Reproducibility of the Semiflexed (Metatarsophalangeal) Radiographic Knee Position and Automated Measurements of Medial Tibiofemoral Joint Space Width in a Multicenter Clinical Trial of Knee Osteoarthritis

J. CHRIS BUCKLAND-WRIGHT, RUPERT J. WARD, CHARLES PETERFY, CHRISTOPHER F. MOJCIK, and RICHARD L. LEFF

ABSTRACT. ***Objective.*** To determine the baseline and longitudinal consistency in reproducibility of the semiflexed metatarsophalangeal (MTP) position in repeat examinations of patients with knee osteoarthritis (OA) recruited for a multicenter clinical trial that terminated within one year (mean duration 0.81 yr), based on precise measurements both of minimum medial tibiofemoral compartment joint space width (JSW) and of tibial inter-rim distance.

Methods. Two technologists from 8 and one technologist from 14 clinical radiology units had received previous training in performing nonfluoroscopic semiflexed MTP knee examinations and in quality control criteria for film acceptance. Patients (N = 402; F = 269) were recruited from 58 rheumatology sites and referred to 22 centers, or "x-ray hubs," across North America. At baseline and at study exit, both knees were x-rayed twice on the same day. All films had quality control, and accepted films were digitized at the Central Radiographic Facility and transmitted to the Central Analysis Facility for computerized measurement of minimum medial compartment JSW and tibial inter-rim distance. JSW loss was calculated in the placebo group for the study period.

Results. The median SD of the difference in JSW between same-day test/retest film pairs was 0.9 mm for 767 baseline film pairs (knees with JSW > 0 mm), and 0.08 mm for 631 exit film pairs. JSW reproducibility was unaffected by subject's sex, age, and degree of JSW loss. Among all x-ray hubs, JSW reproducibility was excellent in 14 (SD < 0.1 mm), good in 6 (0.1 < SD < 0.2 mm), and moderate in 2 hubs (0.2 < SD < 0.3 mm). No statistical difference was found in technologists' ability either in positioning OA knees or in their test/retest reproducibility in repositioning joints at baseline and at study exit. JSW did not alter significantly during the study period.

Conclusion. The protocol for the semiflexed MTP knee position provides a highly reproducible method for anatomically repositioning the knee and for measuring JSW, necessary for OA clinical trials. It is a simple method that can be employed readily at clinical radiology units, as shown by the similarity in JSW precision between x-ray hubs. The results from this large dataset show that throughout the study precise measurements of JSW were obtained from same-day repeat radiographs, findings that together with previous single-center studies confirm the reliability of this method for clinical trial use. (J Rheumatol 2004;31:1588–97)

Key Indexing Terms:
OSTEOARTHRITIS KNEE RADIOLOGY CLINICAL TRIAL

From the Department of Applied Clinical Anatomy, King's College London, School of Biomedical Sciences, London, UK.

Supported by Bayer Corporation, West Haven, Connecticut, USA.

J.C. Buckland-Wright, PhD, DSc, Professor of Radiological Anatomy at the University of London, King's College London; R.J. Ward, MPh, Research Associate, Department of Applied Clinical Anatomy, King's College London; C. Peterfy, MD, PhD, Synarc, San Francisco, California, USA; C. Mojcik, MD, PhD; R.L. Leff, MD, Bayer Corporation, West Haven, Connecticut.

Address reprint requests to Prof. J.C. Buckland-Wright, Department of Applied Clinical Anatomy, King's College London, Hodgkin Building, School of Biomedical Sciences, London Bridge, London SE1 1UL, UK. E-mail: chris.buckland-wright@kcl.ac.uk

Submitted April 7, 2003; revision accepted March 24, 2004.

Primary outcome measures in clinical trials for knee osteoarthritis (OA) that employ radiography to assess the effect of structure modifying OA drugs (SMOAD) quantify changes in tibiofemoral articular cartilage thickness from measurements of the joint space width (JSW)[1-3]. Measurement of this feature assesses the combination of both the material thickness of articular cartilage and its compressibility when the joint is radiographed in the standing position[2]. Standardized radiographic protocols are employed to minimize variations in obtaining the radiographic image, and computerized methods of measurement are employed to limit the effects of observer variability[1] and to improve the precision of radiographic joint space narrowing (JSN) as a primary outcome measure in clinical trials.

Initially, radiographic protocols relied upon fluoroscopy to assist in reproducibly repositioning the knee within and between patient examinations[3-6]. Fluoro-assisted radiography of the knee in the semiflexed view has been found to be transferable between centers[7] and is now used in several clinical trials in North America[8,9] and Europe[9,10]. Nevertheless, this method has a number of limitations, which include the demands placed upon the technologists to perform consistently throughout the study duration, use of sophisticated radiographic equipment, and the need to correct for the effect of radiographic magnification when measuring JSW[11]. Nonfluoroscopically assisted protocols have been developed that ensure reproducible radioanatomical positioning of the joint[11,12] and that are simpler to perform than the fluoro methods.

At the time of undertaking this study the only published report on these methods was the semiflexed MTP (metatarsophalangeal) view of the knee[11]. This radiographic knee protocol resulted in a remarkable precision in both JSW measurement and reproducibility of radioanatomic joint positioning[11], factors that led to the adoption of this method for the multicenter, double blind, placebo controlled study to investigate the efficacy of the metalloproteinase inhibitor BAY 12-9566 (Bayer Corporation, West Haven, CT, USA) in the treatment of patients with mild to moderate knee OA, over 3 years. This study was terminated after one year, following detection of unfavorable parameters in cancer patients enrolled in another study. Recent single center studies have confirmed that the MTP method produces accurate and precise JSW measurements[13,14], and reproducibly repositions the joint at repeat examinations[14], leading to its superiority, compared to other methods, in assessing JSW and osteophytosis for routine clinical practice[15].

We describe results as to the applicability of the MTP method in a multicenter study in which patients were recruited from 58 rheumatology sites and referred to 22 centers, or "x-ray hubs," across North America for radiography, twice in one day, of both knees in the MTP position at baseline and exit visits. From duplicate films we determined the baseline reproducibility of JSW measurements for all patients and those from each of the hubs. Baseline and longitudinal consistency in JSW measurement precision and in the technologists' performance in positioning the knees and their reproducibility in the radioanatomic joint repositioning were determined from the baseline and exit films in the placebo group of patients. These data were used to determine whether variation in radioanatomic joint repositioning affected JSW precision.

MATERIALS AND METHODS

Patients. Ethical Committee approval for this study was obtained at each of the 58 institutions participating in the trial. Patients were selected from those attending one of 58 rheumatology sites across North America; they were aged 45 years and older, one or both knees had primary or post-traumatic (due only to remote, > 6 months, trauma) OA as defined by American College of Rheumatology clinical and radiographic criteria[16,17]; pain for at least 50% of the days in the month prior to baseline visit; radiographic evidence of Kellgren and Lawrence[18] Grades 2 and 3 in the AP extended knee radiograph, and in the study knee a minimum medial tibiofemoral compartment JSW ≥ 2 mm, measured at the Radiographic Quality Control Center (RQCC) from radiographs of the knees taken in the MTP position[11]. Key exclusion criteria comprised knees with OA secondary to known disorder, lower limb surgery within the last 6 months, patients who have received matrix metalloproteinase-inhibitory medication, those with marked chondrocalcinosis, evidence of other types of arthritis and metabolic bone disease. For each patient, the study knee was defined as the symptomatic joint with a minimum medial compartment JSW ≥ 2 mm at baseline. In those cases in which both knees met the inclusion criteria, the study knee was the joint that had the lower minimum JSW. Patients were randomly allocated to receive either BAY 12-9566, at one of 2 dose levels, or placebo in a double-blinded, parallel group design.

Radiographic procedure. Patients recruited at the rheumatology sites were referred to one of 22 "x-ray hubs" distributed across North America. Both knees of all patients were radiographed at the same time and twice on the same day, within a 2 hour interval so that day-to-day variation of knee pain intensity and/or ease of movement would not affect the positioning. Following the initial radiographic exposure the outline of the foot was drawn on a large sheet of paper taped to the floor. The foot map was used to reposition the joint at the repeat examination. The x-ray film cassette was held in a vertical film-holder with a film-to-focus distance of 100 cm. Stationary grids were not used for any of the exposures since the grid lines, recorded in the image, interfered with the computerized JSW measurement procedure. Patients were provided hand support if required. The same procedure was followed at all subsequent radiographic examinations.

Radiography of the knee in the standing semiflexed or MTP position[11]. The x-ray tube was positioned so that the central ray of the x-ray beam was horizontal, parallel to the floor, and perpendicular to the x-ray film. The radiography technician identified the position of the tibiofemoral joint space located midway between the inferior border of the patella and the superior margin of the tibial tuberosity. The line of the joint space was traced around to the side of the knee and the skin marked with a felt-tip pen. This mark was used to help align the center of the x-ray beam with the joint space. The patients stood with both knees facing the film cassette, their feet slightly externally rotated, with an angle between the feet of approximately 15°, as recommended by Ravaud, *et al*[4] in their assessment of the optimum foot position for knee radiography. The first MTP joint of each foot was positioned immediately below and in line with the front edge of the film cassette (Figures 1A and B). The patients bent their knees (about 7°–10°) so that the anterior surface of each knee touched the middle and front of the film cassette. The tube was positioned so that the x-ray beam was directed midway between the popliteal surface of the knees, and the tube's positioning light was aligned with the horizontal plane of the joint space, identified by the pen mark. This plane lay above the horizontal skin crease of the popliteal fossa. Both knees were recorded on one film at each exposure. All films were forwarded to the Regional Quality Control Center (RQCC) at Synarc (San Francisco, CA, USA) to confirm eligibility.

Technologists' training procedure. Participating radiologists and technologists were required to have in-depth knowledge and extensive experience in their respective fields. There were a total of 30 clinical x-ray technologists participating from the 22 x-ray hubs, 2 technologists from 8 hubs, and one from each of the remaining 14 hubs.

Each of 2 groups of 15 technologists was trained in half a day at a radiographic facility by one of the authors (CB-W) and an experienced senior x-ray technologist, Cyndi Hayashi (Synarc). The training commenced with a slide presentation describing the scientific basis to the radiographic method

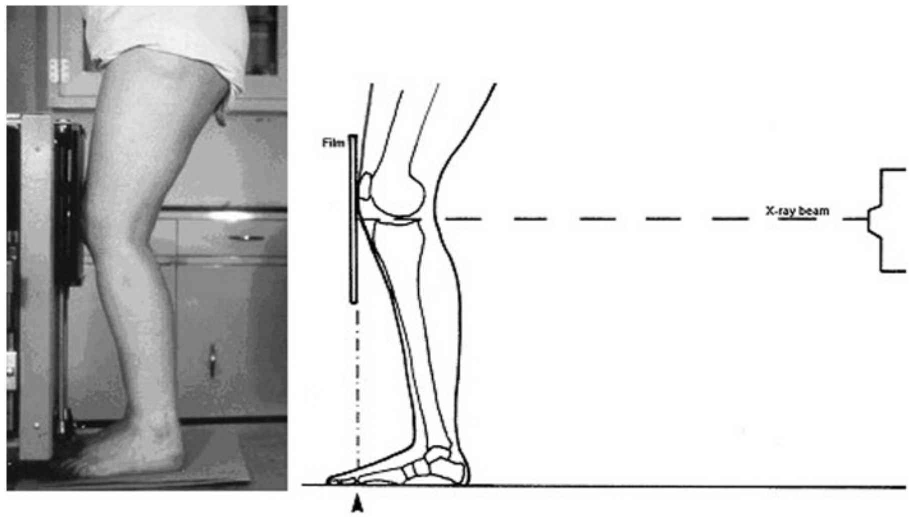

Figure 1. General view (A) and diagram (B) of the x-ray equipment for the posteroanterior view of the knee in the semiflexed or MTP position showing the alignment of the leg relative to the x-ray tube and the film cassette mounted in the vertical holder. The first metatarsophalangeal (MTP) joints are placed in line with the front of the film cassette, and the knees are flexed until they touch the cassette; the arrow marks the position of the first MTP joint, which is in line with the front of the film cassette. The patient's envelope or card is used to draw a map of the feet to help reposition the patient at the repeat visit.

and quality control criteria (Table 1). The technologists were provided with a detailed manual describing the radiographic process and quality control issues and containing illustrations of the optimum knee position and the technologist's exclusion criteria that included film under/over exposure and the position of labels on the film. Afterwards, the technologists commenced hands-on training. Each technologist identified and marked the anatomical landmarks on a colleague corresponding to the position of the knee's joint space. These landmarks were later used to align the x-ray tube's positioning light and hence the center of the x-ray beam with the joint space of the knee. Following a demonstration by one of the instructors, each technologist practiced positioning knees in the MTP view on a colleague until they felt confident in the procedure. An instructor checked the correct positioning of the colleague for radiography. No radiographic exposure was taken. All technologists were encouraged to observe their colleagues performing the procedure, thereby increasing their experience.

Quality control. All films produced by the technologists were sent to the RQCC at Synarc, where they were inspected by an experienced radiologist who assessed their acceptability according to the quality control criteria (Table 1) and their eligibility for study inclusion from minimum medial compartment JSW measurement, which had to be ≥ 2 mm in at least one knee. This measurement was carried out using a transparent template

Table 1. Quality control criteria for film acceptance: technologist's checklist. Once the radiograph has been developed, check the following points. The radiograph must meet all the following criteria to ensure that it conforms to the quality control standards necessary for this study.

1. Both knees must appear on each film
2. The knees must appear in the *middle* of the film
3. The long axis of the tibia must be parallel to the margin of the film
4. All of the joints, including osteophytes, must appear on the film
5. Cone the beam to the size of the film
6. Do not use stationary grids
7. Right and left markers must be properly placed and imaged clearly
8. Check that the study label is correctly filled out
9. The exposure should be optimal for bone detail

marked with a circle, whose outer dimension was 2 mm, which was used to determine if the interbone distance in the medial compartment fell below 2.0 mm at any point. The radiographic quality assurance (QA) was not as important an issue in the semiflexed positioning of the knee as it is in the methods for fluoroscopically assisted knee radiography[3,7,9], since all that was required in the MTP view was for the knee to be centrally placed in the radiograph that was neither under- nor over-exposed. A greater effect upon film acceptance/ rejection was the QA using the template measurement to determine minimum JSW, as part of the patient inclusion/exclusion procedure. It has not been possible to report the values for film rejection for these 2 QA procedures, as these had not been forwarded to the Central Analysis Facility at King's College London. All qualifying films were digitized with a Lumiscan 200 laser film digitizer (Lumisys, Inc., Sunnyvale, CA, USA) to a resolution of 100 µm. Prior to digitization all films were bar-coded to ensure that on digitization the computer database linked patient visit data to the JSW measurement obtained from each radiograph. All digitized film images were stored on magnetic tape and sent to the Central Analysis Facility at King's College London for JSW measurement.

Joint space width measurement. A semi-automated computerized method of JSW measurement[19,20] was used in this study to measure minimum JSW in the medial compartment from each of the radiographs. The coefficient of variation for JSW measurement was 1% for test/retest repeat radiographs of the knee in the semiflexed position[3]. JSW measurement reproducibility was determined from the paired baseline films. Images were measured individually and not in serial pairs and were examined blind to patient information and the chronology of the images. JSN was determined from the difference in JSW between the baseline and exit film, blind to the sequence in which they were obtained.

Reproducibility in the radioanatomic repositioning of the joint. The radioanatomic position of the knee, recorded in the radiograph, is determined by the angle between the plane of the tibial plateau and the central ray of the x-ray beam and is represented by the tibial inter-rim distance (TIRD). This is calculated from measurements taken at the middle of the medial tibial compartment from the anterior and posterior rims of the plateau to the floor of the tibial plateau (Figure 2). Since it was not always possible to identify which rim was anterior and which posterior, the absolute difference of these distances was used as the TIRD. Thus, TIRD is

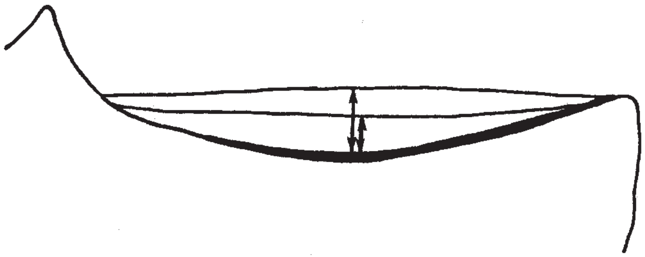

Figure 2. Diagram of the radiographic appearance of the medial tibial plateau showing the measurements taken, in each radiograph, from the floor of the articular fossa to the anterior and posterior rims, respectively. The degree of similarity in the tibial inter-rim distance between repeat radiographs determines the reproducibility in repositioning the joint radioanatomically.

the same quantity that the fluoro-assisted semiflexed method of positioning the knee aims to minimize. In the latter, the TIRD must be ≤ 1.0 mm in order for the radiographic quality control criteria to be met[7,9]. This condition is not appropriate for the MTP view, since in this method the aim is not to minimize the angle between the tibial plateau and central ray of the x-ray beam, but to ensure that the angle subtended is reproducible. We undertook an assessment of this reproducibility since variability in radioanatomic repositioning the knee may adversely affect the precision of JSW measurements.

An operator (RJW) used specially written software to measure the inter-rim distance from digitized images. The measurements were taken pairwise so that the location of the measurements was consistent both within test/retest radiograph pairs and between baseline and exit film pairs. The reproducibility of TIRD measurement, expressed as the median standard deviation (SD) and 95% confidence interval (CI) was 0.14 mm (0.13, 0.30) obtained from measurements of 20 OA patient films repeated 4 times on separate occasions.

Data analysis. Reproducibility of JSW measurement for each knee at each visit was calculated as the SD of the measurements taken from the 2 radiographs at that visit. The distribution of SD for each group of knees is represented by the median SD and 95% CI, and also by the median coefficient of variation (SD for each knee-visit expressed as percentage of mean JSW for that visit) and root mean square error (RMSE, the square root of the mean within-subject variance of Bland and Altman[21]) for comparison with other studies. The mean and 95% CI minimum medial compartment JSW and the mean and SD of the difference in JSW between test and retest was calculated for the knees in each category, and between-category comparisons conducted using t tests. Between-group SD were compared using the Kruskal-Wallis test, and within-knee SD using paired t tests (since the distributions of differences were normal in these cases). The significance level was 0.05 for all tests, and all tests were 2 sided. The effect of patient characteristics upon the reproducibility of JSW measurement was evaluated for sex and age.

To determine the reproducibility in radioanatomic repositioning of the knee joint the absolute difference between anterior and posterior medial tibial rim heights was calculated. For all pairs of test-repeat radiographs in the placebo group, at both baseline and exit, the mean and SD of the TIRD values were calculated and used to represent the tibial position and its repeat visit reproducibility, respectively. For both means and SD, the difference between baseline and exit TIRD values was calculated for each knee and used to represent the technologists' longitudinal consistency in tibial positioning and in reproducibility of tibial repositioning, respectively. Because these means and SD were not normally distributed, medians and 95% CI were used to summarize their distribution.

To assess the relationship between the technologists' performance in tibial positioning and JSW measurement at different x-ray hubs, both knee position (TIRD) and reproducibility and JSW measurement and its reproducibility were summarized by means of test/retest means and SD, for all baseline and exit film pairs from hubs with sufficient number of knees for statistical analysis (n ≥ 8). Spearman correlation coefficients were calculated between these hub-based TIRD and JSW variables, to see if there was a relationship between JSW reproducibility and either tibial position or its reproducibility.

RESULTS

Four hundred and two patients that met the radiographic inclusion criteria (269 were women) were recruited into the study. They had a mean age (95% CI) of 63.7 (62.8, 64.6) years, with no age difference between men and women. Of the total number of 804 knee radiographs measured, 37 (10 right, 27 left) knees had a medial tibiofemoral compartment that was bone on bone, i.e., with no measurable JSW, leaving a total of 767 (392 right) knees with a measurable minimum JSW, i.e., > 0 mm.

The combined x-ray hubs' mean JSW, median SD, RMSE, and coefficient of variation for test/retest, for the study knees and for the right and left knees separately and combined, are given in Table 2 for radiographs obtained at baseline and at study exit. For the 767 baseline film-pairs obtained of both knees the median SD (95% CI) of paired test/retest JSW measurements was 0.09 mm (0.08, 0.10). For the 399 study knees, the equivalent figure was also 0.09 mm (0.07, 0.10). The values obtained for the patient exit films were similar and not statistically different from those at baseline. Importantly, the similarity in JSW measurement precision between the baseline and exit films confirmed the longitudinal consistency in test/retest precision of this measurement in patients' knees. Further, patients' minimum medial compartment JSW was found to be significantly larger in the right than in the left knee (p = 0.004) by a mean of 0.2 mm; however, right and left knee JSW measurement reproducibility values were similar.

Factors affecting JSW measurement reproducibility. The effect of patient characteristics upon the reproducibility of JSW measurement was evaluated for all knees as well as for the study knee. The results for all knees are presented in Table 3; study knee results were similar and are not shown in this table. There was no statistically significant difference in the JSW measurement reproducibility either for sex or between the different age groups. Further, no statistically significant difference in the JSW measurement reproducibility was detected between any of the categories of JSN (Table 4). These findings indicate that the technologists could reliably reposition patients' legs at repeat examinations and that this was independent of sex, age, and the severity of knee OA as determined by the degree of JSN.

Between-x-ray hub reproducibility. The values for the reproducibility of JSW measurements for paired radiographs at the 22 x-ray hubs are presented in Figure 3. No statistically significant difference in JSW measurement reproducibility was detected between any of the hubs. Between-x-ray hub

Table 2. Combined x-ray hub minimum medial compartment JSW and test-retest reproducibility, for knees with non-zero JSW, in the study and non-study knees and for the right and left separately and combined, at baseline and exit visits.

Visit	Knee Group	No. of Knees	Mean JSW, mm (95% CI)	Median SD, mm (95% CI)	CV, %	RMSE†, mm
Baseline	Study	399	3.67 (3.59, 3.57)	0.09 (0.07, 0.10)	2.44	0.21
	Non-study	370	3.77 (3.63, 3.91)	0.09 (0.08, 0.11)	2.39	0.20
	Right	393	3.79 (3.67, 3.96)*	0.08 (0.07, 0.09)	2.18	0.22
	Left	375	3.67 (3.56, 3.77)	0.11 (0.09, 0.12)	2.96	0.20
	Both	767	3.73 (3.65, 3.81)	0.09 (0.08, 0.10)	2.50	0.21
Exit	Study	333	3.60 (3.51, 3.70)	0.07 (0.07, 0.09)	2.41	0.20
	Non-study	299	3.76 (3.60, 3.92)	0.09 (0.08, 0.11)	2.39	0.19
	Right	318	3.79 (3.66, 3.92)*	0.08 (0.08, 0.09)	2.32	0.21
	Left	313	3.58 (3.45, 3.70)	0.09 (0.08, 0.11)	2.58	0.19
	Both	631	3.64 (3.59, 3.77)	0.08 (0.07, 0.09)	2.47	0.20

* Right > left JSW p = 0.004 (t test). JSW: joint space width; CI: confidence interval; CV: coefficient of variation; SD: standard deviation; RMSE: root mean square error. † RMSE is included for the purpose of comparison with published data. However, we consider it less easy to interpret and less appropriate (because of the non-normal distribution of the variances) than the median SD.

Table 3. The effect of patient characteristics upon the reproducibility of JSW measurement was evaluated for sex and age. There was no statistically significant difference in the JSW measurement reproducibility between either sex or the different age groups.

Sex/Age Group, yrs	No. of Knees	Mean JSW, mm (95% CI)	JSW Difference for Test/Retest Median SD, mm (95% CI)	CV, %	RMSE, mm
Female	538	3.59 (3.49, 3.69)	0.09 (0.07, 0.09)	2.37	0.19
Male	266	3.49 (3.31, 3.68)	0.09 (0.07, 0.11)	2.55	0.21
45–50	46	3.79 (3.42, 4.17)	0.07 (0.06, 0.13)	1.89	0.28
50–60	230	3.68 (3.51, 3.84)	0.10 (0.09, 0.12)	2.67	0.21
60–70	314	3.60 (3.45, 3.75)	0.09 (0.07, 0.11)	2.35	0.19
70–80	180	3.30 (3.10, 3.51)	0.07 (0.06, 0.08)	2.07	0.16
80–91	34	3.35 (2.95, 3.74)	0.08 (0.04, 0.15)	2.77	0.18

JSW: joint space width; CI: confidence interval; CV: coefficient of variation; SD: standard deviation; RMSE: root mean square error.

Table 4. For all patients, the effect of the degree of joint space narrowing (JSN) upon the reproducibility of joint space width (JSW) measurement was assessed. No statistically significant difference in the JSW measurement reproducibility was detected between any of the categories of JSN.

			JSW Difference for Test/Retest, mm		
JSW, mm, range	No. of Knees	Mean JSW, mm	Median SD, mm	CV, %	RMSE, mm
0–1	47	0.14	0.00	0.00	0.11
1–2	39	1.56	0.09	5.08	0.22
2–3	134	2.55	0.08	3.32	0.18
3–4	260	3.58	0.08	2.19	0.18
4–5	250	4.41	0.09	2.15	0.21
5–6	55	5.39	0.11	2.19	0.22
6–7	19	6.31	0.16	2.48	0.37

JSW: joint space width; CV: coefficient of variation; SD: standard deviation; RMSE: root mean square error.

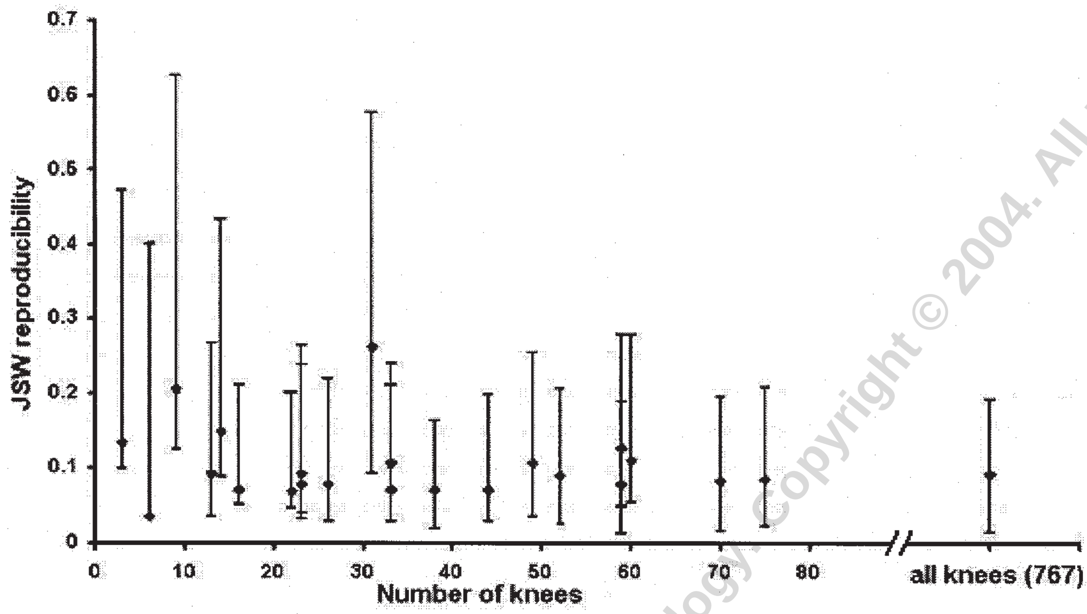

Figure 3. Joint space width measurement reproducibility expressed as median SD and 95% CI of the difference in minimum medial compartment JSW between test/retest obtained from paired baseline films of OA knees at each of the 22 x-ray hubs ranked according to the number of measurable knees at each hub.

JSW reproducibility was excellent at 14 sites, where the median SD in the difference in JSW measurement for test/retest was < 0.1 mm, good in 6 hubs with a median SD < 0.2 mm, and moderate in 2 hubs with a median SD < 0.3 mm.

Joint space narrowing in the placebo group. By study termination, exit films had been obtained for 112 patients (75 women) whose mean (95% CI) age and study duration were 61.4 (59.7, 63.0) years and 0.81 (0.78, 0.84) years, with the latter ranging from 0.1 to 1.31 years. In this patient group 212 knees (109 right) had a baseline JSW > 0 mm. The mean rate of JSN for the study knee and for the right and left knees separately and combined is given in Table 5. Differences in the number of knees between right and left were due to the presence of prostheses in the joints excluded from measurement. Both knees in one patient had a minimum medial compartment JSW < 2 mm on automated computerized measurement and were excluded from the study knee group.

Table 5. Combined x-ray hub mean annual rate of joint space narrowing (JSN) calculated from the difference in minimum medial compartment JSW between baseline and exit films of patients from the placebo group.

Knees*	Number	JSN (95% CI), mm/yr		
		Mean	SD	95% CI
Study	112	–0.08	0.86	–0.25, 0.08
Right	109	–0.07	0.75	–0.21, 0.08
Left	103	–0.05	0.91	–0.23, 0.13
Both	212	–0.06	0.83	–0.17, 0.05

* Knees with non-zero joint space width at baseline. JSW: joint space width; CI: confidence interval; SD: standard deviation.

Radioanatomic knee positioning in the placebo group. The 224 knees of the placebo group from which TIRD measurements were obtained were typical (not significantly different) of the overall patient group with respect to JSW and JSW reproducibility. The placebo group mean (95% CI) baseline JSW mean was 3.72 (3.57, 3.86) mm and a JSW precision with a median (95% CI) baseline JSW SD of 0.08 (0.07, 0.09) mm.

The radioanatomical position of the tibia, as measured by TIRD, is represented by the median of the within-knee means for both baseline and exit films (Table 6). These values are greater than the 1.00 mm that is acceptable for fluoro-assisted semiflexed radiography, which is to be expected since the non-fluoro MTP method does not seek specifically to minimize TIRD. The change between baseline and exit knee positions, as represented by the difference between baseline and exit mean TIRD values, is given in the last column of Table 6. These were small and not statistically significant, showing that knees were positioned similarly in the MTP view over the course of the study. The technologists' ability to reproducibly reposition the tibia is given by the median within-knee TIRD SD for both baseline and exit test/retest film pairs (Table 7). The reproducibility is very good, being very similar to that for repeat measurements. The change in the technologist performance over time, as represented by the difference between baseline and exit TIRD SD values in the last column of Table 7, was also small and not statistically significant, showing that their ability to reproducibly reposition the tibia was maintained throughout the course of the study.

Table 6. Radioanatomic positioning of OA knees (tibial inter-rim distance, TIRD). For the different knee groups the positioning is represented by the median within-knee mean TIRD for both baseline and exit repeat film pairs. Longitudinal change in positioning is represented by the median difference between baseline and exit means.

Knee Group	No. of Knees	Knee Positioning: Median (95% CI) of Within-knee TIRD Means, mm		Median (95% CI) Change in TIRD, mm
		Baseline	Exit	Baseline – Exit
All	224	1.80 (1.38, 2.06)	1.73 (1.26, 2.15)	0.05 (-0.05, 0.10)
Study	112	1.63 (1.25, 2.14)	1.75 (1.31, 2.19)	0.05 (-0.04, 0.20)
Non-study	112	1.85 (1.36, 2.15)	1.65 (1.41, 2.19)	0.00 (-0.10, 0.15)

CI: confidence interval.

Table 7. Reproducibility of radioanatomic repositioning of OA knees. For the different knee groups the technologist's reproducibility in repositioning knees is represented by the median within-knee tibial inter-rim distance (TIRD) SD for each of baseline and exit repeat-film pairs. Longitudinal change in reproducibility is represented by the median difference between baseline and exit SD.

Knee Group	No. of Knees	Reproducibility of Repositioning: Median (95% CI) of Within-knee TIRD SD, mm		Median (95% CI) Change in SD, mm
		Baseline	Exit	Baseline – Exit
All	224	0.21 (0.14, 0.21)	0.14 (0.14, 0.21)	–0.01 (–0.07, 0.0)
Study	112	0.14 (0.14, 0.21)	0.14 (0.13, 0.21)	0.00 (–0.07, 0.0)
Non-study	112	0.21 (0.14, 0.28)	0.14 (0.08, 0.21)	–0.07 (–0.07, 0.0)

CI: confidence interval.

Within the placebo group, 13 of 21 x-ray hubs provided ≥ 8 knee films at both baseline and exit (total of 192 knees). There was no statistically significant difference between hubs for either tibial position (TIRD) or JSW summary variables (Kruskal-Wallis test). One hub only was found to have increased variability in both JSW measurement reproducibility (Figure 3, 11th site along abscissa) and TIRD reproducibility. Tibial position (TIRD mean) was found not to be correlated with JSW reproducibility ($r = -0.11$, $p = 0.72$) but did correlate with JSW mean ($r = 0.64$, $p = 0.02$). By contrast, reproducibility in tibial positioning (TIRD SD) was correlated with JSW reproducibility ($r = 0.63$, $p = 0.02$) but not with JSW mean ($r = 0.20$, $p = 0.49$).

DISCUSSION

In the nonfluoroscopic MTP method, reproducible positioning of the tibiofemoral joint is determined by the anatomy of the limb when positioned with respect to a fixed position for the patient's feet, the film/screen cassette, and the horizontal x-ray beam. Anatomically the effect of controlling joint flexion by this method results in a tibiofemoral angle that is similar within and between patients at successive radiographic examinations, irrespective of the normal variability in the posterior inclination of the medial tibial plateau between patients[22] (Figure 4). With time, progressive changes in joint structure may subtly alter this tibiofemoral angle. Nevertheless, the reliability of the MTP method in repositioning the knee is very good, since the baseline JSW measurement reproducibility, from multiple centers across North America gave a median SD of the difference in minimum medial compartment JSW between repeat films of 0.09 mm (Table 2). Although there was no statistically significant difference in JSW measurement precision between hubs, JSW reproducibility within each of the 22 hubs was excellent in 14 [median SD (SD_m) < 0.1 mm], good in 6 ($0.1 < SD_m < 0.2$ mm), and moderate in 2 hubs ($0.2 < SD_m < 0.3$ mm), values similar to that reported in the literature from other North American centers that had achieved excellent ($SD_m = 0.08$ mm)[11,13] or moderate precision[14]. Comparing the values from our study with published values for OA knee JSW measurement reproducibility, those for the MTP protocol were all smaller, apart from one center[14], than for the fluoroscopic semi-flexed[9], and similar to those for the nonfluoroscopic fixed-flexion technique[12,23].

Baseline reproducibility of a radiographic protocol does not necessarily predict its consistency during the study period. For this reason JSW measurement reproducibility was obtained from the study patient's duplicate exit films; these values were found to be the same as those for the baseline visit (Table 2), demonstrating that the quality of the technologist's performance, as reflected in repeat examinations on the same day, did not deteriorate over time. The consistency in the technologist's performance over the study period is central to the radiographic protocol's sensitivity in detecting progression and/or therapeutic effect. The simplicity of the MTP method, incorporating procedures well known to technologists, is less costly with respect to

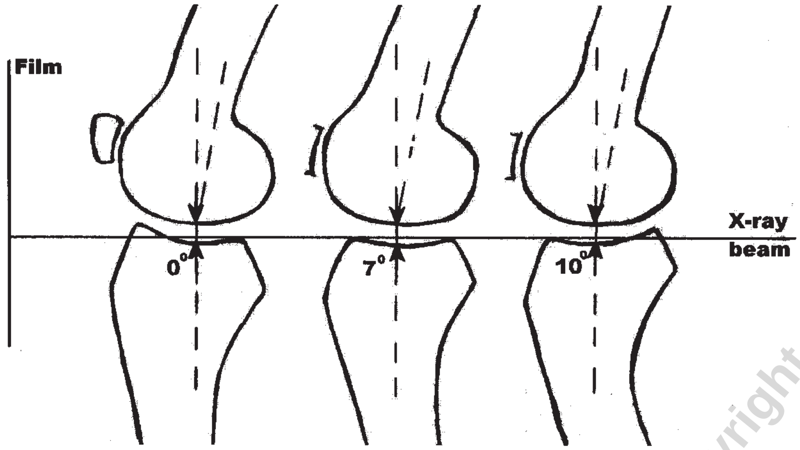

Figure 4. Diagram illustrating the normal variability in the posterior inclination of the medial tibial plateau (range 0°–10°) among knees positioned for radiography in the semi-flexed MTP view. The tibiofemoral angle is determined by the radiographic position. The angle between the 2 limb bones is similar between examinations and is only changed if the patient unusually alters their pelvic tilt. The site of JSW measurement is constant between knees and coincides with the load transmission region across the joint (arrows)[11,23], and is parallel to the film and perpendicular to the femoral and tibial margins. The difference between the tibial plateau alignment and the x-ray beam among some knees results in a tibial inter-rim distance that is measurable in anteroposterior radiographs of the knee.

their training and in subsequent supervision by experienced technologists than is required for protocols employing fluoroscopic guidance for positioning the knee[9]. The facility technologists have in carrying out the MTP procedure will have contributed to the consistency in the JSW measurement reproducibility over the study period.

Our results confirm those of a previous investigation of JSW measurement precision for a multicenter clinical trial[9], which showed that JSW precision was unaffected by patient age, sex (Table 3), and radiographic severity of OA (Table 4). In the latter, we used an improvement upon the method of Kellgren and Lawrence for categorizing disease severity by employing degrees of JSN measured in millimeters (Table 4). We also found that there was no difference, between the "study" and all knees, in mean JSW, in JSW measurement reproducibility at baseline versus exit (Table 2), and in joint space narrowing (Table 5), indicating that the results for study group knees, selected on the basis of symptomatic criteria, were not significantly different from those of all knees. The absence of a significant change in JSW over the period of assessment in the different knee groups (Table 5) was attributed mainly to the brevity of the study period, since a recent analysis of all 333 patients recruited into the same study, comprising both the treatment and placebo groups (there was no statistically significant difference in the rate of JSN between study groups), detected a statistically significant reduction ($p \leq 0.05$) in the mean (95% CI) annual rate of joint space narrowing of –0.144 (–0.257, –0.031) mm/yr in both 325 right knees and of –0.108 (–0.185, –0.031) mm/yr in right and left knees combined from patients with non-zero JSW at baseline (n = 634). The slower rate of JSN in the latter may be due to changes in the left knee (n = 309) not reaching significance [mean (95% CI) –0.069 (–0.174, 0.035) mm/yr] (manuscript in preparation). The difference in the rate of JSN between knees may be associated with the larger JSW in the right than the left joint (Table 2). However, with a greater number of patients the MTP method measured joint space loss within a one-year period. Studies in progress, including one funded by the US National Institutes of Health, are expected to provide further information on the sensitivity of the MTP method in detecting JSW changes over a number of years.

Reproducibility in radioanatomic joint positioning. All protocols for knee radiography undertake to fix the degree of knee flexion, since variation in the tibiofemoral angle of the joint between examinations has a marked effect upon JSW measurement reproducibility. Assessment of the TIRD was devised by one of us (CB-W) as a method for assessing radioanatomic joint positioning[3,11], specifically for fluoroscopic semiflexed methods, in which the central ray of the x-ray beam is aligned with the tibial plateau. In that view, therefore, the degree of superimposition of the anterior and posterior tibial rims as measured by TIRD was used as the radiographic quality control criterion. In the nonfluoroscopic MTP method, where the tibial rims are not imaged during the radiographic procedure, assessment of how close they are to superimposition should not be used for determining successful joint positioning, as reported elsewhere[14,24]. Our finding is supported by Sheldon Cooper's group in their assessment of the precision and accuracy of JSW measurements obtained from MTP semiflexed knee radiographs[13]. The more appropriate method, since the degree of superimposition can vary between knees radiographed in the non-fluoro semiflexed methods, is to determine the reproducibility of the TIRD at test/retest and between timepoints; this assesses the degree to which the knee has been reproducibly repositioned between radiographs. Further, the middle of the medial tibial plateau, employed here, is anatomically a more valid location for measuring the TIRD[9,11] than at the site of the minimum JSW measurement used by others[14,25], since at the latter site the tibial rims converge towards one another, reducing the sensitivity in the TIRD measurement; additionally, as the site of the minimum JSW alters with disease so also will the site for measuring this distance.

The results for this multicenter study confirmed our previous findings[11] that technologists were able to reliably and consistently position the knees radioanatomically in the MTP view at both baseline and exit visits (Table 6), and that they were able to reproducibly reposition the joints at each visit (Table 7). The positive correlation between the size of TIRD and JSW ($r = 0.64$) could be due to a simple relationship between tibial plateau size and JSW thickness, in that large joints have larger tibial plateaus and thicker articular cartilages, measured as JSW, than smaller joints. There was, however, no correlation between TIRD reproducibility and JSW measurement. Further, the angle of the tibial plateau relative to the center of the x-ray beam, as measured by TIRD, did not correlate with JSW measurement reproducibility, demonstrating that aligning the tibial plateau with the x-ray beam so that the tibial margins are superimposed did not improve JSW measurement precision. Whereas TIRD reproducibility did correlate with JSW measurement reproducibility ($r = 0.63$), confirming that the crucial factor in knee radiography for clinical trials is to ensure reproducible repositioning of the knee between visits, and not that the tibial plateau should in all knees be level with the x-ray beam as suggested elsewhere[14,24,25]. Differences in radioanatomical position of the joint in the MTP view due to normal human variability did not adversely affect JSW measurement reproducibility. However, variability in repositioning the joint does affect JSW precision, as observed at one site in this study. In an OA knee clinical trial such a site would benefit from monitoring so as to improve its performance.

Our study reaffirms the relevance of the nonfluoroscopic MTP view as a reliable method for quantifying the extent and progression in knee OA. The key question of the choice of radiographic protocol for multicenter OA knee clinical trials can be addressed. Essentially there was no major difference in the radiographic quality obtained from either the fluoroscopic semiflexed[9] or nonfluoroscopic MTP procedures. The greatest differences between these 2 methods were in the radiological factors[23] relating to the fluoroscopic procedures, which in the future will probably be made even more difficult by the replacement of fluoroscopic tubes by digital imaging systems, introducing additional technical challenges.

ACKNOWLEDGMENT

The authors thank their colleagues, in particular Drs. T. Taylor, J. Magner and D. Bradway at Bayer Corporation, Dr. D. Lissin at Synarc, and Dr. C. Bird at King's College London. We also thank all the patients, x-ray technologists, and the staff at the different x-ray hubs across North America that took part in this study.

REFERENCES

1. Altman R, Brandt K, Hochberg M, Moskowitz R. Design and conduct of clinical trials in patients with osteoarthritis: recommendations from the task force of the Osteoarthritis Research Society. Osteoarthritis Cartilage 1996;4:217-43.
2. Buckland-Wright JC, Macfarlane DG, Lynch JA, Jasani MK, Bradshaw CR. Joint space width measures cartilage thickness in osteoarthritis of the knee: high resolution plain film and double contrast macroradiographic investigation. Ann Rheum Dis 1995;54:263-8.
3. Buckland-Wright JC, Macfarlane DG, Williams SA, Ward RJ. Accuracy and precision of joint space width measurements in standard and macro-radiographs of osteoarthritic knees. Ann Rheum Dis 1995;54:872-80.
4. Ravaud P, Auleley G, Chastang C, et al. Knee joint space width measurement: an experimental study of the influence of radiographic procedure and joint positioning. Br J Rheumatol 1996;35:761-6.
5. Piperno M, Hellio M-P, Conrozier T, Bochu M, Mathieu P, Vignon E. Quantitative evaluation of joint space width in femorotibial osteoarthritis: comparison of three radiographic views. Osteoarthritis Cartilage 1998;6:252-9.
6. Buckland-Wright JC. Protocols for precise radio-anatomical positioning of the tibiofemoral and patellofemoral compartments of the knee. Osteoarthritis Cartilage 1995;3 Suppl A:71-80.
7. Mazzuca SA, Brandt KD, Buckland-Wright JC, et al. Field test of the reproducibility of automated measurements of medial tibiofemoral joint space width derived from standardized knee radiographs. J Rheumatol 1999;26:1359-65.
8. Mazzuca SA, Brandt KD, Buckwalter KA. Longitudinal study of the variability of joint space narrowing (JSN) in osteoarthritic (OA) knees imaged over 30 months with fluoroscopically standardized knee radiography [abstract]. Arthritis Rheum 2002;45 Suppl:S568.
9. Buckland-Wright JC, Bird CF, Ritter-Hrncirik CA, et al. X-ray technologist's reproducibility from automated measurement of medial compartment JSW in knee OA for clinical trial. J Rheumatol 2003;30:329-38.
10. Buckland-Wright JC, Macfarlane DG, Lynch JA, Jasani MK. Quantitative microfocal radiography detects changes in OA knee joint space width in patients in placebo-controlled trial of NSAID therapy. J Rheumatol 1995;22:937-43.
11. Buckland-Wright JC, Wolfe F, Ward RJ, Flowers N, Hayne C. Substantial superiority of semi-flexed (MTP) views in knee osteoarthritis: a comparative radiographic study, without fluoroscopy, of standing extended, semi-flexed (MTP) and Schuss views. J Rheumatol 1999;26:2664-74.
12. Peterfy C, Li J, Zaim S, Duryea J, et al. Comparison of fixed-flexion positioning with fluoroscopic semi-flexed positioning for quantifying radiographic joint-space width in the knee: test-retest reproducibility. Skeletal Radiol 2003;32:128-32.
13. Dupuis DE, Beynnon BD, Richard MJ, et al. Precision and accuracy of joint space width measurements of the medial compartment of the knee using standardized MTP semi-flexed radiographs. Osteoarthritis Cart 2003;11:716-24.

14. Mazzuca SA, Brandt KD, Buckwalter KA, Lane KA, Katz BP. Field test of the reproducibility of the semiflexed metatarsophalangeal view in repeat radiographic examinations of subjects with osteoarthritis of the knee. Arthritis Rheum 2002;46:109-13.
15. Wolf F, Lane NE, Buckland-Wright JC. Radiographic methods in knee OA: a further comparison of semiflexed (MTP), schuss-tunnel, and weight bearing AP views for joint space narrowing and osteophytes. J Rheumatol 2002;29:2597-601.
16. Dieppe PA. Osteoarthritis: introduction. In: Klippel JH, Dieppe PA, editors. Rheumatology. London: Mosby; 1994:7.2.5.
17. Cooper C. Osteoarthritis: epidemiology. In: Klippel JH, Dieppe PA, editors. Rheumatology. London: Mosby; 1994:7.3.1.
18. Kellgren JH, Lawrence JS. Radiological assessment of osteoarthrosis. Ann Rheum Dis 1957;16:494-501.
19. Lynch JA, Buckland-Wright JC, Macfarlane DG. Precision of joint space width measurement in knee osteoarthritis from digital image analysis of high definition macroradiographs. Osteoarthritis Cartilage 1993;1:209-18.
20. Buckland-Wright JC, Macfarlane DG, Jasani MK, Lynch JA. Quantitative microfocal radiographic assessment of osteoarthritis of the knee from weight bearing tunnel and semi-flexed standing views. J Rheumatol 1994;21:1734-41.
21. Bland JM, Altman DG. Measurement error. BMJ 1996;313:744.
22. Yoshioka Y, Siu DW, Scudamore RA, Cooke TDV. Tibial anatomy and functional axes. J Orthop Res 1989;7:132-7.
23. Buckland-Wright C. Review of the anatomical and radiological differences between fluoroscopic and non-fluoroscopic positioning of osteoarthritic knees. Osteoarthritis Cartilage 2004;(in press).
24. Mazucca SA, Brandt KD, Buckwalter KA. Detection of radiographic joint space narrowing in subjects with knee osteoarthritis: longitudinal comparison of the metatarsophalangeal and semiflexed anteroposterior views. Arthritis Rheum 2003;46:385-90.
25. Vignon E, Piperno M, Hellio Le Graverand MP, et al. Measurement of radiographic joint space width in the tibiofemoral compartment of the osteoarthritic knee. Comparison of standing anteroposterior and Lyon Schuss views. Arthritis Rheum 2003;48:378-84.