Imaging and Submission Guideline

The Pfizer aNGF/Tanezumab Program
Pfizer, Inc.
Tanezumab Phase 3 clinical program in Osteoarthritis (OA), Chronic Low Back Pain (CLBP), and Cancer Pain clinical trials.

Pfizer

Final Version 2.0
Date: 13Apr2016

CONFIDENTIAL

Version 2.0 of this Imaging Guideline has been approved by Pfizer and Bioclinica, Inc. (Bioclinica). Any subsequent amendments to the Protocol may result in the revision of this guideline.

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Revision History

Revision Number and Date	Summary of Change(s)	Reviewed by:	Prepared by:
Final Version 1.0 16Jun2015	Finalized for signature by Bioclinica and Pfizer personnel	Bioclinica and Pfizer	Ann Marie C. Leach
Sponsor Draft 2.0 Version 2.0 25Mar2016	Global/general changes: • Updated Bioclinica logo and spelling • List of Abbreviations: changed FID to FFD; retained SID • Update QC'd to QC checked • Update subtype of subjects to subset of subjects • Marker preparation instructions – remove prepare study specific imprint marker (8-digit subject identification) • SynarcConnect replaced with SMART Portal • Corrected header numbering • Updated Marker Preparation to delete marker for 8-digit subject ID • Font and alignment corrections Section 1.1: update magnetic resonance images to MRI exams Section 3.1: added note that AP neutral is substituted for Grashey view in case of total joint replacement; alternative positioning for Grashey view added to subject positioning instructions; correction made to central ray instruction, and updated text added to Figure 4 Section 3.2.1: Clarifications added to AP Pelvis radiograph instructions in case of single or bilateral hip replacement; Figures realigned for better viewing Section 3.2.2: added note that totally replaced hip does not require frog leg lateral view at screening visit, alternative positioning for frog leg view added to subject positioning instructions; corrections made to Figures 9 and 10 showing acceptable and unacceptable positioning	BioClinica and Pfizer	Sharon Hedrick

Revision Number and Date	Summary of Change(s)	Reviewed by:	Prepared by:
	Section 3.2.3: added note that a knee having undergone total knee replacement requires only one standing PA radiograph (in positioning frame) at screening visit, and follow visits only required at Investigator request. Updates made to marker preparation instructions, knee preparation, feet positioning in Synaflexer, central ray placement, change of central ray placement for successive images, and number of images. Corrected image placed for Figure 21 Section 4: Headers added to PA Knee Radiograph Modified Lyon Schuss Troubleshooting table, text added to Beads row; update made to Flexion row, clarification on number of images required added to comment Section 4.1: Updates to text for radiographic criteria for follow-up exams Section 4.2: updated example of optimal acceptable knee image, text added to example of unacceptable knee image, updates to images of unacceptable joint space centering and marker placement Section 4.3: Updates to text under image First IMD is best Sections 5.1.1, 5.2.1, 5.3.1: added notes for imaging techs in the parameter table headers Section 5.1.2: Added note that flex coil is acceptable if should coil not available Section 5.3.1: Spacing gap corrected (decimal previously omitted) Section 10: Technologist Training, new section added to document Section 14: updates made to Pfizer and Bioclinica signatories		
Sponsor Draft Version 3.0 07Apr2016	Deleted terms not present in document from list of abbreviations. Updated formatting to reflect consistent fonts and spacing.	Bioclinica and Pfizer	Sharon Hedrick

Revision Number and Date	Summary of Change(s)	Reviewed by:	Prepared by:
	Added figure numbers and updated numbering throughout document. Section 3.2.3: Feet Positioning in Synaflexer – replace "include bunions" with "metatarsophalangeal". Central Ray Placement – add "take care to set mode to degrees as opposed to percentage" to inclinometer information.		
Final Version 2.0 13Apr2016	Finalized for signature by Bioclinica and Pfizer personnel.	Bioclinica and Pfizer	Sharon Hedrick

LIST OF ABBREVIATIONS

Term/Acronym	Definition
ACR	American College of Rheumatology
ASIS	Anterior Superior Iliac Spine
aNGF	Anti-Nerve Growth Factor
AP	Anteroposterior
CD	Compact Disc
CR	Central Ray
DCF	Data Clarification Form
DICOM	Digital Image and Communication in Medicine
DTF	Data Transmittal Form
eCRF	Electronic Case Report Form
EDT	Electronic Data Transfer
EU	Europe
Fat Sat	Fat Saturated
FDA	Food and Drug Administration
FFD	Focus to Film Distance
FOV	Field of View
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
ID	Identification
IMD	Inter-margin Distance
IR	Imaging Receptor
JSN	Joint Space Narrowing
KLG	Kellgren and Lawrence Grade
MRI	Magnetic Resonance Imaging
NCR	Non-Carbon Required
OA	Osteoarthritis
ON	Osteonecrosis
Non-fat Sat	Non-fat saturated
PA	Posteroanterior
QC	Quality Control
RPOA	Rapidly Progressive OA
SID	Source to Image Distance
US	United States

1. INTRODUCTION

1.1. Bioclinica Overview

Bioclinica, Inc. (Bioclinica) is an international company, headquartered in the US, providing global central imaging core laboratory services. Bioclinica has established procedures in accordance with the principles of Good Clinical Practice (GCP) as stated in the International Conference on Harmonization (ICH) in order to receive and process all protocol-required clinical imaging data for subjects participating in this program.

Bioclinica's primary objective for Pfizer's anti-Nerve Growth Factor (aNGF) program is to ensure the consistent acquisition and processing of high quality images across numerous imaging modalities obtained from participating imaging facilities.

Bioclinica will be responsible for the following:

- Imaging facility: Provide imaging acquisition training and remediation.
- Process, perform quality control (QC) checks, and archive all imaging data (radiograph and MRI exams).
- Provide feedback to clinical sites, imaging facilities, and Pfizer clinicians regarding concerns with image quality.
- Provide alerts to stakeholders (clinical sites, imaging facilities, Pfizer designees) on missing scans and queries.
- Maintain subject confidentiality.
- Provide training venue and calibration meetings for musculoskeletal radiologists (central readers) as necessary.
- Report endpoint data to program-specified adjudication or safety committees.

Bioclinica has established rigorous processes recognizing that each image acquisition is an important and unique data point for safety in all studies conducted in this program. In the event data does not meet required minimal quality standards, Bioclinica will notify the site and other stakeholders as needed and provide remediation. This process of identifying problems and providing solutions early during the program is an effective means of preventing possible loss of data.

2. IMAGING

2.1. Standardized Image Collection and Review

The radiographic and magnetic resonance images obtained in this program will be subject to QC checks, processed for central radiology review, and centrally databased.

Image data sets obtained from imaging facilities will be standardized with validated methodologies that will enable reproducibility and reliability of measurements across the program. To achieve consistency, imaging methodologies (see Sections 3 and 4) contained in this guideline must be adhered to and may differ slightly from techniques used in the clinical care setting.

Images collected at imaging visits will be QC checked before submission to central readers (hereafter, referred to as Reader[s]) for their review and assessment. Clinical information will be limited to the Reader in order to ensure the objectivity of data.

It is critical that technologists comply with the guidelines presented in this document to ensure consistency in data thereby increasing the value of the imaging data provided to the sponsor.

2.2. Radiographic Imaging for Eligibility

During the Screening Period in Pfizer's aNGF studies, subjects will undergo radiographs of the protocol-specified major target joints (shoulders, hips, and knees). Other joints considered at-risk as determined by the Investigator and, although, not specified a target joint (e.g., ankle, elbow) will undergo radiographic review as well. A major target joint having undergone a joint replacement is required to have at least one radiograph of that joint. All radiographs will be processed at Bioclinica and assessed by Readers to aid the Investigator in the determination of radiographic eligibility for study participation.

2.3. Eligibility Reporting

Radiographs obtained during the Screening Period for all covered studies in the aNGF program will be reviewed centrally for eligibility. The radiographic results of the eligibility review will be sent to each clinical site within 3 business days following receipt of a complete imaging data set at Bioclinica providing a query(ies) has not been generated or one remains outstanding.

2.4. Baseline Imaging

In selected osteoarthritis (OA) study(ies) MR images are required at the baseline visit for all subjects slated for randomization. A subset of subjects will require further MR images at scheduled imaging visits discussed in the next section.

2.5. Imaging for Safety (Post-Baseline Period)

Once randomized, subjects will be assessed for joint safety endpoints through serial radiographs of the target joints at every imaging visit. Should one of the target joints

show signs and symptoms of rapid joint failure at any time, the Investigator may order an unscheduled visit for additional imaging, which also may include a request for MRI, Such a visit is termed a "*for-cause*" visit. Any additional radiographs and/or MRIs for a *for-cause* event will be processed and reviewed by the Reader and assessed for program-specified joint safety endpoints. Once *for-cause* is initiated, that joint will be radiographically, and possibly MRI-followed, at every scheduled visit thereafter.

A non-target joint (e.g. Other joint) considered at-risk in the post-baseline period by the Investigator may be considered a *for-cause* event requiring radiograph and/or MRI and will be assessed in a manner consistent with a major target-level joint. These images will be centrally read and results reported to the Investigator.

A Reader also may request a *for-cause* MRI to provide more information around an equivocal radiograph or for an unexplained anomaly (e.g., acute or chronic increase in pain in an otherwise benign looking joint). Any post-baseline MRI and/or radiograph may be compared back to any previous MRIs and radiographs before reporting to an Investigator.

As discussed previously a subset of subjects having a Kellgren Lawrence Grade (KLG) three (3) or four (4) hip or knee at the initial screen visit will require follow-up MRIs of both hips and knees at all post-baseline scheduled imaging visits.

2.6. Follow-Up Safety Reporting

Images obtained during the six (6)-month Safety Follow-up Period will be processed, centrally read, and results sent to each clinical site within three (3) business days following receipt at Bioclinica providing a query(ies) has not been generated or one remains outstanding.

2.7. Imaging Time Points

Imaging visits vary from study to study. The target joints and the methodologies used to image them will not change across the program. It is imperative that images be sent to Bioclinica immediately after processing at the imaging facility as a decision will be made to dose a subject based on the radiographic outcome.

2.8. Imaging Facility Technologist Proficiency

The first subject's set of radiographs at each imaging facility will serve as a technologist's test of proficiency. The purpose is to ensure that each facility's technologist understands and is in compliance with their instruction/training pursuant to this imaging guideline.

The first set of radiographs will be QC checked and a notification of acceptance or corrective measures or a repeat request will be initiated from Bioclinica. In the event the images do not meet minimal standards, the clinical site/imaging facility and the Pfizer clinician or designee will be notified and the site may be requested to hold further enrollment at the clinical site until remediation has been completed.

Please note: A second prospective screen subject should not be imaged until this first test image or repeat is approved by Bioclinica. In the event a second subject's images are received at Bioclinica prior to the first subject's images having been approved, the second subjects' images may be held for processing.

3. IMAGING THE TARGET JOINTS

3.1. Anteroposterior Standing Grashey Shoulder Radiograph

The anteroposterior (AP) Grashey view will profile the joint space between the humeral head and the glenoid fossa (Figure 1). Both shoulders need to be imaged regardless of arthroplasty. If a subject has a total joint replacement, a neutral AP may be substituted for the Grashey view. A totally replaced shoulder will not require a follow-up image unless requested from the Investigator.

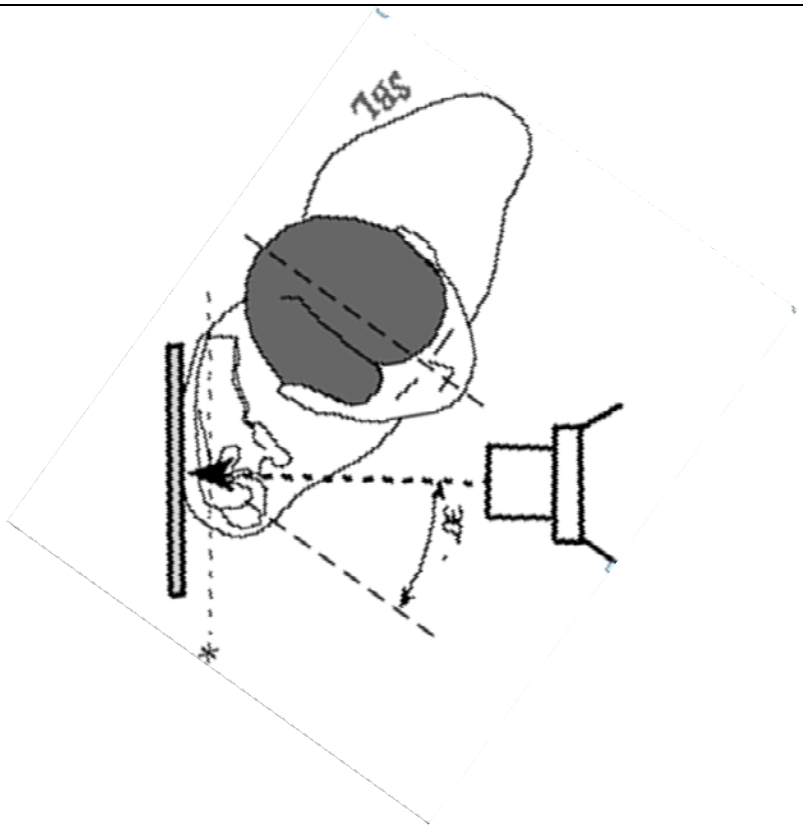


Figure 1: Standing AP shoulder Grashey View

Left and Right AP Shoulder Grashey View	
Marker Preparation	• Left or Right lead markers.
Imaging Receptor	• Insert a 10- by 12-inch (24 by 30 cm) cassette crosswise.
Focus to film Distance (FFD)/Source to Image Distance (SID)	• 40 inches (100 cm) perpendicular to the Imaging Receptor (IR).
Clothing	• Hospital gown/remove brassiere/optional males shirtless.
Subject Positioning (Figures 2-4)	• Rotate body 35-45 degrees toward affected side. • Center the glenoid joint to the central ray (CR) position and center the IR to the CR. • Adjust the cassette so the top of the IR is about 2 inches (5 cm) above the superior border of humerus. • Abduct the target-side arm slightly and internally rotate to rest palm-of hand on the abdomen. • Place markers on the IR to the lateral side of the anatomy. • Alternative positioning for the Grashey: If the subject is kyphotic, you may lie the subject on the table and roll them to the affected side to place the scapula parallel to the table surface. Occasionally while in the supine position, the body may need to be rotated more than 45 degrees. A support under the elevated shoulder may be used. • Abduct the target arm slightly in internal rotation resting the humerus on the table surface.
Central Ray	• Direct the CR 2 inches (5 cm) medial and 2 inches (5 cm) inferior from the superolateral border of the shoulder. • Position the IR to the center CR location.
Exposure	• Set exposure to optimally visualize the glenoid joint • Suspend respiration.
Number of Images	• One per shoulder • Perform at screening and one at every follow-up visit.
Shielding	• Shield reproductive areas as per department policy.

Figure 2: Proper positioning examples for AP Grashey view

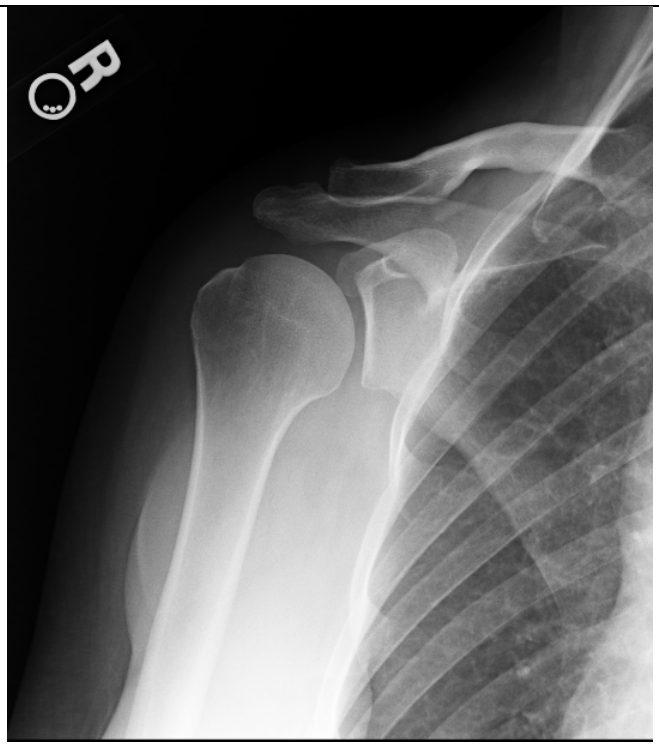


Figure 3: Acceptable AP Grashey view

The joint space between the humeral head and the glenoid cavity is open.

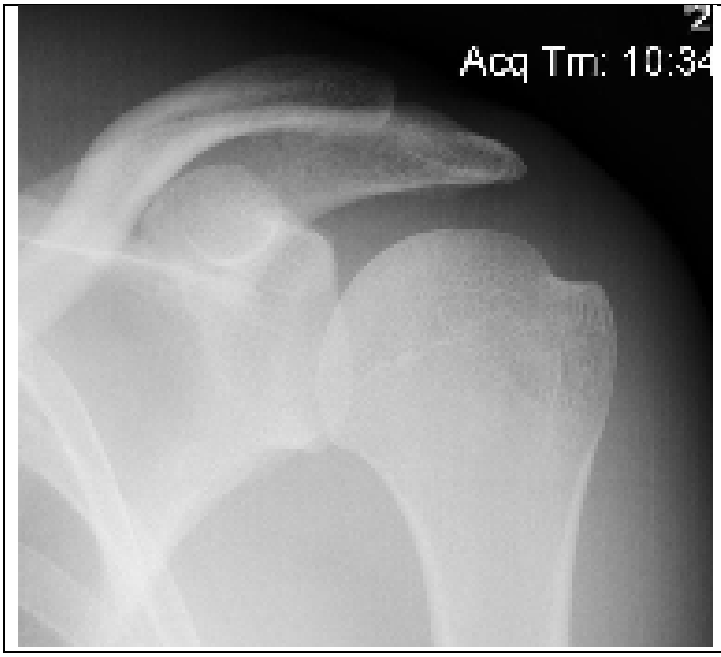


Figure 4: Unacceptable AP Grashey view

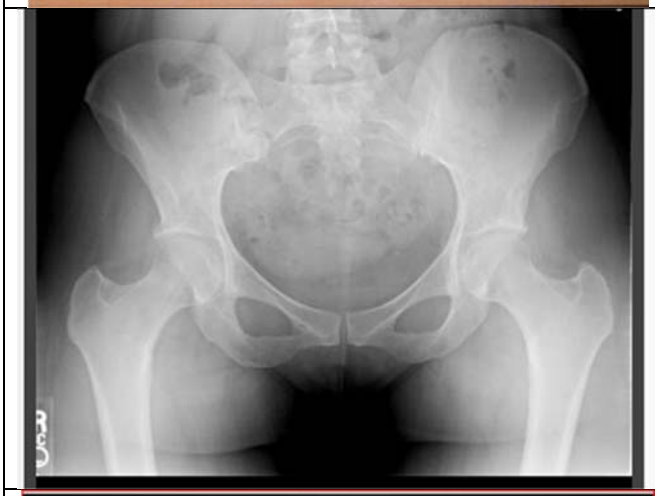
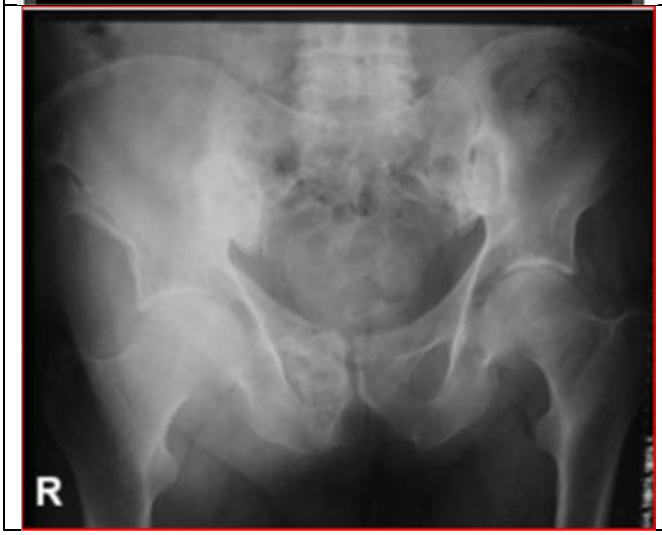
The joint space between the humeral head and the glenoid cavity is **NOT** open. Bony overlap is present making the image unacceptable.

3.2. Pelvis and Hip Radiographs

3.2.1. AP Pelvis

The AP pelvis view is critical for the measurement of joint space width and assessing OA disease severity. It will be performed at screening and at every scheduled follow-up imaging visit. A unilateral total hip replacement will require the AP pelvis at every follow-up visit. A bilateral total hip replacement will only require the screen AP pelvis and no follow-up unless the Investigator requires one.

AP Pelvis	
Marker Preparation	• Left or Right lead markers.
Imaging Receptor	• Insert a 14- x 17-in (36 x 43 cm) cassette crosswise.
Focus to film Distance (FFD)/Source to Image Distance (SID)	• 40 inches (100 cm) perpendicular to the IR.
Clothing	• Hospital gown
Subject Positioning (Figures 5-7)	• Align mid-sagittal plane of subject to center of the table and to the CR. • Place arms across upper chest. • Ensure subject is not rotated. • Use pillow under head. • Separate the legs and space the feet about eight (8) to ten (10) inches (20 to 25 cm) apart. • Internally rotate the toes fifteen (15) to twenty (20) degrees. Secure the feet in this position with straps or tape. • Place markers on the table to the lateral side of the anatomy.
Central Ray	• Align the CR perpendicular, midway between the Anterior Superior Iliac Spine (ASIS) and pubic symphysis (approximately two (2) inches [4-5cm] inferior to the ASIS). • Position the IR to the center CR location.
Exposure	• Set exposure to optimally visualize the pelvis. • Suspend respiration.
Number of Images	• Perform at screening and one at every follow-up visit
Shielding	• Shield reproductive areas as per department policy.

	**Figure 5: Proper AP Pelvis position**
	**Figure 6: Acceptable AP Pelvis**
	**Figure 7: Unacceptable AP Pelvis** The right hemipelvis, right acetabulum and sacroiliac joint is underpenetrated

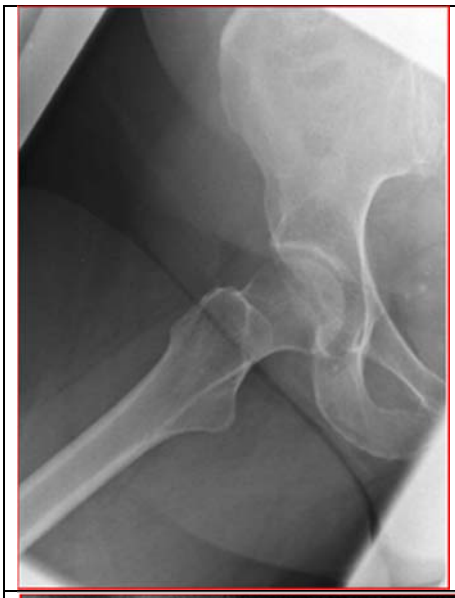
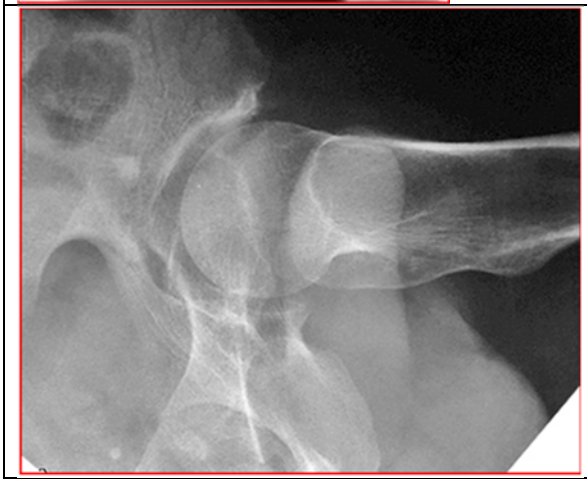
3.2.2. Frog Leg Lateral

The frog leg lateral views will aid the Reader in assessing OA disease severity at the initial screen visit only. Both the right and left hips will be imaged separately; however, a totally replaced hip will not require this view at the screen visit, but should be a comment on the Data Transmittal Form.

Frog Leg Lateral	
Marker Preparation	• Left or Right lead markers.
Imaging Receptor	• Insert a 10- x 12-inch (24 x 30 cm) cassette.
Focus to film Distance (FFD)/Source to Image Distance (SID)	• 40 inches (100 cm) perpendicular to the IR
Clothing	• Hospital gown
Subject Positioning (Figures 8-10)	• Instruct subject to lie supine on the table. • Use pillow under head. • Position subject so the center of the ASIS of the target hip is mid-line to the table. • Flex the knee on the target hip and place the heel of the foot against the opposite leg in the area of the knee. • Abduct the thigh laterally approximately forty-five (45) degrees by dropping the knee towards the table. • Use a sponge to comfort the knee as needed. • Place arms across upper chest. • Place markers on the table to the lateral side of the anatomy. Alternative positioning: If a subject is unable to adequately achieve the frog view, place the subject in an oblique lumbar position. A sponge or positioning device may be placed behind the subject to support the side. Flex the knee into the frog position.
Central Ray	• Align the CR perpendicular to the target hip joint, between the ASIS and pubic symphysis (approximately two [2] inches [4-5cm] inferior to the ASIS). • Position the IR to the center CR location.
Exposure	• Set exposure to optimally visualize the hip joint.

	• Suspend respiration.
Number of Images	• One of each hip • Perform at screening only.
Shielding	• Shield reproductive areas as per department policy.

Figure 8: Proper positioning examples for Frog Leg Lateral

	**Figure 9: Acceptable Frog Leg Lateral**
	**Figure 10: Unacceptable Frog Leg Lateral** Lesser Trochanter in rotated.

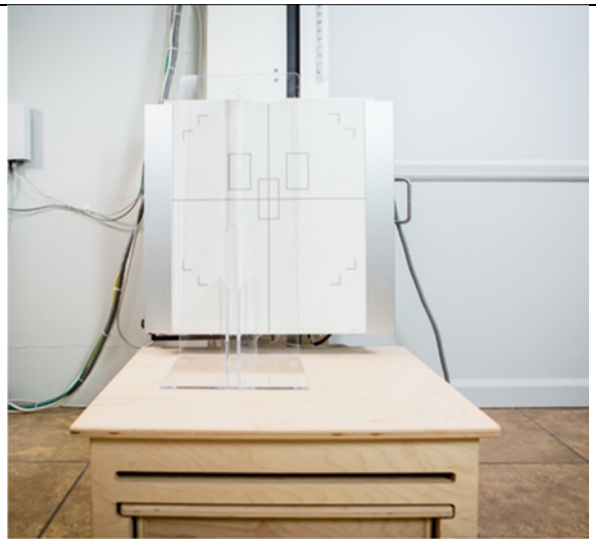
3.2.3. Knee Radiograph

Acquisition of quality radiographs will be achieved through the posteroanterior (PA) modified Lyon Schuss methodology. This methodology requires a set of three (3) radiographs per knee at each visit. Each knee image will require an initial read by the technologist to ascertain if any corrective action in knee position or tube angle is needed for the next image. A knee having undergone a total knee replacement will require only one standing PA radiograph in the positioning frame (Synaflexer™) at the screening visit. A follow-up image would not be required unless requested by the Investigator (Figures 11-24).

PA Knee Radiograph Modified Lyon-Schuss	
Marker Preparation	• Prepare study specific imprint marker containing the SID (40). • Tube angle must be identified on each image knee radiograph using lead marker from kit placed lateral to the anatomy being imaged. • Include Left or Right lead markers (reversed since this is a PA projection but read in the AP setting).
Imaging Receptor	• Insert a 10- x 12-inch (24 x 30 cm) cassette lengthwise.
Focus to film Distance (FFD)/Source to Image Distance (SID)	• 40 inches (100 cm) to the IR
Clothing	• Hospital gown • Remove shoes
Shielding	• Shield reproductive areas as per department policy.
Wood Platform and Step	• The optional wood platform will raise a subject in the event that the radiograph tube or IR does not fully lower to the level of the knee. The step can be added to the platform for additional height. • Be mindful of subject-safety while on the platform.
Refining the Synaflexer™ Position and Platform	• Place Synaflexer™ on top of the wood platform, if needed. Depending on the knee to be imaged; the position of the Synaflexer™ frame will vary. • The anterior (vertical) wall of the Synaflexer™ should be in contact with the vertical wall of the IR (Figures 16-18).

	• The Synaflexer™ will be placed off center (to the left or right) to the IR depending on the knee being radiographed.
Knee Preparation	• Position subject in the Synaflexer™ so the back of their knees are facing you. • Locate the joint line crease along the width of the knee. This should align with the apex of the patella. At the midpoint of the crease, make a mark with a marker pen. This mark will always be the point for the CR placement on every adjustment of tube angulation.
Feet Positioning in the Synaflexer™	• Subject must be barefoot or in socks. In the case of a leg-length discrepancy, a shoe should be worn to correct the leg lengths; however, the same shoe should be worn at every follow-up time point. • Have the subject place their feet on each side of the V-support such that the entire medial aspect (metatarsophalangeal joint and heel) of the knee being imaged is in contact with the V-shaped support of the Synaflexer™. • The medial aspect of the other foot may be aligned with the V-shaped support but does not need to make contact with it. • The great toes (big toe, hallux) or the longest toes of both feet must make contact with the vertical wall of the Synaflexer™.
Subject Positioning	• Position the IR so the knee center is on the midline of the IR. • Once the feet are firmly in place, the knees and thighs must be pressed directly against the vertical wall of the Synaflexer™ (Figure 17). To ensure the hips are square, the technologist should gently guide the hips forward by placing their hand on the small of the subjects back. • Ensure that the knees and thighs are not pressed inward (medially) or outward (laterally) but are pressed "straight" against the Synaflexer™. This will result in both knees being semi-flexed at a fixed angle of 10-20 degrees. This is the Schuss position. • The subject's body weight must be equally distributed between both legs. Place markers to the lateral side of the anatomy.
Central Ray Placement	• Use the supplied inclinometer on top of the x-ray tube; ***take care to set mode to degrees as opposed to percentage.*** • Locate the mark established during knee preparation. This mark will always be the point for the CR placement on every adjustment of the tube angle. Once the Bucky/IR is in position it never moves again with the tube angle changes.

Change of Central Ray Placement for Successive Images	• Start with a 10-degree PA caudal angulation at screening and take Image #1. • For Image #2, adjust the angulation either to twelve (12) or eight (8) degrees remembering to change the angle designation lead marker. Do not move the IR. • Re-center the CR to the mark at the midpoint of the back of the knee crease. • Process both images and assess whether you have achieved an optimal image according to the Optimal Image section below. If you determine that an optimal image has not been achieved, adjust accordingly for the third angle image. • Once again, center the CR to the mark on the back of the knee and take the image without moving the Bucky/IR. Adjust the tube so that the CR is centered to the Bucky/IR. • A fourth image may be performed if necessary to obtain an optimal image.
Optimal Image	• Inter-margin Distance (IMD) ≤1.5 mm. • Rotation. The tibial spines should be centered within the femoral notch. There should be a normal inter-bone space between the tibia and fibula without internal or external rotation. • Flexion. Check for consistency in the femoral notch configuration. • Knee joint space must be equidistant from top to bottom and side to side. • Minimum of 5 inches (10-12 cm) or the distance of 5 calibration beads of bone above and below the knee joint space. • Markers should not obscure anatomy. • Both columns of calibration beads are visible in the image. • Optimal exposure for bony detail.
Exposure	• Set exposure to optimally visualize the knee.
Number of Images	• 3 of each knee at every visit. If subject has a total knee replacement, then only one image of that knee is required (standing PA view in the Synaflexer) at screening only. No angulation of the tube is necessary.
Shielding	• Shield reproductive areas as per department policy.

	**Figure 11: Synaflexer™ Positioning Device**
	**Figure 12: Wood platform**
	**Figure 13: Wood platform with optional step**

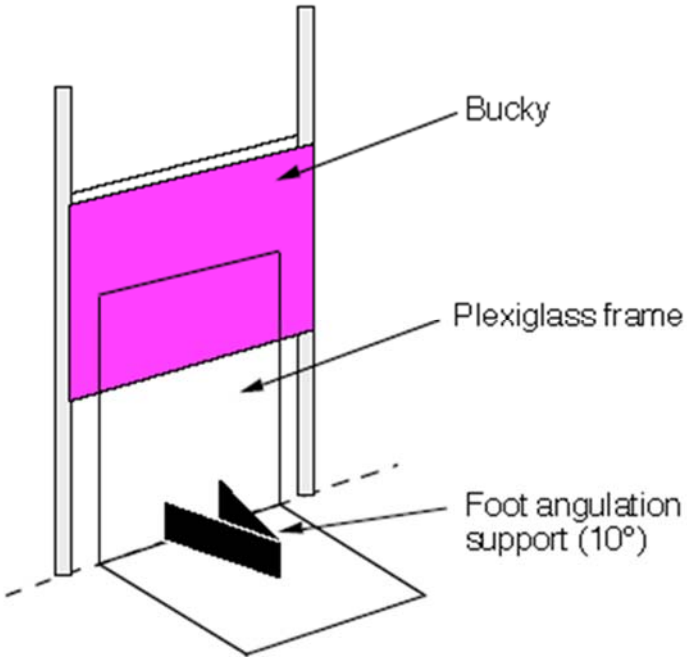


Figure 14: Wood Platform Synaflexer™ against the Imaging Receptor (Bucky)

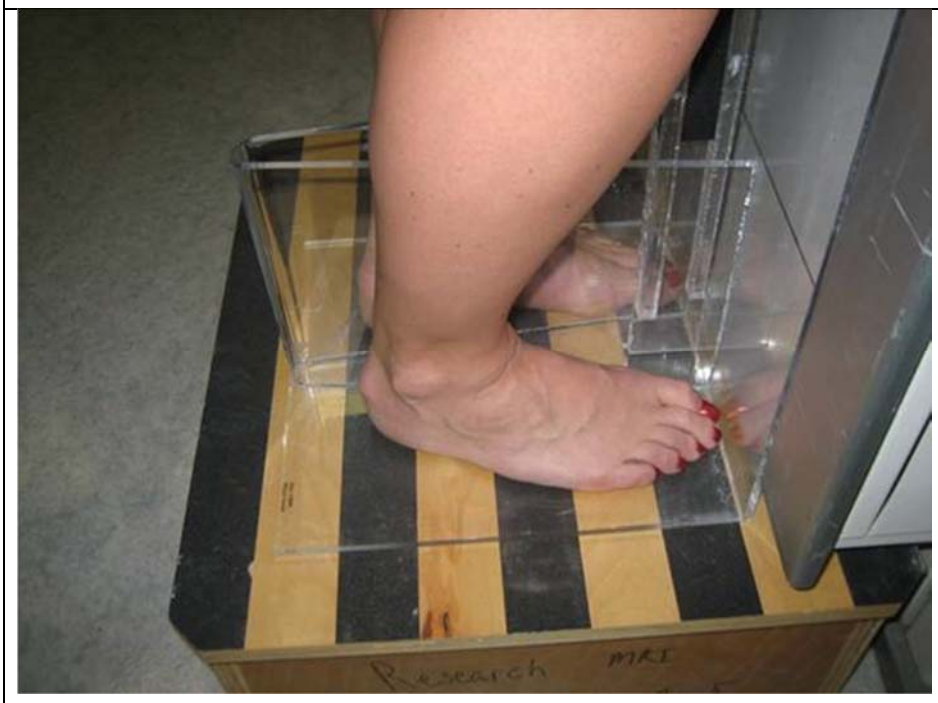


Figure 15: Proper foot position

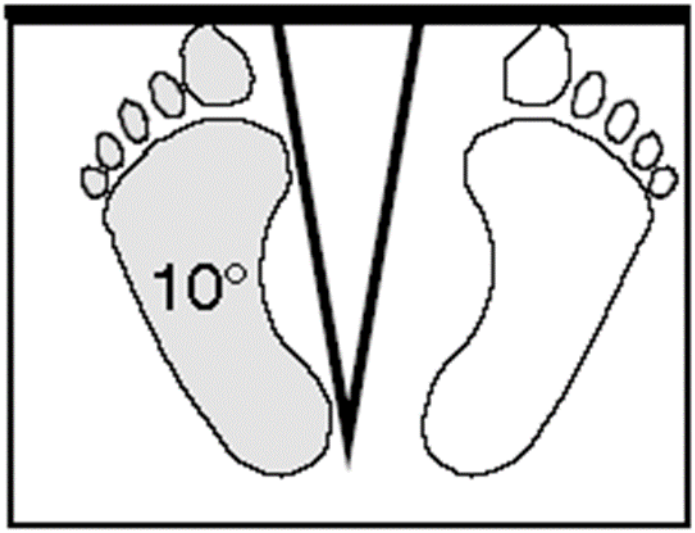


Figure 16: Proper knee and thigh position

	**Figure 17: Subject positioned against IR**
	**Figure 18: Body weight distributed evenly**

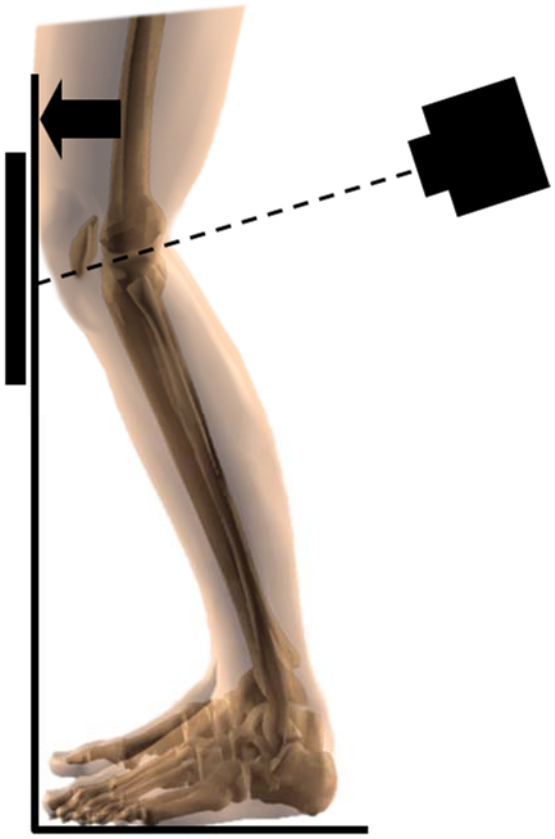
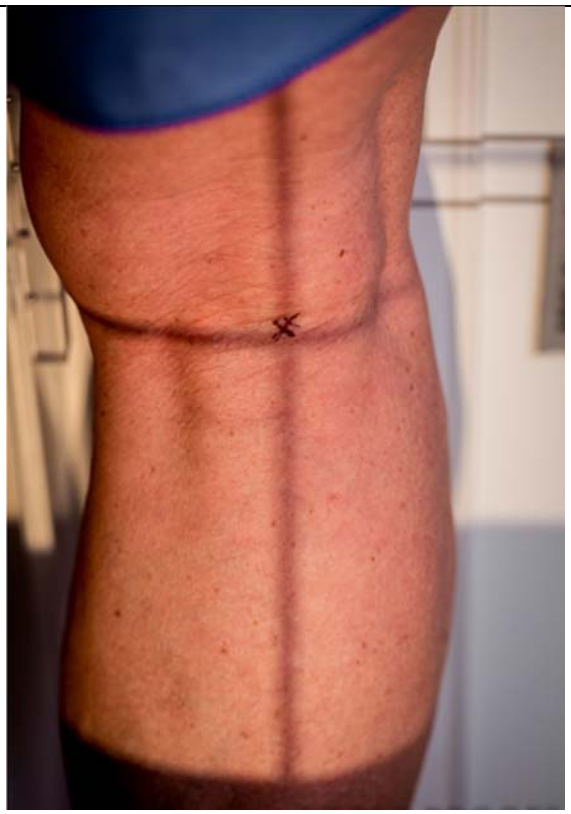


Figure 19: Radiograph beam angle and targeted anatomy

	**Figure 20: Point for CR placement marked behind knee**
	**Figure 21: Digital inclinometer**

Note: The “40” represents “inches”, which correlates to “100 cm”

The degree angle **does not need** to slide into the imprint marker and it **should read as SID**

Figure 22: Permanent imprint markers with personal identifiers

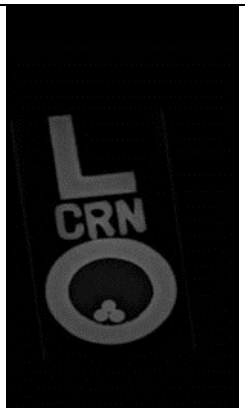


Figure 23: Left/Right markers

Figure 24: Proper positioning examples for knee view

4. ASSESSING A RADIOGRAPHIC IMAGE FOR QUALITY

To assess an image for quality after processing, numerous elements must be considered. As you standardize a subject within the Synaflexer™ frame you are automatically building in the quality, and to verify this, you need to review the image and make any corrections before the next image is acquired. The following table may give some insight on how to correct some quality issues. Examples of optimal, sub-optimal, and unacceptable images are shown in Figures 25-30.

PA Knee Radiograph Modified Lyon Schuss Troubleshooting		
	Problem	**Solution**
Inter-Margin Distance	IMD>1.5 mm	Adjust tube angle
Rotation	Fibula and Tibia space closing or overlapping	Hips not square to vertical wall of Synaflexer™. Foot not positioned correctly in the V-support.
Patella	Patella rotated	Ensure there is no rotation. Tibial spines centered within the femoral condyles notch
Flexion	Inadequate flexion	Knees, thighs, and hips are not pressed directly against the vertical wall of the Synaflexer™. Ensure that both knees are semi-flexed at a fixed angle of 10-20 degrees. (This is the Schuss position).
Tibial position	Tibia not parallel to long axis of film	Ensure that both legs have equal weight distributed between them. This ensures good tibial alignment.
Anatomy centering	Target anatomy not centered	Include 5 inches (10-12 cm) of visible bone above and below the knee joint space.
Exposure	Over/Underexposure of bone detail	Adjust exposure techniques.
Markers	Marker overlapping anatomy	Move marker to lateral side of anatomy.

Beads	Two (2) columns of beads not visible on image.	Collimate to include two (2) columns of beads taking care to include the distance of 5 beads (5 inches or 10 cm) above and/or below the knee joint.

4.1. Criteria for Follow-Up Radiographic Time Points

Radiographic Criteria for Follow-Up Exams	At any follow-up visit, prior to starting the knee sequence again, **the technologist must review the most optimal screening radiograph and start with the angle recommended by Bioclinica. This is available in a Time Point Package that will be sent to the clinical site and imaging facility before the next imaging visit. Remember, when referencing the optimal angle, you are trying to reproduce the image obtained at that angle. The angle at follow-up may not be the same as the original angle (at screening) and that is acceptable. The goal is to reproduce the screening image – not the acquisition angle.** Ensure that all parameters of the follow-up image exactly "match" the most optimal screening radiograph. The follow-up IMD, flexion, rotation, and knee joint centering, tibia-to-fibula spacing must identically match the selected best optimal screen radiograph. *For example: if the most optimal image selected at screening is a slightly rotated knee such that the tibial spines are off center; or there is an overlapping of the fibula and tibia, those conditions need to be duplicated for an accurate reading of joint space width.*

Comment:

Submit three (3) images of each knee to Bioclinica at each visit. If an optimal image is obtained in one or two images that is acceptable, but a third image is always necessary (e.g., consider the third image only two degrees from the second image). Remember that you must **reproduce the same image** at each follow-up time point.

Fill out a Data Transmittal Form (DTF) for each subject.

Images must be submitted at 100% (true to size).

4.2. Knee Optimization

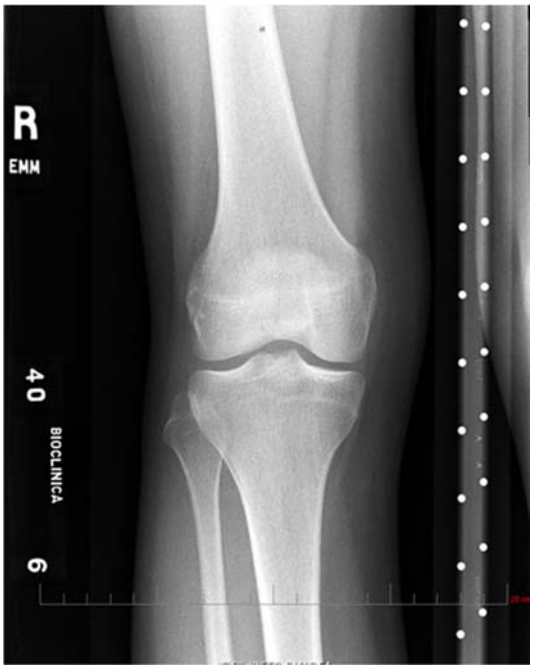
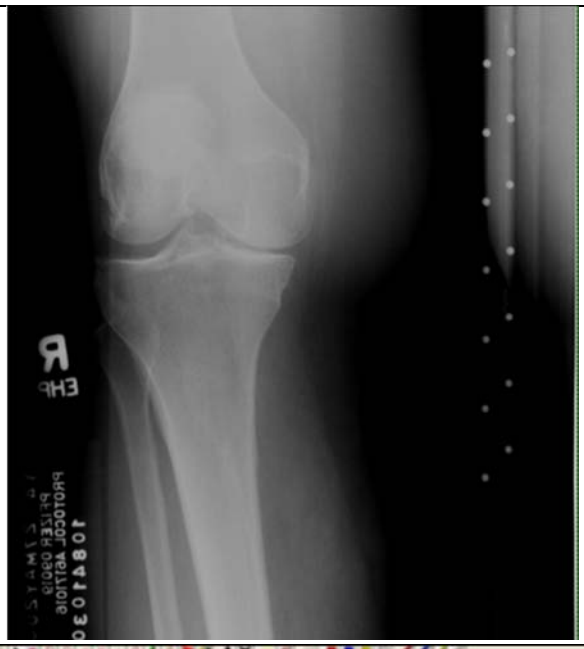
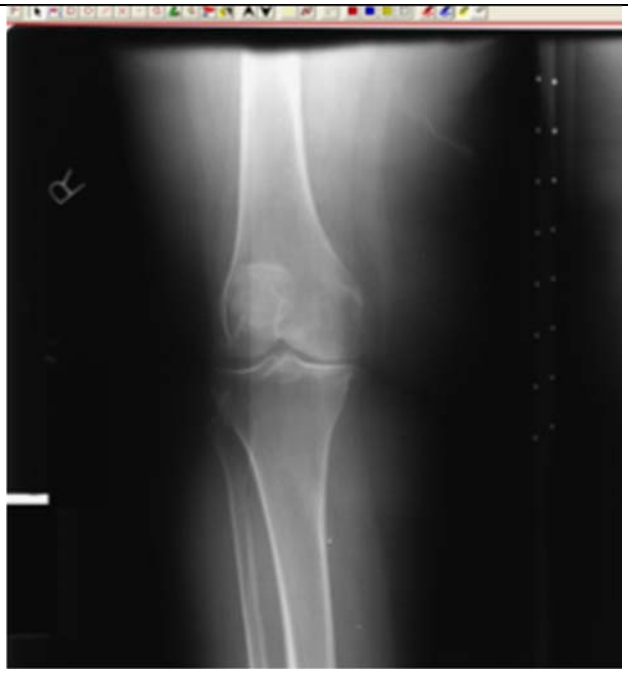


Figure 25: Example of an Optimal, Acceptable Knee Image:

- There is no rotation. Tibial spines are centered within the femoral notch.
- The interbone distance between the tibia and fibula indicates no internal or external rotation.
- Knee joint space centered from top-to-bottom and left-to-right on the film and the distance of at least five (5) beads (5 inches/10 to 12 cm) of bone above and below knee joint space.
- Outer margins of femur and tibia clearly visible.
- Optimal exposure for bone detail.
- Both columns of calibration markers from Synaflexer™ frame visible on radiograph.
- Markers outside the anatomy (lateral side).

	**Figure 26: Example of an Unacceptable Knee Image:** Rotation as evidenced by the profile of both femoral condyles (lateral showing thinner profile) and narrowed tibia-fibula interbone spacing. Improper centering (top-to-bottom, left-to-right). Brings into question where the central ray may have been placed. This will invoke a request for a repeat image. Markers inverted. Inadequate exposure.
	**Figure 27: Example of a Sub-Optimal (but readable) Knee Image:** Rotation as evidenced by profile of lateral femoral condyle and tibia-fibula interbone spacing. This may invoke a request for a repeat image.

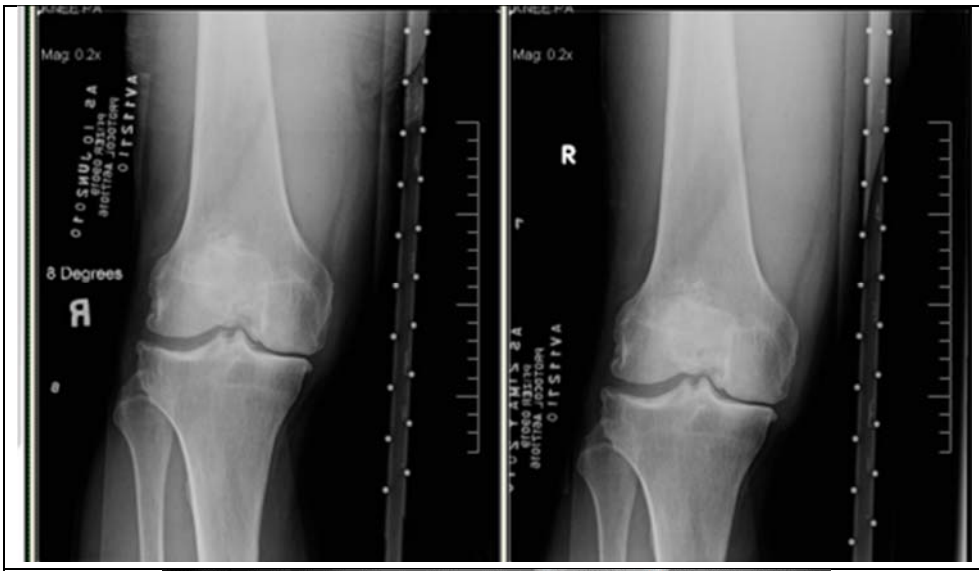


Figure 28: Example of Unacceptable Joint Space Centering: Top-to-bottom, right-to-left. The image on the far left shows inverted marker placement.

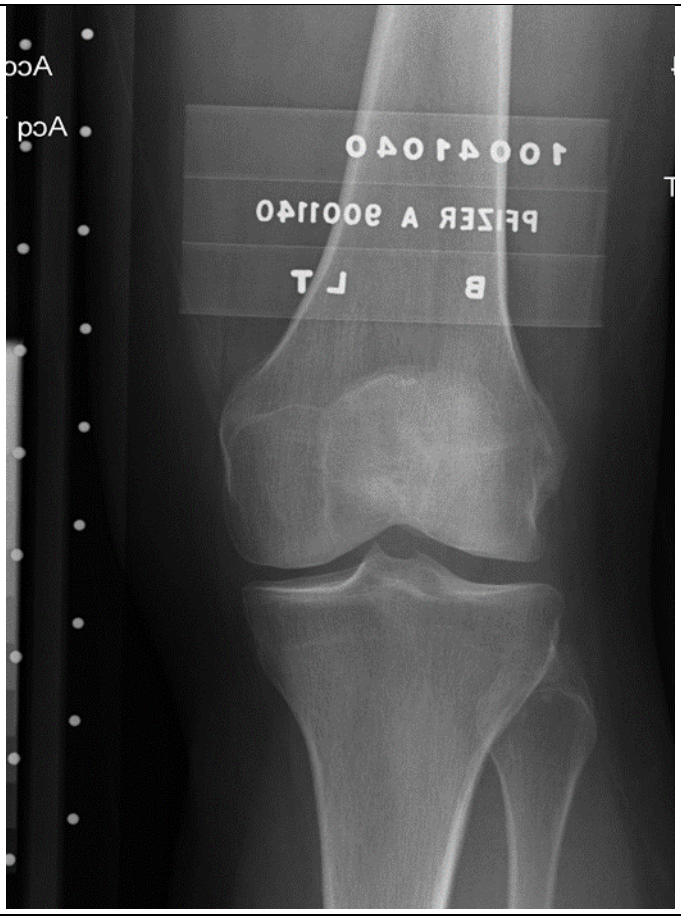


Figure 29: Unacceptable Marker Placement: Marker over bone and inverted.

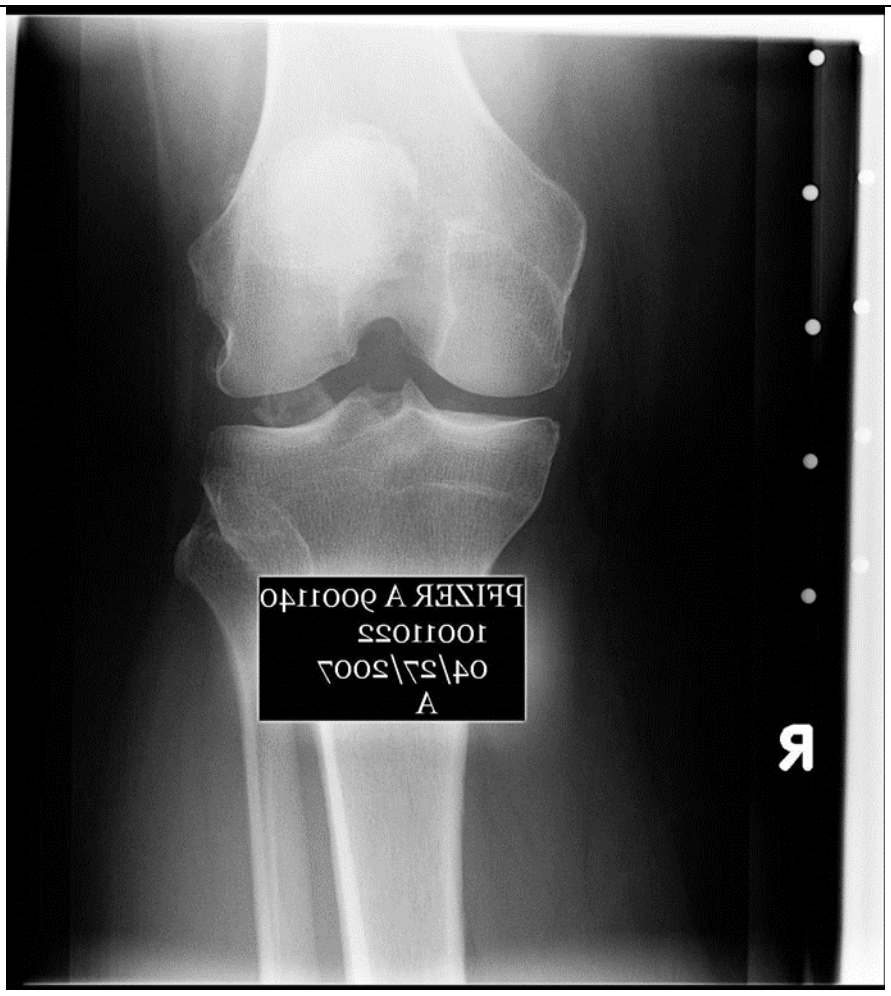
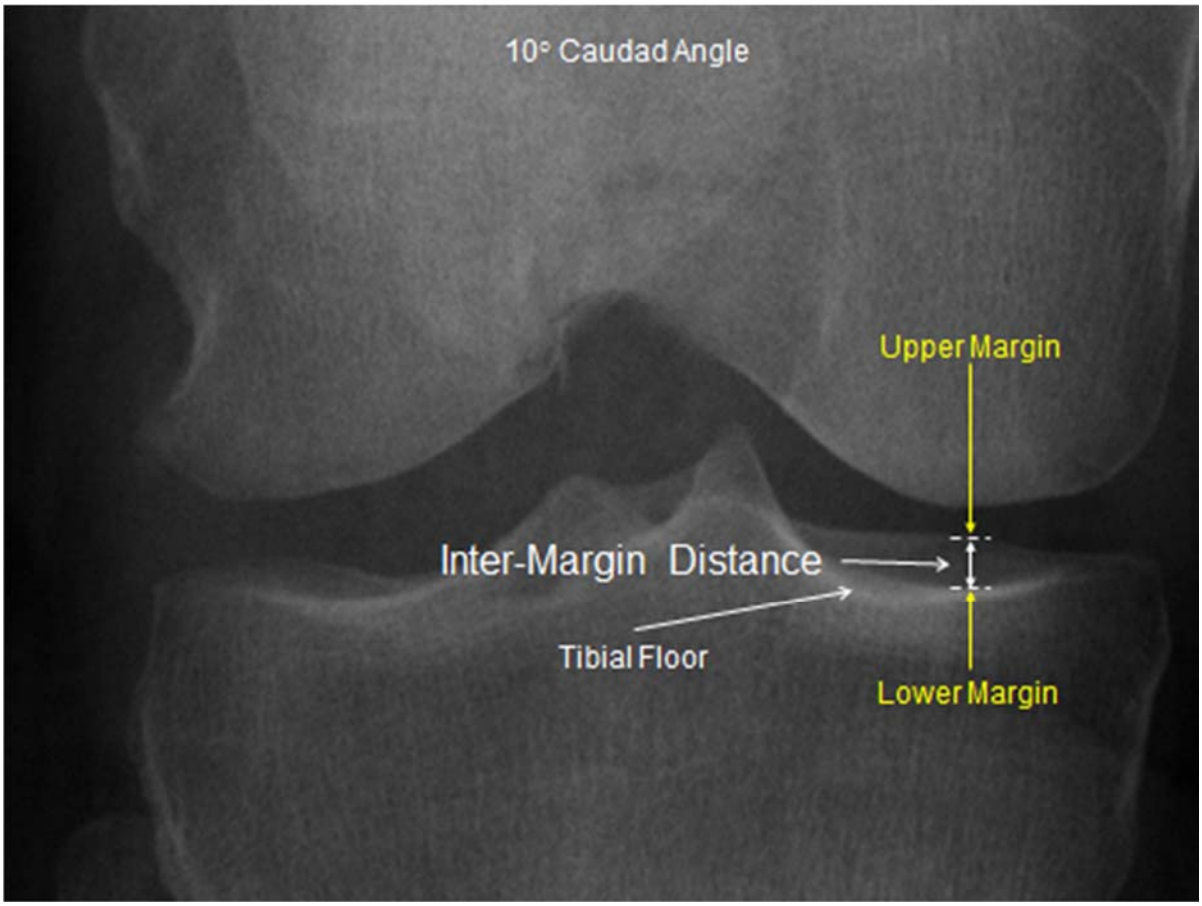


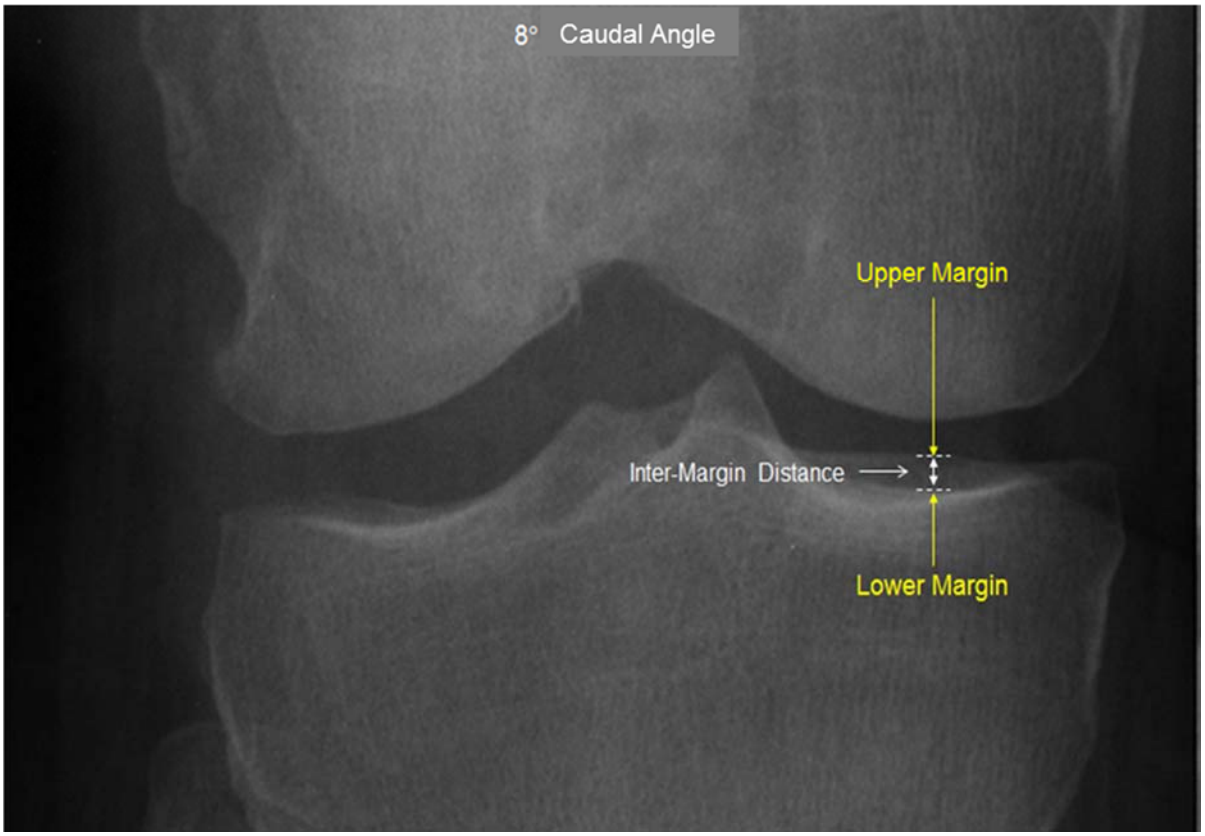
Figure 30: Unacceptable Centering and Marker: Top-to-bottom centering and marker over bone and inverted. Two columns of beads not adequately included. Inadequate anatomical coverage of the femur.

4.3. Inter-Margin Distance

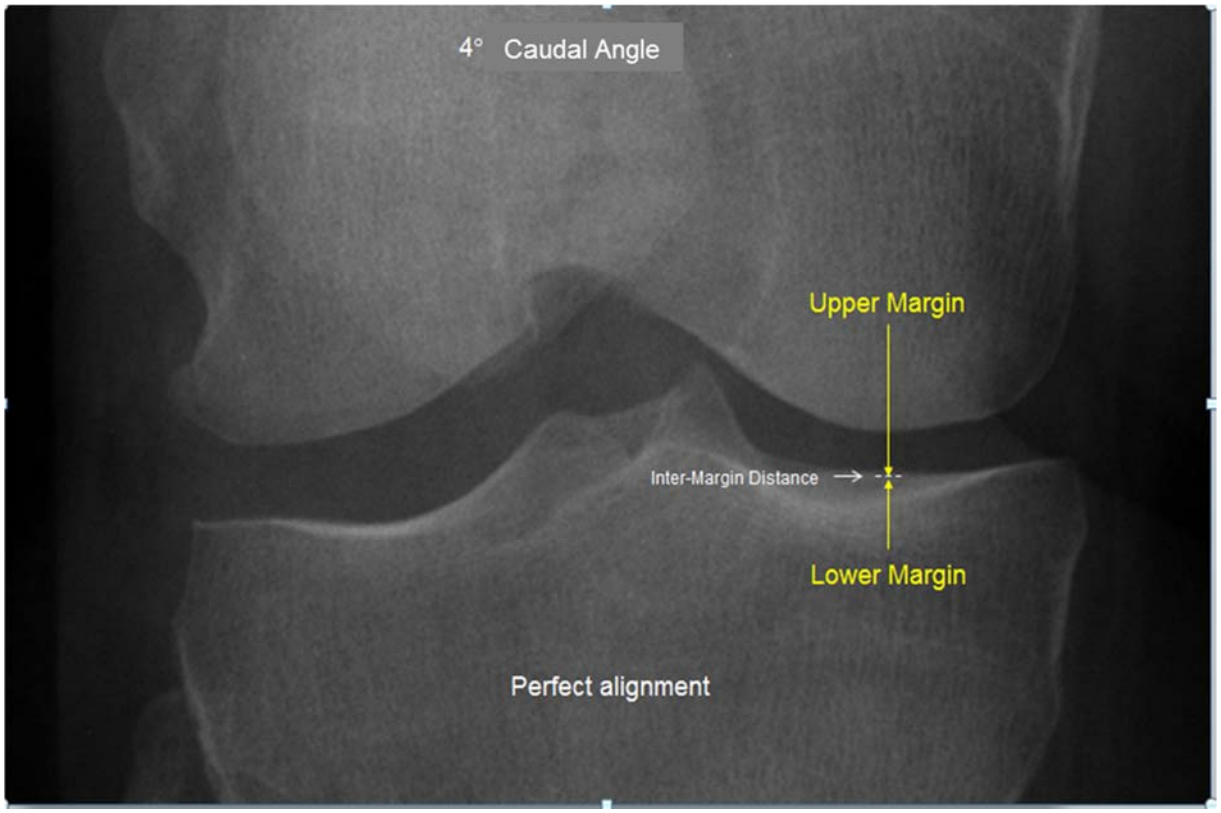
The Inter-margin Distance (IMD) is defined as the distance in millimeters between the upper and lower margins along a tilted tibial plateau. The IMD is measured at a point along the tibial plateau approximating at the midpoint of the medial femoral condyle. A perfect IMD is when the tibial plateau (upper and lower margins) is in perfect alignment, where the IMD = 0 mm; however, a variance in tilt between 0 and 1.5 mm will be acceptable. Joint space width is always measured at the narrowest width between the edge of the femoral condyle to the tibial floor (which seats the base of the meniscus). The following examples showcase various IMDs (Figures 31-35).



In **Figure 31** above, this 10-degree angle depicts an IMD >1.5 mm. Not ideal for measuring joint space width. The IMD must be improved by bringing margins to within ≤1.5 mm in next image.

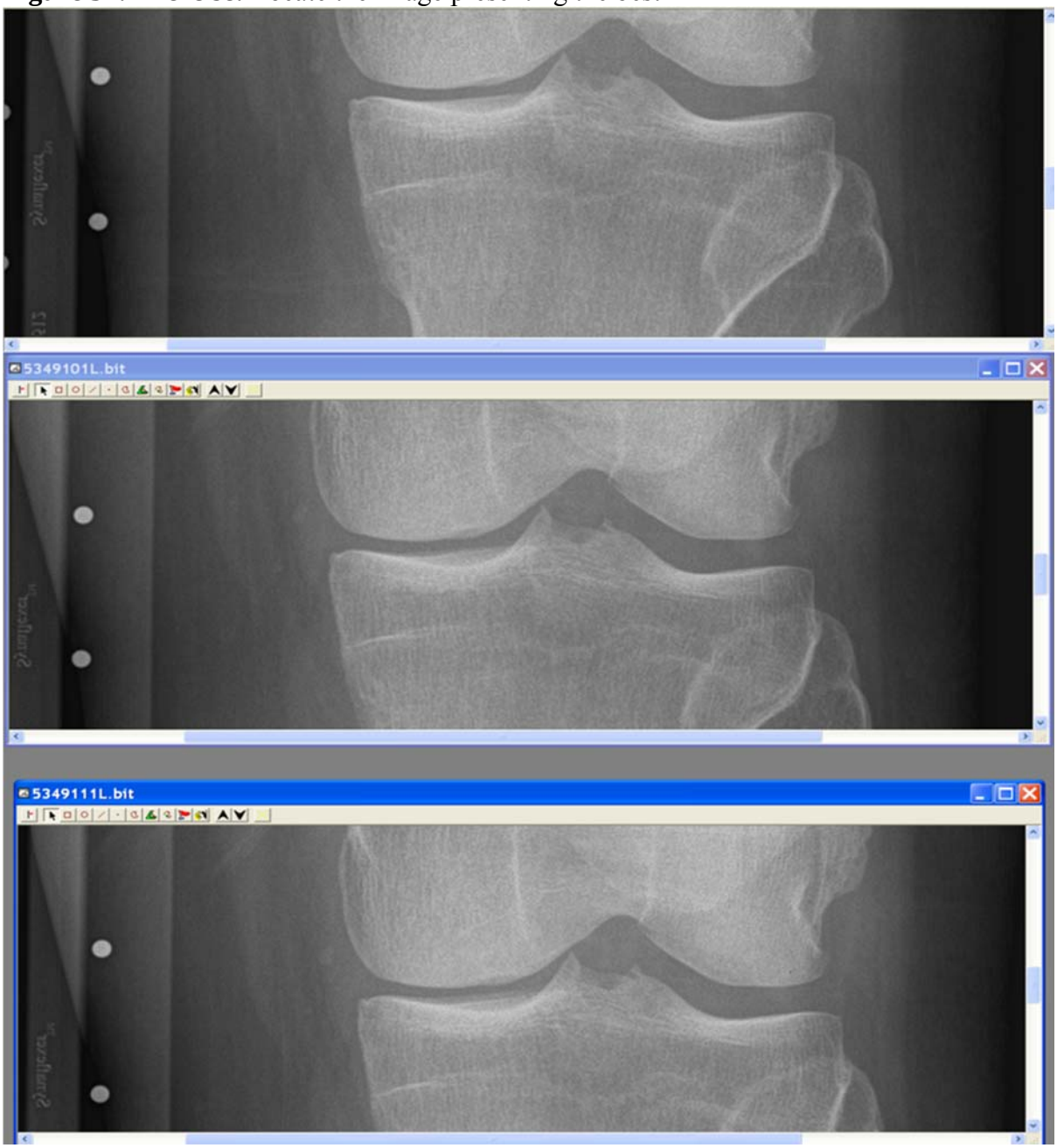


In **Figure 32** above, a tube angle upward correction to eight (8) degrees is improving the IMD but it still remains >1.5 mm. Decreasing the angle is improving the IMD; however, a decrease of two (2) degrees was not enough of a change. Continue decreasing the angle but at a larger incremental change (maybe to four [4] degrees).



In **Figure 33** above, an upward tube angle decrease to four (4) degrees improves the IMD to perfectly align both margins on top of each other. That is the ultimate goal; however, a margin of error to ≤1.5 mm is acceptable. In six (6) months this subject will come back for repeat images and the four- (4) degree tube angle in this knee will be the preferred angle for the first image.

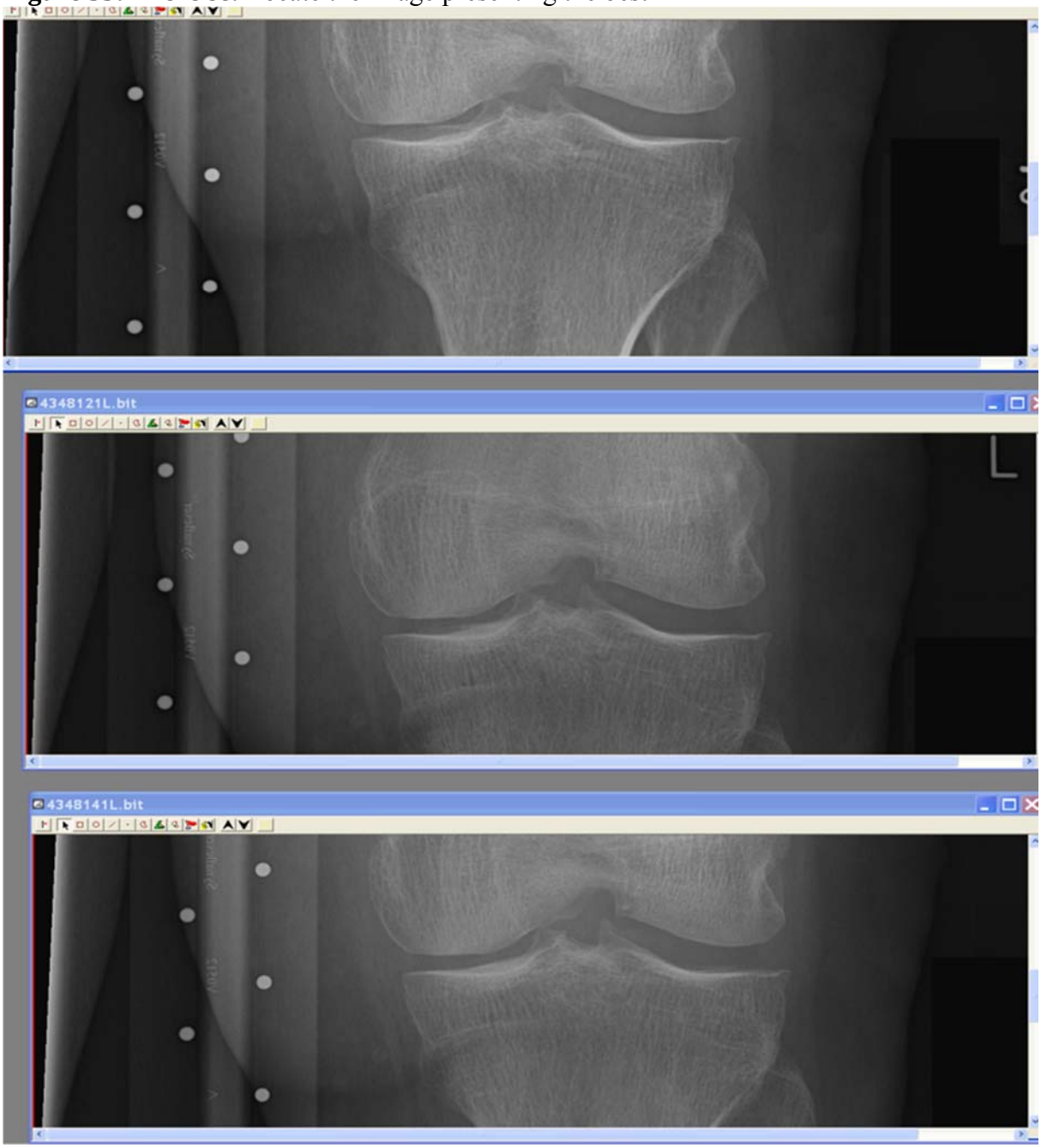
Figure 34: Exercise: Locate the image presenting the best IMD



First IMD is best

Middle image was the starting image (10-degree caudal angulation) with small and acceptable IMD (≤1.5 mm). In an effort to improve the IMD the technologist adjusted tube downward by one (1) degree (**bottom image**). Note the IMD worsened (widened) —wrong direction. For the 3rd image, the technologist adjusted the tube two (2) degrees upward to nine (9) degrees (**top image**). **The smaller the IMD the smaller the incremental tube change. The most optimal image was obtained in three (3) attempts.**

Figure 35: Exercise: Locate the image presenting the best IMD



Top image: (10-degree caudal angulation) IMD >1.5 mm.

Middle image: The technologist adjusted the tube downward to twelve (12) degrees (as noted by the improving IMD, the down direction was correct.

Bottom image was another two (2) degrees down direction (fourteen [14] degrees) —perfect alignment. **The larger the IMD the larger the incremental tube change. Completed in three (3) attempts.**

5. MAGNETIC RESONANCE IMAGING

Post-baseline MRIs may be requested by the Central Radiologist at Bioclinica (Reader) or the Investigator for a "*for-cause*" event (e.g., equivocal radiographic findings) for a joint (targeted and non-targeted) considered "*at-risk*".

In selected OA studies, subjects having a KLG three (3) or four (4) hip or knee at the initial screen visit will require MRIs of both hips and knees prior to randomization and at all post-baseline scheduled imaging visits.

Any sequence that demonstrates subject motion or other significant artifacts must be immediately repeated and documented on the Data Transmittal Form (DTF) in the comment field (e.g., "Patient motion - repeated T1 two times").

When acquiring MRI data, all the images acquired need to have the following characteristics of a good quality examination suitable for the purposes of the clinical trial:

- Adequate Signal to Noise
- No motion artifact
- No phase wrap
- Torso phased array or large flex coil, shoulder coil, or knee coil

The protocols below are based on suggested MRI acquisition parameters that are typical for 3T scanners. Please use the similar parameters for 1.5T scanners. Depending on specific hardware/software versions and magnet brand, some settings may vary. Bandwidth, FOV, NEX, TR, and TE settings can be optimized on your patient/scanner to achieve an optimal signal-to-noise ratio, anatomic coverage and image quality. Deviations from the requested slice thickness or spacing/gap will result in re-scan requests. Please save the imaging protocol on the scanner at study initiation and use for all subjects. Consistency in acquisition across all visits is especially very important.

Proper subject preparation is critical for obtaining high-quality images. The following comments will help achieve the best subject preparation:

1. Provide pads, positioning aids, blankets and cushions to make the subject as comfortable as possible and to ensure immobility during imaging.
2. Use earplugs or music through headphones along with pillows, blankets, and verbal reassurance. These measures usually help alleviate some of the subject's anxiety.
3. All loose metal objects including metal-containing clothing (zippers, hooks, belts, snaps) and jewelry should be removed.
4. If possible, the subject should be dressed in a hospital gown for the MRI exam.
5. Monitor the subject during imaging at all times.

When imaging the left and right knee, left and right shoulder and pelvis, a quick 3-plane localizer should be first obtained for accurate anatomical orientation and positioning of slices in the subsequent sequences.

5.1. Shoulder

5.1.1. Shoulder MRI Parameters

Sequences: Left and Right Shoulder Exams (each shoulder imaged separately) **Please note: Deviations from the requested slice thickness or spacing/gap will result in re-scan requests.**				
Plane	**Type**	**Thickness (mm)**	**Spacing/gap (mm)**	**Comments**
Oblique Coronal	T1-weighted TR=450-500 ms TE=15-30 ms	3.0	0.5-1.0	Non-fat sat
Oblique Coronal	Intermediate weighted/proton density-weighted TR=3000-4000 ms TE=12-35 ms	3.0	0.5-1.0	Fat sat ETL (turbo factor) 7-9
Comments: Field of View (FOV) must be appropriate to subject size, usually around 16 cm; Matrix=512 x 256; 2 averages (NEX); bandwidth~250 Hz/pixels.				

5.1.2. Shoulder MR Subject Preparation and Positioning

Proper subject preparation is critical for obtaining high-quality images. Follow these guidelines and make sure to consistently cover all preparatory steps during each subject-visit (Figure 36).

- The laterality of the target shoulder for imaging should correctly be entered through the scanner console.
- The subject should be positioned supine with the hand extended by the side of the torso or on the stomach.
- A dedicated shoulder coil should be used for imaging. A flex coil will be acceptable if a shoulder coil is not available.
- The target shoulder should be as close as possible to the center of the magnet bore.

- The padding should be used to elevate the elbow and align the humerus parallel to the table.
- When moving the table inside the scanner, use laser lights to zero in on the shoulder joint.

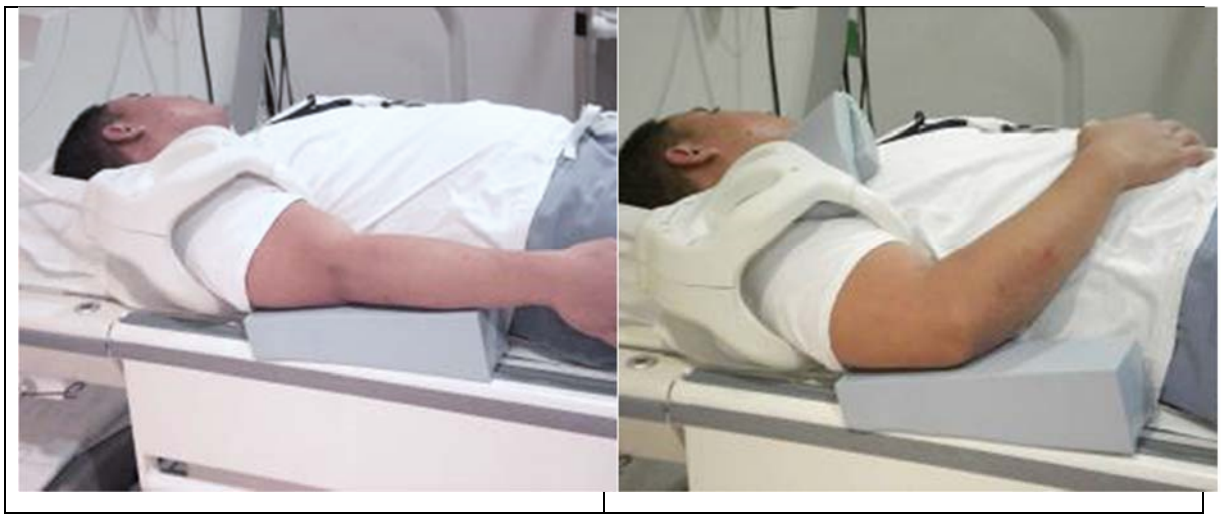


Figure 36: Shoulder MR Preparation and Positioning

5.1.3. Shoulder MR Anatomical Coverage and Slice Prescription

Shoulder Oblique Coronal Scan

- On an axial localizer identify the slice on which the supraspinatus muscle can be well observed. The slices should be prescribed parallel to the axis of the supraspinatus muscle/tendon.

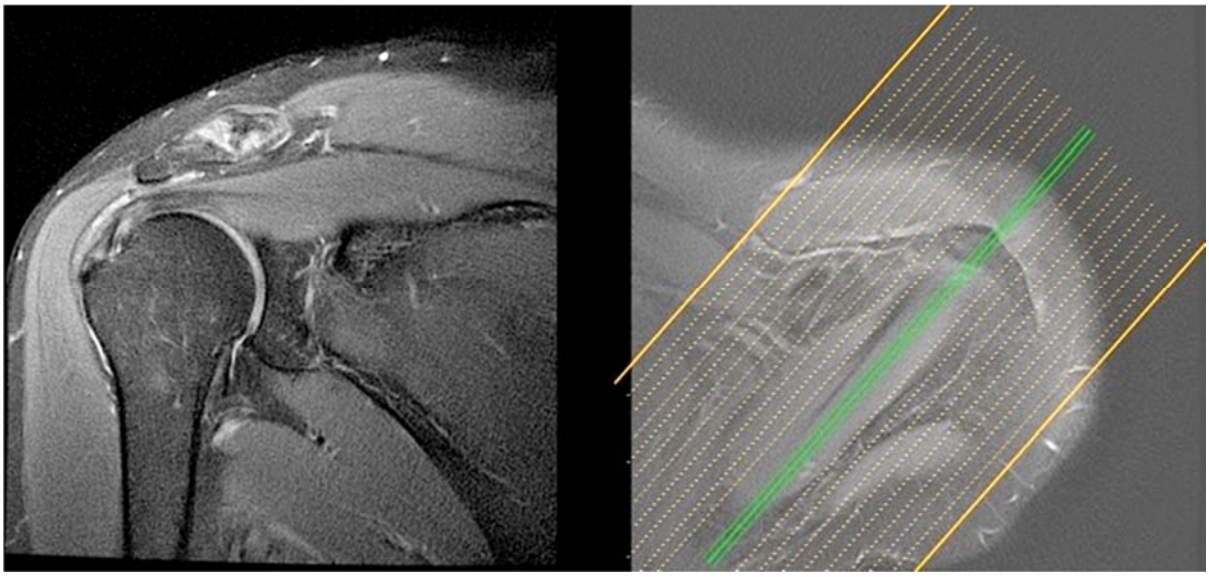


Figure 37a **Figure 37b**

The green line shows the orientation of the slices parallel to the long axis of the supraspinatus muscle and also the perfect anatomical coverage including the subscapularis muscle anteriorly and infraspinatus muscle posteriorly (Figure 37b). Figure 37a shows a perfect oblique coronal intermediate-weighted fat-suppressed MRI of the shoulder.

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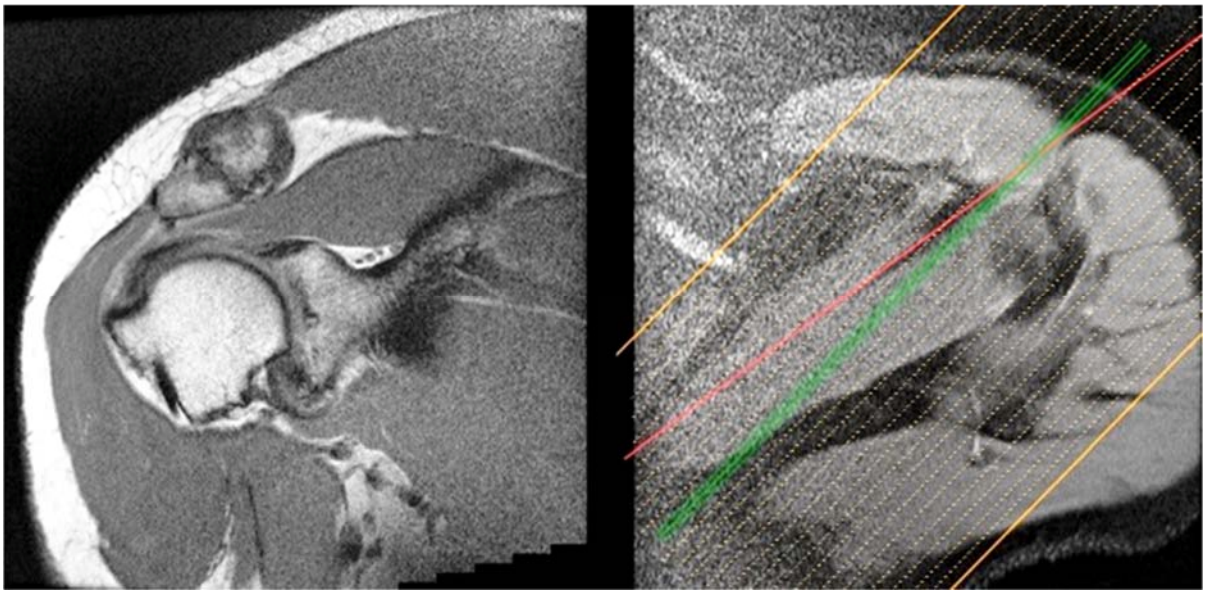

Figure 38a **Figure 38b**

The red line shows theoretical perfect orientation of coronal slices parallel to the long axis of the supraspinatus muscle. The green line shows the actual slices orientation which oblique and are not parallel to the long axis of the supraspinatus (Figure 38b). Figure 38a shows a non-acceptable oblique coronal T1-weighted MRI of the shoulder with suboptimal visualization of the glenohumeral and acromioclavicular joints.

Figures 39-41 show suboptimal but still readable shoulder images.

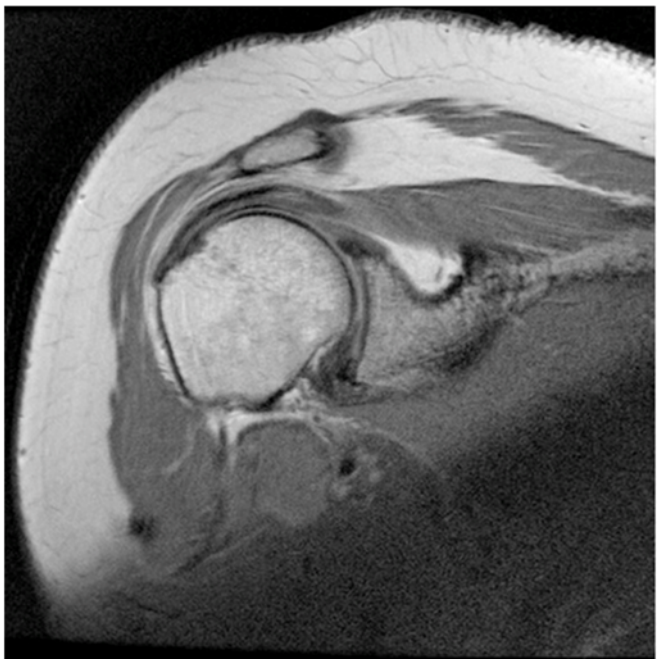

Figure 39: Suboptimal but still readable coronal T1-weighted MRI of the shoulder with non-visualization of the inferior shoulder soft tissues secondary to coil misplacement.

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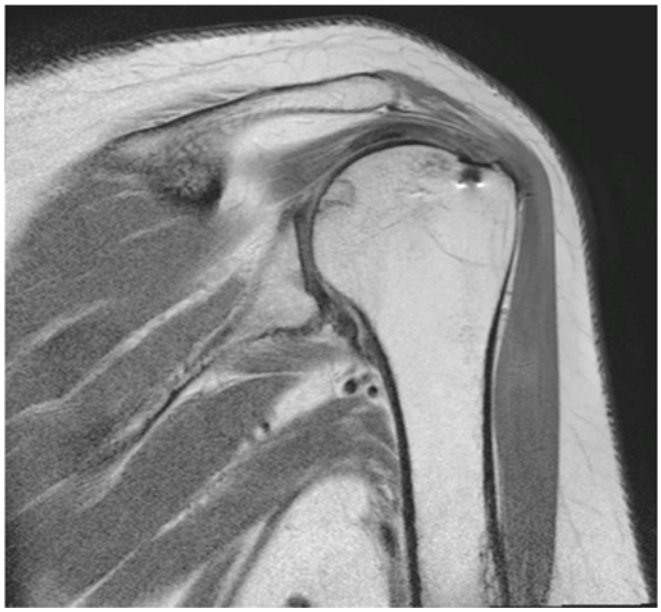

Figure 40: Suboptimal but still readable coronal T1-weighted MRI of the shoulder with small surgical metallic artifact at the greater tuberosity not interfering with the assessment of the shoulder joint.

(Images Copyrighted by Dr. Ali Guermazi, MD, PhD, 2015 © and used with permission)

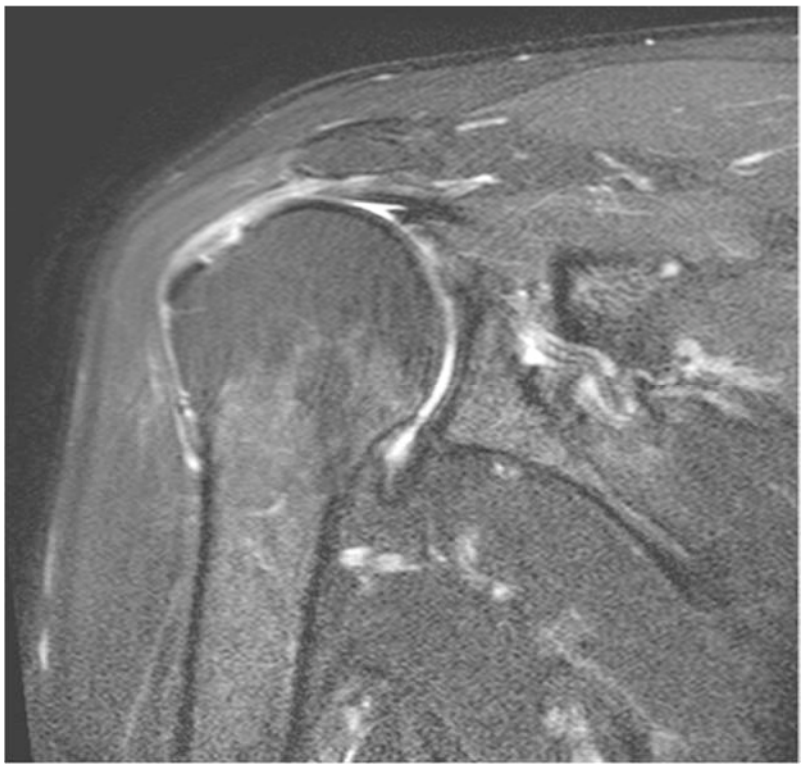

Figure 41: Suboptimal but still readable coronal intermediate-weighted fat-suppressed MRI of the shoulder with motion artifact (zebra artifact). Please repeat sequence if possible.

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5.2. Hip

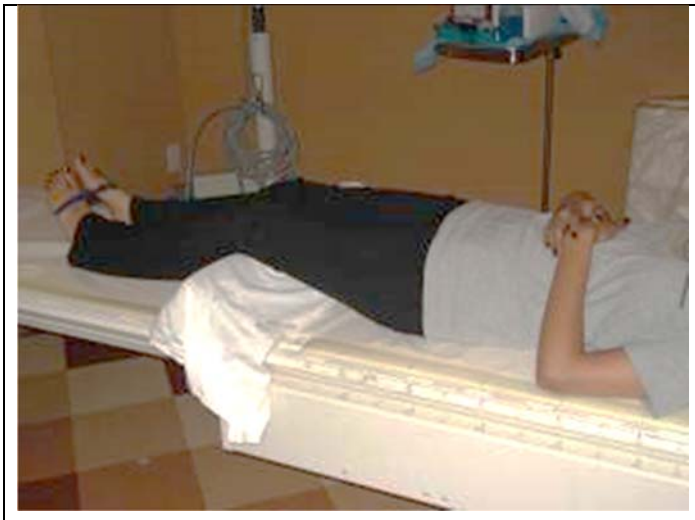
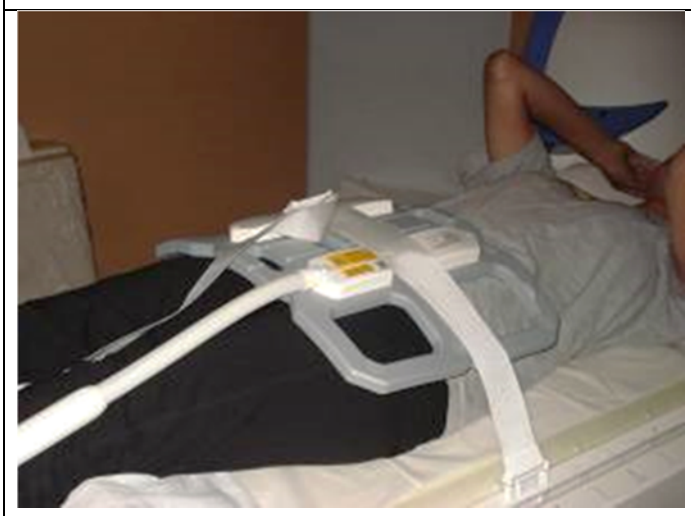
5.2.1. Hip MRI Parameters

Sequences: Bi-lateral Hip Exam **Please note: As the hip scanning is a bi-lateral acquisition, if the subject has Right and Left total joint replacement, do not image the hips and indicate this on the MRI DTF in the comments field. If the subject has only Right or Left total joint replacement follow the standard imaging procedure.** **Deviations from the requested slice thickness or spacing/gap will result in re-scan requests.**				
Plane	**Type**	**Thickness (mm)**	**Spacing/gap (mm)**	**Comments**
Coronal	T1-weighted TR=400-600 ms TE=8-15 ms	3.0	0.5-1.0	Non-fat sat
Coronal	Intermediate or proton density-weighted TR=3000-4000 ms TE=30-40 ms	3.0	0.5-1.0	Fat sat Echo train length (ETL)=5-7
Axial	Intermediate weighted/proton density-weighted TR=3000-3800 ms TE=25-40 ms	3.0	0.5-1.0	Fat sat Echo train length (ETL)=5-7
Comments: • FOV must be appropriate to subject size, in general 35 x 28 cm. Matrix=256 x 256. • Both hips should be captured in a single field-of-view. • Torso phased array or large flex coil. • Average NEX=1				

5.2.2. Bi-lateral Hip (Pelvis) MR Subject Preparation and Positioning

- The subject and coil should be centered to the table.
- The pelvic or body (phased-array) coil should be used for imaging.
- Subject positioning inside the scanner should be (feet- or head-first) supine.
- The feet should be strapped to provide immobility and correct positioning (Figure 42).

- When moving the table inside the scanner, use laser lights to center midway between the ASIS and pubic symphysis (Figures 43-44).

	**Figure 42: Positioning – strap feet**
	**Figure 43: Positioning/ centering**
	**Figure 44: Positioning/ centering**

5.2.3. Hip MR Anatomical Coverage and Slice Prescription

5.2.3.1. Hip Coronal Scan

- On an axial localizer find the slice with the largest cross-section through femoral heads and identify the line connecting inferior margins of femoral heads.
- Make sure the slices are parallel to the aforementioned line.
- The stack should be centered over the femoral head and the acetabular socket.

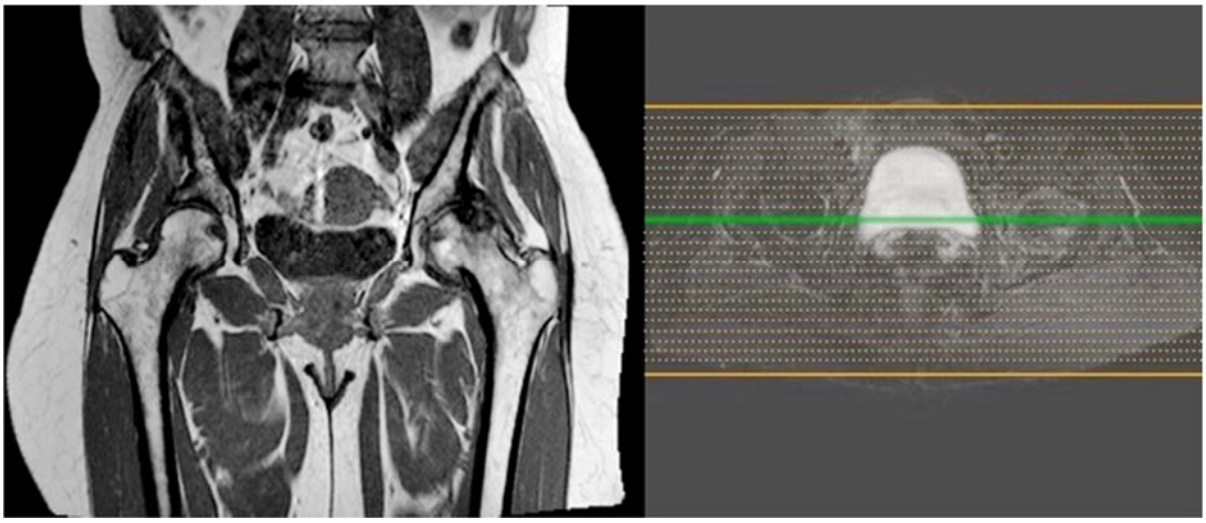


Figure 45a **Figure 45b**

The green line shows the orientation of the slices parallel to the femoral heads and the line connecting the inferior margins of the femoral heads. The slices cover the entire pelvis anteriorly and posteriorly (Figure 45b). Figure 45a shows a perfect coronal T1-weighted MRI of the pelvis with left femoral head osteonecrosis.

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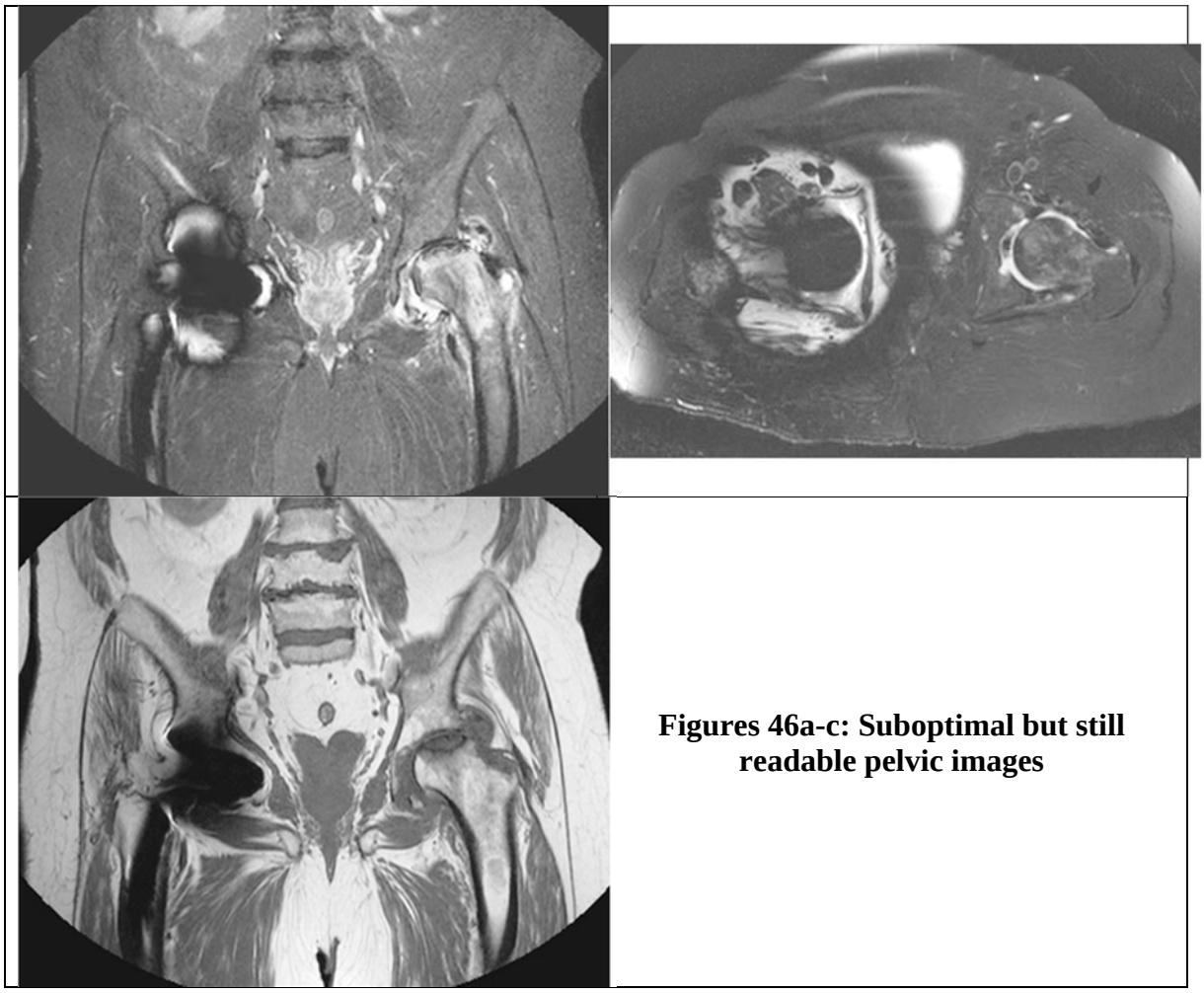

Figures 46a-c: Suboptimal but still readable pelvic images

Suboptimal but still readable coronal (Figure 46a) and axial (Figure 46b) intermediate-weighted fat-suppressed and coronal T1-weighted (Figure 46c) MRI of the pelvis with metallic susceptibility artifact secondary to right total hip replacement. Note the left shows an avascular necrosis of the femoral head with important likely reactional proximal femoral bone marrow edema and large effusion-synovitis.

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5.2.3.2.Hip Axial Scan

- On a coronal localizer find the slice on which you can clearly see the femoral heads and the lesser and greater trochanters. Identify the line connecting the superior margins of the femoral heads.
- Make sure the slices are parallel to the aforementioned line.
- The stack of slices should cover 2 cm below the lesser trochanter and at least 5 cm above the acetabulum.
- The stack should be centered over the femoral head and the acetabular socket.

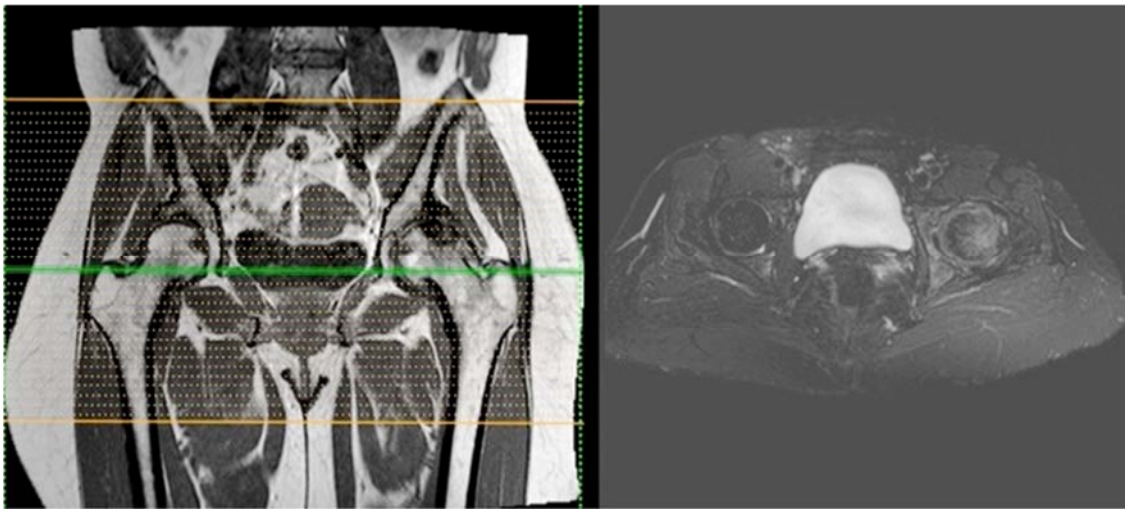

Figure 47a **Figure 47b**

The green line shows the orientation of the slices parallel to the line connecting the superior margins of the femoral heads. The slices should cover at least 2 cm below the lesser trochanter and 5 cm above the acetabulum (Figure 47a). Figure 47b shows a perfect axial intermediate-weighted fat-suppressed MRI of the pelvis.

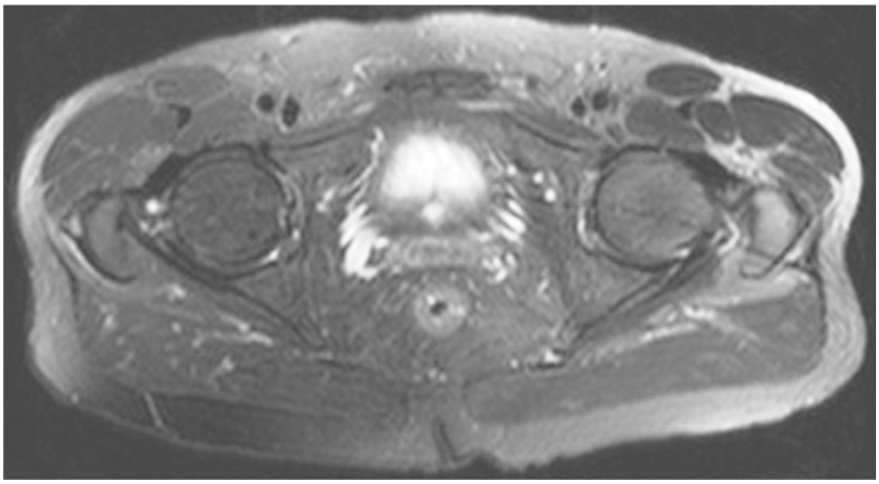

Figure 48: Suboptimal but still readable axial intermediate-weighted fat-suppressed MRI of the pelvis with inhomogeneous fat suppression.

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5.3. Knee

5.3.1. Knee MRI Parameters

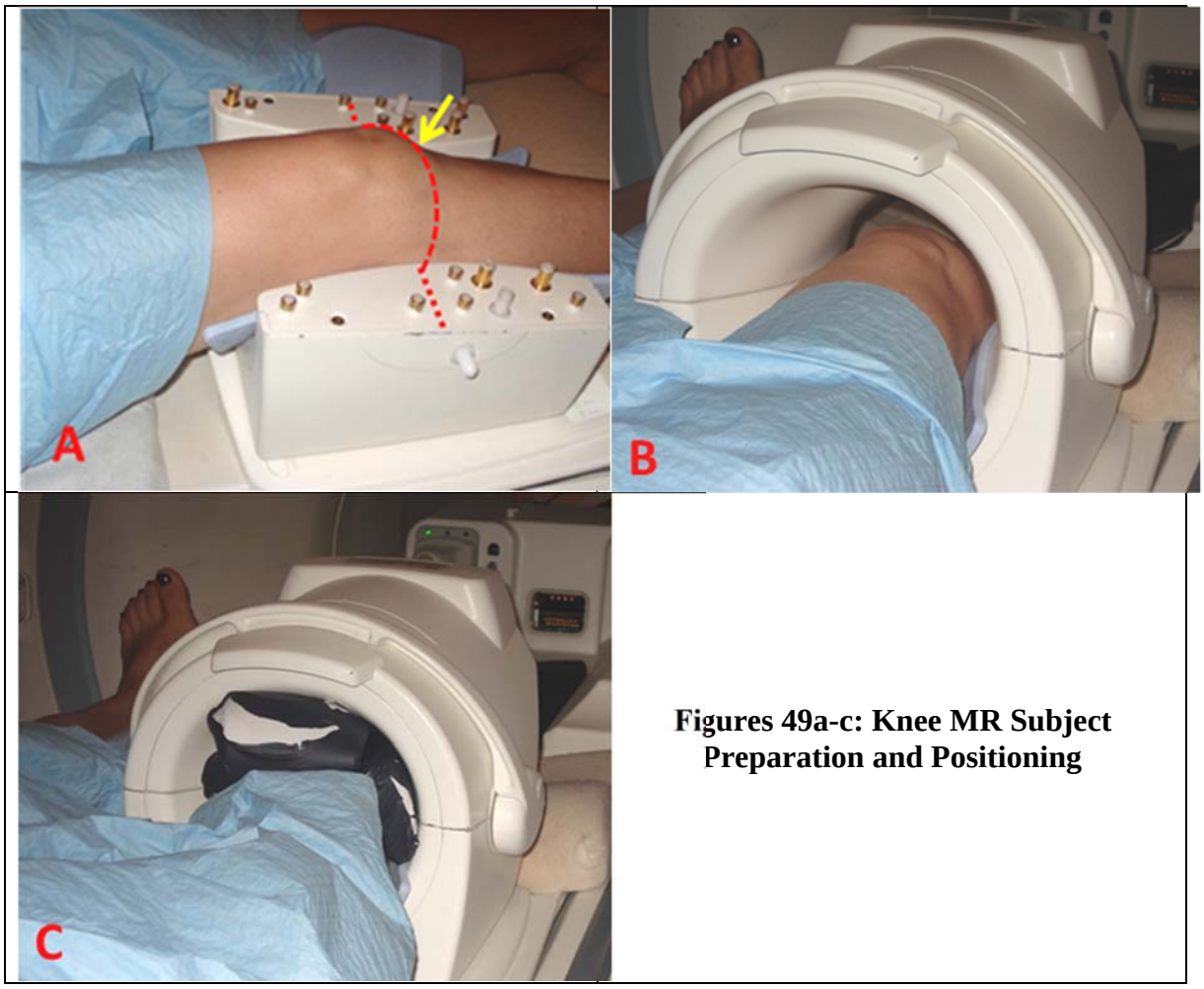
Sequences: Left and Right Knee Exams (each knee imaged separately) **NOTE: If a subject has a Right or Left total joint replacement, do not image the joint and indicate this on the MRI DTF in the comments field.** **Note: Deviations from the requested slice thickness or spacing/gap will result in re-scan requests.**				
Plane	**Type**	**Thickness (mm)**	**Spacing/gap (mm)**	**Comments**
Coronal	T1-weighted TR=400-600 ms TE=8-15 ms	3.0	0.5-1.5	Non-fat sat
Coronal	Intermediate weighted/proton density-weighted TR=2800-4000 ms TE=25-40 ms	3.0	0.5-1.5	Fat sat Echo Train Length (ETL)=5-7
Sagittal	Intermediate weighted/proton density-weighted TR=2800-4000 ms TE=25-40 ms	3.0	0.5-1.0	Fat sat Echo Train Length (ETL)=5-7
Comments: Field of View (FOV) must be appropriate to subject size, in general between 14-18 cm. Matrix=256 x 256. Average NEX=1.				

5.3.2. Knee MR Subject Preparation and Positioning

- The laterality of the target knee for imaging should correctly be entered through the scanner console.
- Subject positioning inside the scanner should be Feet First Supine.
- In the coil the knee should be positioned so that the apex of the patella is aligned with the center of the coil (Figure 49a).
- The leg should be in a relaxed, neutral position. The most comfortable (and sustainable) one is attained when the knee is slightly flexed. Many coils are designed to accommodate this. However, if the base of your coil is flat, use

the pads/pillows to slightly elevate and flex the knee to attain optimal positioning.

- Once the knee is comfortably oriented and centered inside the base of the coil, attach the top (Figure 49b). Use pads as needed to immobilize the knee (Figure 49c).
- NEVER insert a cushion or pad under the heel (ankle).
- Position the coil as close as possible to the center of the table. To achieve this, offset the subject toward the contralateral side.
- When moving the table inside the scanner, use laser lights to zero on the center of the coil (apex of the patella).



Figures 49a-c: Knee MR Subject Preparation and Positioning

5.3.3. Knee MR Anatomical Coverage and Slice Prescription

5.3.3.1. Knee Coronal Scan

- Based on the axial localizer find the slice with the largest cross-section through femoral condyles and identify the line connecting the posterior tips of the femoral condyles. The slices should be aligned with (parallel to) the aforementioned line. Figure 50a.
- Based on the mid-sagittal localizer prescribe the slices parallel to the femoral shaft. Make sure to also include the patella. Figure 50b.
- Based on the coronal localizer make sure the FOV is well positioned and the target knee is completely covered. Figure 50c.

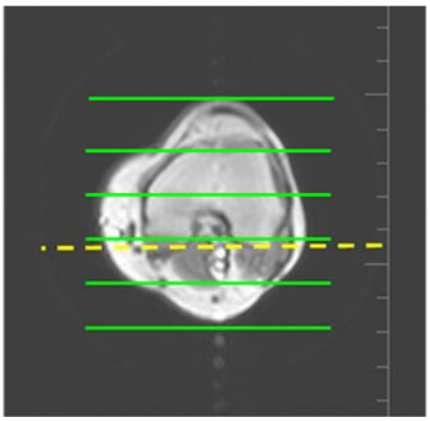


Figure 50a

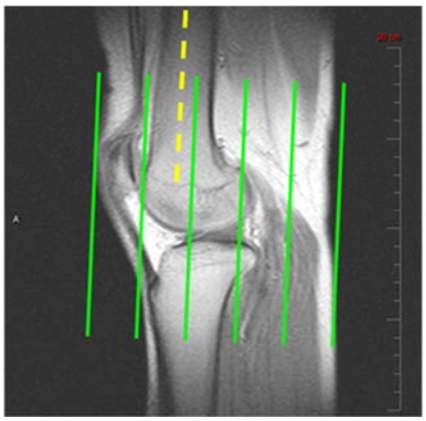


Figure 50b

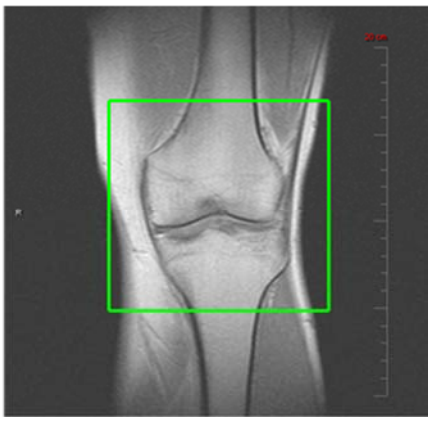


Figure 50c

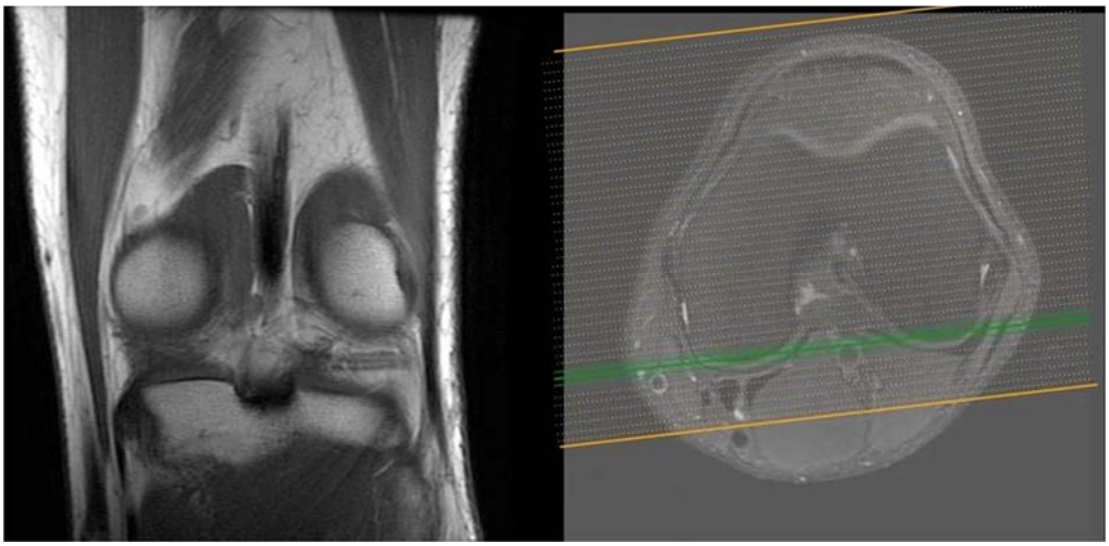


Figure 51a **Figure 51b**

The green line shows the orientation of the slices parallel to the line connecting the posterior tips of the femoral condyles. The slices should cover the knee from the anterior tip of the patella anteriorly to the level of the gastrocnemius muscles posteriorly (Figure 51b). Figure 51a shows a perfect coronal T1-weighted MRI of the knee with identical size of the posterior tip of the femoral condyles.

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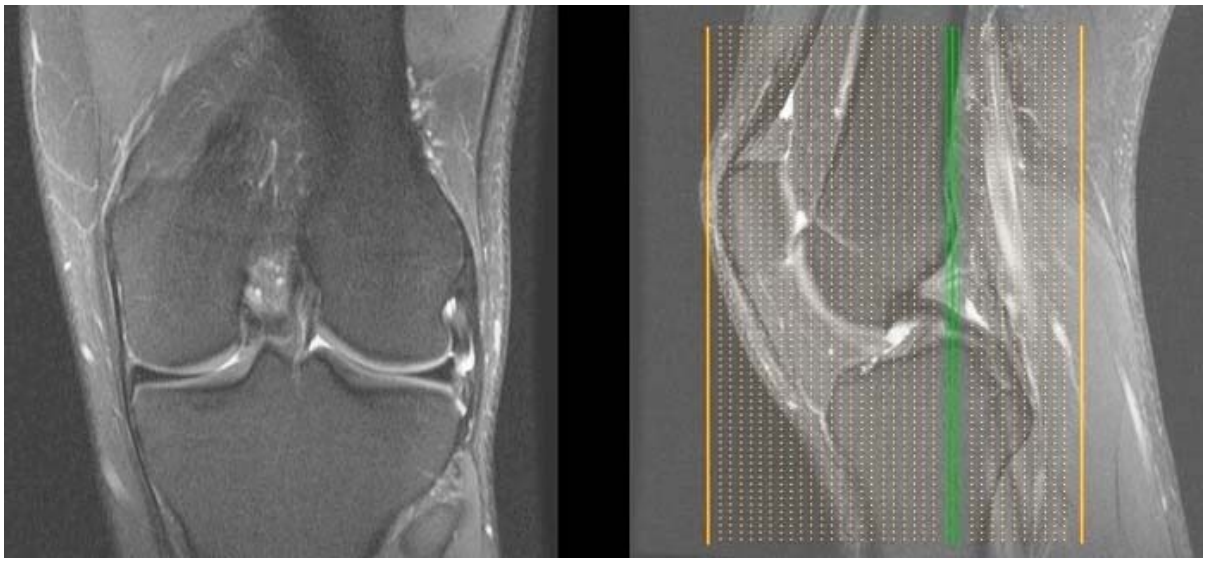

Figure 52a **Figure 52b**

The green line shows the orientation of the slices parallel to the femoral shaft line. The slices should cover the knee from the anterior tip of the patella anteriorly to the level of the

gastrocnemius muscles posteriorly (Figure 52b). Figure 52a shows a perfect coronal intermediate-weighted fat-suppressed MRI of the knee with identical size of the posterior tip of the femoral condyles.

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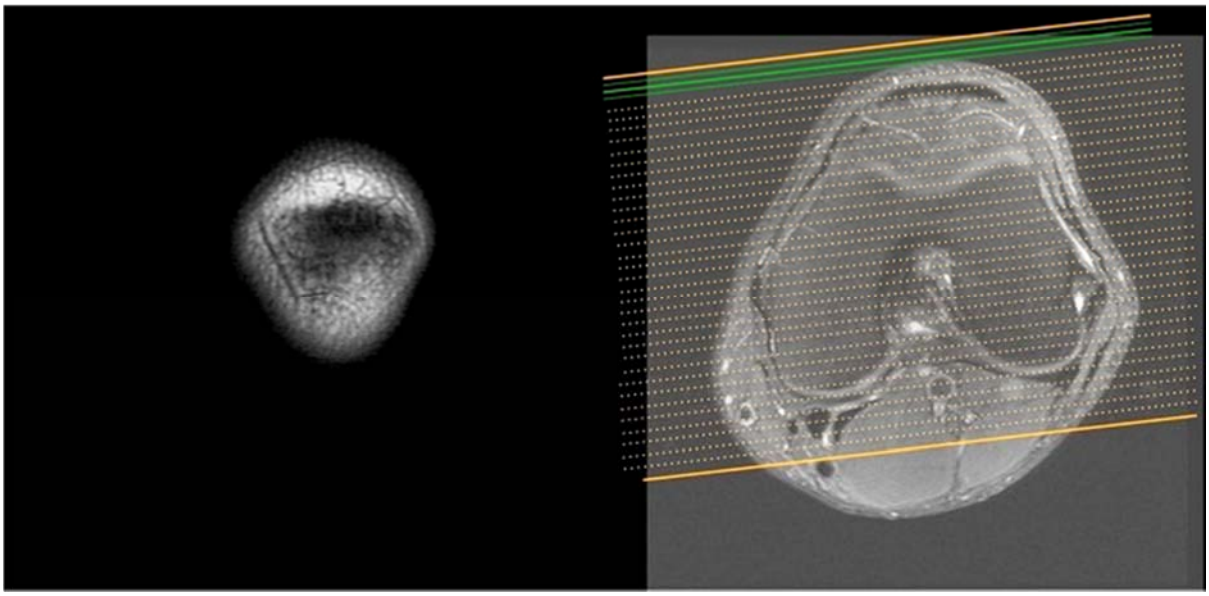

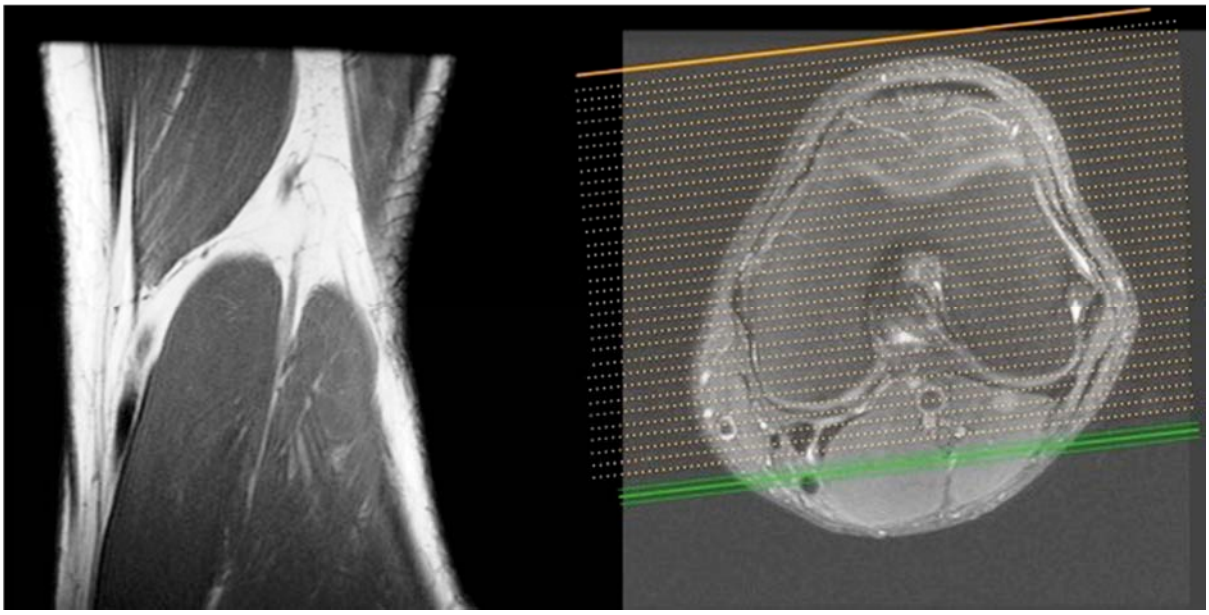

Figure 53a **Figure 53b**

The 2 images show normal anterior (Figure 53a) and posterior (Figure 53b) coverage of the coronal slices represented by the green lines.

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Figures 54-55 illustrate suboptimal but still readable knee images.

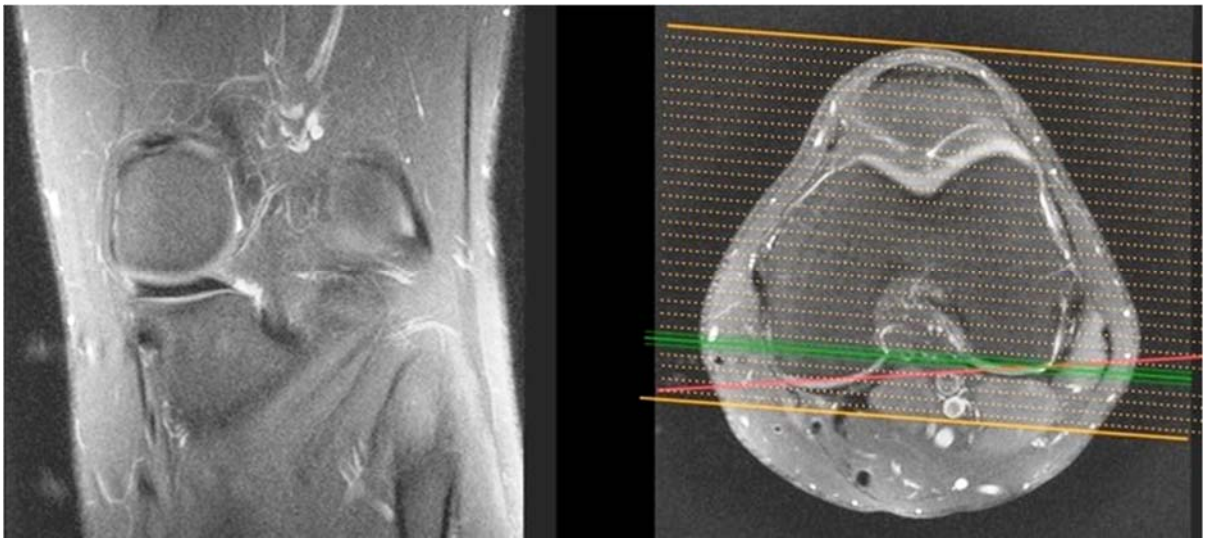

Figure 54: Suboptimal but still readable coronal intermediate-weighted fat-suppressed MRI of the knee with the red line showing the perfect orientation parallel to the line connecting the tips of the femoral condyles and the green line showing the actual slices orientation. As a result the medial posterior femoral condyle is visible while the lateral is not with at least 2 slices deviation. Repeat sequence if possible.

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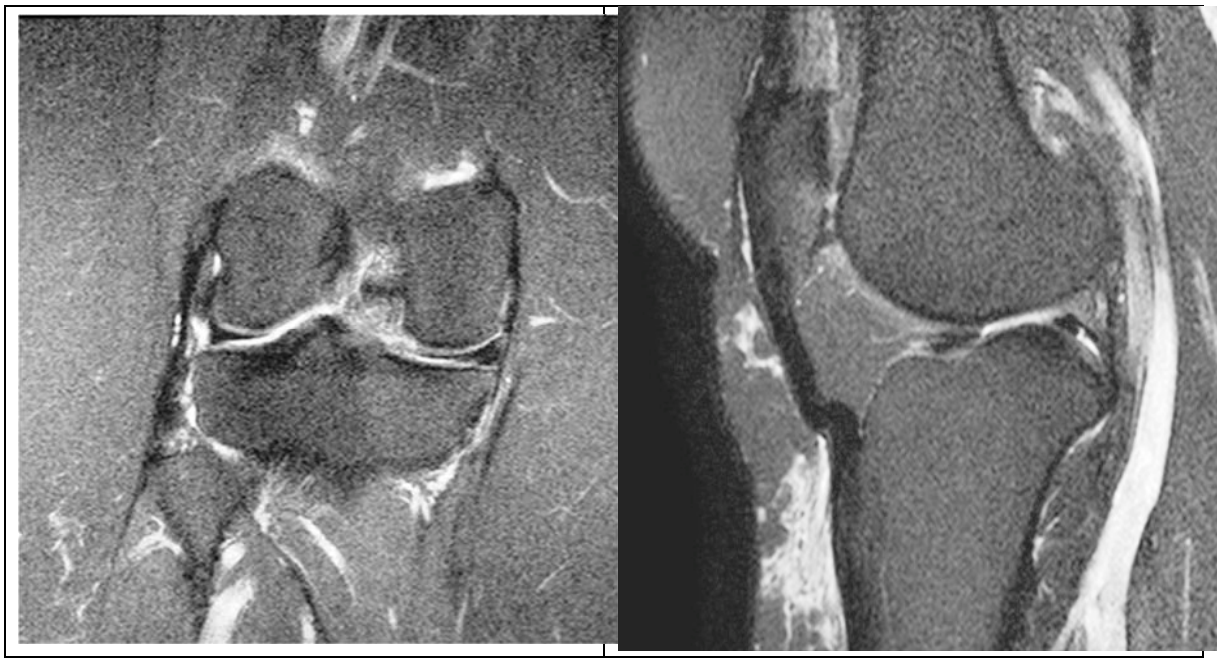

Figure 55: Suboptimal but still readable coronal (a) and sagittal (b) intermediate-weighted fat-suppressed MRI of the knee with low signal to noise ratio in an obese subject. In this

case please use flex coil and if necessary increase NEX to 2. In this case, the sequence time will increase but images will be of better quality. Repeat sequence if possible.

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5.3.3.2. Knee Sagittal Scan

- Based on the axial localizer find the image with the largest cross-section through femoral condyles and identify the line connecting the posterior surfaces of the condyles. The slices should be perpendicular to the aforementioned line (Figure 56a).
- Based on the mid-sagittal localizer make sure the tibial joint is in the center of the FOV and the patella is also included (Figure 56b).
- Based on the coronal localizer prescribe the slices parallel to the femoral shaft. Also make sure the femur-tibia joint is in the center of the stack (Figure 56c).

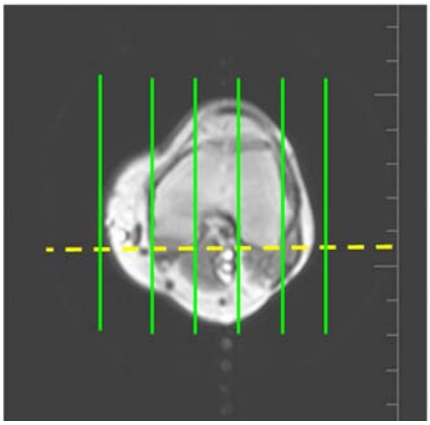

Figure 56a

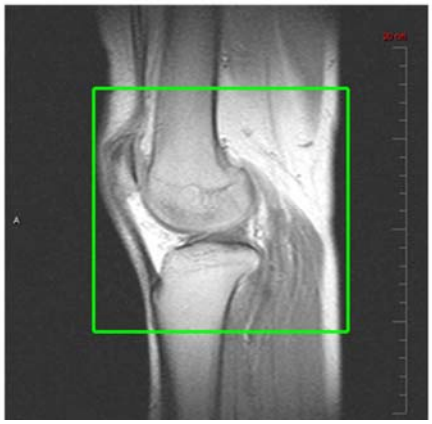

Figure 56b

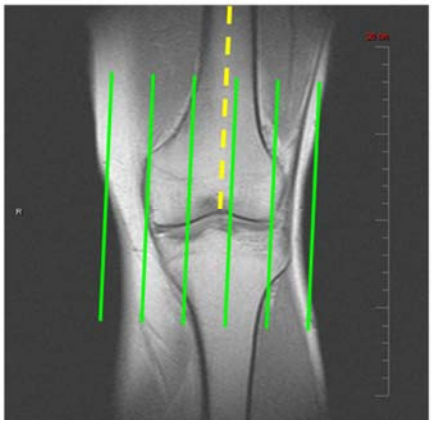

Figure 56c

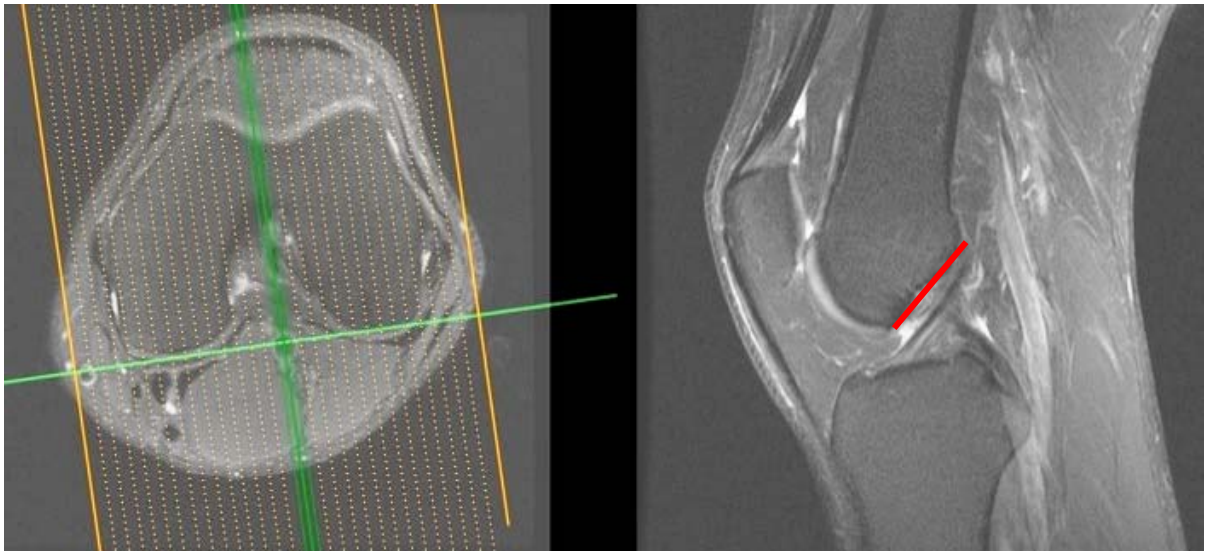

Figure 56d **Figure 56e**

The green line shows the orientation of the slices perpendicular to the line connecting the posterior tips of the femoral condyles. The slices should cover the knee from the soft tissues around the medial collateral ligament medially to the soft tissues around the lateral collateral ligament laterally (Figure 56d). Figure 56e shows a perfect sagittal intermediate-weighted fat-suppressed MRI of the knee with the ACL shown on one slide parallel to the Blumensaat line (red line). (Images Copyrighted by Dr. Ali Guermazi, MD, PhD, 2015 © and used with permission)

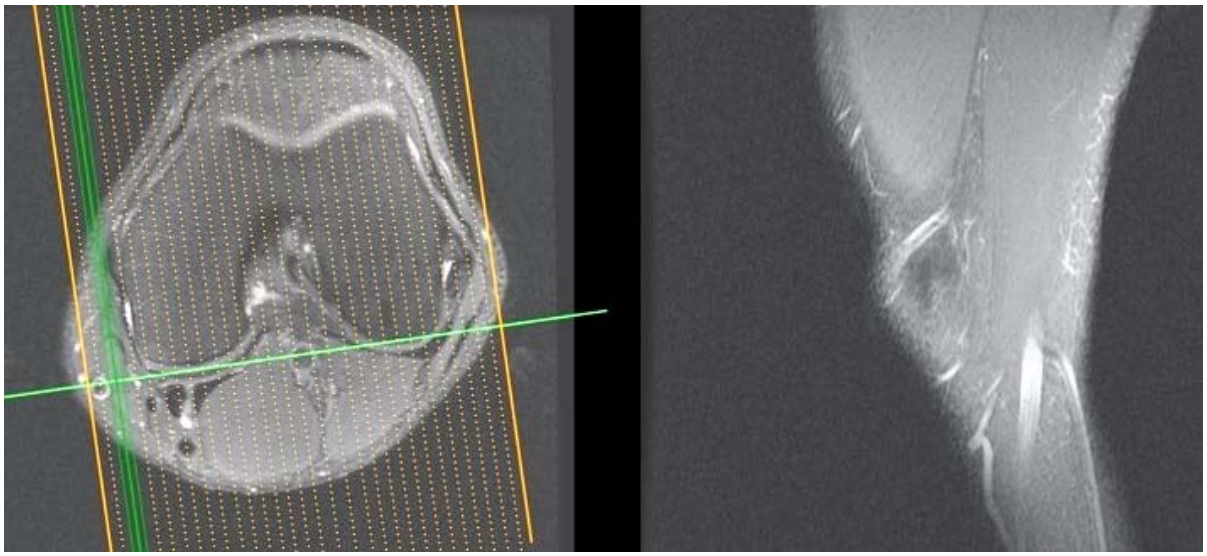

Figure 57a **Figure 57b**

This image show normal medial knee coverage of the sagittal slices represented by the green line (Figure 57a). The same applies to the lateral side of the knee (Figure 57b). (Images Copyrighted by Dr. Ali Guermazi, MD, PhD, 2015 © and used with permission)

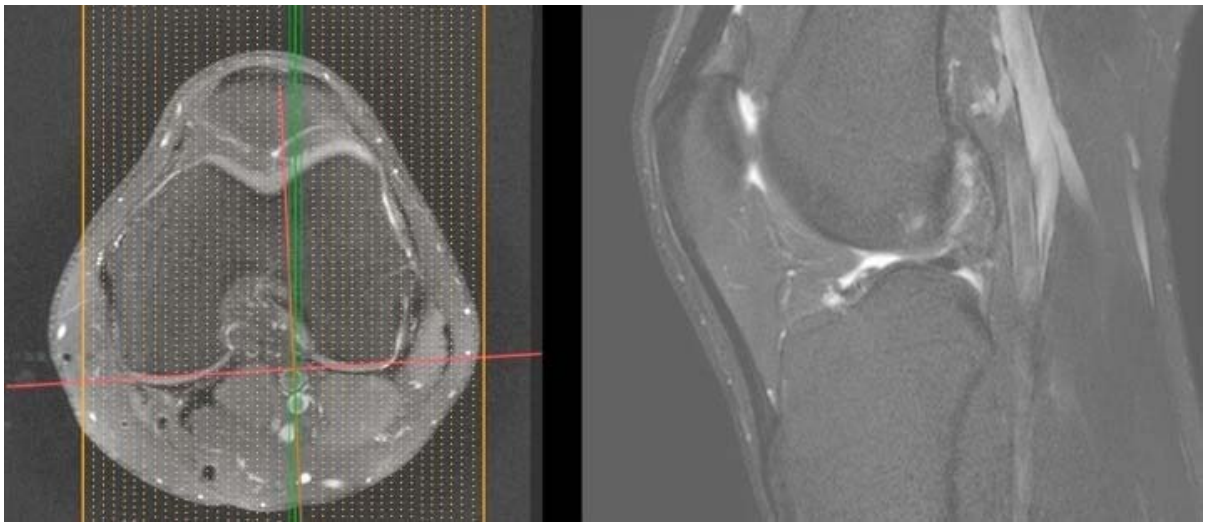

Figure 58a **Figure 58b**

Figures 58a-b show suboptimal but still readable sagittal intermediate-weighted fat-suppressed MRI of the knee with the red line showing the perfect orientation perpendicular to the line connecting the tips of the femoral condyles and the green line showing the actual slices orientation. As a result the knee notch is not perfectly visualized. Repeat sequence if possible.

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5.4. Evaluation of For-Cause MRI Scans at Bioclinica

Bioclinica's imaging technologist and/or the imaging physicist will evaluate the quality of each MRI study. A QC report listing results of quality review will be e-mailed to the clinical site within three (3) business days from receipt of data.

The following will be checked to assess the quality of the exam:

- Imaging sequences
- Subject positioning in the scanner (orientation of the MRI sequence planes)
- Anatomical coverage
- Parameters related to signal- and contrast-to-noise (correct TR, TE, flip angle, etc.)
- Image resolution related parameters (the FOV, slice thickness/gap, matrix, etc.)
- Absence/presence of artifacts: motion/flow, fat saturation, aliasing, susceptibility (e.g. from metallic objects), etc.
- Subject number/ID related information in electronic header.

5.5. MRI Safety Tips

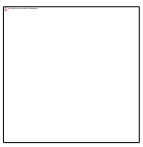
MRI is a potential safety risk for subjects for whom the following situations are applicable:

- Implants: Pacemakers, nerve stimulators, implantable cardioverter-defibrillators loop recorders, insulin pumps, cochlear implants, deep brain stimulators and other similar forms of medical or biostimulation implants that have no official labeling of being "MRI safe."

- (Ferromagnetic) foreign bodies (e.g. shell fragments or glass) especially ocular, or metallic implants (e.g. surgical prostheses, aneurysm clips) are also potential risks, and safety aspects need to be considered on an individual basis.

Interaction of the magnetic and radio frequency fields with such objects can lead to: trauma due to movement of the object in the magnetic field, thermal injury from radio-frequency induction heating of the object, or failure of an implanted device. These issues are especially problematic when dealing with the eye.

In 2006, a new classification system for implants and ancillary clinical devices has been developed by American Society for Testing and Materials International and is now the standard supported by the Food and Drug Administration (FDA):



MR Unsafe sign

***MR-Unsafe*:** Nearly self-explanatory, this category is reserved for objects that are significantly ferromagnetic and pose a clear and direct threat to persons and equipment within the magnet room.

MR Conditional sign

***MR-Conditional*:** A device or implant that may contain magnetic, electrically conductive or RF-reactive components that is safe for operations in proximity to the MRI, provided the conditions for safe operation are defined and observed

MR Safe sign

***MR-Safe*:** The device or implant is completely non-magnetic, non-electrically conductive, and non-RF reactive, thereby eliminating all of the primary potential threats during an MRI procedure.

Please note that in all situations, it is the responsibility of each Hospital/Site Investigator to determine the standard Protocol for MRI safety for the subjects involved in this clinical program.

6. MASKING DATA

Bioclinica will maintain subject confidentiality at all times. All site and subject identifiers will be removed before processing at Bioclinica.

6.1. Masking Procedure for Digital Images

Personal identifiers should be removed from both the images and the Digital Imaging and Communication in Medicine (DICOM) header file before submission to Bioclinica. When changing the header information, the technologist should replace the personal information with a unique Pfizer identifier (e.g., 8-digit subject number assigned as part of the clinical study) for subject verification at Bioclinica. Exact procedures for accessing header information will vary depending on the scanner or system. It is crucial to avoid masking any of the imaging parameters that may be embedded in the digital files.

Any personal identifiers that remain on the digital images will be masked by Bioclinica to ensure subject confidentiality at all times.

6.2. Masking Procedures for Film Images

For radiographs only, be sure to complete a film label with the unique Pfizer identifier (e.g., eight [8]-digit subject number assigned as part of the clinical study) before masking the personal information on the film. When masking or blinding personal identifiers, use indelible ink ONLY. Do not use tape, labels, or other devices to mask personal information. Ensure that none of the imaging parameters that are printed on the films are masked.

Any personal data that remain on the filmed images will be masked by Bioclinica to ensure subject confidentiality at all times.

7. IMAGE SUBMISSION

7.1. General

The acquired images are submitted along with the corresponding documentation to Bioclinica for QC and subsequent processing. The following steps outline the modalities for submitting data to Bioclinica for this trial.

7.2. Electronic Submission

The ***preferred*** method for transferring imaging data from the imaging facility to Bioclinica is electronically using Bioclinica's SMART Portal electronic data transfer system. The electronic transfer user guide and Quick Reference Guide provided with the study kit describe the processes for transferring digital images to Bioclinica.

For sites unable to submit electronically, please follow the following instructions.

7.3. Courier Submission

For centers submitting data via courier, please ensure you correctly label your data and submit with a DTF as defined below.

7.4. Data Transmittal Form

For shipping data via a courier, the DTF is a form used to identify image data and provide specific subject and imaging information. The information is critical for optimal image processing. One DTF must be completed and forwarded with every imaging study or modality submitted to Bioclinica.

The comments section on the DTF is provided to document any imaging-specific details that may provide additional information for Bioclinica.

7.5. Labels

All imaging data submitted to Bioclinica must contain a completed study-specific label. The label must be attached to the CD or films.

When completing the labels, care must be taken to ensure that the data entered on the label is consistent with data entered on all corresponding forms (DTFs). An example is provide below.

BIOCLINICA	**Pfizer Protocol #: XXXXXX**
Site ID: _____	**DOB:** _____
Subject ID: _____	**Exam Date:** _____
Visit Number:	

7.6. Courier Air Waybills

All image data must be sent to Bioclinica via the overnight courier selected for this study.

Pre-printed courier air waybills are provided for the submission of image data to Bioclinica. Ensure to keep a copy of the tracking number any time you courier data to Bioclinica.

Log on to the courier website for local pick-up scheduling and information. For international shipping, commercial invoices can be downloaded from the courier website.

7.7. Digital Image

All digital images should be stored in duplicate on two separate CDs in an **uncompressed** or lossless compressed DICOM format or through an alternative long term archival solution implemented at your site. One will serve as the source CD to be stored at the imaging facility and one will serve as the identical copy to be submitted to Bioclinica according to the instructions in Section 7.1.

Imaging data submitted to Bioclinica will be retained for the duration of the study.

CD – Standard writable CDs should be utilized. Always use one storage medium (e.g., one CD) per subject and time point. Radiograph Film Archival (Analog) Data

Imaging facilities using analog films should submit only original films. Film copies are not acceptable (loss of detail occurs when copies are made).

7.8. Digital/Computed Radiograph Data

When printing images to film, the images should be anatomically true-to-size with zero magnification and zero minification (scaled at 100%). Digital data can also be archived to CD in generic uncompressed DICOM format. Please contact the manufacturer or your center's service engineer with any questions regarding this process.

8. IMAGE ARCHIVAL

The source data should remain at the agreed upon location between the clinical site and imaging facility and will serve as the original clinical data or source documentation for the aNGF program (in accordance with ICH/GCP for record retention for research in human subjects).

There are regulations governing the retention of research records and primary trial documentation (source data) in order to protect the rights of the subjects enrolled in clinical trials. Following closure of the study, the principal investigator must maintain all site study records in a safe, secure location. The records must be maintained to allow easy and timely retrieval, when needed (e.g., audit or inspection), and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, of supporting systems, and of staff. Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The investigator must assure that all reproductions are legible, are a true and accurate copy of the original, and meet accessibility and retrieval standards, including regenerating a hard copy if required. Furthermore, the investigator must ensure there is an acceptable backup of these reproductions with an acceptable QC process in place for making these reproductions.

Pfizer will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, or Pfizer standards/procedures. Otherwise, the retention period will default to fifteen (15) years.

9. QUALITY CONTROL

During the course of the study, there may be instances where Bioclinica will need to communicate to you in reference to the imaging data that was submitted. There are two types of data quality correspondence that Bioclinica will send: Quality Control Reports and Data Clarification Queries

9.1. Quality Control Report

Bioclinica's imaging technologist will evaluate the quality of each data set submitted. A QC report listing results of the quality review will be e-mailed to the clinical site within three (3) business days from receipt of data presuming there are no outstanding queries.

The Quality control report will outline if the data was considered acceptable quality for the study. If the data was considered poor quality, supporting feedback will fall into two categories:

- Corrective action may be required to re-submit or re-acquire the image. When there is a corrective action, a DCF will always be raised in parallel (see section 9.2)
- Scope of improvement may be provided and will serve as a reminder of the protocol guidelines and suggest corrective action for a particular aspect of the imaging procedure the next time that subject is imaged **This is are for informational purposes and do not require a response by the clinical site.**

9.2. Data Clarification Queries

This query may request information, such as a clarification of a scan date, or a request for additional data (e.g., when the images are not acquired according to the study-specific Imaging Guidelines). The query will request specific action to correct or clarify the outstanding issue. **These are for clarification and require a response by the clinical site or imaging facility**. The issues indicated on the query must be addressed immediately as they could stop the processing of an image and hold up a subject's dosing or, be needed to inform the Reader of a critical safety issue. A description of the resolution of the problem/issue is to be completed by the site, and each query must be responded to. The site is required to print a copy of the query and provide a response to Bioclinica along with the requested information/data.

Table 1 is a tabulation of some, but not all, types of queries that may be generated (Query Reason/Topic) with specific Comments on what the issue is and any Actions a facility may take to avoid repeats in the future.

Table 1

Query Reason/Topic	Comments	Actions to avoid Query or comment on returned Query
DTF incomplete or not received	DTF identifies the subject, time point, and possibly imaging parameters for the data being submitted	Check shipment package prior to sending; review DTF
DTF and data discrepancies	Information on DTF does not match imaging data (e.g., subject DOB, date of scan)	Site review should compare DTF and imaging data prior to submission if possible
Data not received	Data either missing on digital CD or film was not included with DTF	Confirm data are stored on digital CD prior to shipment
Incomplete data set	Imaging protocol anatomical regions are not submitted or are missing	If not performed, needs to be documented on DCF or comment section of DTF
Technically inadequate imaging – repeat scan	Based on the imaging parameters for the clinical trial, exceptional quality may be required	If unable to improve, document this on DCF or in the comment section of DTF
Follow-up time point does not match screening	Consistency is critical for clinical trials to perform evaluations	Refer to the screening scan for consistency; if not possible, document on DCF or in the comment section of DTF
Missing time point	Tracker received from client indicates a time point was performed, but Bioclinica has not received the image	Ensure that as subjects are scanned, the data is immediately forwarded to Bioclinica

The Imaging Facility can expect to receive three (3) types of data clarification forms from Bioclinica when issues arise that Bioclinica cannot address without documented clarification from the Imaging Facility.

- Discrepant Data: sent if there is any biographical discrepancy, e.g. visit information, exam date.
- Incomplete Package Received: sent if a package was received without any transmittal form, a missing radiograph or incomplete labeling of the X-ray images.
- Rejected Images: Resubmission/Repeat Request: sent in case of poor quality or non-compliance to the study protocol; each repeat has to be submitted with a new transmittal form to Bioclinica. It is very important that responses to the queries issued by Bioclinica are returned within one week of notification. It is

also important that all queries contain an appropriate response to the question(s) asked and that they are signed and dated.

Bioclinica cannot process incomplete queries. If responses are incomplete, another query follow up will be issued to request clarification.

The Investigator site or monitor may become involved as necessary to resolve a query.

10. Technologist Training

Training of the X-ray Imaging technologists is required and may be accomplished in numerous venues through or by:

- Investigator Meeting/Technologist Training venues
- Country-specific regional trainings
- Individual x-ray facility trainings
- A trained and *authorized* (i.e., passed their first test image) surrogate (e.g., x-ray facility manager, supervisor, radiologist).
- A trained and *authorized* facility technologist.

Training in the A409 program is universal, meaning that a technologist trained in one of the venues mentioned above will be permitted to perform imaging in all A409 protocols that require imaging. At all imaging facilities and following their training, technologists must first be assessed for proficiency by submitting their first set of subjects' images to Bioclinica. After undergoing successful quality assessment of the submitted images, an Authorization Letter will be issued to the clinical site giving permission to continue enrolling subjects. The Authorization Letter at a site covers any trained technologist to do any A409 protocol requiring imaging. For example:

- If a clinical site is only conducting the A4091058 study and their technologist has been trained, the clinical site will be issued an A4091058 Authorization Letter. This allows the clinical site to continue enrolling subjects. If in the future another A409 study were to be added at the clinical site, that tech would be authorized, and a study specific Authorization Letter provided to, do imaging for that study as well since the training across the A409 program is the same.
- If a clinical site is only conducting the A4091059 study and their technologist has been trained, the clinical site will be issued an A4091059 Authorization Letter. This allows the clinical site to continue enrolling subjects.
- If a clinical site is conducting both the A4091058 and A4091059 studies and their technologist has been trained, the clinical site will be issued both an A4091058 and an A4091059 Authorization Letter. This allows the clinical site to continue enrolling subjects in both studies.

Study personnel changes (transitions and/or additions) are expected through the duration of a clinical trial. This is also true for the imaging technologists acquiring images in this program. The steps below show the steps that should be followed when you learn of a personnel change (eg, a technologist leaving or a new one joining) at your site:

- Immediately notify Bioclinica of the change and the need to have a new technologists trained. To do this please contact the A409 Bioclinica support team (Pfizer_aNGF_Support@bioclinica.com). In addition, notify your CRA and CMPL.

- Bioclinica will review your facility's image submission history (eg, repeat rate, Authorization Letter) to confirm there have been successful images submitted from your facility to date.
- If your site is confirmed as "authorized," you will be notified that it is acceptable to move forward with allowing site imaging personnel to perform the additional training.
- Once additional training has been completed, please provide a record of the training to the Bioclinica team (Pfizer_aNGF_Support@bioclinica.com). If needed a training form to record this training can be provided to you by the Bioclinica personnel.
- The newly trained technologist will be added to your site's training record at Bioclinica and an updated Authorization letter adding this new technologist will be provided to your site.
- Once received, this additional technologist will be able to acquire X-rays at your site.

11. BIOCLINICA AND SUPPLY CONTACT INFORMATION

For study assistance email or call our Help Desk, 24 hours a day, 7 days a week:
US and Canada sites dial: 1-888-ASK-BIO2 (1-888-275-2462)
International sites dial: +1-267-757-3330
E-mail: helpdesk@bioclinica.com

International AT&T Direct Access codes and dialing instructions can be found at http://www.business.att.com/bt/access.jsp.

Re-order supply forms have been provided in the Imaging Binder if additional study materials or supplies are needed.

12. STUDY KIT CONTENTS

Various supplies have been provided, in the form of an Imaging Kit, to assist each clinical site with the submission of image data to Bioclinica.

- Imaging Binder for storage of study-related forms and documents
- Imaging and Submission Guidelines (this document)
- Electronic Data Transfer User guide (SMART Portal)
- Quick reference guides (QRG)
- Labels
- Data Transmittal Forms
- Sample forms
- Pre-addressed courier air waybills
- Re-order Supply Form
- Mailer envelopes
- Training video/DVD
- Synaflexer™ (knee radiograph positioning device)
- Bioclinica wood platform and step
- Lead marker kit

13. REFERENCES

1. Merrill's Atlas of Radiographic Positioning and Procedures
Eleventh Edition, Volume 1
Eugene D. Frank, Bruce W. Long, Barbara J. Smith

14. IMAGING GUIDELINES SIGNATURE PAGE

Protocol Number: Pfizer aNGF Program

Title of Protocol: Tanezumab Phase 3 clinical program in Osteoarthritis (OA), Chronic Low Back Pain (CLBP), and Cancer Pain clinical trials.

Final Version 2.0 13April2016

Pfizer has reviewed this Imaging Guideline and agrees to the content herein that the procedures and processes outlined in this Imaging Guideline satisfy all Pfizer required site and imaging requirements. Any major changes to this Imaging Guideline, either those initiated by Pfizer or Bioclinica, will be addressed in writing, amended to the Imaging Guideline and contract (if necessary), and agreed to by both parties.

For Pfizer:

By: _____	By: _____
Name: Ray S. Clemmer, MS	Name: Sarah Sherlock, PhD
Title: Tanezumab Imaging Lead	Title: Tanezumab Imaging Lead
Date: _____	Date: _____

For Bioclinica, Inc.:

By: _____	By: _____
Name: Mark W. Tengowski, DVM, MS, PhD	Name: Michelle Montalto
Title: Scientific Director, Musculoskeletal Medical Affairs	Title: Global Program Manager
Date: _____	Date: _____
By: _____	By: _____
Name: Sonia Morges	Name: Ami Marano
Title: X-Ray Imaging Analysis Technologist	Title: MR Imaging Analysis Technologist
Date: _____	Date: _____