Workshop Report

# Which Is the Best Radiographic Protocol for a Clinical Trial of a Structure Modifying Drug in Patients with Knee Osteoarthritis?

Until recently, the development of pharmacologic agents for treatment of osteoarthritis (OA) has focused exclusively on the relief of joint pain and improvement of function. Interest is growing, however, in pharmacologic agents whose primary action is directed at inhibition of pathogenetic processes related to the breakdown of articular cartilage or, in some instances, to the changes in subchondral bone in the OA joint. Such agents were originally designated "chondroprotective" drugs. However, because of the recognition that OA is not merely a disease of cartilage but involves all of the tissues of the affected joint, more recently they have been called "disease modifying OA drugs" (DMOAD)[1].

A number of pharmaceutical companies and regulatory agencies hold high interest in the development of DMOAD — and of suitable outcome measures that are essential for their evaluation in a clinical trial. Such outcome measures must be sensitive to change in the thickness of articular cartilage, based on evidence of reproducibility[a] and accuracy[b].

Ideally, the outcome measures should also be simple and inexpensive. Although attention has been directed to magnetic resonance imaging, arthroscopy, and measurements in body fluids of the concentration of molecules derived from cartilage or bone as surrogate "biomarkers" of OA activity or predictors of OA progression, none of these has been validated. The widely accepted view today is that radiography remains the method of choice for evaluation of the efficacy of a DMOAD[2-4].

Which radiographic variable(s) linked to joint structure should be chosen as a primary outcome measure for a DMOAD study? A variety of methods have been proposed, but assessment of radiographic JSW is generally accepted as the most relevant[2-4]. In a study of 20 knees of patients with OA and 14 radiographically normal knees[5], JSW in microradiographs taken in the weight-bearing "tunnel" view showed a highly significant correlation with the sum of the thicknesses of the femoral and tibial articular cartilage in the medial tibiofemoral (MTF) compartment, as measured in a non-weight-bearing lateral view of a double contrast macroarthrogram of the same knee. Notably, JSW was smaller than the summed thickness of the cartilages, reflecting compression of the cartilage in weight bearing. Thus, JSW in a standing knee radiograph reflects both the degree of compressibility of the cartilage in weight-bearing (which increases in OA) and the thickness of the cartilage (which may either increase or decrease in OA, depending on the stage of the disease).

In the hope that knee radiography can serve as a satisfactory outcome measure in DMOAD trials, a number of investigators have recently attempted to develop improved radiographic methodology. To discuss the current status of radiologic/radiographic techniques for DMOAD studies in patients with knee OA, NEGMA-LERADS convened an *ad hoc* advisory board and held a workshop in Toussus-le-Noble, France, January 17-18, 2002. The participants, all of whom had developed relevant methodologies and had generated data relevant to imaging of the OA knee that had been published in peer reviewed journals, were asked to address the following questions:

- Are any of the radiographic protocols that have been recommended for use in DMOAD studies suitable for demonstrating the efficacy of a drug that significantly slows the rate of loss of articular cartilage in patients with knee OA in a randomized placebo controlled trial involving a "reasonable" number of subjects and a "reasonable" duration of treatment?
- If the answer to the above question is "no," might additional analyses be performed on existing databases that could result in an affirmative answer?
- Are none of the existing radiographic techniques suitable for studying the efficacy of a putative DMOAD in patients with knee OA?

A summary of the discussion and the conclusions reached by the Board are presented below.

[a]Reproducibility is precision in measurement. An instrument affords reproducible measurement to the extent that repeated estimates of an object of constant value [e.g., joint space width (JSW) in multiple radiographs obtained on the same day] yield identical results.

[b]Accuracy is *validity* in measurement. An instrument is accurate to the extent that a measurement in question and variation in measurements between subjects correspond closely to the true values, as determined by the accepted criterion or 'gold standard.' The accuracy of radiographic JSW as a measure of articular cartilage thickness may be determined at autopsy in cadaver knees or by arthrography in living subjects.

## THE CONVENTIONAL STANDING EXTENDED VIEW KNEE RADIOGRAPH. CAN ITS INHERENT LIMITATIONS BE OVERCOME?

For more than 30 years the standing anteroposterior (AP) knee radiograph (i.e., a bilateral weight-bearing view of both knees in full extension) has been the conventional image employed for plain knee radiography (Figure 1)[6,7] and the accepted radiographic technique for characterizing the bony changes of OA (e.g., osteophytosis, subchondral sclerosis). This technique is severely limited, however, as a means by which to visualize reproducibly the thickness of the articular cartilage, an estimate of which is usually made from the interbone distance in the MTF compartment[8]. This limitation stems from numerous shortcomings of the technique with respect to variability in the positioning of the knee in serial examinations [e.g., changes in extension, nonstandardized alignment of the x-ray beam and medial tibial plateau (Figure 2), variable distance between the knee and x-ray cassette].

Further, changes in joint pain from examination to examination affect the positioning of the knee in serial standing AP radiographs (i.e., the greater the severity of standing knee pain, the less the extension of the joint) and thereby alter radiographic JSW[9]. This finding is relevant to recent reports that concluded that, in comparison with placebo, treatment with glucosamine sulfate over 3 years prevented joint space narrowing (JSN) in paired radiographs obtained with the standing AP technique[10,11]. It is possible that the concomitant reduction in joint pain seen in the glucosamine arm, relative to the placebo arm, altered the positioning of the knee, resulting in a change in JSW that might have confounded estimates of JSN in individual knees and exaggerated the difference in mean rate of JSN between treatment groups.

Nonetheless, because the standing AP radiograph can be readily obtained in any clinical radiology department, before considering less universally available alternatives for use in multicenter studies of a DMOAD, it is important to examine whether its limitations can be circumvented. Possible solutions include the use of uniform guidelines for performance of the examination, use of an optimal approach to measurement of radiographic JSW, and an increase in sample size and/or duration of treatment in a DMOAD trial to compensate for the magnitude of error in measurement of JSW associated with changes in joint position in serial examinations.

*Guidelines for uniform positioning*. Examination by Ravaud, *et al*[12] of the effects on radiographic JSW of variations in positioning of the knee (i.e., knee flexion, external foot rotation) and in the radiologic procedure (i.e., angle and

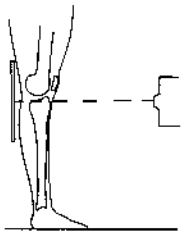
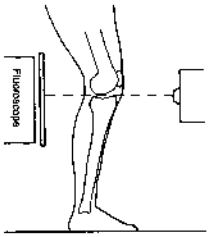
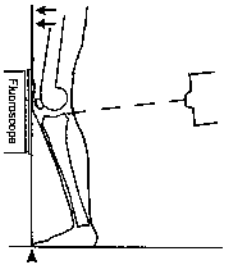
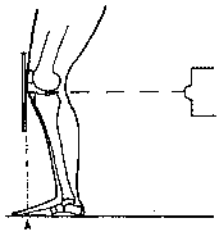
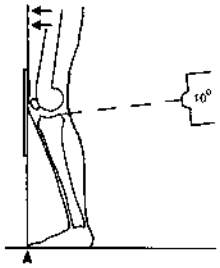
| | Standing AP View | Semiflexed AP View | Lyon Schuss View | Semiflexed Metatarsophalangeal (MTP) View | Fixed-flexion PA view |
|---|---|---|---|---|---|
| |  |  |  |  |  |
| **Fluoroscopically Assisted?** | No | Yes | Yes | No | No |
| **Position of the knee** | Extension of the knee to make contact with the x-ray cassette | Knee flexion, as needed, to superimpose (±1 mm) the anterior and posterior margins of the medial tibial plateau | Patellae and thighs in contact with film cassette (arrows) and coplanar with the tips of the great toes (arrowhead) | 1st MTP joints beneath the front surface of the film cassette (arrowhead); patellae in contact with the cassette and aligned vertically with 1st MTP joints | Patellae and thighs in contact with film cassette (arrows) and coplanar with the tips of the great toes (arrowhead) |
| **Flexion of the knee** | 0° | 7–10° | 20–35° | 7–10° | 20–35° |
| **Angulation of the x-ray beam** | Horizontal | Horizontal | As needed, to align the medial tibial plateau with the beam | Horizontal | 10° downward |
| **Rotation of the foot** | No standard | As needed, to center the tibial spines beneath the femoral notch | As needed, to center the tibial spines beneath the femoral notch | 15° external | 10° external |

*Figure 1*. Comparison of positioning of the subject for the conventional standing AP knee view and for fluoroscopically and nonfluoroscopically assisted protocols designated to standardize the positioning of the knee.

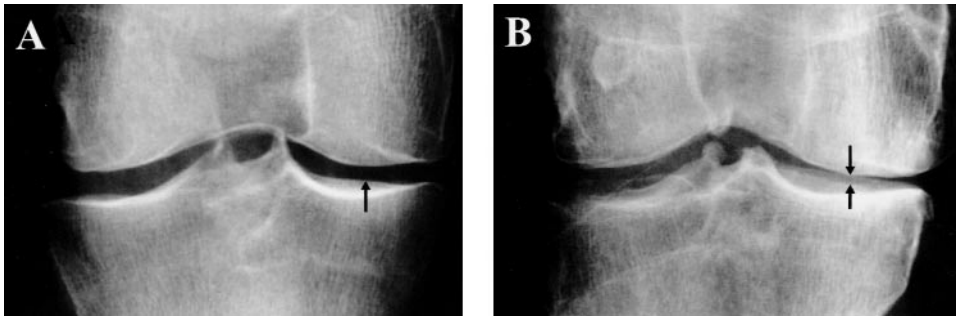



*Figure 2*. Conventional standing AP radiographs in which the medial tibial plateau and x-ray beam are (A) aligned in parallel [anterior and posterior margins of the plateau superimposed (±1 mm, arrow) and (B) not aligned (intermargin distance > 1 mm, arrows].

focus of the x-ray beam) in the standing AP knee examination led to the conclusion that 0° knee flexion, 15° external foot rotation, and 5° downward beam inclination improved the precision of JSW measurements in repeated examinations by 50%, in comparison with the conventional standing AP examination performed without positioning guidelines (Table 1)[12,13]. However, no published evidence exists to indicate whether the sensitivity of the standing AP radiograph to JSN is improved by the use of these guidelines.

*Method of measurement of JSN*. Previous studies of JSN in the conventional standing AP view of the OA knee have employed a variety of manual and automated methods of measurement of radiographic JSW (Table 2)[10,11,14-20]. Manual procedures entail the use of a calipers, ruler and/or magnifying lens to measure JSW at either its narrowest point (i.e., minimum JSW) or at a predetermined location (e.g., the midpoint) within the MTF compartment (Figure 3). Automated systems of JSW measurement use digital

*Table 1*. Studies of comparative reproducibility of conventional and standardized protocols for knee radiography.

| Reference | X-ray Protocol(s) | Measurement Procedure | Site of Medial JSW Measurement | No. of Repeated Exams | Interval Between Exams | No. and Types of Knees | Mean JSW, mm | $SE_m$, mm | CV of JSW, % |
|---|---|---|---|---|---|---|---|---|---|
| 12 | Conventional extended view without positioning guidelines | Magnifying glass | Midpoint | 2 | 2 wks | 20 normal | 6.36 | 0.66 | 10.3 |
| 12 | Extended view with guidelines (without fluoroscopy) | Magnifying glass | Midpoint | 2 | 2 wks | 20 normal | 6.36 | 0.37 | 5.8 |
| 12 | Extended view with guidelines and fluoroscopy | Magnifying glass | Midpoint | 2 | 2 wks | 20 normal | 6.36 | 0.30 | 4.7 |
| 13 | Extended view with guidelines (without fluoroscopy) | Magnifying glass | Midpoint | 2 | 2 h | 36 OA | 4.31 | 0.32 | 7.4 |
| 24 | Standing AP | Automated | Minimum | 4 | 4 wks | 10 normal, 25 OA | ? | 0.29<br>0.37 | 6.2<br>8.9 |
| 24 | Semiflexed AP | Automated | Minimum | 4 | 4 wks | 10 normal, 25 OA | ? | 0.11<br>0.19 | 3.2<br>5.5 |
| 31 | Standing AP | Automated | Minimum | 2 | < 2 h | 41 normal, 33 OA | ? | 0.19 | 3.7 |
| 31 | Tunnel PA | Automated | Minimum | 2 | < 2h | 41 normal, 33 OA | ? | 0.11 | 2.3 |
| 31 | Semiflexed MTP | Automated | Minimum | 2 | < 2 h | 41 normal, 33 OA | ? | 0.08 | 1.6 |
| 32 | Fixed-flexion PA | Graduated lens | Minimum | 2 | < 1 h | 18 normal, 10 OA | 5.2<br>2.5 | 0.3<br>0.2 | 5.8<br>8.0 |
| 32 | Fixed-flexion PA | Automated | Minimum | 2 | < 1 h | 18 normal, 10 OA | 5.3<br>2.8 | 0.1<br>0.1 | 1.9<br>3.6 |
| 35 | Fixed-flexion PA with SynaFlex™ Frame | Automated | Minimum | 2 | < 1 mo | 30 OA | 3.58 | 0.18 | 5.0 |

$SE_m$: Standard error of measurement ($SE_m$), i.e., the standard deviation of a theoretical distribution of JSW measurements from repeated examinations. CV of JSW: Coefficient of variation of JSW ($SE_m$/mean JSW × 100%).

*Table 2*. Longitudinal studies of joint space narrowing (JSN) in knee OA.

| X-ray Protocol/Reference | System/Location of JSW Measurement | Mean Duration, yrs | Groups/Subgroups Analyzed | No. of OA Knees | JSN, mm, mean ± SD | Rate of JSN, mm/yr | CV of JSN, % | SRM of JSN |
|---|---|---|---|---|---|---|---|---|
| Standing AP | | | | | | | | |
| 14 | Automated/area | 2 | Combined chondroitin sulfate and placebo (PBO) groups from a RCT | 323 | 0.18 ± 0.69 | 0.09 | 383 | 0.26 |
| 15 | Manual/minimum | 2.6 | Combined OA cohorts from the US & UK | 402 | 0.37 ± 1.25 | 0.14 | 338 | 0.30 |
| 16 | Manual/midpoint | 3 | Bristol OA 500: right knee | 145 | 0.29 ± 0.92 | 0.10 | 317 | 0.32 |
| | | | Bristol OA 500: left knee | 145 | 0.31 ± 1.06 | 0.10 | 342 | 0.29 |
| 10 | Automated/area | 3 | PBO group from a glucosamine RCT | 106 | 0.31 ± 0.90 | 0.10 | 290 | 0.34 |
| | Manual/minimum | | | | 0.41 ± 1.21 | 0.14 | 295 | 0.34 |
| 11 | Manual/minimum | 3 | PBO group from a glucosamine RCT | 101 | 0.19 ± 0.50 | 0.06 | 263 | 0.38 |
| 17 | Manual/minimum | 3 | Clinical OA cohort | 150 | 1.80 ± 1.75 | 0.60 | 97 | 1.03 |
| 18 | Manual/minimum | 4 | Population based cohort (BLSOA) | | | | | |
| | | | Women with OA at baseline | 19 | 0.24 ± 0.56 | 0.06 | 233 | 0.43 |
| | | | Men with OA at baseline | 17 | 0.36 ± 0.68 | 0.09 | 189 | 0.53 |
| 19 | Manual/minimum | 8 | Population based cohort (Farmingham) | 40 | 0.81 ± 1.05 | 0.10 | 130 | 0.77 |
| 20 | Automated/area | 11 | Clinical OA cohort | 63 | 0.38 ± 1.96 | 0.03 | 516 | 0.19 |
| Semiflexed AP | | | | | | | | |
| 28 | Automated/minimum | 2.5 | Clinical OA cohort | | | | | |
| | | | 16 mo followup | 285 | 0.31 ± 0.64 | 0.23 | 206 | 0.48 |
| | | | 30 mo followup | 199 | 0.55 ± 0.75 | 0.22 | 136 | 0.73 |
| Lyon schuss | | | | | | | | |
| 25 | Automated/area | 1 | Clinical OA cohort | 19 | 0.41 ± 0.70 | 0.41 | 171 | 0.59 |
| Semiflexed MTP | | | | | | | | |
| 34 | Manual/minimum | 1.2 | Clinical OA cohort | 27 | –0.16 ± 0.84 | –0.13 | 525 | 0.19 |
| Fixed flexion PA | | | | | | | | |
| 35 | Manual/minimum | 1 | Clinical OA cohort | 39 | 0.18 ± 0.51 | 0.18 | 283 | 0.35 |

CV of JSN: Coefficient of variation of JSN: an estimate of the sensitivity of an instrument to true change (see Footnote c). SRM: Standardized response mean: an alternative expression of the sensitivity of an instrument (SRM = mean/SD). The SRM of JSN in treatment groups is directly related to the statistical power of a DMOAD trial.

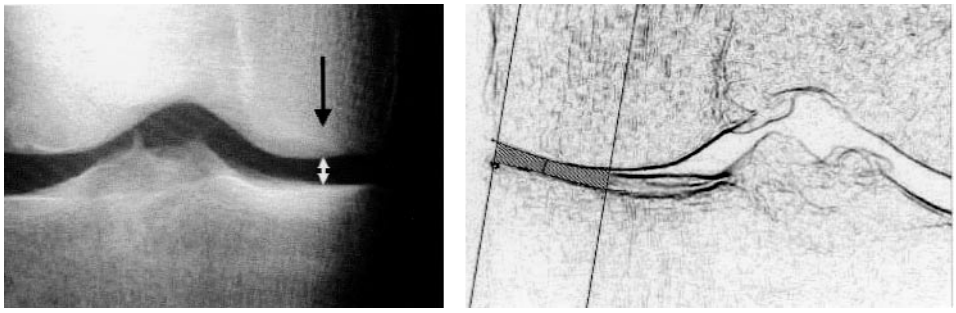


*Figure 3*. Illustrations of minimum joint space width (JSW, arrow) in the medial tibiofemoral compartment (left) and digital image analysis of joint space area (between the parallel lines), within which mean JSW can be estimated (right).

image analysis with specialized edge detection software[21-23] to identify the margins of the joint space (Figure 3) and quantify joint space area, mean JSW or minimum JSW across a horizontal span of predetermined width (e.g., 1 cm).

Table 2 presents a summary of the methods and results of 9 previous longitudinal studies of the radiographic progression of knee OA that employed the standing AP view[10,11,14–20]. The mean annual rate of JSN varied 20-fold (i.e., 0.03–0.60 mm/yr) across these studies over mean intervals of followup ranging from 2–11 years. However, because the Advisory Board considered 3 years to be the practical limit for the duration of treatment in a DMOAD trial, 6 studies of 2–3 years duration conducted in clinical OA populations were considered to be particularly relevant to the design of a DMOAD trial[10,11,14-17]. With only one exception[17], in which the annual rate of narrowing was > 4-fold more rapid than any of the others, estimates of the annual rate of JSN over 2–3 years fell within a fairly narrow range (0.06-0.14 mm/yr)[10,11,14-16]. Similarly, the coefficient of variation[c] (CV) of JSN in these studies varied within a relatively narrow range (263–383%).

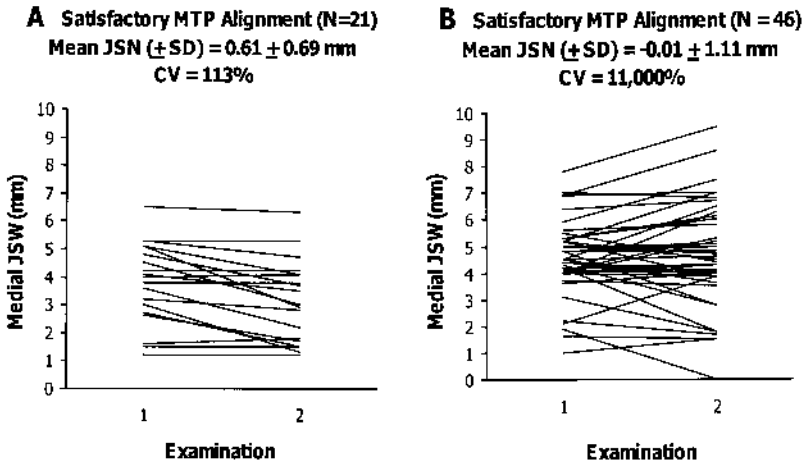



*Figure 4*. Plots of joint space narrowing (JSN) in paired conventional standing AP knee radiographs (mean interval between examinations 1 and 2 = 2.6 yrs) when radioanatomic alignment of the medial tibial plateau is present in both (A) and absent in both (B). Note the heterogeneity of within-subject changes in radiographic joint space width (JSW) in radiographs that do not exhibit satisfactory alignment of the medial tibial plateau and x-ray beam, compared to radiographs in which satisfactory parallel alignment is uniform.

Two of the studies of clinic patients with OA[10,14] employed automated measurement of mean JSW, and one[10] used both automated and manual measurements of JSW. In comparison with descriptions of radiographic JSN over 2 to 3 years based on manual measurements of the minimum or midpoint JSW, studies using automated measurements of JSW were no more likely to result in either a consistent annual rate of JSN within the observed range or, more importantly, a decrease in within-subject variability in JSN, relative to the mean (Table 2). Therefore, for detection of a significant difference in the rate of JSN among treatment groups in a DMOAD trial, the limitations of the conventional knee radiograph are not likely to be overcome by the method chosen to measure JSW.

*Sample size*. In principle, a given degree of error variance in measurements of radiographic JSN in a DMOAD trial can be overcome by an appropriate increase in the number of subjects randomized to treatment groups. However, the large values for the CV of JSN (263–383%) in previous studies of 2 or 3 year OA progression measured in serial standing AP radiographs (Table 2) suggest that overcoming the limitations of conventional knee radiography solely with increased numbers of subjects will be prohibitively costly and time-consuming.

[c]The CV of JSN is an estimate of the magnitude of between-subject variability in JSN (including true narrowing and error variation), relative to the mean of JSN (the unbiased estimate of the true change in JSW) in a sample. The CV of JSN in the placebo group of a DMOAD trial is inversely related to statistical power; i.e., the larger the CV (or more heterogeneous the variability) of JSN within the placebo group, the more subjects and/or the longer duration of treatment will be needed to detect a significant difference between treatment groups with respect to mean JSN. [CV of JSN = SD of JSN ÷ mean JSN × 100%.]

This conclusion is best illustrated by a recent analysis of radioanatomic positioning and JSN in paired standing AP radiographs from 3 research cohorts (Indianapolis, Bristol, Nottingham), in which parallel alignment of the medial tibial plateau and x-ray beam in both images of the pair occurred by chance in only 14% of 402 OA knees[15]. In this select subsample, JSN over 2 to 3 years progressed at a mean annual rate of 0.26 mm/year, with a CV of JSN of 104%, i.e., at almost twice the rate and with only one-fourth the variability, observed in the remaining 86% of knees, in which alignment of the plateau was unsatisfactory in one or both images.

The effect of uniform alignment of the medial tibial plateau and x-ray beam (defined as superimposition ± 1 mm of the anterior and posterior margins of the plateau in serial radiographs) is illustrated in data from one of the 3 cohorts examined by Mazzuca, *et al*[15] (Figure 4). Uniform alignment in 21 OA knees (19% of all knees in the cohort with radiographic evidence of OA at baseline) resulted in remarkable homogeneity in the rate of JSN over a mean interval of 2.6 years (CV = 113%). In comparison, in 46 OA knees in which misalignment of the medial tibial plateau (i.e., distance between anterior and posterior margins > 1 mm) was apparent in both members of the paired radiographs, the underlying annual rate of JSN was obscured (–0.004 mm/yr) and the SD of JSN was 61% larger than that in knees in which alignment was satisfactory (1.11 mm, 0.69 mm, respectively)[15].

What are the practical consequences for a DMOAD trial of the degree of homogeneity of JSN? The effect of the CV of JSN in the placebo group of a DMOAD study is illustrated in Figure 5, which considers a theoretical 30 month trial in which the mean rate of JSN in the placebo group is

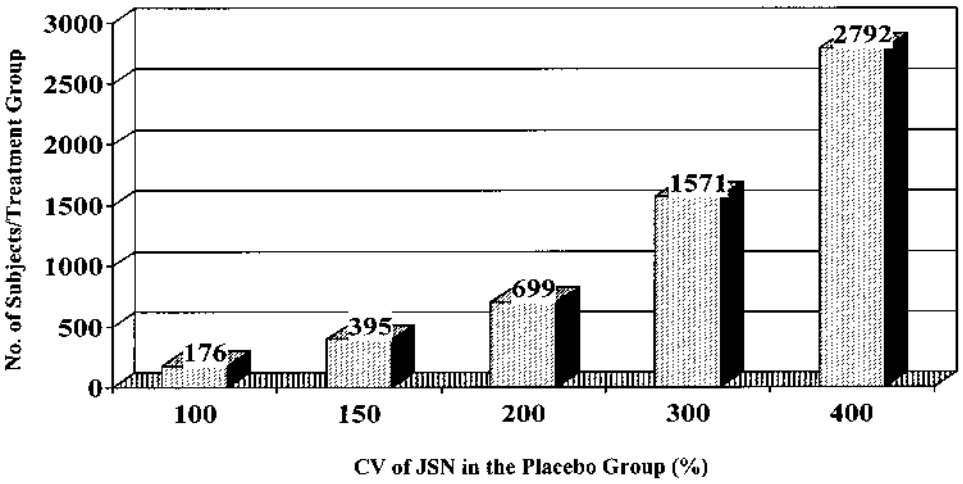



*Figure 5*. Effect of the coefficient of variation of cumulative joint space narrowing (JSN) in the placebo group on sample size requirements for a fictitious 30 month DMOAD trial designed to detect a 30% decrease in the annual rate of JSN in the active treatment group, compared to that in the placebo group in which the rate of JSN in the placebo group is assumed to be (0.10 mm/yr).

0.10 mm/yr, as suggested by previous studies in clinic populations (Table 2). Under ideal conditions of uniform alignment in all radiographs (CV of JSN = 100%), only 176 subjects per treatment group would be needed for an intent-to-treat analysis to detect a 30% DMOAD effect (i.e., a 30% decrease in the rate of JSN in the active treatment group, in comparison with the placebo group) with 80% power and $\alpha = 0.05$. As the radiographs become more heterogeneous (less standardized) with respect to alignment, and as the CV of JSN in the placebo group rises accordingly into the range found in conventional radiographic studies of JSN over 2-3 years (i.e., 300–400%), the sample size requirements increase nearly *16-fold*, i.e., to nearly 3000 subjects per treatment arm.

The Advisory Board recognized that any increase in sample size in a DMOAD trial would bring with it a proportional increase in the number of participating clinical centers, demands for multicenter coordination and quality control, and associated costs. Therefore, given the magnitude of the effect on overall sample size requirements imposed by heterogeneity of JSN in the placebo group (Figure 5), the Board concluded that it would be impractical and prohibitively costly to attempt to overcome the limitations of the conventional standing AP knee view in a 2-3 year DMOAD trial by increasing the number of subjects enrolled.

*Duration of treatment*. The precision with which JSW can be measured with a given set of radiographic and mensural procedures can be used to define a tolerance (e.g., a 95% confidence interval) around individual estimates of baseline JSW, within which changes observed in a followup examination should not be interpreted as being "true" JSN (i.e., beyond the margin of measurement error). However, as the interval between examinations increases and true biological (or pathological) change in JSN has more time to manifest itself, the finite magnitude of the error associated with serial measurements of JSW should represent a smaller proportion of the total variance in JSN. Some rationale exists, therefore, for considering that the limitations of the conventional standing AP radiograph with respect to reproducibility of JSW measurement might be overcome by the length of a DMOAD trial.

The Advisory Board examined the results of 5 longitudinal studies[10,11,14-16] of radiographic JSN in knee OA in which the duration of followup was ≤ 3 years, the practical limit for the duration of a DMOAD trial. In one study of 2 years' duration,[15] the CV of JSN was 383%; in another, in which the mean duration of treatment was 2.6 years, it was 338% (Table 2)[15]. Among 3 studies of 3 years' duration[10,11,16], the average CV of JSN was about 300%. Consistently smaller CV of JSN in measurements taken from serial standing AP radiographs have been achieved only in epidemiologic studies of the natural history of knee OA over intervals of 4-8 years[18,19].

While it appeared that the overall effect of measurement error, as a component of the between-subject variability in JSN, diminishes as the time between examinations increases, practical considerations would generally limit the duration of a DMOAD trial to 3 years. The degree of heterogeneity of JSN associated with 3 year studies of JSN in knee OA[10,11,16] (CV = 300%) suggests that data from at least 1571 subjects per treatment arm would be required for an intent-to-treat analysis of a 30% DMOAD effect (Figure 5) in a study of maximum practical duration. Further reductions in sample size could be achieved only by extending the duration of treatment beyond the practical limit.

## STANDARDIZED RADIOANATOMIC POSITIONING OF THE KNEE. FLUOROSCOPICALLY ASSISTED PROTOCOLS

Fluoroscopically assisted protocols for standardized knee radiography have been described (Figure 1)[12,24,25]. Their strengths and limitations, relative to ensuring an accurate and reproducible image of the MTF compartment joint space, are summarized in Table 3.

*Extended AP view obtained with positioning guidelines.* Ravaud, *et al*[12] examined in detail the possibility that performance of the extended view radiograph obtained with positioning guidelines (see above) can be improved by use of fluoroscopy to adjust knee flexion and rotation and angulation of the x-ray beam on a patient-by-patient basis. Based on their analysis, they concluded that the addition of fluoroscopy increased the reproducibility of JSW measurements only marginally (Table 1)[12,13].

*Semiflexed AP view.* Buckland-Wright, *et al*[24] have described a fluoroscopically assisted protocol in which the positioning standards for alignment of the tibial plateau with a horizontally directed x-ray beam result in semiflexion (7-10° of flexion) of the knee in most subjects (Figure 1). Horizontality of the beam prevents distortion of the joint space due to parallax. However, semiflexion of the knee draws the joint away from the x-ray cassette and introduces radiographic magnification, a potential obstacle to accurate JSW measurement. Therefore, the semiflexed AP protocol requires use of a foot map to reproduce the joint-to-film distance and a magnification marker (i.e., a small steel ball affixed to the skin over the head of the fibula) to permit correction of JSW estimates for variations in radiographic magnification, which may be as great as 35%.[24]

The semiflexed AP view, with magnification correction, has been shown to permit remarkable precision in the measurement of JSW, compared to the conventional standing AP view (Table 1)[24]. A field test of this protocol in 5 clinical radiology units showed that radiology technologists varied with respect to the ease with which they could learn to perform the examination according to its standards for radioanatomic positioning of the knee[26]. However, when the examination was performed according to specifications, the reproducibility of magnification-corrected JSW measurements compared well to that originally demonstrated by Buckland-Wright, *et al*.[24] In a recent field test of this protocol in 50 radiology centers in North America and Europe, 6% of centers experienced difficulty acquiring expertise with fluoroscopic positioning; however, in a study of 146 knees, 45% of repeated measurements of JSW were within 0.1 mm, and 92% within 0.3 mm[27]. Further, because the standards for knee flexion dictate the position of the joint for imaging, the semiflexed AP view (and perhaps other standardization protocols) may be free of the confounding effect on JSW of longitudinal changes in knee pain that is seen in the standing AP radiograph[9].

Although the semiflexed AP protocol has been implemented in several industry sponsored DMOAD clinical trials, published reports of its sensitivity to JSN over time are not available. This protocol is currently in use also in investigator initiated studies sponsored by the National Institutes of Health (NIH). Because one is a placebo controlled multicenter RCT that continues to operate under an experimental blind, the sensitivity of the semiflexed AP examination with respect to rates of JSN in that study is unknown. However, preliminary data from the second study, a non-interventional study of the radiographic progression of knee OA in 253 subjects[28], indicate that the semiflexed AP view permits consistent estimations of the rate of JSN (0.22–0.23 mm/yr), based on followup examinations performed 16 months and 30 months after the baseline examination (Table 2). Indeed, the CV of JSN over 30 months (136%) in 199 OA knees examined to date is less than half as large as that in studies using conventional standing AP radiographs obtained over a similar interval. This finding is particularly notable in light of the fact that

*Table 3.* Strengths and limitations of current protocols for standardized knee radiography with respect to assuring an accurate and reproducible image of the medial tibiofemoral compartment joint space.

| | View in Fluoroscopic Positioning | | | View in Nonfluoroscopic Positioning | |
|---|---|---|---|---|---|
| Standard for Radioanatomic Positioning | Extended, with Positioning Guidelines[12] | Semiflexed AP[24] | Lyon Schuss[25] | Semiflexed MTP[31] | Fixed Flexion PA[32] |
| Parallel radioanatomic alignment of the medial tibial plateau | + | + | + | +/–* | +† |
| Knee rotation | + | + | + | + | + |
| Reduction of magnification effects | | +†† | + | + | + |
| Fixation of the femorotibial angle | | | + | | + |
| Negation of parallax distortion | | + | | + | |

* Parallel alignment achieved in only 32% of knees; alignment was highly reproducible in repeat examinations performed on the same day, but not in serial examinations > 1 year apart.

† Supporting data have been presented only in abstract form.

†† Requires use of a magnification marker to correct for radiographic magnification.

7% of knees exhibited significant increases in radiographic JSW over 30 months (i.e., ≥ 0.5 mm) despite uniformly high quality with respect to alignment, knee rotation, and control for radiographic magnification (Figure 6).

The advance in standardized knee radiography represented by the semiflexed AP view was recognized by the Advisory Board. However, some concern was expressed about the extent to which several aspects of this protocol may limit its potential to detect JSN with optimal sensitivity (CV of JSN = 100%) within the time frame of a DMOAD trial: First, the correction of JSW values for radiographic magnification may be compromised by variation in x-ray penetration of plain radiographs,[29] although, this limitation may be circumvented as digital radiography becomes more common. Second, the femorotibial angle is not standardized in this protocol, permitting changes in the contact point between the femoral and tibial articular cartilage on serial examinations (Figure 7). Finally, the protocol for the semiflexed AP view does not prevent changes in weightbearing and the resulting degree of compression of articular cartilage in serial examinations. The latter two limitations may help explain the increase in the apparent thickness of articular cartilage seen occasionally in serial semiflexed AP radiographs of high technical quality (Figure 7). It is important to point out, however, that the frequency with which significant increases in JSW occur with the other protocols described here is unknown; no direct comparisons of the mean annual rate and variability of JSN have been made in subjects imaged concurrently with alternative protocols.

*Lyon schuss view.* Vignon, *et al*[14] have developed a protocol that requires a greater degree of flexion (28-35°) than the semiflexed AP view and, in contrast to a radiograph obtained in full knee extension or to the semiflexed AP view, provides contact between the femur and tibia in the posterior aspect of the femoral condyle, i.e., the region in which cartilage damage in OA is usually most prominent (Figure 7)[30]

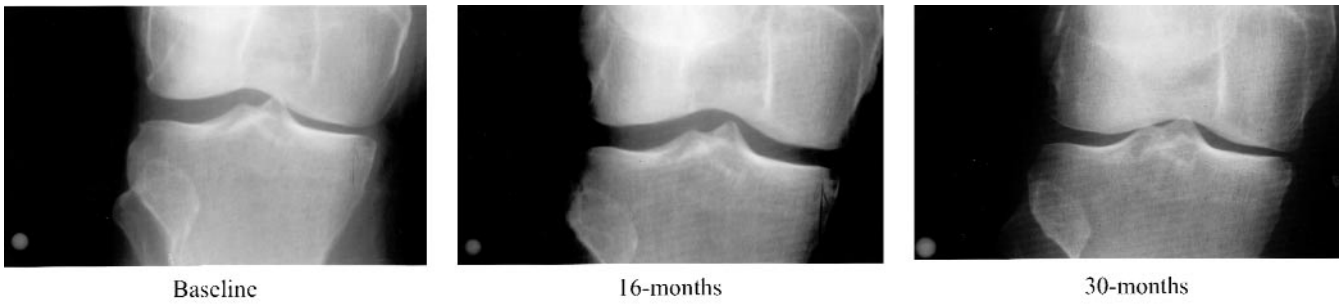



*Figure 6.* Serial semiflexed AP radiographs of knee obtained at baseline, 16 months, and 30 months. All radiographs were satisfactory with respect to parallel alignment of the medial tibial plateau and x-ray beam [i.e., anterior and posterior margins superimposed (± 1 mm), knee rotation (tibial spines centered under the femoral notch), and placement of the radioanatomic magnification marker (affixed to the skin over the head of fibula)]. Nonetheless, joint space width in the 16 month image is clearly larger than that in the baseline or 30 month images.

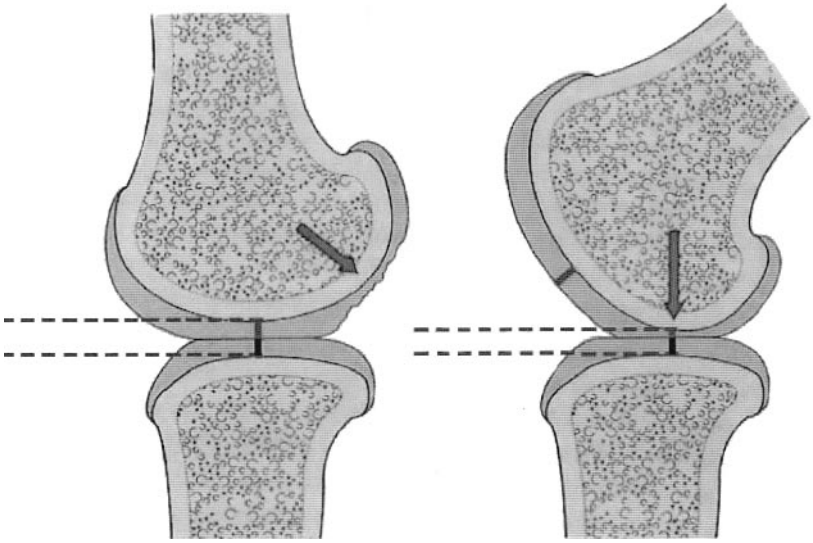


*Figure 7.* Effect of variation in the femorotibial angle on the point of contact and, therefore, on the apparent thickness of the articular cartilage between tibia and femur (broken lines), even when the medial tibial plateau and x-ray beam are in parallel alignment. The marked thinning of the cartilage as a reduction in the interbone distance (i.e., joint space width) at the posterior aspect of the femoral condyle (arrow) would be apparent if the femorotibial angle were increased (right), in comparison with an image obtained with the knee in full extension (left).

.In the posteroanterior (PA) Lyon schuss view (Figure 1) the patella is coplanar with the anterior aspect of the hip and tip of the great toe and in contact with the x-ray cassette. To compensate for the effect of this position on the angle of the medial tibial plateau, relative to the horizontal, fluoroscopy is used to adjust the angle of the x-ray beam downward to bring the tibial plateau into sharpest focus. Positioning of the knee against the x-ray cassette minimizes the degree of radiographic magnification and placement of the hip against the vertical x-ray table (coplanar with the patella) fixes the femorotibial angle.

Although alignment of the tibial plateau with the x-ray beam is seen in only about 60% of Lyon schuss examinations, this technique affords a high degree of precision: the CV of JSW on 3 examinations performed on the same joint within a single day was 3.5%.[25] In a 1 year study of a small clinical OA cohort (N = 19 knees), the CV of JSN (171%) was notably smaller than that in studies of 2–3 years duration that employed conventional standing AP radiographs (Table 3).

*Limitations of fluoroscopy in a multicenter clinical trial*. An appraisal of the fluoroscopically assisted protocols with respect to the precision of measurement of JSW and resulting sensitivity in detection of JSN must include several practical limitations of these techniques when they are exported for use in multicenter clinical trials. Notably, many clinical centers with strong track records of recruitment of subjects with knee OA for clinical trials of pain medications (which may require only a conventional standing AP radiograph to confirm eligibility of the subject at baseline) do not have ready access to the required fluoroscopic equipment. In the United States, even among clinical centers that have access to such equipment, a shortage and high rates of turnover of radiology technologists make maintenance of quality control of radiographs with respect to criteria for radioanatomic positioning difficult. Further, ethical and practical considerations (e.g., cumulative radiation exposure, willingness of subjects) may limit attainment of uniformly high technical quality by precluding repetition of substandard examinations. Finally, fluoroscopic positioning increases the cost of a radiographic knee examination 3- to 4-fold.

## STANDARDIZED RADIOANATOMIC POSITIONING OF THE KNEE. NON-FLUOROSCOPICALLY ASSISTED PROTOCOLS

For the reasons listed above, considerable effort has been devoted to development of non-fluoroscopically assisted radiologic procedures[31,32] that use empirically derived standards for knee flexion, foot rotation, and angulation of the x-ray beam as an alternative to fluoroscopically guided positioning of the joint (Figure 1).

*Semiflexed MTP view.* Buckland-Wright, *et al*[31] have developed a non-fluoroscopic alternative to their semiflexed AP view of the knee, namely the semiflexed metatarsophalangeal (MTP) view, which provides a PA radiograph of both knees with the subject standing so that the MTP joints of both great toes are directly beneath the front surface of the x-ray cassette and the patellae in contact with the cassette, directly above the MTP joints (Figure 1).

The reproducibility of the semiflexed MTP view has been demonstrated by its author with respect to minimum JSW and alignment of the medial tibial plateau and x-ray beam in examinations repeated on the same day[33]. In comparison with the conventional standing AP view and a non-fluoroscopic PA tunnel view obtained with the knee flexed to 30º, it exhibited superior precision in JSW measurements (CV of JSW = 1.6% vs 2.3% and 3.7%, respectively; Table 1) and reproducibility of positioning of the medial tibial plateau[31]. (NB: Although the tunnel view in this article was called a schuss view by the authors, this technique should not be mistaken for the Lyon schuss view described above. In contrast to the latter, the tunnel view that was evaluated did not fix the femorotibial angle or provide fluoroscopically assisted angulation of the x-ray beam.) Notably, nearly 70% of the initial MTP examinations resulted in non-parallel alignment of the medial tibial plateau and x-ray beam[31], a finding of concern in view of recent evidence that misalignment of the medial tibial plateau in the conventional standing AP view (even when the intermargin distance is reproduced ± 1 mm in the followup examination) greatly impairs sensitivity in the detection of JSN[15].

A field test of the semiflexed MTP view, currently in progress[34], has confirmed that this view results in parallel alignment of the tibial plateau and x-ray beam in only about 30% of cases. Consistent with the findings of Buckland-Wright, *et al*[31], alignment of the medial tibial plateau in the initial semiflexed MTP examination was highly correlated with that in a second examination performed on the same day (r = 0.89). However, preliminary data indicate that reproducibility of positioning with the semiflexed MTP protocol was not as good in examinations performed 14 months apart[33]. In results from serial examinations of 27 OA knees, the correlation between JSW measurement in serial radiographs was only moderate (r = 0.52). Changes in JSW in these knees were heterogeneous and often large; the mean rate of JSN over 14 months (–0.16 mm) suggested an improbable increase in JSW (Table 2). In contrast, in fluoroscopically assisted semiflexed AP radiographs of the same knees obtained on the same day as the MTP view, mean JSW decreased 0.20 mm.

*Fixed flexion PA view.* Peterfy, *et al*[32] have described a fixed flexion PA view in which both knees are in contact with the cassette (negating magnification effects) and coplanar with the hips, patellae, and tips of the great toes (Figure 1). In essence, the fixed flexion PA protocol places the patient in a position identical to that in the Lyon schuss view. However,

in the fixed flexion view the x-ray beam is angled downward 10°, whereas the beam angle in the Lyon schuss view is varied with each examination in an attempt to align the beam with the medial tibial plateau. Positioning of the knee is facilitated by use of the SynaFlex™ positioning frame (Synarc, Inc.; San Francisco CA, USA), an L shaped platform on which the subject stands and leans forward to fix the femorotibial angle, as well as the angle of foot rotation.

Like other standardization protocols, the fixed-flexion PA view permits highly precise measurements of JSW.[32] Although it is currently in use in several industry and NIH supported studies of the radiographic progression of OA, no accounts of the longitudinal performance of this protocol have been published. Unpublished data from a study of 39 OA knees, however, suggest that sensitivity to JSN over one year (CV = 283%) is only marginally better than that achieved with conventional knee radiography (Table 2)[35].

Given the similarities between the Lyon schuss and fixed-flexion PA views with respect to positioning of the subject, a comparison of the performance of these two protocols is informative: longitudinal studies of one-year duration have been performed with both techniques in separate cohorts of patients. Data have been reported for only 19 OA knees in which serial images were obtained with the Lyon schuss protocol, but are available for 5 times as many knees imaged with the fixed flexion PA view. Although the annual rate of JSN appears considerably greater with the Lyon schuss than with the fixed flexion PA view (0.41 mm/yr, 0.18 mm/yr, respectively), the two patient populations may have differed with respect to underlying OA pathology and risk factors for OA progression. It is notable, however, that the CV of JSN with the Lyon schuss view was considerably lower than that with the fixed-flexion PA view (171%, 360%, respectively).

*Limitations of non-fluoroscopically assisted knee radiography.* The Advisory Board recognized that, all else being equal, the value of practicality in a DMOAD trial weighs heavily in favor of protocols that do not require fluoroscopy to standardize the position of the knee in serial examinations. It should be emphasized, however, that the use of non-fluoroscopically assisted positioning methods does not reduce the demand for the training of radiology technologists that is needed to achieve the requisite high level of technical proficiency or reduce the need for meticulous quality control throughout the conduct of the trial. Unfortunately, it is impossible at this time to determine whether all else is equal because the published evidence supporting the appraisal of specific protocols is meager.

Table 4 provides a comparison of the semiflexed MTP[31] and the fixed flexion PA[32] protocols, which differ importantly in several respects: The semiflexed MTP protocol requires only 7–10° of flexion and may, therefore, be less likely than the fixed flexion PA view, which provides > 20° of flexion, to reveal significant cartilage thinning. However, these protocols have not been compared directly (i.e. concurrently in the same subjects under the same conditions). Although both of the respective authors have published or presented a demonstration of short-term reproducibility of their technique,[31,32] only the semiflexed MTP protocol has been field tested by independent investigators[34]. Further, data on the longitudinal performance of both of these techniques are only preliminary and are based on observations of fewer than 40 knees. The semiflexed MTP view may not afford either reproducible positioning or sensitive detection of JSN in longitudinal examinations, while the sensitivity to JSN of the fixed flexion PA appears only marginally superior to that of the conventional standing AP view.

*Table 4.* Comparison of 2 nonfluoroscopically assisted protocols for standardized knee radiography.

| Protocol Features/Track Record | Semiflexed MTP View[31] | Fixed Flexion View[32] |
|---|---|---|
| Knee flexion, degrees | 7–10 | 20–30 |
| External foot rotation, degrees | 15 | 10 |
| Fixation of femorotibial angle? | No | Yes |
| Evidence of reproducibility published by investigator(s) in a peer reviewed journal? | Yes[25] | No |
| Reproducibility confirmed by independent investigators? | Yes[27] | No |
| Evidence of sensitivity to JSN published in a peer reviewed journal? | No | No |
| Preliminary data on sensitivity to JSN | | |
| No. of OA knees | 27 | 39 |
| Duration of followup, yrs | 1 | 1 |
| JSN, mm, mean ± SD | –0.16 ± 0.84 | 0.18 ± 0.51 |
| CV of JSN, % | –525 | 283 |

## CONCLUSIONS

The task of the Advisory Board convened by NEGMA-LERADS was to ascertain whether any of the current radiographic protocols is suitable as an outcome measure in clinical trials of DMOAD involving a "reasonable" number of subjects with knee OA and "reasonable" duration of treatment. The following conclusions were based on the extent to which each protocol represented a favorable balance between performance, practicality, and cost.

With regard to evaluating performance, the Board considered the extent to which the various protocols permitted (a) reproducible measurement and (b) sensitive detection of JSN. Particularly relevant in these deliberations were the results of previous studies of the radiographic progression of OA conducted with patients from clinic populations (rather than community cohorts) over intervals ranging from 2 to 3 years, the target population and time frame relevant to a DMOAD trial.

Although several studies permitted direct comparisons of

alternative protocols with respect to reproducibility of JSW measurement[12,24,31], none offered a longitudinal comparison of competing approaches to standardized positioning of the knee during the x-ray examination. Consequently, the Advisory Board could consider only longitudinal studies of single protocols in specific populations.

While it is possible that minor inconsistencies across studies with respect to the underlying mean and variability of the rate of JSN (Table 2) may, to some extent, reflect small, but true, differences between distinct subpopulations of OA patients, variation in the quality of radiographic data was considered to be a major source of this variation. In the absence of studies contrasting the longitudinal performance of alternative radiographic methods, comparisons of alternative protocols were based on the sensitivity of each to JSN in separate populations over differing intervals of time. The homogeneity of longitudinal changes in JSW, relative to the mean of changes (i.e., the CV of JSN), was considered a useful basis on which to make these comparisons. In support of this approach, it should be noted that the CV of JSN varied between studies in a fashion consistent with the principle that, as the interval between examinations increases, error variance from measurement error becomes a smaller proportion of total variance, and sensitivity to true JSN increases. Further, as an indicator of comparative performance, the CV of JSN showed that fluoroscopically standardized protocols detect JSN with greater sensitivity in less time than conventional radiographic procedures.

• Are any of the radiologic/radiographic protocols that have been recommended for use in DMOAD studies suitable for demonstrating the efficacy of a drug that significantly slows the rate of loss of articular cartilage in patients with knee OA in a randomized placebo controlled trial involving a "reasonable" number of subjects and a "reasonable" duration of treatment?

Using performance, practicality and cost as criteria, the Advisory Board concluded that none of the protocols discussed could confidently be endorsed for use in a DMOAD trial at the present time.

The major obstacle to a definitive answer to this question was the scarcity of peer reviewed descriptions of the performance of available protocols for standardizing the radioanatomic positioning of the knee in examinations occurring over an interval of 2 to 3 years. Current studies are limited by small numbers of knees and/or short intervals of followup. Nonetheless, the available data permit the elimination of several approaches to knee radiography, are useful in evaluating the strengths and weaknesses of the remaining candidates, and help identify gaps in our knowledge that are necessary to inform such a decision.

Based on the wealth of information available regarding the performance of the conventional standing AP radiograph in assessing JSN in knee OA, the Board concluded that because of its inability to provide reproducible measurement of JSW and the extent to which estimates of JSN are influenced by changes in the radioanatomic alignment of the joint in serial examinations, its use in DMOAD trials cannot be endorsed.

Fluoroscopically assisted protocols for standardizing the radioanatomic position of the knee[12,24,25] afford superior reproducibility of JSW measurement, in comparison with the conventional standing AP view. However, only limited longitudinal data are available in peer reviewed publications to permit an evaluation of the suitability of these protocols for a DMOAD trial. Further, currently available accounts of the longitudinal performance of fluoroscopically assisted protocols (Table 2) are based on only a small number of knees[25] or preliminary analyses of larger studies that will not be completed for at least a year.[28]

Even less is known about the cost/benefit tradeoffs of more recently described non-fluoroscopically assisted protocols for standardizing the positioning of the knee[31,32]. While the short term reproducibility of positioning of the knee by empirically derived standards compares well to that obtained with fluoroscopic positioning, preliminary data on the longitudinal performance of non-fluoroscopic positioning standards (i.e., reproducibility of position, sensitivity to JSN) are still scant.

• Might additional analyses of existing film archives permit a recommendation that one or more protocols is suitable for use in a DMOAD trial?

The Board felt unanimously that the answer is yes.

The Board noted that the pharmaceutical industry has supported phase III multicenter clinical trials of purported DMOAD[36] that have employed protocols to standardize knee radiography, but were terminated prematurely because of adverse events or lack of efficacy. If a sufficient number of subjects from the placebo groups of these trials underwent followup x-ray examinations before the trials were halted, measurement of JSW in serial knee radiographs and longitudinal analysis of these JSW data could quickly provide essential information about the performance of current radiologic/radiographic protocols with respect to their sensitivity to JSN in a multicenter trial. These data would be of immediate benefit to sponsors and designers of DMOAD trials who must consider, for example, whether the technical benefits of fluoroscopically assisted knee radiography outweigh its practical disadvantages and costs.

Similarly, current multicenter studies of OA progression contracted by the NIH (the Health ABC Study, the GAIT trial) should provide evidence of the longitudinal performance of the fixed flexion and semiflexed MTP protocols, respectively, within the next 1 to 2 years.

• Are none of the existing protocols suitable for studying the effects of a putative DMOAD in patients with knee OA?

The question cannot be answered today.

Whether the analyses of existing radiographs recommended above will provide reassurance that a trial of

reasonable size and duration can be designed to evaluate the effect of a potential DMOAD in subjects with knee OA remains to be seen. Possibly, the problems of standardizing the radioanatomic position of the hip in subjects enrolled in a DMOAD trial would be less daunting than those associated with imaging of the knee. Analysis of the existing data related to JSN in hip OA would be a useful exercise.

*Supported by an unrestricted grant from NEGMA-LERADS.*

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