Osteoarthritis and Cartilage

Review

OARSI Clinical Trials Recommendations: Knee imaging in clinical trials in osteoarthritis


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S U M M A R Y

Significant advances have occurred in our understanding of the pathogenesis of knee osteoarthritis (OA) and some recent trials have demonstrated the potential for modification of the disease course. The purpose of this expert opinion, consensus driven exercise is to provide detail on how one might use and apply knee imaging in knee OA trials. It includes information on acquisition methods/techniques (including guidance on positioning for radiography, sequence/protocol recommendations/hardware for magnetic resonance imaging (MRI)); commonly encountered problems (including positioning, hardware and coil failures, sequences artifacts); quality assurance (QA)/control procedures; measurement methods; measurement performance (reliability, responsiveness, validity); recommendations for trials; and research recommendations.

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Introduction

Significant advances have occurred in our understanding of the pathogenesis of knee osteoarthritis (OA) and some recent trials have demonstrated the potential for modification of the disease...
course. Current regulatory requirements for disease modification require that alongside the assessment of structural effects symptom improvement be demonstrated. The previous guidelines for clinical trials published in 1996 included recommendations for imaging with a predominant focus on radiography (commensurate with the era) with some detail in the appendices on methods of acquiring radiographs and use of magnetic resonance imaging (MRI). There was little if any detail on the different imaging methods available, the pitfalls inherent no performance metrics of different imaging markers.

The purpose of this data-based expert opinion, consensus driven exercise is to provide detail to anyone involved in clinical OA trials, imaging scientists and their respective teams on how one might use and apply this knowledge in disease modifying clinical trials utilising knee imaging assessments. It includes information on acquisition methods/techniques (including guidance on positioning for radiography, sequence/protocol recommendations/hardware for MRI); commonly encountered problems (including positioning, hardware and coil failures, sequences artifacts); quality assurance (QA)/control procedures; measurement methods; measurement performance (reliability, responsiveness, validity); recommendations for trials; and research recommendations.

Methods

This paper is the work of a large multidisciplinary group who were invited to participate in the Osteoarthritis Research Society (OARSI) Clinical Trials Imaging Working Group. This review began with a search of PubMed using terms of OA, knee, and imaging. We also conducted general searches for manuscripts covering general imaging and randomized control trial (RCT) methods, covering each of the sub-topics below; from this literature we identified designs and methods, as well as other manuscripts of high relevance. It should be noted that the vast majority of this manuscript is based upon expert opinion of the diverse multidisciplinary group involved in this exercise. Authors of this review included multiple experts familiar with different approaches for imaging of the knee joint, including radiologists, rheumatologists, and engineers. This expert opinion was generated via a series of teleconference and email exchanges followed by generation of a series of recommendations. This correspondence allowed the working group to identify additional topics and manuscripts for inclusion and to develop and reach concurrence on a set of recommended principles for inclusion of knee imaging methods in OA trials. Given the potential for divergent perspectives for the trial recommendations and research recommendations a survey was conducted of these members to determine the strength of recommendation for each point raised. Final recommendations were obtained by averaging the responses to a survey among the 14 authors for the strength of recommendation from 0 to 100. At the commencement of this exercise all members of the working group were asked about conflicts of interest and the results from those who were conflicted were not included in the survey results. The focus of the content is on radiography and MRI as the preferred imaging techniques with some content on ultrasound when appropriate.

Image acquisition

Imaging of the knee can be obtained by a variety of modalities. X-ray, ultrasound, computed tomography (CT) and MRI are most widely used and well developed at this time. New trials are using PET and SPECT/scintigraphy to evaluate knee OA. There continue to be limitations in the application of arthroscopy, ultrasound and bone densitometry techniques in clinical OA trials; hence, their acquisition methods are not discussed below.

X-ray of the tibiofemoral joints

Radiography of the tibiofemoral joints is most often evaluated with anteroposterior (AP) positioning. Although supine (non-weight bearing) AP images are easily and frequently obtained, the joint space width (JSW) cannot be adequately estimated in that position. The AP standing view is the most frequently used view in clinical practice, but not in clinical trials. Both knees can be included using a 36 × 43 cm (14 × 17 in) detector system if the thighs are not heavy or significant varus is not present. Otherwise, a single knee can be imaged with a suitable (e.g., 24 × 30 cm) detector system. For the standing X-ray, care must be taken that the knees be fully extended and against the cassette to avoid distortion. The X-ray beam should be 6° caudal and a 180 cm (72 in) focus to film distance, utilizing 65–72 kVp and a small focal spot. With feet pointed straight ahead, the X-ray beam should be centered midway between the knees (bilateral) or horizontally at mid-patella (single knee) and about 1 cm below the apex of the patella.

In cross sectional epidemiologic or symptom modifying clinical trials, the posteroanterior (PA) X-ray is useful for supporting a diagnosis of knee OA. For longitudinal epidemiologic or structure (disease) modifying trials, the standing or radiograph of the knee does not adequately define joint space narrowing (JSN), as the most severe changes in condylar articular cartilage are often somewhat posterior. To more accurately determine the narrowest point in the medial compartment, Buckland-Wright developed a method of fluoroscopically positioning the knee. This and several other techniques have been developed in order to have reproducible positioning for semi-quantitative OARSI grading of JSN and quantitative measurements of the medial joint space. The basic principle of these methods are to fix the alignment of the medial tibial plateau, while flexing the knee at a reproducible angle in order to capture the narrowest region of cartilage of the medial condyle. The most commonly used techniques utilized at this time are the fixed-flexion PA view and the fluoroscopically aligned Lyon-Schuss PA view, with the use of a SynaFlexer positioning frame (BioClinica (formerly Synarc), San Francisco, CA) and the Lyon Schuss view, the patellae and thighs are in contact with the film cassette and coplanar with the tips of the great toes. In the MTP fixed flexion view the patellae are in contact with the cassette and aligned vertically with the first MTP joints with the feet externally rotated 5°. This results in reproducible flexion of the knee at approximately 20°. The X-ray beam is angled 10° caudal and centered on a reproducibly identifiable point in the popliteal fossa of a single knee or midway between the two knees at the level of the popliteal fossa if both knees are imaged simultaneously, with the aim of aligning the beam tangential with the floor of the medial tibial plateau. The Lyon Schuss technique uses the same positioning and beam centering, but fluoroscopically aligns the anterior and posterior rims of the medial tibial plateau. Magnification correction is assisted by a projection phantom on the SynaFlexer frame or by placing a ball bearing of known dimension in the same position medial to the knee if imaging without the SynaFlexer. Fluoroscopic guidance, if done correctly, provides high quality and optimally aligned images. However, this requires more training and is not available at most sites in a multicenter trial. A modified Lyon-Schuss (mLS) technique has been used successfully, requiring imaging the knee three times with a 2° difference in tube head angle to ensure optimum positioning as observed with the inter-margin distance. It should be noted that special images (long limb films) were historically recommended to adequately judge varus or valgus deformities, but more recently, the knee film alone has been found to be sufficient.
X-ray of the patello-femoral joint

A lateral view of the patellofemoral (PF) joint can be used to supplement the findings on the AP view. In addition, measurement of the lateral view radiographic patellofemoral JSW may also be of value\textsuperscript{29}. The lateral PF view is often obtained with the patient lying supine on the table, hips and knees flexed with the heels on the table enough to flex the knees to 45°. Additionally, determination of PF alignment and specific of PF JSW (adequate determination of medial vs lateral PF involvement) are often viewed with an axial (skyline, sunrise, sunset) image of the knee, obtained with the X-ray beam parallel to the table and perpendicular to a

Quantitative cartilage morphometry MRI acquisition techniques

Due to the limitations of radiography, MRI has been identified by the Outcome Measures in Rheumatologic Clinical Trials (OMERACT) and OARSI as the most appropriate imaging modality to assess joint status in OA research studies\textsuperscript{20}. MRI can detect structural pathology associated with pain\textsuperscript{21,22} and other tissues involved in the disease process such as cartilage damage, osteophytes, subchondral cysts, joint effusions, ligament and tendon tears, Baker’s cysts, synovitis, meniscal tears, and subchondral bone marrow lesions\textsuperscript{13–31}. MRI is
becoming more widely available and requires no exposure to ionizing radiation\textsuperscript{14}. The mechanisms of pain and mechanical dysfunction in OA are not completely understood but are believed to involve multiple interrelated pathways involving all joint structures\textsuperscript{3,26,33–37}. MRI protocols in OA research studies should be tailored for optimized visualization of the tissue of interest and take into account the image analysis method such as semi-quantitative scoring, quantitative assessment of tissue dimensions (volume, thickness) or biochemical composition\textsuperscript{20,30}. For 3D volumetric cartilage analysis \textit{in vivo} to perform comprehensive joint assessment, two-dimensional fluid sensitive sequences such as fat-suppressed intermediate-weighted or T2-weighted FSE or short tau inversion recovery should be performed in at least one plane to allow improved detection of ligament tears, bone marrow lesions, and joint effusions. Protocols are optimally performed on 3.0 T scanners providing image quality sufficient for reproducible analysis for most protocols.

MRI protocols should include 3D sequences if \textit{quantitative}, volumetric evaluation of articular cartilage is to be performed (see Table II). Fat suppression is typically added to these sequences to reduce chemical shift artifact and to optimize the overall dynamic contrast range of the image. 3D sequences are acquired with high in-plane spatial resolution and thin continuous slices which reduce partial volume averaging. Many 3D sequences have near-isotropic resolution which allows articular cartilage and other joint structures to be evaluated in any orientation through the creation of high quality multi-planar reformat images. Various three-dimensional sequences have been used for cartilage assessment within the knee joint including T1-weighted, fat-suppressed gradient-echo\textsuperscript{38–40} and dual-echo in the steady-state (DESS)\textsuperscript{41}. Although the three-dimensional FSE/TSE techniques are improving, there are still numerous drawbacks compared to the more widely available 2D techniques: (1) image blurring when using 3D FSE sequences secondary to T2 modulation of the point spread function, (2) decreased contrast for evaluating soft tissue structures including bone marrow lesions, ligaments, tendons, and menisci \textit{(3)} greater variation between manufacturers, (4) longer image acquisition time which increases likelihood of motion, (5) increased susceptibility to metallic artifacts. Although, 3D gradient-echo sequences have been validated and applied for volumetric cartilage assessment for over a decade\textsuperscript{42}, there are few studies available using 3D FSE/TSE sequences for semi-quantitative assessment\textsuperscript{43}.

Gradient-echo sequences were the first 3D sequences used to evaluate articular cartilage. Gradient-echo sequences can be divided into dark fluid sequences and bright fluid sequences based upon the signal intensity of synovial fluid. Dark fluid sequences include T1-weighted spoiled gradient recalled-echo (SPGR, GE Healthcare), fast low angle shot (FLASH, Siemens Medical Systems), or steady-state free precession (SSFP, GE or 3D-FISP, Siemens) and T1-fast field echo (T1-FFE, Philips Healthcare). Bright fluid sequences include T2*-weighted gradient recalled-echo acquired in the steady-state (GRASS, GE Healthcare), gradient recalled-echo (GRE, Siemens Medical Systems), and fast field-echo (FFE, Philips Healthcare). These sequences have been combined with a variety of fat-suppression techniques including frequency selective fat-saturation\textsuperscript{44,45,46}, water excitation\textsuperscript{47,48} and iterative decomposition of water and fat with echo asymmetry and least squares estimates (IDEAL)\textsuperscript{39–41}. Bright fluid gradient-echo sequences have been found to be the most useful for detecting cartilage lesions in clinical practice and OA to perform cartilage thickness measurements in OA research\textsuperscript{39–41,45,46,52}. The main disadvantage of using dark fluid sequences for clinical cartilage imaging is that the low signal intensity of synovial fluid may decrease the conspicuity of superficial cartilage lesions\textsuperscript{39,51}.

Driven equilibrium fourier transform (DEFT) and DESS are additional three-dimensional sequence used to evaluate articular cartilage. DEFT uses a 90° pulse to return transverse magnetization to the $z$-axis which increases the signal intensity of tissues such as synovial fluid with long T1 relaxation times. Cartilage signal is relatively preserved on DEFT images due to the use of short echo times\textsuperscript{53,55,56}. DESS acquires two gradient echoes separated by a refocusing pulse which are combined into a single image. Adding the two echoes enhances the T2*-weighting of the image and increases the signal intensity of both cartilage and synovial fluid\textsuperscript{44,45,46}. DEFT and DESS utilize frequency selective fat-saturation\textsuperscript{53} or water excitation\textsuperscript{47,48} to suppress signal from adipose tissue. Both sequences produce multi-planar images of the knee joint with bright synovial fluid which creates an arthrogram-like effect that increases the conspicuity of superficial cartilage lesions. A water excitation DESS sequence with 0.4 mm $\times$ 0.5 mm in-plane spatial resolution and 0.7 mm slice thickness is currently being used in the Osteoarthritis Initiative to provide detailed cartilage assessment\textsuperscript{22}.

Three-dimensional FSE sequences such as fast spin-echo Cube (FSE-Cube, GE Healthcare) and sampling perfection with application optimized contrasts using different flip angle evolutions (SPACE, Siemens Medical Systems) have also been used to evaluate...
articular cartilage. These sequences utilize flip angle modulation to constrain T2 decay over an extended echo train which allows intermediate-weighted images of the knee joint with isotropic resolution to be acquired with minimal blurring. Three-dimensional FSE sequences typically use frequency selective fat-saturation to suppress signal from adipose tissue. FSE-Cube and SPACE have lower in-plane spatial resolution and greater image blurring when compared to other three-dimensional cartilage imaging sequences with similar acquisition times which may decrease the conspicuity of superficial cartilage lesions. However, these sequences have highly versatile intermediate-weighted contrast which can be used to evaluate all joint structures. In fact, three-dimensional FSE sequences with multi-planar reformatations has been shown to provide near identical “whole-organ” knee joint assessment in OA research studies as axial, sagittal, and coronal two-dimensional FSE sequences in shorter periods of time by eliminating the need to acquire images with identical tissue contrast in multiple planes. It should be noted, however, that the image quality of the reformations is not comparable with the acquired source images and that reformations cannot fully substitute 2D images obtained in the same orientation.

For cartilage quality studies quantitative mapping techniques have been used to measure MRI parameters that are sensitive to early changes in the composition and structural organization of the extra-cellular matrix that precede loss of tissue detected with standard MRI techniques. Techniques that have been applied in clinical trials include cartilage T2 mapping, T1rho mapping, and delayed gadolinium enhanced MRI of cartilage (dGEMRIC) and have been the focus of several review articles. dGEMRIC can provide sensitive and specific information regarding the proteoglycan content of cartilage, but the technique requires a long waiting period between contrast administration and image acquisition and carries the risk of nephrogenic systemic sclerosis. T2 and T1rho mapping have been shown to be sensitive for detecting early cartilage degeneration in human subjects without the inconvenience and risks associated with the use of exogenous contrast agents. However, both techniques are not chemically specific, but are influenced by concurrent changes in water content, macromolecule content, and anisotropic organization that occur during early cartilage degeneration. As such it is important when interpreting the results of these techniques to realize that the measured response to tissue degeneration is nonlinear and that biochemical specificity of the response will generally decrease with more advanced degeneration.

CT arthrography

CT arthrography can also be used to provide knee joint assessment in OA research studies. CT is a widely available and relatively inexpensive imaging modality which can rapidly acquire high resolution volumetric source data that can be used to create reformatted images in multiple planes. CT imaging has high sensitivity for detecting various features of joint degeneration including meniscus and ligament tears, cartilage loss (these first three features following the injection of iodinated contrast into the knee joint), subchondral cysts and sclerosis, and osteophyte formation. The technique can also be used to measure the thickness of cartilage and proteoglycan concentration of cartilage. However, CT arthrography is an invasive technique requiring radiation exposure and intra-articular contrast administration which has limited its use in longitudinal OA research studies. Also evaluation of bone marrow and ligaments is limited with CT compared to MRI. A more recent study suggested CT may also have promise for evaluation of calcium crystal deposition in the knee.

Commonly encountered problems: positioning, hardware and coil failures, sequences artifacts

Commonly-encountered problems in radiography

Projection

Radiography is a projectional technique in which 3D anatomy is projected onto a 2D receptor, and therefore subject to morphological distortion, magnification and superimposition of overlaying structures. A reproducible radiographic image of the tibiofemoral joint space thus requires adherence to exacting standards of centering and angulation of the X-ray beam, and positioning of the knee, which include specifications for flexion and rotation of the joint. In a majority of patients, the anatomy of the knee is such that full extension of the joint (as is required for a conventional weight-bearing extended-knee radiograph) tilts the tibial plateau to an angle that is skew (i.e., not parallel) to a horizontally directed X-ray beam. Skewed radio-anatomic alignment of the tibial plateau in an AP or PA knee radiograph is apparent in the excessive floor angle that is skew (i.e., not parallel) to a horizontally directed X-ray beam. Skewed radio-anatomic alignment of the tibial plateau in an AP or PA knee radiograph is apparent in the excessive displacement of the anterior and posterior margins of the medial plateau. When the alignment of the plateau is notably skewed, the floor of the joint space can become indistinct, and a key reference point for the measurement of minimum JSW (minJSW) is less reliably ascertained. Typically it is recommended that the inter-marginal distance (IMD) should be ≤1.5 mm or even ≤1 mm. Although, other studies suggest that while stability of the IMD between visits matters, as a metric of reproducible projection, small differences in absolute IMD may not empirically affect JSN.

1. Flexion of the knee, rotation of the knee

If the articulating surfaces of tibia and femur overlap or the anterior and posterior tibial rims are grossly malaligned, unclear visualization or artificial variation of the JSW may result.
Different degrees of knee flexion between time points cause problems in longitudinal studies. Further, articular cartilage loss in the knee most commonly begins along a region of the femoral condyle that is posterior to that which articulates with the tibial surface when the knee is in full extension. Since radiographic joint-space width reflects cartilage thickness only where the femoral and tibial articular surfaces are in direct contact, positioning the knee in full extension can be insensitive to early cartilage loss. Mild flexion is thus needed to articulate this active portion of the femur with the central tibia and detect early cartilage loss. Moreover, since cartilage loss progresses heterogeneously in the knee, knee flexion as well as beam centering and angulation must be exactly the same on serially acquired radiographs for longitudinal assessments of JSN to be valid.

Different degrees of rotation of the knee may cause different degrees of overlap between osteophytes and the margin of femur/tibia, leading to non-visualization of previously seen osteophytes, exposure of previously obscured osteophytes, or a discrepancy in their apparent size between timepoints when in fact there has been no real change in size.

### 2 Weight bearing

As noted above, radiographic joint-space width can be valid as a measure of cartilage thickness only when the two opposing cartilage surfaces of interest are in direct contact with each other. The knee must therefore be loaded in order to ensure this. However, weight bearing during radiography poses a number of additional challenges. For example, longitudinal changes in weight bearing (for example, due to weight gain or loss) may affect the extent of voluntary knee extension. Accordingly, effort must be taken in serial examinations to fix the degree of flexion reproducibly. Changes in the distance between the knee and radiographic cassette may alter the degree of radiographic magnification in the image. These sources of error seriously limit the utility of the knee radiograph to detect true reduction in JSW, the cardinal indicator of progression of knee OA. While these challenges are recognized, recent studies have demonstrated that with careful site technologist training, using a weight bearing acquisition technique, careful unilateral imaging of each knee (not a bilateral knee radiography), proficient quality control (QC) of the radiography by a core lab experienced in the technique, either the fixed flexion or mLS technique can provide reproducible images to allow evaluation of a disease modifying osteoarthritis drugs (DMOAD) in a large multi-center clinical trial.

### 3 X-ray beam angle

Variation in X-ray beam angle can result in apparent difference in the JSW (Fig. 3). This can also cause artificial variation in JSW in longitudinal studies.

### Commonly-encountered problems in MRI

In clinical trials of knee OA, the images need to cover the whole knee joint. For optimal images, the joint should be centered at the midpoint of the coil and the iso-center aligned caudal to the distal end of the patella. That guarantees full coverage of the knee. However, if the synovial fluid is to be measured, the field of view (FOV) must be shifted proximally to ensure that all parts of the joint capsule are covered in both the proximal-distal and medial-lateral directions.

#### Imaging plane alignment

The curved shape of the femoral condyles and the patella requires selection of an imaging plane perpendicular to the curvature to provide clear views of the cartilage surface and to minimize partial volume effects. Imaging planes should provide the best views of articulating cartilage, bones and soft tissue structures both for scoring and quantitative assessment of cartilage, bone marrow lesions, and meniscus. Selection of an oblique imaging plane aligned with the anterior cruciate ligament may be helpful for

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**Fig. 2.** Radiographs at baseline and 2-year follow-up of a 61-year-old woman with OA. At two time points, radiographs were taken with 5°, 10°, and 15° angulation of the knee. (a) AP radiograph taken at 5° angulation shows medial JSN (OARSI grade 2 and KLG 3). (b) However, AP radiograph taken at 10° angulation shows OARSI grade 3 JSN (KLG 4). (c) Similarly, at follow-up, AP radiograph taken at 5° angulation shows OARSI grade 2 JSN (KLG 3) whereas that taken at 15° angulation (d) shows OARSI grade 3 JSN (KLG 4). If images (b) and (c) are compared longitudinally, one observes a paradoxical ‘joint space widening’.
between cartilage and all adjacent tissues and fluid. Many of the techniques are manufacturer-dependent, but most include some type of fat suppression or selective water excitation and 3D FSE or gradient echo sequence, although 2D FSE is sometimes used for semi-quantitative scoring. All of those sequences have been validated for imaging of cartilage. Their ability to show the boundaries between bone-cartilage, cartilage-cartilage, cartilage-degenerated meniscus, cartilage-inflamed synovium, and cartilage-inflamed synovial fluid varies. While selecting a sequence it is important to take care that the imaging parameters are also chosen in such a way that the visualization of those interfaces are optimized, particularly those with the greatest impact on study endpoints.

MRI is used for compositional assessment including techniques such as T2 imaging, dGEMRIC and T1 rho imaging. This imaging has similar resolution dependencies as quantitative morphologic imaging. Thick slices and low in-plane resolution will limit detection to generalized changes and prevent detection of local abnormalities and their progression. For T2 measurements the ideal slice thickness is 2 mm, but for practical purposes 3 mm resolution may be needed. There are varying opinions of the number of echoes needed in the multi-echo spin echo series for repeatable T2 calculations, varying from two echoes to 11 echoes. The practical issue is that the larger the number of echoes the smaller the number of slices, subsequently limiting coverage of the knee. Regardless of the number of slices, however, assessments are only useful for comparison if the area covered and the imaging plane used are the same from time point to time point. Standardization (consistency of image acquisition parameters within the study) of image acquisition cannot be overemphasized.

The variability of T2 measurements between different manufacturers and different imaging units is a well-known confounding factor. The effect of the variability can be minimized by using small, standardized T2 phantoms, which are positioned in the imaging field of view of the T2 series acquired for each subject at each time point. This will enable pooling of T2 data across multiple sites and equipment and verify possible change between time points. At this time, T1 rho sequences have not been validated for use in OA trials, therefore their use is currently limited to experimental tertiary endpoints.

Since both quantitative and qualitative assessments may use fat suppressed/saturated sequences, heterogeneous fat suppression due to field heterogeneity will affect analysis results. Since the cartilage thickness changes over time are generally relatively small, geometric distortion can affect the reliability of the results. The stability of field homogeneity should be monitored by scanning special uniformity and linearity phantoms at the start of the study and periodically throughout. Transmit/receive as well as receive only coils, which are used for knee imaging have a tendency to start failing slowly. Therefore, phantom scanning also should monitor their performance throughout the study. Although a relatively rare occurrence, changes in imaging performance can be caused by software or hardware upgrades to the scanner, or problems requiring a re-shim to correct. Periodic phantom scanning can detect these issues before too much study data has been acquired.

In addition to the difficulties outlined above there can be difficulties in safely putting patients with pacemakers or imbedded metal foreign objects inside the magnet. A small proportion of patients have problems with claustrophobic reactions. The size of the joint being imaged—for example a large knee in an obese patient—may be too large for the cylindrical RF coil typically used, leading to potential impaired image quality. Researchers need to be aware of commonly encountered issues MR artifacts. Screening for artifacts that potentially hinder adequate and appropriate image assessment should be part of standardized QA procedures that are discussed in detail in the next section. The challenges in conjunction with MRI
artifacts have been reviewed extensively. A detailed discussion of these would be beyond the scope of this manuscript.

**QA/control procedures**

Clinical trials are becoming more complex, and from a regulatory perspective, they are underpinned by an over-arching quality process or Good Clinical Practice (GCP). The understanding of the GCP framework is critical to ensure the management of all aspects of clinical trials, not least of which is the imaging. Essentially, this is twofold: data integrity and subject protection. From an imaging perspective, more recently the requirements specifically for medical imaging in clinical trials, including the necessary documentation, such as an Imaging Charter have been detailed by the Food and Drug Administration (FDA). Potentially more practical details for the charter and review of read systems have been described in detail recently. A systematic approach is required to ensuring quality as detailed below:

- Personnel roles and responsibilities
- Training
- Policies and procedures
- QA and auditing
- Document management, record retention, and reporting
- Corrective and preventive action (CAPA)

There is a major difference between QC and QA:

Quality control, as stated by the ISO definition, is the summarizing term covering the operational techniques that are used to fulfill requirements for quality. In the context of medical imaging in clinical trials, this includes the framework of the documents described and the checking of the medical imaging data by a third party such as an imaging core lab. A diagrammatic representation is shown in Fig. 4.

Quality Assurance comprises the overarching procedures that are put in place to ensure quality, which includes the checking and audit of the process and QC systems that have been instigated.

**Medical imaging QC in clinical trials**

When evaluating the QC procedures one needs to understand the key aspects of the use of medical imaging in medicine in general: (1) Diagnosis; (2) Prognosis or screening; (3) Monitoring of therapy and (4) Monitoring of natural history in order to initiate, refrain from or change therapy. In clinical trials one usually considers efficacy measures, which are items 3 & 4 (monitoring therapy, and monitoring natural history for placebo controlled studies). For eligibility, items 1 and 2 are relevant. There are different metrics that have to be considered for each of these uses. KLG is used for eligibility but it does not have the sensitivity or precision for efficacy and hence the radiographic QC may differ when applying radiographic KLG for eligibility compared to reduction in radiographic JSW being used as an outcome in longitudinal studies looking at efficacy.

The challenge at screening in regard to required image quality is to account for both, the requirements of eligibility and efficacy; e.g., if JSW loss is the primary end point in a clinical trial, then the acquisition of the knee X-ray has to be of sufficient quality for the JSW measurement, but for a pure screening KLG acquisition, a standard AP film may be adequate, as when an analgesic is being developed without DMOAD properties.

**Cross-calibration**

Depending on the end-point, cross-calibration may be an optional requirement. For many outcomes in clinical trials the key end point is percentage change from baseline. If each subject is used as their own control (i.e., compare follow up with baseline or previous follow-up visits), then cross calibration is not required. This is certainly the case with all radiographic and MRI endpoints in DMOAD studies. However, it has to be ensured that image acquisition at serial visits is performed in identical fashion including technical aspects such as MRI or radiography system, sequence protocols used, positioning and others. This leads to a set of QC features that are required regardless of the anatomical area being evaluated:

1. Radiographs. If a grading scale is being used, then no calibration is required, but the above mentioned items in regard to reproducibility of image acquisition apply also for studies using ordinal outcomes. If JSW or another quantitative end point is being used, then a calibration marker or markers have to be placed and be visible in the FOV at about the same distance to the detector as the joint is located, to minimize the effects of beam divergence and magnification.
2. MRI. If a scoring or grading system is being used, no calibration is required (other than the routine standard ones conducted at the site for correct instrument use). However, full anatomical coverage and comparable sequence protocols are a requirement for longitudinal comparison. If cartilage volume, thickness or other quantitative parameters are being measured, very specific calibration phantoms should be used, which are anatomic and end-point specific. For continuous biomarkers such as these quantitative measures then multivendor trials should demonstrate and document that the biomarker values are comparable across vendors and across centres. Subjects must always be scanned on the same instrument on which they had their baseline measurement, and using identical imaging parameters, regardless of methodology being applied. If change in quantitative cartilage is to be measured, then 3 T with phased-arrays is recommended, while if whole-organ scoring is the primary aim, then any 1.5 T or 3 T system which passes QA can be used.
3. Ultrasound. Ideally all the equipment should be standardized across all sites. If not, then each subject must be scanned using

![Fig. 4. QC](http://www.transition-support.com/Quality_control.htm) accessed 05 February 2014.
the same equipment at each visit. The technologist acquiring the data has to be very conscientious in marking up the scans so the technologist providing QC can follow the joint and positioning.

**Instructions manual**

For all imaging, instruction manuals or “cheat sheets” must be provided to all sites detailing the specific acquisition requirements. Without this set of details, QC cannot be conducted.

**Reader “training” or calibration**

For all the imaging evaluations performed in OA clinical trials, radiologists or radiologist-trained readers may be involved in the clinical study as readers. If only one reader is used, a regular calibration process is needed during the course of a longitudinal study to avoid shift/drift in readings. If more than one reader is to read the images (highly recommended, except for small studies), then it is important to bring the readers together for a calibration meeting for the following specific reasons:

1. Training on the reading protocol
2. Training on the reading interface (unless they have used the same specific software and hardware configuration in prior work).
3. To gain concordance in understanding the grading requirements
4. To undertake intra- and inter-reader agreement evaluation. It is important that the reliability assessment is performed on an adequate number of cases that takes into account the characteristics of a specific cohort. It is important to assess reliability in a cross-sectional as well as longitudinal fashion as detection of change is the most important parameter in clinical trials. Further an adequate number needs to be included in reliability exercises. During the course of the study, inter-reader concordance exercises should be conducted in an on-going manner. In general the concepts provided here are outlines in the FDA draft Guidance entitled “Guidance for Industry on Standards for Clinical Trial Imaging Endpoints”.

**Knee X-ray specific QC**

All knee acquisitions need to use a weight bearing fixed flexion technique, such as fixed flexion or MFL using a positioning device, such as the Synaflexer equipped with a calibration standard.

There are a number of factors that need to be considered when evaluating QC for the knee for both eligibility and efficacy:

1. Is there a single knee imaged per radiograph?
2. Are there calibration beads visible?
   a. If not JSW cannot be measured
3. Is the knee in the center of the image?
4. Is there minimal rotation (as evaluated by the patellar position)
5. Is the cortex of the medial tibial plateau sharply delineated in its entirety
   a. Some studies suggest inter-margin distance should be ≤ 1.5 mm
6. Does the inter-margin distance vary between visits?
7. Is anatomical coverage 10 cm above and below the tibial spines?
   a. Is there correct alignment (defined by anatomical angle axis) and is it within protocol limits? (if needed for eligibility)

**Knee MRI specific QC**

After checking the identification of the participant, sequences relative to the study protocol should be verified. Then, for each acquisition, image quality should be validated according to the following criteria:

- Integrity of all sequences (legible and complete sequences)
- Position of the knee in the FOV
- Contrast of tissues
- Motion artifact
- Other artifacts
- At follow-up visit, it is important to check that it is the same knee as the knee that was imaged at baseline and that the imaging parameters are identical.
- QC results should be documented and archived in the participant’s file.
- According to the study, the rejection of a QC may necessitate the new submission of images, resumption of the MRI or dismissal of the participant.

**Measurement methods**

**Semi-quantitative radiographic scores**

Radiography can be used to visualize osteophytes, subchondral cysts and sclerosis, alignment, and cortical irregularities. Radiography does not directly visualize articular cartilage, menisci, cruciate or collateral ligaments, synovium, bursae, or the periarticular muscles and ligaments, all of which can be better assessed by MRI. Moreover, JSW is nonspecific, as it includes not only articular cartilage but meniscal tissue. Radiography is also limited by providing only a 2D projection of the knee, which has a complex, 3D structure.

In clinical trials, the PA radiograph is useful for supporting a diagnosis of knee OA. Although the KLG system is over 60 years old, it continues to be a useful method for eligibility screening for clinical trials. According to the KLG the presence of a definite osteophyte is consistent with the diagnosis of OA (KLG 2). The presence of definite JSN and osteophytes is consistent with moderate OA (KLG 3).

There are more detailed methods for defining individual radiographic features (including the OARSI atlas) that are useful in more specifically defining the study population and ascertaining progression of JSN. Other radiographic scoring methods are available (including the Spector Atlas and Doherty’s line drawing atlas), however, they are less widely used.

**Quantitative radiographic measures**

Traditionally the progression of knee OA has been assessed by measuring changes in JSW (typically in millimeters), i.e., the distance between the medial femoral condyle and medial tibial plateau on plain radiographs, as the medial compartment is the most common site of involvement in knee OA. Among the various radiographic features of OA, JSW is considered the surrogate for articular cartilage thickness although it also reflects the integrity of the meniscus. Methods of measurement of JSW can be either manual using callipers or a simple graduated ruler and a micrometer eyepiece, or semi-automated using computer software.

**MRI semi-quantitative scores**

Semi-quantitative assessment of the joints by expert interpreters of MRI data has increased our understanding of the natural history of this complex disease. These are usually in ordinal scales although for some features they are dichotomous/binary (e.g., ACL disruption). Several reliable and validated semi-quantitative scoring systems now exist and have been applied to large-scale, multicenter, cross-sectional and longitudinal observational epidemiological studies. Semi-quantitative MRI outcome
measures have also been applied in several clinical trials in OA. These include WORMS, BLOKS, and MOAKS, which have been extensively reviewed elsewhere recently.

**MRI — quantitative measurements**

There is a wide variety of quantitative MRI measurement methods including compositional measures such as (T1rho, T2 (sec) and T2* relaxation time measurements, GAG CEST, Sodium, Diffusion and DTI, and dGEMRIC), as well as quantitative measurements of cartilage (such as cartilage thickness, denuded area, and morphological (CALS) score) or other joint tissues for quantitative morphological assessment (including 3D statistical shape models and bone shape and dynamic contrast-enhanced and non-contrast MRI synovitis). There are a range of methods used for quantitative assessment of cartilage morphometry (volume (typically measured in mm³), thickness (typically measured in mm), denuded area (typically measured in mm²)) ranging from fully manual to fully automatic. There is no clear data demonstrating measurement performance superiority of one method over another after direct comparison. Similarly, quantification of the knee bone marrow lesions, osteophytes, meniscus, muscle volume, bone area and shape, synovitis and synovial fluid are possible and are demonstrating some important findings.

**Measurement performance (reliability, responsiveness, validity)**

**Reliability of radiography in the knee joint**

Reliability assessments for observer based measures include both inter and intra-observer measures as provided in ICCs or kappa scores. There are different review articles available which provide relatively consistent numbers with intra-reader variability of about 0.95—0.97 (ICC) and only slightly lower inter-reader variability of about 0.93—0.95 (ICC) for JSW. However, these values are highly influenced by the quality and grades of the radiographs being evaluated, so should not be used as a gold standard, unless the same set of images are being used to compare another set of radiologists. The radiographic method did not affect the reliability, however the positioning of the knee joint plays a very important role.

**Reliability of MRI in the knee joint**

Concerning MRI the literature gets much more inconsistent and the reliability is in part very much dependent on what one is measuring and how one is doing this. To this end we would assert that reliability is study specific and should be tested and reported for each endeavour. The inter-reader and intra-reader ICCs are high for quantitative as well as semi-quantitative morphological MRI (range 0.80—0.94) in OA. However, the results are very much dependent on the specific anatomical area within the knee joint which is analysed with an increased range of ICCs e.g., for the quantitative assessment of the synovium (range 0.61—1.00) or the semi-quantitative assessment of the meniscus (range 0.49—1.00). For quantitative cartilage morphometry the ICC ranges in various studies for intra- and inter-rater reliability in between 0.86 and 0.95. In compositional MR techniques, the range of the reliability is higher and even more heterogeneous. So far there is no systematic review on reliability issues in compositional MRI available. Existing studies are reporting on ICC values for T2 mapping in between 0.61 and 0.98. The reproducibility of T1-p values for example was higher in the thicker patellar cartilage (ICC range, 0.86—0.93) than in the femoro-tibial joint with a large range of ICC values in between 0.20 and 0.84.

**Responsiveness of radiography in the knee joint**

The responsiveness of radiographic JSW can be assessed by calculating the standardized response mean (SRM). The SRM is one of several available effect size indices used to gauge the responsiveness of scales to clinical change. The overall pooled SRM was 0.33. Responsiveness of change in JSW measurement was improved substantially in studies of greater than 2 years duration (0.57). Further stratifying this result in studies of greater than 2 years duration, radiographs obtained with the knee in a flexed position yielded an SRM of 0.71 although, like MRI this is likely study specific.

**Responsiveness of cartilage morphometry:** thickness, area, volume in the knee joint

The pooled SRM for quantitative measures of cartilage morphometry for the medial tibiofemoral joint was reported as –0.86. For the quantitative analysis, SRMs are negative because the quantitative value, indicating a loss of cartilage, goes down. The pooled SRM for the semi-quantitative measurement of cartilage morphology for the medial tibiofemoral joint was 0.55. For the semi-quantitative analysis, SRMs indicating a loss in cartilage are positive (increase in score).

**Responsiveness of compositional measures: (T2, T1-rho, dGEMRIC, Na) in the knee joint**

The responsiveness as an instrument’s ability to detect change over time has so far not been assessed in the literature for compositional MR techniques. Nevertheless for quantitative T2 mapping, recent reports from the incident and normal cohort of the OA1 support the use of cartilage T2 as an early marker of cartilage degeneration, demonstrating responsiveness to cartilage change over time. Comparably also in other studies T2 mapping is seen to provide stable and subtle longitudinal data. A comparable promising detection of longitudinal results can be found for dGEMRIC. For T1rho a number of studies also showed responsiveness.

For all other compositional sequences, the availability of possible responsiveness to change is not yet available in literature. Additionally the possibility of a real quantification of most of the compositional MR techniques enables them to reliably detect changes of cartilage micro-structure.

**Validity of radiography in the knee joint**

The validity or accuracy is the degree to which an instrument measures what it is supposed to measure is assessed here. In OA progression can be assessed validly. For radiography, there is some evidence for construct and predictive validity, with good evidence for reliability of metric measurement of JSW. It is important to note that radiographic assessment concurrent and predictive validity for clinical outcomes is weak and that JSW reflects a number of structures not just hyaline articular cartilage.

**Validity of MRI in the knee joint**

Concurrent validity of MRI in OA has been examined compared to different parameters. The relation of bone marrow lesions, synovitis and effusion to pain was moderate to strong. There was a weak or no relation of cartilage damage or meniscal tears to pain. The relation of cartilage morphology to radiographic OA and radiographic joint space was inconsistent. There was a higher frequency of meniscal tears and extrusion, synovitis and other
features in persons with radiographic OA. The relation of cartilage to other constructs including histology and arthroscopy was stronger. Predictive validity of MRI in OA has been examined for ability to predict total knee replacement (TKR), change in symptoms, radiographic progression as well as MRI progression\textsuperscript{13}. Compositional MR techniques have been validated against histological samples with very promising results in exactly quantifying and detecting changes e.g., in the collagen matrix or the GAG content of cartilage\textsuperscript{14}.

**Recommendations for trials (Table IV)**

Trial recommendations are contingent on the goals of imaging in clinical trials. For example imaging may play a role in: subject selection; or monitoring progression/improvement; or determining the complications of disease or treatment.

Further to this the role of imaging in the clinical trial maybe for internal decision making or for definitive proof of efficacy. Internal decision making studies may include proof of concept studies, design considerations for phase III trials or phase IV (patient subgroups or different practice settings).

For image acquisition (whether radiography or MRI) we would recommend.

i. Site training
ii. Image data-quality checks (completeness, correctness)

Regarding image analysis process we would recommend:

i. Central reading
ii. Multiple readers of the same images
iii. Individual patient images grouped for processing for multi-visit studies
iv. Adjudication

In reporting imaging studies in OA we strongly advocate that authors describe in sufficient detail the methods of acquisition, image processing/analytic methods, QA and QC that authors describe in sufficient detail the methods of acquisition, image processing/analytic methods, QA and QC that the methods section of the manuscript. This will enhance both the readers ability to appraise the work and others ability to replicate it. To facilitate clear and transparent communication we would advocate careful and correct use of terminology\textsuperscript{15}.

**Experience with radiography**

The current hierarchy of claims for structural outcome as defined by the FDA Clinical Development Programs for Drugs, Devices and Biological Products Intended for the Treatment of OA draft guidance is as follows:

1. Normalise the X-ray (reverse progression)
2. Improve the X-ray (halt progression)
3. Slow JSW loss by at least a pre-specified amount (slow the rate of progression) accompanied by symptom improvement.

We support the continued use of JSW as one option for assessing structural OA change, taking all the previous points into account when deciding on study end-point.

**Research recommendations (Table V)**
**Table V**
Summary of research recommendations

<table>
<thead>
<tr>
<th>Process</th>
<th>Strength of recommendation (range 0—100)*</th>
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<tr>
<td><strong>Conventional radiography</strong></td>
<td></td>
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<tr>
<td>With conventional radiography a special focus and further work should be on: JSW: Measurement performance (reliability and responsiveness) dependency on projection technique, dependency on axial loading JSW: Measurement performance (reliability and responsiveness) in the lateral femorotibial compartment Bony changes (osteophytes, erosions, cysts, attrition): dependency of reproducibility on projection technique Further investigation of the correlation of MRI cartilage thickness change, MRI meniscus change (position and size), and radiographic JSW change in different stages of radiographic disease (i.e., healthy, pre-radiographic, early radiographic, advanced radiographic should be analysed). This knowledge is required to achieve a paradigm shift from radiographic JSW to MR measurements. What is their reliability (test-retest precision) and sensitivity to change across different (radiographic) stages of knee OA (i.e., from healthy, to pre-radiographic, early radiographic, advanced radiographic). What is their ability to predict the onset of pain in non-symptomatic subjects with and without radiographic change. What is their ability to predict the onset of functional limitations in non-symptomatic subjects with and without radiographic change. What is their ability to predict the onset of radiographic or other structural changes in subjects without definite radiographic change (KLG 0 or 1, with and without symptoms). What is their ability to predict a worsening in pain (progression) in subjects with mild to moderate pain levels (with and without radiographic change). What is their ability to predict an increase in functional limitations (progression) in subjects with mild to moderate limitations (with and without radiographic change). What is their ability to predict the progression of radiographic or other structural changes in subjects with definite radiographic change (KLG ≥ 2) with and without symptoms</td>
<td>72.2  60.3  51.8  74.1  71.3  62.7  72  70.2  69.5  69.8  73.5</td>
</tr>
<tr>
<td><strong>MRI</strong></td>
<td></td>
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<td>Although there exists a comparison between quantitative cartilage volume/thickness with semi-quantitative scoring further comparison with scoring systems such as — WORMS, BLOKS, KOSS and MOAKS should be performed. Further investigation should also be done for compositional MR methods such as T2 mapping and gagCEST to find correlations between macro-and microstructure changes in the knee joint. A correlation with clinical scores, clinical importance of individual variables in the semi-quantitative scoring systems as well as with quantitative values of the compositional MR techniques should be performed. Develop and appraise methods that will allow qualitative (semi-quantitative) measures to be quantitatively assessed as well as semi-automated to fully automated: cartilage; bone (osteophytes, erosions, cysts, attrition, fractures, BML); menisci (surface, morphology, thickness, volume). Evaluation of age dependence of structural changes (cartilage thickness and others) due to mechanical stress in different age groups (20–30, 30–40, 40–50 etc) Improved detection, quantification and measurement performance of structural, compositional changes of hyaline and fibrocartilage (GAG, fibre orientation, water content) with the use of: T2 relaxation time measurements, T2* relaxation time measurements, gagCEST, T1rho, DWI, Sodium imaging, dGEMRIC Development of semi-quantitative and quantitative as well as fully automated evaluation of inflammatory changes of the synovium, with the use of synovitis score, non-contrast-enhanced sequences, dynamic contrast-enhanced perfusion studies, development of reproducible, standardized quantification of perfusion Evaluation of “inflammatory” changes in the subchondral bone marrow with the use of: DWI, T2*, dynamic contrast-enhanced perfusion studies. Evaluation of muscle cross sectional areas (thigh), inter-muscular adipose tissue, intramuscular adipose tissue, and other imaging measures of muscle quality (in context of muscle strength measurements) which are thought to play a potential role in the onset and progression of knee OA, but in particular for intra-muscular adipose tissue and muscle quality, it is currently unclear which imaging technique is most accurate and precise for its evaluation. Clinical validation of MRI methods and techniques in general: What is their ability to predict virtual knee replacement endpoints? What is their ability to predict real knee replacement? How sensitive are different imaging measures to drug treatment (with different modes of action: i.e., affecting cartilage resorption, cartilage anabolism, bone resorption, other) once DMOAIs with these modes of action become available?</td>
<td>55.4  69.6  78.8  77.8  63.5  73.8  81.8  72.8  75.2  91.2</td>
</tr>
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</table>

* Mean response from the 13 persons on the working group who responded to the survey. Results of participants who were conflicted are not included. Strength of recommendation scale ranged from 0 (don’t Recommend) to 100 (strongly recommend).
Summary and conclusion

The goals of imaging the knee in clinical trials can include subject selection, monitoring disease progression and treatment effect, and/or identifying complications of the disease or the treatment. For acquisition we have provided guidance with regards both plain radiographic and MRI protocols. MRI protocols must be optimized around the scientific objectives and unique practical constraints of the specific study in question, particularly with respect to the study centers. This manuscript includes a number of recommendations for clinical trials that we would advise anyone planning on using imaging in knee OA trial to follow.

Author contributions

All authors were involved in collecting data, reviewing the literature and drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published.

Disclosure

The comments and editorial expressed herein represent those of the author/s and do not reflect those of any official scientific role or institution that the author/s may be hold or be affiliated with. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Conflict of interest

1. David Hunter has royalties from DJO for a patent granted for a patellofemoral buttress. Has grants from the NIH, Australian Research Council and NHMRC. Associate Editor for Osteoarthritis and Cartilage.
2. Roy D. Altman is a consultant to Cytori, Ferring, Iroko, Johnson and Johnson, Novartis, Oletec, Pfizer, Q Med, Rotapharma, Strategic Sciences and Technologies, and Teva.
3. Flavia Cicuttini – Receives honoraria from Jansen. Has grants from the NHMRC for Statin RCT, Zoledronic Acid RCT and ACL study. Holds a volunteered paid position in Repatriation Medical Authority as a Medical Officer and as an Associate Editor in the BMC Musculoskeletal Journal, ART Journal.
4. Michel D. Crema – has shares in Boston Imaging Core Lab, LLC a company providing image assessment services to academia and the pharmaceutical and medical device industry.
5. Jeffrey Duryea – has a grant from NIH/NIAMS for a Quantitative MRI analysis method for longitudinal assessment of knee OA.
6. Felix Eckstein receives honoraria from Mariel Therapeutics, MerckSerono, and Medtronic. Is CEO and co-owner of Chondrometrics Gmbh, a quantitative image analysis company and is involved in, clinical trials including FGF 18 from MerckSerono. Holds a voluntary unpaid position in Annals of Anatomy, Cell Tissue Organs as an associate editor and in Osteoarthritis & Cartilage as part of the editorial board.
7. Ali Guermazi receives honoraria from Genzyme, TissueGene, OrthoTrophiX and Merck Serono. He has shares in Boston Imaging Core Lab, LLC. Deputy Editor of Radiology.
8. Richard Kijowski has grants from the National Institute of Health for NIAMS/Rapid MRI for Assessing Joint Degeneration, for the NAIMS/Cartilage Contact and for Early degeneration after ACL Injury.
9. Thomas M. Link receives honoraria from Springer. He has grants from the National Institutes of Health (NIAMS and NIBIB) and General Electric for the MAVRIC protocol and Insightec Exablate protocols. Holds a paid position in Current Radiology Reports as Editor-in-Chief. He is on the editorial boards of Osteoarthritis and Cartilage, Radiology, AJR and Skeletal Radiology. He is also section editor for European Radiology.
10. Johanne Martel-Pelletier & Jean-Pierre Pelletier — receives honoraria from ArthroLab/ArthroVision, Bioiberica, Elanco, Ferring, Merck, Pfizer, Servier, TRB Chemedica. Has grants from The Arthritis Society (as co-investigators), Canadian Institutes of Health Research (CIHR) (as co-investigator). Has investment in non-medical industry at ArthroLab/ArthroVision and is a Shareholder. Holds a volunteered lecturer position at the ESCEO13-IOF European Congress on Osteoporosis and Osteoarthritis (travel grant).
11. Colin G. Miller- Senior vice president at Bioclinica.
12. Timothy J. Mosher receives honoraria from Medical Metrics, Depuy Orthopaedics, elimage, Pirima Healthcare, has shares in Johnson & Johnson, holds a voluntary paid position in Radiological Society of North America (RSNA), Academy for Radiology Research and the Society for Skeletal Radiology.
13. R. Elena Ochoa Albizetegui — no conflict of interest to disclose.
14. Charles Peterfy — has shares in Spire Sciences, Inc., which provides Image analysis for clinical trials to multiple pharmaceutical and medical device companies. He holds a volunteered paid position in The International Society for Musculoskeletal Imaging in Rheumatology as treasurer.
15. Jean-Pierre Raynauld receives honoraria as a consultant for ArthroLab/ArthroVision.
16. Frank Roemer — has shares in Boston Imaging Core Lab, LLC, a company providing image assessment services to academia and the pharmaceutical and medical device industry. Associate Editor for Osteoarthritis and Cartilage.
18. Garry E. Gold receives honoraria as a consultant from Zimmer Inc., Isto, Inc. and Boston Scientific. Has a grant from GE Healthcare for improved MR Systems and one from the NIH for advanced MRI of Osteoarthritis.

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