity and a timed up and go test.

Once these baseline measures are completed, the patient is randomized. Randomization is performed in real time on MeTeOR's secure website. Subjects are randomized in blocks of varying size within each site, stratified by the extent of osteoarthritis on the baseline plain radiograph (Kellgren Lawrence grade 0-2 (no joint space narrowing) versus Kellgren Lawrence grade 3 (< 50% joint space narrowing).

Interventions:

Surgical arm: Surgical investigators from five MeTeOR centers discussed the surgical protocol in two face-to-face meetings and arrived at a standardized approach. The surgeon performs an arthroscopic partial meniscectomy, trimming the damaged meniscus back to a stable rim. Surgeons trim loose fragments of cartilage and bone but they do not attempt to stimulate a healing response by penetrating the subchondral bone (microfracture technique). Intraarticular corticosteroid injections are not permitted at the time of surgery. Preoperative antibiotics are

used routinely. Patients are scheduled for physical therapy (PT) following surgery. The PT regimen is analogous to that provided in the nonoperative arm (see below).

Nonoperative arm: The investigators opted for a standardized nonoperative protocol rather than 'usual care.' The latter makes the comparisons less incisive, as there are many variations of usual care for knee problems.[18] The physical therapy protocol was developed by a team of physical therapists from the various trial centers based on evidence in the literature supporting land-based, individualized physical therapy with concomitant progressive home exercise for patients with knee OA.[19, 20] The program was designed to address range of motion, concentric/eccentric muscle strength, muscle length restrictions, aerobic conditioning (e.g. bicycling), functional mobility and proprioceptive/balance training. Patients progress through three stages with increasing demand. Criteria for progression from Stages I to II and II to III include the level of self-reported pain, observed strength, range of knee motion, knee effusion and functional mobility. In each stage, the patient attends PT sessions approximately twice weekly and performs a follow-up home exercise program in between sessions.

In both the nonoperative and operative arms, subjects use acetaminophen and nonsteroidal anti-inflammatory agents as needed. Subjects with persistent pain or who are unable to tolerate these medications may receive codeine as needed. Intraarticular injections of corticosteroids are permitted at the discretion of the surgeon. Use of these medications and injections is documented carefully, permitting analysis of the role of these concomitant treatments on outcome and differential use of these treatments across randomized groups.

Outcome measures:

The WOMAC functional status scale,[21] assessed at six months, is the primary outcome measure. We gathered preliminary data on the performance of this scale in a pilot study among patients with OA and meniscal tear. In these patients, the WOMAC function scale was highly reliable (Cronbach's alpha 0.97) and valid, had little missing data (just 1%) and no ceiling or floor effects (unpublished pilot data). .

We measure secondary outcomes in several domains including pain, generic functional status, quality of life, and health care utilization. We measure pain and symptoms with the KOOS (Knee injury and Osteoarthritis Outcome Scale) pain and symptom scales.[22, 23] Each has been extensively validated. In our pilot work in subjects receiving APM, the WOMAC pain scale had a ceiling effect, with the top 25% of patients scoring a perfect 100. The KOOS pain scale (comprised of the five WOMAC pain items and four other items that tap symptoms typical of internal derangements) did not have this limitation. Both scales had Cronbach's alpha greater than 0.85. Therefore, we use the KOOS scale as our pain measure. We include the Physical Activity Scale of the SF-36, a widely used, reliable, valid generic health status measure shown to capture the functional burden of patients following APM.[24] We also include the five-item mental health index contained in the SF-36, which has been validated against clinical assessments of depression.[25] We administer the Euroqol (EQ-5D) for economic analyses. This five-item instrument assesses health-related quality of life in five domains and has been calibrated to measure utility in large national samples. It has been validated for use in samples with knee osteoarthritis.[26]

Assessments:

Timing (see Figure): We chose times of assessment to capture key milestones in the management of patients with meniscal tears in the presence of OA. We assess subjects prior to randomization and at three months to capture the early response to surgical or nonoperative therapy. The principal endpoint is at six months, at which point subjects have typically reached maximum improvement. We also evaluate subjects with questionnaires at 12, 18 and 24 months to characterize the trajectory of pain and function over the first two years. We contact subjects by phone every two weeks for the first three months after randomization and then quarterly until two years. (Of note, the time of reference is the date of randomization. These calls elicit data on health resource utilization, compliance with physical therapy, and pain and function to provide a detailed temporal profile of response to each intervention. Physical examinations are performed at enrollment and three months to document baseline impairments and the extent to which they are influenced by treatment. We are seeking funding to follow this cohort beyond two years to evaluate longer-term functional outcomes, subsequent surgeries and structural OA progression.

Blinding: MeTeOR is not a blinded study. Subjects know whether they were randomized to the surgical or nonoperative arms, as do the surgeons and research staff. While blinding with a sham control would have averted potential observer bias, our investigators were uncomfortable conducting sham surgery, felt that patients would not accept randomization to a sham procedure and felt that the hospitals would potentially be troubled by the legal and billing aspects of the sham procedure. The primary outcome measures are obtained from validated self-report questionnaires, with no involvement by the operating surgeon. This feature reduces the

possibility of observer bias, though we acknowledge that the subjects' own knowledge of their randomization status poses potential bias. All analyses will be performed with the analysts blinded to treatment assignment in order to avoid subtle biases in the interpretation of the findings.

Crossover, noncompliance and termination:

Crossover is defined as switching from the randomly assigned treatment arm to the other arm of the study. In a surgical RCT such as MeTeOR, a crossover occurs when a study subject assigned to the nonoperative arm undergoes surgery or when a subject assigned to the surgical arm does not have surgery but rather is treated nonoperatively. Because the primary analysis is "intention to treat," crossovers dilute the estimates of efficacy, if indeed there is a true difference in the treatment arms. While "as treated" analyses can be performed to compare the treatments actually received, these analyses lose the unique benefits of randomization – the random allocation of all measured and unmeasured patient characteristics across the treatment groups. We attempted to minimize crossover in both directions. For subjects randomized to surgery, we attempted to deliver the procedure within three weeks of randomization. For those randomized to nonoperative therapy, we attempted to maintain the treatment assignment at least until the primary endpoint was assessed at six months. We also did a full assessment at three months in order to capture all outcome measures on subjects that did cross over before the six-month mark. Crossover from nonoperative therapy to APM is informative because it likely reflects failure of nonoperative therapy to control symptoms and restore function. We anticipate that crossovers from surgery to nonoperative therapy will be less informative of the patient's clinical status and more reflective of logistical barriers in scheduling APM promptly.

Sample size and power:

The principal outcome measure is the WOMAC function scale at six months. We powered the study to detect a 10-point difference between the operative and nonoperative arms. This was the difference we noted in observational pilot data and was also in the range of the minimal clinically important difference in the WOMAC function scale among OA patients estimated by Angst et al.[27, 28] We adopted a Type I error rate of 5% and power of 80%. The sample size calculation took into account two sources of sample degradation: losses to follow-up and crossover from the assigned arm to the other arm prior to the primary outcome assessment at six months. We powered the study for one pre-planned subgroup analysis in which patients with KL Grade 3 (joint space narrowing) will be analyzed in one subgroup and those with KL Grades 0-2 in the other. The subgroup analysis is a formal multiplicative interaction and is powered as such.[29] On the basis of these considerations, we set the target sample size at 340 patients.

Analytic approach:

The primary analysis is a comparison of improvement in WOMAC function score between the surgical and the nonoperative groups, using the "intention to treat" approach, in which subjects are analyzed in the same group to which they were randomly assigned. Secondary analyses will use an "as treated" approach, in which patients are analyzed according to the treatments actually received. We will also perform a secondary "intention to treat" analysis in which the dependent variable is a failure indicator defined as failing to achieve a minimal clinically important improvement in WOMAC function score (8 points[27, 28]), or electing to cross

over to the other treatment arm. This analysis provides an estimate of efficacy of the patient, rather than group.

A formal economic analysis is planned as well, to determine the cost-effectiveness of APM as compared with nonoperative therapy in patients with symptomatic meniscal tear and concomitant OA. The analysis will incorporate accepted principles of cost-effectiveness analyses including a societal perspective and discounting of all costs and health benefits.[30]

Data management:

Study data are managed by the Data Coordinating Center (DCC) at Boston University School of Public Health. The DCC developed a secure, password-protected MeTeOR website for this trial, which is used for randomization, direct entry of some data (including screening and eligibility information, terminations, crossovers and serious adverse events) and communication across centers. The phone interviews, questionnaires, physical examination and surgical forms are sent to the DCC in hard copy. All data are housed on a secure network drive and backed up nightly.

Imaging assessment:

The research team received funding from the American Rehabilitation and Recovery Act to add an imaging component to MeTeOR. The principal goal of the imaging component is to determine whether either of the treatment arms is associated with more rapid progression of osteoarthritis. This is a critically important clinical policy question, as any effect of surgery on short-term outcomes should be viewed in the context of potential long-term risk of accelerated

progression of osteoarthritis. All MeTeOR patients are invited to an 18-month visit in which they undergo a knee MRI and a plain radiograph and complete an additional questionnaire. The MRI is performed on 3T scanners whenever possible and uses the same sequences as were used in each patient's baseline scan. Baseline and 18-month scans are de-identified and sent to the DCC for uploading to a secure imaging database.

The baseline and 18-month MRIs are scored using the MOAKS (MRI Osteoarthritis Knee Score) scoring system. MOAKS is a semiquantitative scoring system that incorporates elements from the WORMS (Whole Organ MRI Score) and BLOKS (Boston Leeds Osteoarthritis Knee Score) scoring systems.[31-34] It has undergone preliminary reliability testing and validation. Scans will be read paired (baseline and 18-month), but not blinded to order.[35] The readers will, however, be blinded to the subjects' treatment arm. The analyses of these data will examine whether the surgical and nonoperative groups differ with respect to loss of cartilage, change in the size or number of bone marrow lesions, synovitis/effusion, or size of osteophytes. The scans were obtained using clinical protocols and therefore do not have the appropriate cartilage-sensitive, three-dimensional sequences that would facilitate quantitative cartilage morphometry.

The 18-month radiographic exams use a SynaFlexer™ (Synarc Inc., San Francisco) frame for a standard fixed flexion views.[36] We hope to repeat the radiographs at five years using the same technique, permitting an analysis of longitudinal progression in joint space narrowing from 18 months to five years. The imaging component presented several challenges, including the lack of standardized baseline scans at the seven clinical scanners, the limitations of routinely

obtained knee MRIs for three-dimensional cartilage segmentation, and the possibility of secular change in equipment or sequences over the course of this longitudinal study. We note that routine clinical MRIs typically provide excellent assessment of cartilage defects.[37]

Summary:

MeTeOR asks a fundamental question: whether arthroscopic partial meniscectomy combined with physical therapy leads to better pain and functional outcomes than physical therapy alone for middle-aged and older patients with a symptomatic meniscal tear in the setting of mild to moderate osteoarthritis. Study staff enrolled 351 subjects at seven clinical centers between June, 2008 and August, 2011. Key challenges have included the issues of patient and physician equipoise, blinding, crossover and non-compliance and examination of imaging studies that were done originally for clinical rather than research purposes. We have addressed each of these challenges in our work with the intention of limiting their potential to threaten validity. We acknowledge that no single trial can resolve an important question unequivocally, but hope that MeTeOR helps clinicians and patients to make wise, evidence-based decisions about the common problem of symptomatic meniscal tear in the setting of knee osteoarthritis.

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Figure Legend: Flow diagram depicting enrollment and follow up procedures in MeTeOR trial.

Table One: Entry and Exclusion Criteria for the MeTeOR Trial	
Entry Criteria	*Rationale*
-age 45 years or greater	- higher likelihood of coexisting OA
-symptoms for at least four weeks, managed with one or more of: medications, activity limitations or PT	- unreasonable to operate prior to trying conservative therapy
-symptoms consistent with torn meniscus (at least one of: clicking, catching, popping, giving way, pain with pivot or torque, pain that is episodic, pain that is acute and localized to one joint line)	- surgery generally not done in absence of symptoms suggesting meniscal tear
-availability of knee radiograph and MRI	- required to ascertain eligibility
-evidence on knee MRI of osteophytes or full-thickness cartilage defect; *or* plain radiographic evidence of osteophytes or joint space narrowing	- documents signs of early OA
-evidence on knee MRI of a meniscal tear that extends to the surface of the meniscus	- documents meniscal tear
-willingness to undergo randomization and ability to understand and sign an informed consent document	
Exclusion criteria	*Rationale*
- a chronically locked knee (e.g. patient cannot reduce locking; a clear-cut indication for APM)	- locked knee is an indication for surgery
- Kellgren-Lawrence Grade 4 (far advanced OA)	- TKR typically more appropriate than APM in this setting
- inflammatory arthritis or clinically symptomatic chondrocalcinosis	- alternative source of pain and swelling
- injection with viscosupplementation in past four weeks in index knee	- could obscure treatment effects
- contraindication to surgery or physical therapy	
- bilateral symptomatic meniscal tears	- difficult to follow response to index knee
- prior surgery on same knee	- complex pathoanatomy

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