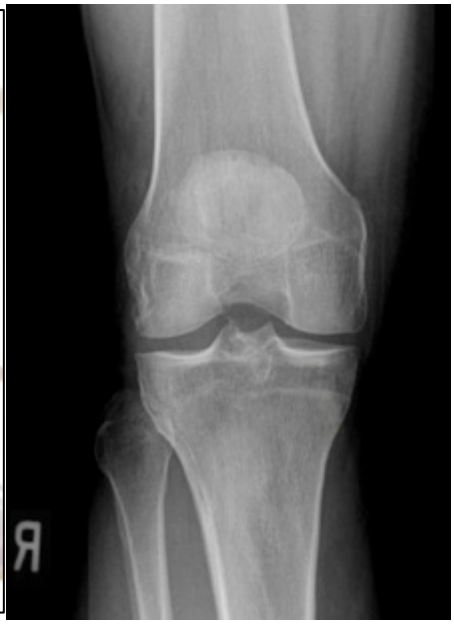
Imaging Procedure Manual

Centrexion CNTX-4975i-OA-304:

A Randomized, Double-blind, Placebo-controlled, 2-Injection 52-Week Study to Evaluate the Efficacy and Safety of Intraarticular Injections of CNTX-4975-05 in Subjects with Chronic, Moderate-to-severe Osteoarthritis Knee Pain

Acquiring the Knee Fixed-Flexion Radiographs



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This imaging manual has been reviewed and approved for use by:

Name / Title	***Signature***	***Date***
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1. Study Objectives and Implications for Imaging

The objective of this phase 3 randomized, double-blind, placebo-controlled, two-injection, 52-week study is to evaluate the safety and efficacy of an initial injection (at Baseline) and a second injection (at Week 26) of 1.0 mg of CNTX-4975-05, compared to placebo, delivered intraarticularly to the index knee.

The study population will consist of adults who are at least 40 years of age with symptomatic OA of the knee. Subjects will all have moderate to severe knee pain, but will otherwise be generally in good health.

Candidate subjects will receive a posterior-anterior (PA) radiograph of both knees at screening, and, if the radiographic criteria are met and the patient meets all other study entry criteria as determined by the principal investigator, the patient will proceed into the trial. The radiographic criteria will be assessed centrally to determine subjects' eligibility to participate. Radiographs will be scored using Kellgren-Lawrence grading for presence of both osteophytes and possible or definite narrowing of the joint space. Follow-up radiographs will be acquired using the same technique at week 52, and evaluated centrally for the development of chondrolysis using the Osteoarthritis Research Society International (OARSI) scoring method. Images will also be evaluated for osteonecrosis and subchondral insufficiency fracture.

Imaging for this and other clinical trials requires the images to support research questions about groups of patients. Images must be pooled from multiple clinical sites. The imaging protocols in this manual have been designed to meet these needs, and may be different from your daily clinical practice. Please contact Spire Sciences if you have questions about the image quality requirements in this manual, which are based on the needs of central reading:

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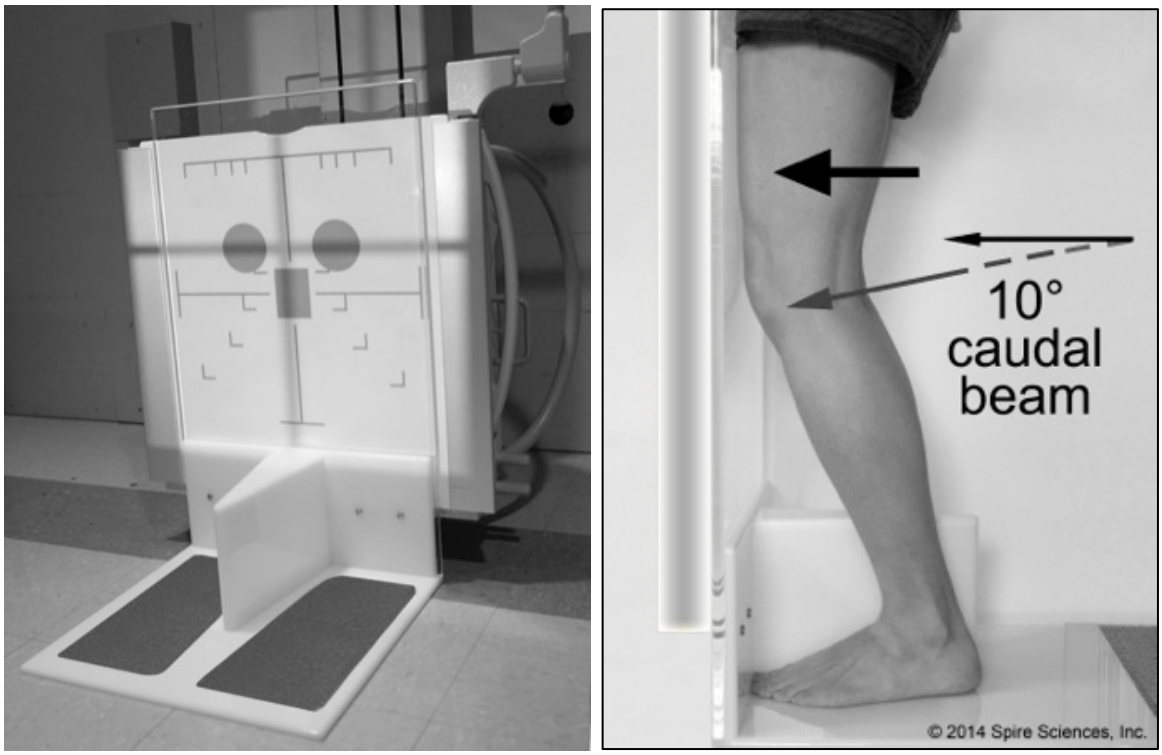
2. Radiography Goals and Technique

Imaging Goals

Fixed-flexion radiography of the knees for clinical trials is similar to radiography in clinical practice, but with a greater focus on patient positioning and beam centering and angulation. Serially acquired radiographs of the index knee of each subject will be compared side-by-side for changes in joint-space width or subchondral bone over time. Even slight variations in how the anatomy is projected can mimic or obscure osteophytes and joint-space narrowing, and thus result in erroneous study results.

Patient Positioning Using the Knee-Flexer Frame

Mild flexion of the knee is required to properly evaluate joint-space narrowing in OA, as femoral cartilage loss typically begins over the posterior horn of the meniscus. A fully extended knee may thus underestimate joint-space narrowing and result patient misclassification and screening failure. Slight external rotation is also beneficial in revealing osteophytes along the medial femoral condyle. The fixed-flexion technique using the Knee-Flexer Frame (Fig. 1) is designed to provide optimal, reproducible flexion and external rotation of the knees for diagnosing OA.

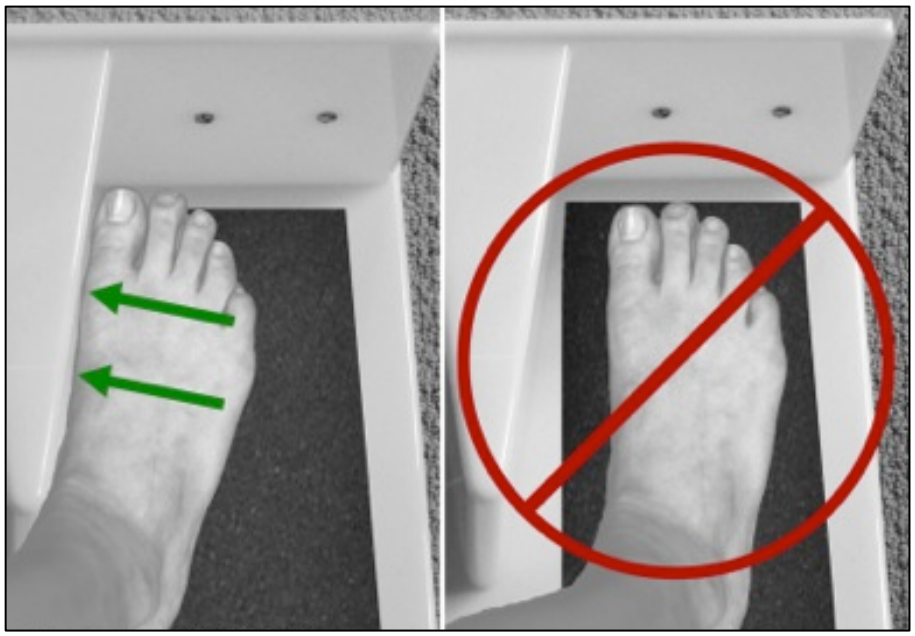


A. B.

Figure 1. The Knee-Flexer Frame™ positioning device.

- Prior to the examination, the Knee-Flexer Frame is placed on the floor, or suitably large platform, so that the cassette holder or reclining table top of the radiographic system rest flush against it.
- The subject is positioned standing on the Knee-Flexer Frame facing the cassette/table top (Fig. 1). The medial aspect of each foot should be against the V-shaped guide on the frame's base with the great toes touching the front wall of the frame (Fig. 2).
- Both knees are flexed until the patellas also touch the front wall of the frame. This fixes the angle of the tibial surface.
- The thighs are then pressed against the same front wall of the frame, taking care to maintain the contact of the knees and great toes. This fixes the angle of the femur. Ensure the subject maintains this position, especially contact of the thighs with the frame wall, throughout the examination, holding a rail for support if necessary.

- The X-ray beam is angled 10 degrees caudad, and centered between the two knees at the level of the joint line (Fig. 3).
- Make sure that left or right markers and labels are in place.
- Make sure that appropriate shielding is used.
- Include both knees on a single PA exposure using the parameters below.



A B

Figure 2. Correct foot alignment on the Knee-Flexer Frame. The medial side of both feet should align with and contact the V-shaped guide on the base of the frame, and the tips of the great toes should touch the front wall (A). This externally rotates the knees slightly. Do not align the feet with non-slip pads (B).

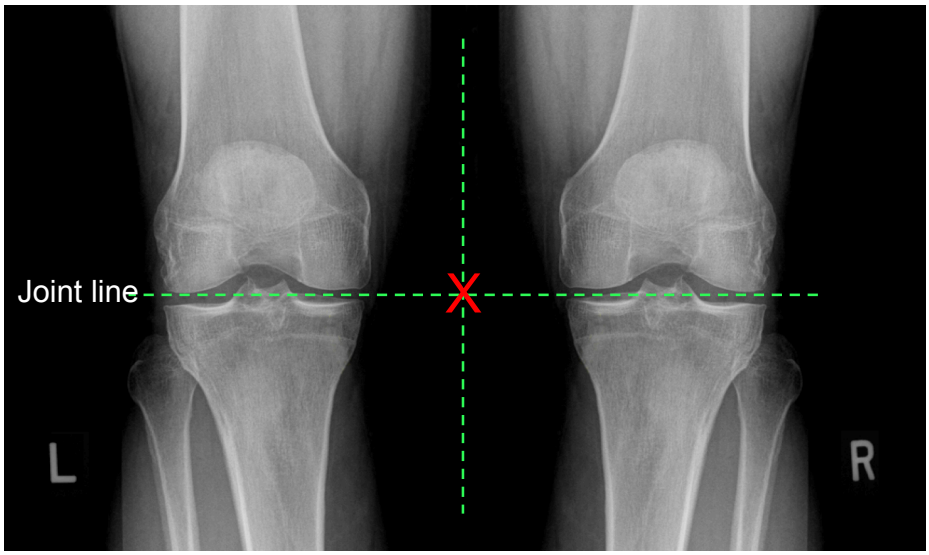


Figure 3. Correct beam centering. Center the X-ray beam midway between the knees at the level of the joint lines.

Radiographic Parameters

Imaging System	Bucky	Recommended
Focus-Film Distance (FFD)	**72 in.**	**Required**
Film Size	**14 in. X 17 in.**	**Required**
mA	*Dependent on film/screen system*	-
KVp	65 – 72 kVp	Recommended
Focal Spot	**Small**	**Required**
Annotation	**Right/Left radio-opaque markers**	**Required**
Tube angulation	**10 degrees caudal (towards feet)**	**Required**

Tube Angulation

A beam angle of 10 degrees has been found to provide the best projection of the tibiofemoral joint space on PA radiographs in the majority of subjects.

Many radiography systems display tube beam angle to the degree. If you have one of these systems, then set the tube angle directly. However, if your system is equipped with only a coarse inclinometer, graduated at 15-degree increments, please let Spire Sciences know, and they will send you a stick-on glass-tube inclinometer with finer increments to allow setting the tube angle at 10 degrees more precisely (Fig. 4).

A B

Figure 4. X-ray beam angulation. While this tube has a needle inclinometer, the markings are in 15-degree increments, making it difficult to set the beam angle to 10 degrees reliably (A). For such systems, Spire Sciences can provide a stick-on glass-tube inclinometer with finer increments (B).

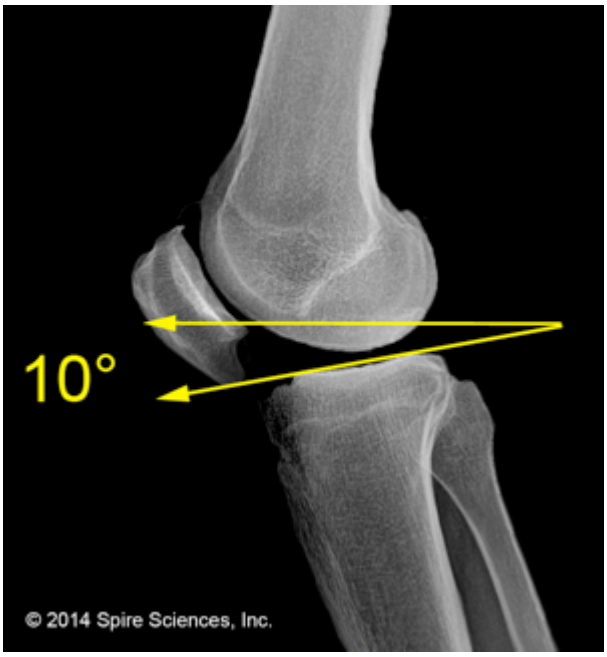
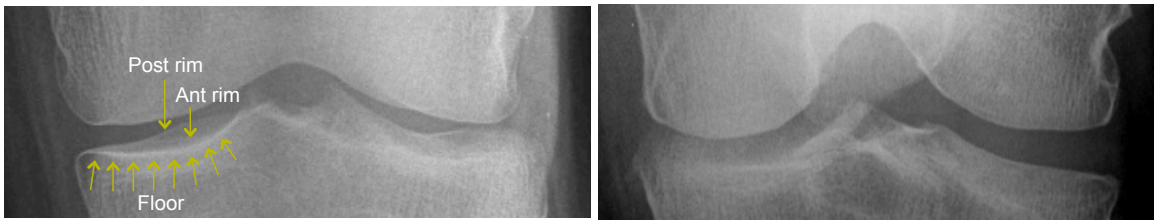


Figure 5. Aligning the X-ray beam with the medial tibial plateau. Lateral knee radiograph (*not required for this study*) illustrates how mild knee flexion and 10-degree beam angulation optimally aligns the beam with the medial tibial floor.



A. B.

Figure 6. Optimal projection of the medial tibiofemoral joint space. The surface of the medial femur is convex, and thus projects as a sharp line regardless of the degree of flexion of the knee or angulation of the x-ray beam. The tibial plateau, however, is concave, and thus, the floor of the plateau projects below the anterior and posterior rims when filmed with the X-ray beam aligned parallel to the floor. Measuring the joint space requires clear delineation of the tibial floor throughout its length (A). Without caudad angulation of the X-ray beam, the tibial plateau is projected en face, and portions of the floor become obscured leaving uncertainty about the actual width of the joint-space.

If the entire length of the floor of the medial tibial plateau is not sharply delineated, please verify that the subject has not moved and is still positioned properly with the great toes, patellas and both thighs firmly against the front wall of the Knee-Flexer Frame, and that the X-ray beam is properly centered midway between the knees and angled 10 degrees caudad. If any of these conditions are not met, please correct them and repeat the exposure before submitting the image to Spire Sciences.