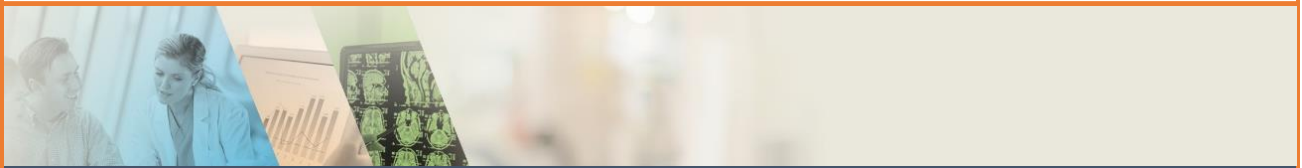




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X-Ray and MRI Imaging and Submission Guidelines

Regeneron Pharmaceuticals, Inc.
Protocol R475-OA-1611

Regeneron Pharmaceuticals, Inc Protocol R475-OA-1611

**A Phase 3 Randomized, Double-Blind, Multi-Dose, Placebo and Naproxen-
Controlled Study to Evaluate the Efficacy and Safety of Fasinumab in Patients
with Pain Due to Osteoarthritis of the Knee or Hip**

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1 LIST OF ABBREVIATIONS AND ACRONYMS

AP	Anterior/posterior
AWB	Air waybills
CR	Central Ray
CD-ROM	Compact Disk – Read Only Memory
CRA	Clinical Research Associate
CRF	Case Report Form[s]
CRO	Contract Research Organization
DCF	Data Clarification Form
DICOM	Digital Imaging and Communication in Medicine
EC	Ethics Committee
eCRF	Electronic Case Report Form
ET	Early Termination
FDA	Food and Drug Administration
FOV	Field of View
FTP	File Transfer Protocol
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IMD	Intermargin Distance
IRB	Institutional review board
IR	Imaging Receptor
JRE	Java Runtime Environment
KLG	Kellgren and Lawrence Grade
MRI	Magnetic Resonance Imaging
PA	Posterior/anterior
PACS	Picture archiving and communication system
PI	Principal Investigator
PTQ	Pre-Trial Questionnaire
QA	Quality Assurance
QAR	Quality Assessment Report
QC	Quality Control
QRG	Quick Reference Guide
TF	Transmittal Form
UDF	Universal Disk Format
UPS	United Parcel Service
US	United States

2 INTRODUCTION

The purpose of this manual is to standardize the imaging acquisition procedures among the sites participating in the Regeneron Protocol R475-OA-1611, “**A Phase 3 Randomized, Double-Blind, Multi-Dose, Placebo and Naproxen-Controlled Study to Evaluate the Efficacy and Safety of Fasinumab in Patients with Pain Due to Osteoarthritis of the Knee or Hip**”. The latest version of the protocol should be consulted for overall inclusion/exclusion criteria and other study details.

All radiologists and technologists contributing to this study are expected to have had appropriate theoretical and practical training in X-RAY and MRI. Study personnel should also satisfy all local requirements for radiology licensing and registration. The qualified radiology personnel are the first step toward the successful use of imaging in the REGENERON R475-OA-1611 study. The procedure manual is designed for the study coordinator and X-RAY and MRI technologists involved in this project. A Quick Reference Guide for X-RAY and MRI acquisition will be provided in a separate document. All new personnel, who join the study after site initiation, are also required to complete training, read and understand the manual.

This manual, taken alone, should not be considered as sufficient training in proper techniques for acquiring or reading of X-RAY or MRI images. The goal of this manual is to define a standard approach to performing X-RAY and MRI that produces images of sufficient quality for achieving the study goals.

Questions regarding this manual, X-RAY or MRI techniques should be directed to:

Primary Contact:

REGENERON R475-OA-1611 (5288) Study Team
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Newark, CA 94560 USA
Email: Regeneron1611@Bioclinica.com

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Newark office HOURS: 8:00 – 17:00 (Pacific Standard Time)

Help Desk HOURS: 24 hours a day call 1-888-ASK-BIOC (888-275-2462) Option 1

3 General Study Information

3.1 Protocol Synopsis

The purpose of this randomized, double-blind, placebo- and naproxen-controlled study is designed to evaluate the efficacy and safety of fasinumab in patients with OA of the knee or hip who have a history of intolerance to or inadequate pain relief with acetaminophen/paracetamol and opioids (or are unwilling to take opioids or have lack of access to opioids). This study will compare the efficacy and safety of fasinumab with placebo and with naproxen, a commonly used member of the class of NSAID medications used for moderate-to-severe pain due to OA. Enrollment of approximately 3640 subjects is planned for this study. Randomization will be stratified according to the affected index joint (hip or knee), the Kellgren-Lawrence (K-L) score (2 to 3 or 4) at the screening visit, and geographical region.

3.2 Expected Radiographic Views

Radiographs of the shoulders hips and knees will be performed in the following manner:

- *Shoulders*
 - Left and right shoulder radiographs will be acquired standing using the Grashey view. Each shoulder will be imaged separately.
- *Hips*
 - Left and right hip radiographs will be acquired in the AP projection and frog-leg lateral projection. If the subject cannot achieve the frog-leg position, a cross-table lateral femur scan can be substituted. Each hip will be imaged separately.
- *Knees*
 - Left and right knee radiographs will be acquired in the PA projection using the standing, semi-flexed fixed flexion method of positioning. In order to ensure adequate images for precise measurement of changes in knee joint space width, subject positioning is aided by use of the SynaFlexer™ positioning device. Acquisition of images may be performed at multiple x-ray beam angles to ensure optimal alignment of the medial tibia plateau. The target criterion is an inter-margin distance between the projected anterior and posterior rims of the medial tibia plateau less than 1.5 mm.

3.3 Expected MRI Sequences

After the patient has otherwise met study eligibility criteria assessed during the screening period, an MRI must be performed before the pre-randomization visit for the index and contralateral joint as well as any knee or hip joint that has a baseline K-L score ≥ 3 .

Expected MRI sequences are shown in the table below. The joint MRI protocols mimic typical clinical protocols and equivalent sequences of diagnostic quality will also be acceptable.

Expected MRI Sequences

Anatomical Region	Required Sequence
Knee (each knee imaged alone)	Coronal 2D T1-weighted FSE Coronal 2D PD-weighted FSE fat sat Sagittal 2D PD-weighted FSE fat sat
Hip (both hips imaged together)	Coronal 2D T1-weighted FSE Coronal 2D STIR Axial PD-weighted FSE fat sat
Shoulder (each shoulder imaged alone)	Oblique coronal 2D PD-weighted FSE Oblique coronal 2D PD-weighted FSE fat sat Oblique sagittal 2D PD-weighted FSE

Bioclinica will prepare a series of imaging guidelines and quick reference guides (QRGs) customized to the study. The QRGs will include:

- Detailed descriptions of the images to be acquired including radiographic projection and coverage and, for MRI, the pulse sequence parameters, slice orientation, slice thickness and coverage
- Techniques for accurate and reproducible subject positioning, proper anatomical coverage, imaging parameters and printing of film images (if applicable)
- Instructions for labeling electronic media with unique, anonymous subject identifiers
- Information on archiving of digital data
- Instructions on completing the transmittal form and data transportation to Bioclinica

3.4 Imaging Time Points

The required X-ray and MRI images obtained for subjects enrolled in the R475-OA-1611 protocol must be archived and forwarded to Bioclinica for processing immediately following acquisition. It is the Principal Investigator (PI) site's responsibility to ensure that any images acquired for this protocol are sent to Bioclinica either by the site or the imaging facility. The PI site is responsible for checking any queries for submitted images have been addressed and followed up on.

Table 1: Screening Period through End of Treatment Period

Imaging Procedure	Screening Period	Treatment Period	Treatment Period	Follow-up Period	Early Termination	JR Pre-Operative ³
Study Week		Week 16	Week 52	Week 72		
Left and right radiographs of knees, hips, and shoulders ^{2,4}	X	X	X	X	X	X
MRI of index joint and contralateral joint as well as any knee or hip with baseline K-L ≥ 3 ¹	X					
Event-triggered imaging ²	On-going					

1. After the patient has otherwise met study eligibility criteria assessed during the screening period, an MRI must be performed before the pre-randomization visit for the index joint and contralateral joint as well as any knee or hip joint that has a baseline K-L score ≥ 3 . Confirmation that the image has been accepted and confirmed query-free by the central reader must be received by the site before the pre-randomization visit. Confirmation from the central reader that there are no exclusionary findings on the MRI must be received before the patient can be randomized.
2. In addition to scheduled imaging, an X-RAY and/or MRI should be considered for any joint following a report of clinically significant worsening or exacerbation of pain in that joint. This imaging will be submitted to the adjudication committee for review as an Event Driven visit. In cases where the joint had previously been treated with TJR surgery, an MRI is not required.
3. Pre-operative imaging for any TJR should be submitted for adjudication, if possible.
4. An MRI may be requested at any follow up visits after review of the X-RAYs.

Table 2: Follow-up for Patients Who Undergo Total Joint Replacement Surgery

Imaging Procedure	Long-Term
Visit	Post-Op Week 20 20 weeks after the date of the joint replacement surgery
Follow -up Study Day	Follow-up Day 140 (± 7)
Left and right radiographs of knees, hips, and shoulders ¹	X
Event-triggered imaging ²	Ongoing

1. An MRI may be requested after review of the x-rays
2. An X-ray and/or MRI should be considered for any joint following a report of clinically significant worsening or exacerbation of pain in that joint. This imaging will be submitted to the adjudication committee for review as an Event Driven visit. In cases where the joint had previously been treated with TJR surgery, an MRI is not required.

3.5 Imaging for Eligibility

During the Screening period, left and right radiographs of the knees, hips, and shoulders will be acquired. All images will be assessed by an independent central radiologist (hereafter referred to as the central reader) to determine radiographic eligibility for study participation. An MRI must be performed for the index joint and contralateral joint as well as any knee or hip joint that has a baseline K-L score ≥ 3 and assessed by the central reader.

- Confirmation that the image has been accepted and confirmed query-free by the central reader must be received by the site before the pre-randomization visit.
- Confirmation from the central reader that there are no exclusionary findings on the MRI must be received before the patient can be randomized.

The radiologic subject inclusion criteria is as follows:

Clinical diagnosis of OA of the knee or hip based on the American College of Rheumatology criteria with radiologic evidence of OA (K-L score ≥ 2) for the index joint at the screening visit.

- The index joint is defined as the joint with OA under evaluation for this study
- A joint previously treated with joint replacement surgery cannot be the index joint
- A joint previously surgically modified within the past year cannot be the index joint (with the exception of cruciate ligament reconstruction surgery, patellar fracture repair surgery, or meniscal repair)
- If a patient has a K-L score of ≥ 2 at more than 1 knee or hip joint, the index joint with the joint with the greatest WOMAC pain subscore at the screening visit
- If 2 or more knee or hip joints have a K-L score of ≥ 2 and the same WOMAC pain subscore, the index joint is the joint with the greater K-L score
- If 2 or more joints have a K-L score of ≥ 2 , the same WOMAC pain subscores, and the same K-L scores, then the investigator may choose 1 of these joints as the index joint

Subject Exclusion based on imaging:

- History or presence on imaging of arthropathy (osteonecrosis, subchondral insufficiency fracture, rapidly progressive osteoarthritis type 1 or type 2), neuropathic joint arthropathy, hip dislocation (prosthetic hip dislocation is eligible), knee dislocation (patella dislocation is eligible), extensive subchondral cysts, significant bone collapse, significant bone loss, or pathologic fractures.
- History or presence on imaging of arthropathy (osteonecrosis, subchondral insufficiency fracture, rapidly progressive OA type 1 or type 2), neuropathic joint arthropathy, hip dislocation (prosthetic hip dislocation is eligible), knee dislocation (patella dislocation is eligible), extensive subchondral cysts, significant bone collapse, significant bone loss, or pathologic fractures.
- Trauma to the index joint within 3 months prior to the screening visit
- Patient is not a candidate for MRI

3.6 Eligibility Reporting

An eligibility report will be sent to the investigator summarizing the results of the X-Ray central assessment of eligibility. A second eligibility report will be sent to the investigator summarizing the results of the MRI central assessment of eligibility.

The results of the eligibility review will be sent directly to the Principal Investigator and Study Coordinator via e-mail within 3 business days following receipt of a complete and query free image set at Bioclinica.

3.7 Site Start Up Check List

Please use this checklist to make sure you are prepared to examine the first subject and that all necessary documentation is in place. It is the responsibility of the lead technologist to ensure that the imaging protocol is followed as well as to ensure that other technologists acquiring images for this study read and understand the procedures detailed in this manual.

	Action	Comment
<input type="checkbox"/>	The Pre-Trial Questionnaire will be collected from each facility participating in the study prior to the beginning of the trial.	Questionnaire to be sent to Bioclinica by E-mail
<input type="checkbox"/>	It is preferred that all sites send images using SMART submit, Bioclinica's web based image transfer portal. Please provide first name, last name and email address of the personnel that will need access.	Enter this information on the The Pre-Trial Questionnaire
<input type="checkbox"/>	Review the supply package contents to ensure receipt of all study materials.	The supplies enclosed are as follows: <ul style="list-style-type: none"> • SynaFlexer™ Knee positioner • X-RAY and MRI Imaging and Submission Guidelines • X-RAY and MRI Quick Reference Guide • Pre-Printed airway bill (AWB) • Transmittal Forms for X-RAY and MRI
<input type="checkbox"/>	Please ensure that all applicable study personnel read this Procedure Manual and QRG.	
<input type="checkbox"/>	Complete the study specific online training for X-RAY and MRI image acquisition. An email invitation to complete the self-directed online training will be sent to the lead technician (s) as indicated on the Pre-Trial Questionnaire.	It is expected that at least one lead technologist involved in the study will complete the online training for X-RAY and MRI acquisition.
<input type="checkbox"/>	After completion of the study specific online training, print and file a copy of the completion certificate for documentation of training per your local regulatory requirements.	

4 Study Roles and Responsibilities

The activities of collecting and analyzing the imaging data for the study are divided between the clinical site, the clinical imaging facility and Bioclinica. Below is an overview of roles and responsibilities as handled by various parties. Note however that the Principal Investigator, Study Coordinator, and X-RAY and MRI Center technologist(s) should agree in advance on their workflow.

4.1 Principal Investigator (PI) or Designee

The PI has overall responsibility for the study at each clinical site and will ensure that clinical site personnel under his/her direction have all the necessary information and resources to properly execute the required study procedures.

The PI determines whether the patient is eligible and can be included in the study and is ultimately responsible for the safety of the patients in the study.

The PI's responsibilities include the following:

- Ensure the patient has been adequately informed of the details of this study and has given and signed their consent to participate prior to commencing of any study related procedures
- Ensure that the patient meets all criteria for the X-RAY and MRI
- Refer the patient to the cooperating imaging facility with all necessary documents, including those provided by the sponsor, to allow correct patient identification, including subject ID and year of birth.
- Ensure that queries sent by Bioclinica to the site are completed. The completed queries should contain the signature of either of the following parties
 - The Principal Investigator (PI)
 - An approved clinical site representative
 - A sub-investigator
 - The study coordinator

The signed queries should be returned to Bioclinica in a timely manner. These queries are initially emailed from Bioclinica to the study coordinator as a data clarification form (DCF).

- The PI, or designee, is responsible for ensuring that the quality standards as outlined in this manual are followed.

4.2 Study Coordinator or Designee

In general terms the Study Coordinator's role is to facilitate communication among Principal Investigator, X-RAY imaging facility, MRI imaging facility, Bioclinica and the Sponsor. In addition they ensure that all procedures associated with each visit have been carried out and associated records completed, distributed and filed appropriately.

In particular, the responsibilities of the Study Coordinator at the clinical site include the following:

- Serve as liaison between clinical site and imaging facility
- Follow up with the imaging facility on a regular basis in order to help facilitate the required items for start-up

- Confirm the receipt of Bioclinica supplies and distribute supplies to the appropriate study personnel based on their roles in the image data acquisition and submission process
- Schedule exams in conjunction with the X-RAY and MRI imaging facility and ensure that a Transmittal Form with demographic and visit information is available at the X-RAY and MRI imaging facility at the time of the exam
- Establish a joint process with the X-RAY and MRI imaging facility for sending digital images and the completed Transmittal Form (referred to hereafter as “package”) to Bioclinica
- Confirm image acquisition was completed and sent to Bioclinica within one (1) business day




The imaging study should be sent to Bioclinica within one (1) business day after the exam!

- Respond to queries about all missing data including image-related data issued by Bioclinica within 1 (1) business days
- Maintain all study records in compliance with sponsor and regulatory requirements
- Facilitate prompt and direct communication between Bioclinica and clinical site personnel when a clinical site requires assistance or consultation

4.3 X-RAY and MRI Imaging Facility Personnel

The major responsibilities of the Imaging Facility personnel include the following:


- Perform radiological examinations according to the procedures detailed in this manual ensuring consistency (i.e. anatomical coverage, use of positioner, etc.) across patients and across visits for a given patient
- Verify that patient demographic information and exam information captured on the Transmittal Form are entered completely and correctly on the electronic image file headers
- Retain a complete archive of the acquired raw data at the facility
- Establish with the study coordinator a joint process for sending data to Bioclinica
- Submit acquired data to Bioclinica via SMART submit or on approved digital media along with corresponding Transmittal Form(s) within one (1) business days of the examination and verify completeness of packages to be sent to Bioclinica upon acquisition of the exam
- **The imaging facility must designate a single Primary Technologist to work on this study.** The responsibility of the Primary Technologist is to ensure that the imaging protocol is followed and other technologists working on this study are qualified to perform the required imaging. and study specific training documentation exists for the technologists working on the trial.
- The imaging facility is responsible for notifying Bioclinica when there is a change in the Primary Technologist and ensuring that all required training is completed so that Bioclinica can notify CRO and Regeneron.
- The facility is considered authorized to conduct the imaging of the first patient-visit after the Primary Technologist completes the online training and prints and files the certificate. Upon approval of the first patient-visit, the imaging facility will be considered qualified for this study.

	<p>Acquisition of radiographs of acceptable quality is an important responsibility of the imaging facility.</p> <p>If you change your equipment during the course of the study, please contact Bioclinica before you do so. We need to evaluate the new equipment to make sure it meets the requirements of this study.</p>
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4.4 Bioclinica

Bioclinica is the central imaging service company for this study. Bioclinica's main responsibilities are outlined below:

- Qualify the imaging facilities and provide training for X-RAY and MRI image acquisition according to procedures and protocols outlined in this manual
- Check incoming packages for completeness and correctness
- Inform the X-RAY and MRI Imaging facility by emails about any issues related to data within three 3 business days of receipt
- Receive and track demographic data and identify data discrepancies
- Review, assess, and monitor the quality of the exams
- Provide clinical sites with a Quality Assessment Report by email for each patient-visit within 3 business days of receipt of a complete package
- Should the initial radiograph be of unacceptable quality, BioClinica will notify the center by email within 3 days of receipt of scan. The center will be instructed how to obtain a second radiograph or MRI
- Archive images and associated study information
- Perform central imaging analysis of X-RAY and MRI data

	<p>Bioclinica does not read images for the purposes of clinical evaluation or patient treatment. Clinical management is the sole responsibility of study patient's locally licensed physicians.</p>
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4.5 Study Supplies

Bioclinica supplies clinical sites with the following study materials:

- Synaflexer™ knee positioning device for X-RAY
- X-RAY and MRI Imaging and Submission Guidelines: one copy each for the radiology/clinical imaging facility or facilities
- X-RAY Quick Reference Guide (QRG): a laminated guideline that summarizes the most important acquisition parameters and data shipment information.
- MRI Quick Reference Guide: a laminated guideline that summarizes the most important acquisition parameters and data shipment information. The MRI QRG sent to the facility is dependent on the field strength of the scanner: either 1.5T or 3T.
- X-RAY and MRI Transmittal Forms: This form must be sent to Bioclinica per subject per visit if sending images via courier.
- Pre-printed air waybills

Please note that courier envelopes for shipment are not provided. Envelopes can be ordered from the courier when scheduling a pick-up.

To request more study supplies, please make a copy of the Supply Order Form at the back of this manual and email it to Bioclinica. Supplies will be sent as soon as possible. Please plan ahead for imaging material needs.

4.6 Technologist Training

SMART Start:

Web training is the primary method of training for this study. There must be a designated Primary Technologist at the facility that will complete the online training. Access details to the SMART Start web portal will be provided via email to all of the imaging technologists listed as working on this study protocol on the Pre-Trial Questionnaire after the PTQ is reviewed and approved by Bioclinica.

It is the responsibility of the Primary Technologist that all technologists working on this protocol are trained on the imaging parameters and requirements. If there is a change to Primary Technologist at the imaging facility it is the responsibility of the imaging facility to notify Bioclinica of the change and confirm that training was completed so that Bioclinica can notify Regeneron and CRO.

Technologist Re-Training:

As part of Bioclinica's contracted, ongoing site support, sites are contacted on an as needed basis by the Bioclinica team when issues are noted with images received. If sites are identified for re-training the technologists at the imaging facility will be contacted by email to complete the SMART Start training again.

Sites that do not show improvement after in their image acquisition and repeat rate completing the re-training via SMART Start will be contact to complete a telephone based training with a Bioclinica imaging technologist.

5 X-RAY and MRI Imaging Facility Qualification and Initiation

5.1 Pre-Trial Questionnaire

All facilities identified as potential imaging centers for this study should complete and submit to Bioclinica the pre-trial X-RAY and MRI questionnaire. Based on the information in the questionnaire the facilities will be chosen for training and initiation for this study. The following requirements should be met before the imaging site personnel is trained:

- Availability of a X-RAY device meeting Bioclinica's approval. If digital, the device must meet Bioclinica's minimum standards for pixel spacing and resolution.
- Availability of a 1.5T (or a 3T) MRI scanner meeting Bioclinica's approval
- Images generated should be of DICOM format
- Digital archival capabilities at the imaging center



To be qualified for this study, the imaging personnel should be able to implement the X-RAY and MRI image acquisition protocol specified by the technical parameters listed in this manual.

5.2 Digital Equipment – X-ray

Digital equipment (computed radiography or digital radiography) may be used. The overall purpose of the assessment of X-RAY equipment is to reduce measurement noise and to minimize differences between sites that could induce measurement errors.

Once the equipment is qualified, it is required that it be used throughout the duration of the study. It is important to not have changes in the operational version during the study. Bioclinica should be notified before any significant hardware changes and/or software upgrades are performed during the study period.

Following the upgrade, Bioclinica will need to evaluate the new equipment/software to ensure study requirements are met. Bioclinica must give the written approval by email before patient imaging is resumed. Please pay attention to the following:

- Spatial resolution must be 100-150 microns
- Gray scale value minimum 12 bit images
- Data should be stored in uncompressed DICOM 3 format.
- Ensure protection of subject information in the electronic header
- For transferring data to Bioclinica, it is preferred that you use SMART submit (see Appendix V)
- If SMART submit can't be used then data may be sent on CD-ROM
- The digital acquired data must be submitted as DICOM files. In the rare case that you are unable to do this, please contact Bioclinica.

5.3 Labeling Patient Exams in Electronic Header

The examination description should include "REGN Protocol 1611".

To preserve patient anonymity and protect patient confidentiality, only the study identifiers should appear in the images. Names and personal ID numbers (for example, Social Security numbers or Medical Record numbers) should NOT be used. The main patient identifiers are the Site Number, Patient ID Number, and Date of Birth (according to local requirements).

The following information should be entered through the scanner or PACS console (depending on the system, the field names may differ from the examples below):

- **"Patient Information"** enter the 3-digit Country Code, 3-digit Site Number followed by the 3-digit Subject Number

Example:

123101-001

- **"Date of Birth"** enter **DD-MMM-YYYY***

Example:

07-MAY-1945

Example for countries not allowed to record DOB:

01-JAN-1945

- **"Patient History"** enter: **Visit Name (Visit and Laterality if applicable)**

Example:

Screening, Left

**Please enter the date of birth as indicated. If regulations prohibit your site from entering the day and month of the date of birth please enter 01 JAN and the correct Year of Birth for the subject. The Year of Birth must be the actual year for the subject.*

6 Procedures and Techniques for MRI

Refer to separate MRI Quick Reference Guides for the specific requirements for MRI acquisition of the hips joints, knee, and shoulder. The QRG used is specific to the field strength of your scanner, either 1.5 T or 3T. The titles and versions of the QRGs are referenced in Appendix II of this document. The image quality criteria in a clinical trial are stricter than in a standard clinical practice. The reliable evaluations of MRI mages require adherence to the standardized acquisition protocol and pre-defined quality standards.

7 Procedures and Techniques for X-RAY

In this section the specific requirements are presented for X-RAY examination of the knees. The image quality criteria in a clinical trial are stricter than in a standard clinical practice. The reliable evaluations of X-RAY images require adherence to the standardized acquisition protocol and pre-defined quality standards.

7.1 Exposure Technique for Knee Radiographs

Imaging System	Bucky	Recommended
Focus-Film Distance (FFD)	47" (120 cm)	<i>Required</i>
Film Size	10"x12" (24 x 30 cm)	<i>Required</i>
mAs	Dependent on Film/Screen system	
KVp Range	70-76 kVp	Recommended
Focal Spot	Small	Required
Other	Use Right/Left Lead Markers	<i>Required</i>
Beam Angle	10 degrees caudal to start, if it is not the correct angle (tibial plateau not flat and IMD > 1.5mm use 8 degrees and 12 degrees	<i>Required</i>
Joint Replacement	In the case of Knee Total Joint Replacement or below the knee amputee the following views of the knee are required: Weight Bearing PA – use the same parameters as when acquiring PA knee radiographs but acquire a single weight bearing exposure; the modified Lyon Schuss technique is not required. Instead, the subject should be standing with the knee joint fully extended.	

7.2 Knee Positioning using the SynaFlexer™

Radiographs of both knees will be acquired using this protocol in all patients at screening. For all radiographs, please concentrate on image quality and optimum positioning of the patients.

- The anterior wall of the SynaFlexer positioning frame (provided by Bioclinica) must be in direct contact with the bucky, cassette holder or reclining table top of the radiographic unit such that there is no angle or gap between them. Lower the bucky or cassette holder so that the center of the film will be at the level of the patient's tibiofemoral joint line.
- Position the patient in a standing upright position on the frame facing the bucky, cassette holder or reclining table top.
- Center the knee on the film and center the beam on the knee (**not** on the column of beads). Be sure the beads are visible on the film. (Figure 1)
- The great toes of both feet are placed in contact with the anterior wall of the frame.
- Both feet are fixed in external rotation by pressing the inner aspects of the foot and heel against the V-shaped support on the base of the frame.
- Both knees are flexed until they touch the anterior wall of the frame. This fixes the angulation of the tibias.
- With the great toes and knees still touching the anterior wall, both thighs are also pressed directly against the wall to fix the angulation of the femurs (Figure 2).
- Gently guide the patient forward with your hand in the small of the back to ensure firm contact of both thighs with the wall of the frame. **IMPORTANT:** the toes, knees and thighs must all be in firm contact with the wall of the frame in order for knee flexion to be reproduced exactly on follow-up radiographs.
- Body weight is distributed equally between the two legs.
- Shield the patient's gonads with a half apron



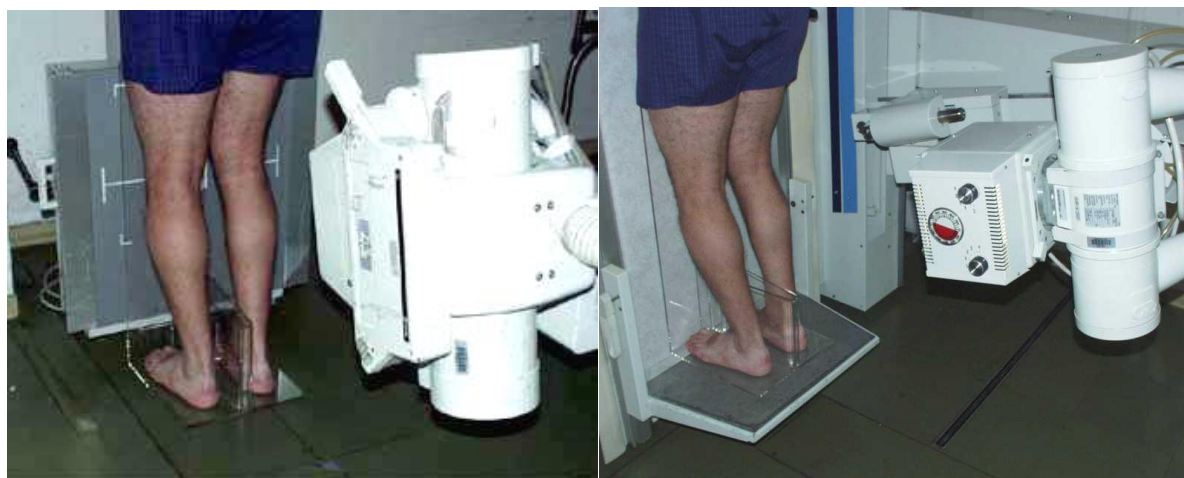


Figure 1: Proper patient positioning and beam angulation for radiography of the knee. The left panel shows proper positioning against a Bucky. The right panel shows proper positioning with a reclining table unit.

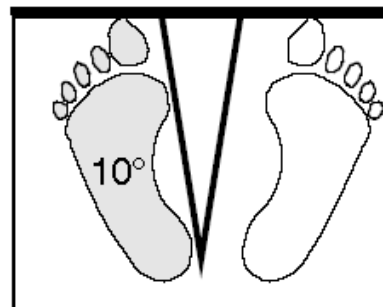
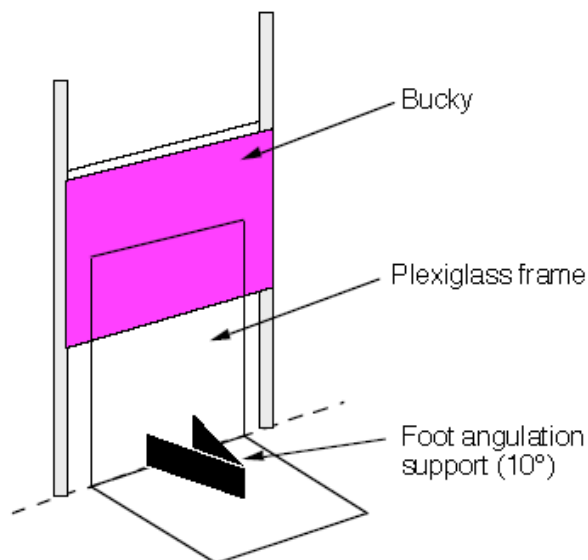


Figure 2: SynaFlexer for reproducible feet fixation and knee flexion. The frame is positioned with its anterior wall in direct contact with the Bucky, cassette holder or reclining table top such that the **target knee** is **centered** on the film. With the great toes touching the anterior wall of the frame, both feet are fixed in external rotation by pressing them against the V-shaped support on the base of the frame. Body weight is distributed equally between the two legs.

7.3 Positioning the X-RAY Tube for Knee Radiographs

- Angle the x-ray tube to 10° caudal centered at the level of the joint line in the popliteal space to start. If that is not the correct angle, and the tibial plateau not flat and IMD is > 1.5 mm, adjust to angle to 8° or 12° (Figure 3)

Beam centering above or below the knee crease will alter the projection of the tibial rims and the joint space on the radiograph and deteriorate the reproducibility of serial measurements. Accordingly, precise beam centering and angulation is critical to the success of the study.

- Collimate to the size of the film. Make sure both columns of beads are included in the image.
- Use a lead (R or L) marker and place it PA on the cassette close to the knee but where it will not obscure the knee anatomy. Properly collimated images will include the entire femoral and tibial metaphysis, the head of the fibula, **at least** 5 vertical sets of metal beads of the SynaFlexer, and the lead laterality marker.
- Expose each knee on a separate **10"x12" (24 x 30 cm)** film.

Special Remarks

- If a patient was difficult to position or has a special consideration, please relay that information in the "comments" section of the Transmittal Form. Bioclinica may decline to request a repeat if the patient's knee posed a difficult positioning situation that would most likely not be corrected with another attempt.

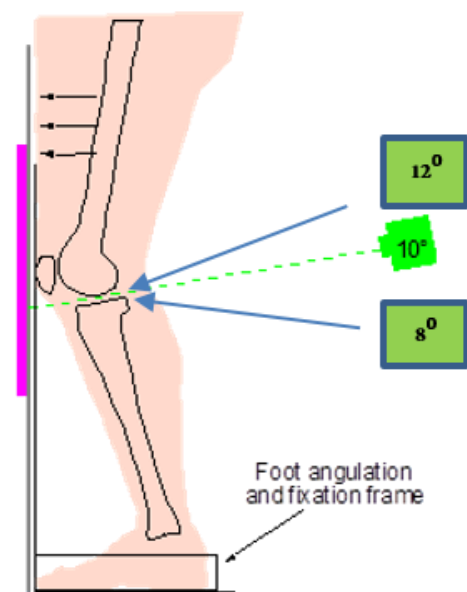


Figure 3: Proper patient positioning and beam angulation for radiography of the knee. Pressing the thigh against the anterior wall of the SynaFlexer and gently pushing the patient forward with a hand in the small of the back fixes the degree of flexion of the femur. Reproducible positioning of the foot in 5° external angulation is maintained using the V-shaped support on a Plexiglas frame. Position the tube so that the X-ray beam is centered on the joint line of the knee in the popliteal space with 10° caudal angulation to start.

7.4 Criteria of Good Quality Knee Radiographs

- Knee joint space must be centered from top-to-bottom- and side-to-side- on the film
- No evidence of subject movement (image only one knee at a time).
- R or L marker must be present and markers should not obscure any anatomy.
- Outer margins of femur and tibia clearly visible.
- Both rows of calibration beads from Synflexer unit must be visible on radiographs.
- The tibial spines should be centered within the femoral condyle notch. There should be no internal or external rotation.
- Knee joint including 10 cm (5 calibration beads) above and below joint space must appear centered on image.
- Check the images by measuring the Intermargin Distance (IMD) of the medial tibial plateau.
- At the mid-point of the medial tibial compartment, the upper and lower margins of the medial tibial plateau must be superimposed or as close as possible to each other (i.e. ≤ 1.5 mm of separation).

7.5 Examples of Knee Projection

For examples of acceptable and unacceptable quality posterior-anterior knee radiographs, see the following pages.

Figure 4: Example of Good Quality

- Medial tibial plateau flat, good positioning and correct angulation of the tube (10° caudal)
- Both columns of the frame beads are visible at the medial margin of the image (medial of the knee)
- Radio-opaque ruler is visible on the film (between both lines of beads)
- Right lead marker properly positioned
- Collimation to the size of the film (frame beads not obscured)



Figure 5: Inappropriate Positioning I

- External Rotation (position of the patella),
- Tibial plateau is not flat and cortical rims poorly aligned
- Incorrect beam angle determined by the position of the double row of beads on the SynaFlexer
- Incorrect centering (joint space of the knee is not in the middle of the cassette)



Figure 6: Inappropriate Positioning II

- Internal rotation
- Medial tibial plateau is not perfectly flat
- Incorrect angulation (> 10 degrees), recognized by the incorrect alignment of the beads



Figure 7: Incorrect Beam Centering

- Incorrect centering of x-ray beam
- Medial tibial plateau is not flat
- None of the two lines of beads is depicted (these should be visible at the medial margin of the image/ medial side of the knee)
- Radio-opaque ruler is missing
- Left/Right Marker is missing



Figure 8: *Incomplete depiction of the frame beads*

- Only one line of the frame beads is depicted (both lines must be visible)
- Radio-opaque ruler is missing
- Underexposure
- Side marker is missing



Figure 9: *Incorrect positioning / beam angulation and Repeat Examination***UNACCEPTABLE:
REPEAT REQUESTED**

- Incorrect angulation of the x-ray tube (more than 10°, recognized by the incorrect alignment of the beads)
- Incorrect positioning
- Missing side marker

**ACCEPTABLE REPEATED IMAGE**

- The x-ray beam was angled correctly
- Both columns of the frame beads are visible
- Side marker on the film
- Medial plateau is flat



7.6 Intermargin Distance (IMD) X-Ray Examples

A perfect IMD is an IMD in perfect alignment, which is an $\text{IMD} = 0 \text{ mm}$; however, a variance between 0 and 1.5 mm will be acceptable. The IMD is always measured at a point approximating the midpoint of the medial tibial plateau. The following examples showcase various IMDs.

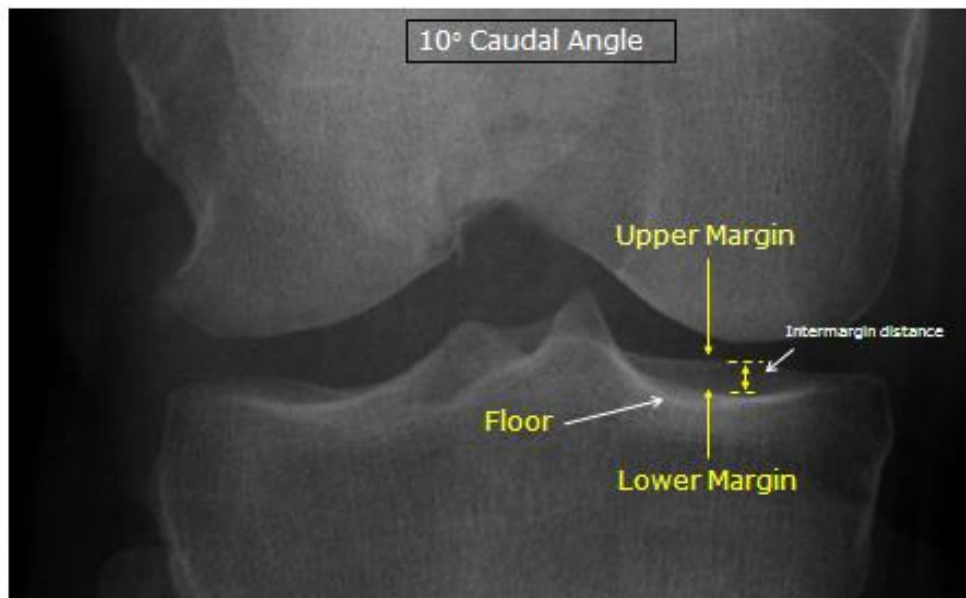


Figure 10: A 10° caudal image with an $\text{IMD} > 1.5 \text{ mm}$

Not ideal for measuring joint space width. Must improve by bringing margins to $\leq 1.5 \text{ mm}$ in next image. Need to change angle to improve IMD.

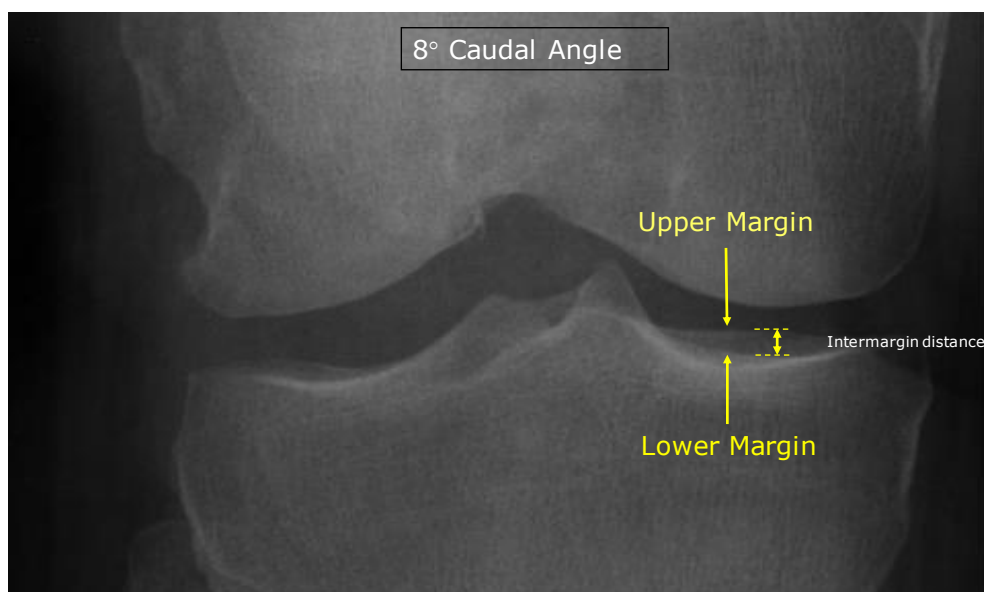


Figure 11: X-Ray Image with a tube angle of 8 degrees

An x-ray tube angle change to 8° caudal seems to improve the IMD but still remains $> 1.5 \text{ mm}$. Since an 8° angle appears to be improving the IMD continue to reduce the tube angle for the next image.

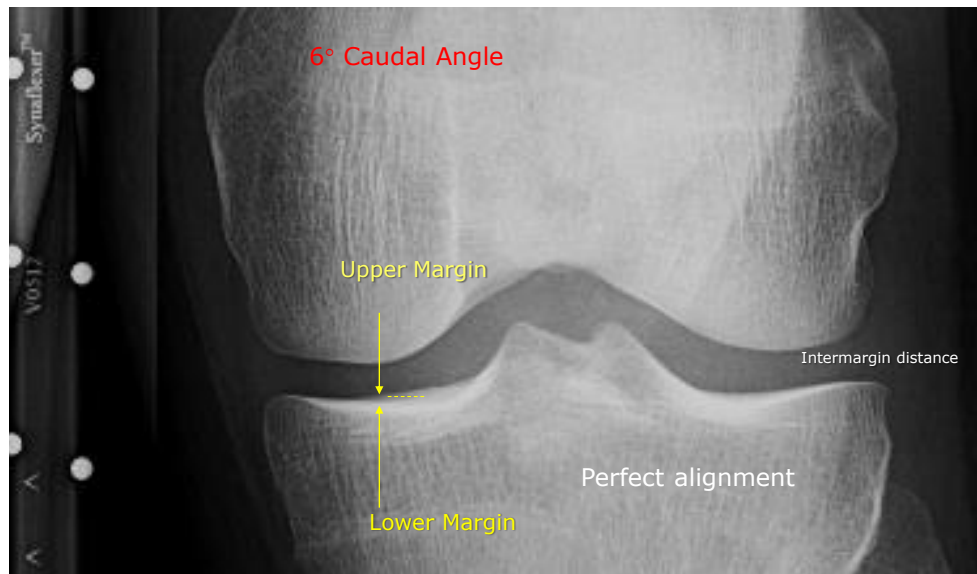
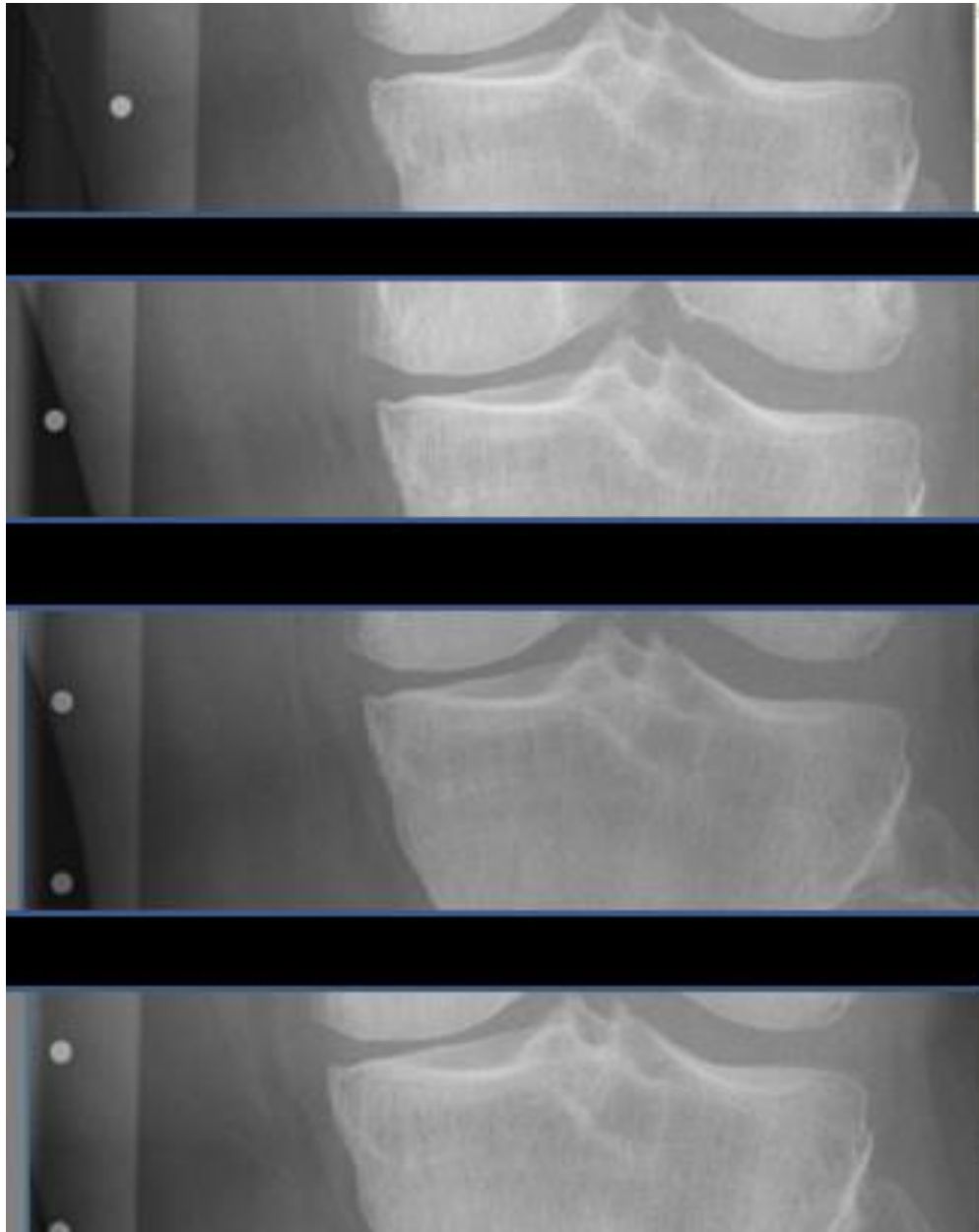


Figure 12: X-Ray Image with a tube angle of 6 degrees

An x-ray tube angle change to 6° caudal improves the IMD to perfect alignment. That is the ultimate target; however, a margin of error to ≤ 1.5 mm is acceptable.

Figure 13: Unacceptable: IMD >1.5 mm for all x-rays



7.7 Imaging parameters for Unilateral AP Hip Radiographs

View	Right and Left AP Hip Consistency in choice of X-ray equipment (either all digital or all film).
Subject Position	<ol style="list-style-type: none"> 1. Instruct subject to lie on the table, arms at sides and adjust the shoulders to lie in the same transverse plane. Cushion subject's head. 2. Align subject to the midline of table in an AP position 3. Ensure the pelvis is not rotated. 4. Separate the legs and feet and internally rotate the thigh and femur by 15 to 20 degrees, aligning the femoral neck horizontal and parallel with the table top. Sandbags may be used to maintain this position. 5. Check the department's policy on shielding the reproductive areas and shield accordingly, being careful not to obscure any anatomy of the proximal femur and hip joint. 6. Collimate the area of interest 7. Place marker placement on outside of pelvic anatomy. 8. Respiration is suspended
Exposure	Recommended: 75 kVp; 20 mAs
Central ray (CR)	Direct the CR perpendicular approximately 2 ½ inches distal to the line between anterior superior iliac spine and the symphysis pubis
film size	10 x 12 (24 x 30 cm) lengthwise
SID/FFD	40 inches (100cm)
Shielding:	Use gonadal shield, but care must be taken to ensure both hip joints are completely visible.
Joint Replacement:	In case of Hip Joint Replacement Surgery the following views are required: AP Hip and Frog Leg Lateral Hip or Horizontal Shoot Through lateral if unable to acquire Frog Leg due to recent (within 3 weeks) replacement surgery

7.8 Example of AP Hip Projection



7.9 Imaging Parameters for Lateral Hip Radiographs (Frog Leg View)

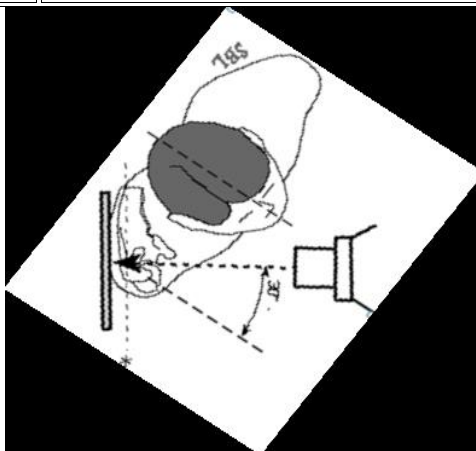
View	Right and Left Lateral Hip- frog leg position Consistency in choice of X-ray equipment (either all digital or all film).
Subject Position	<ol style="list-style-type: none"> 1. Instruct subject to lie on the table. Cushion subject's head. 2. Align subject to and center the affected hip to the midline of the table. Have the subject flex the affected knee and draw the thigh up to a near right angle. Extend the other thigh and support at hip level. The pelvis is rotated posteriorly to prevent its superimposition on the affected hip 3. Check the department's policy on shielding the reproductive areas. 4. Collimate the area of interest 5. Place marker placement on outside of pelvic anatomy. 6. Respiration is suspended
Exposure	Recommended: 75 kVp; 20 mAs
Central ray (CR)	Direct the CR thru the hip joint. This is located midway between the anterior superior iliac spine and the symphysis pubis
film size	10 x 12 (24 x 30 cm) lengthwise
SID/FFD	40 inches (100cm)
Shielding:	Use gonadal shield, but care must be taken to ensure both hip joints are completely visible.

7.10 Example of Lateral (Frog Leg) Hip Radiograph



7.11 Imaging Parameters for AP Shoulder (Grashey View)

View	Shoulder AP Grashey- The joint space between the humeral head and the glenoid cavity should be open
Subject Position	Standing
	<ol style="list-style-type: none"> 1. Raise the Bucky plate to above the shoulder height. 2. Place both shoulders against the Bucky plate and center the target shoulder with the posterior scapular aspect in the center of and against the Bucky plate. 3. Rotate the opposite, non-target shoulder 35° to 45° from the Bucky plate. Readjust the x-ray beam crosshairs as necessary to the target. The target scapula must be parallel to the plate and the humerus in contact with the plate. Abduct the target side arm slightly in internal rotation to rest palm-side down on the abdomen. This position will profile the glenoid cavity at approximately perpendicular to the CR. 4. To align the CR to the glenoid joint on the target shoulder place the x-ray beam crosshair reference point 2 inches (5 cm) medial and 2 inches (5 cm) distal from the superolateral border of the shoulder. 5. Place markers outside the shoulder anatomy on the lateral edge. 6. At the point of imaging have the subject hold an exhalation breath.
Exposure	Recommended kVp: 70-80 kVp; digital 75-85 kVp
Center cassette	Center the cassette to the shoulder joint
Central ray	AP Perpendicular to the IR
Film size	10 x 12 (24 x 30 cm) crosswise
SID/FFD	40 inches (100cm)
Shielding:	Use gonadal shield



7.12 Example of AP Shoulder (Grashey View) Radiograph

Example of acceptable AP Grashey view shoulder x-ray. The joint space between the humeral head and the glenoid cavity is open.



Example of an unacceptable AP Grashey view shoulder x-ray. The joint space between the humeral head and the glenoid cavity is NOT open. Bony overlap.



7.13 Repeat Examinations

Bioclinica's imaging technologist and/or the imaging physicist, and radiologist will evaluate the quality of each X-RAY and 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.

Repeat exams requested by Bioclinica should be performed within 5 days of the original exam date. To facilitate this, Bioclinica will e-mail a Data Clarification Form (DCF) to the site's Study Coordinator, the X-RAY facility and MRI facility. The DCF contains the statement describing the problems associated with image quality as well as the corrective actions including requests for repeat exams.

A repeat exam for a visit is still for that visit (e.g., a repeat exam for Screening is still a Screening exam – the repeated status will be marked on the transmittal form)

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

- Patient positioning and use of Synaflexer™ positioner
- Anatomical coverage and complete representation of the required anatomy
- Proper centering of images
- Image resolution
- Absence of artifacts
- Masked patient information in electronic header

8 Data Handling Procedures

X-RAY and MRI images should be submitted to Bioclinica according to the procedures described in this section.



The Study Coordinator or designee, the Lead X-RAY and MRI Technologist or designee must decide who will be responsible for shipping or uploading the exam data to Bioclinica. This designated person will be responsible for ensuring that the data submitted is complete and accurate.

A data query will be sent to the site Study Coordinator within three (3) business days if there is any discrepancy with the data submitted. Any data discrepancy queries sent to the clinical site from Bioclinica must be resolved and the correct information sent back to Bioclinica by the Study Coordinator within one (1) business days.



The imaging study should be sent to Bioclinica within one (1) business day after the exam!

Two options are available and offered to imaging sites for sending acquired data to Bioclinica. These are:

- Electronic transfer using secure FTP website (SMART submit) – the preferred method of data submission (refer to Appendix V for detailed description).
- Send via courier (UPS)

Both of these options are described below.

8.1 Electronic Transfer (FTP via SMART Submit)

SMART submit is Bioclinica's web-based portal that allows sites to submit images via secure file transfer protocol (FTP). It eliminates delays and expenses associated with shipping images via courier. **In this case, the Transmittal Form is completed and submitted electronically as well.** A complete package for one patient-visit data submitted via SMART submit should contain:

- One correctly labeled upload
- One correctly completed electronic transmittal form

Access to use this portal is given after user names and email addresses are listed on the Pre-Trial Questionnaire. The personnel listed on the PTQ will each be sent an e-mail listing their username, password, and instructions for logging into <https://smart.bioclinica.com/> and navigating the interface.

Access may also be requested at any time during the study by emailing the study support team at Regeneron1611@Bioclinica.com

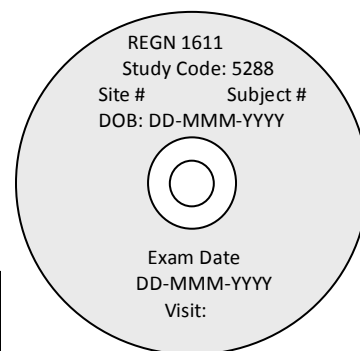
Please refer to Appendix V for detailed instructions on using SMART submit.

8.2 Sending Data on a CD

The images should be submitted on a standard CD (CD-R 640 or 700 MB capacity) in a jewel case to protect the media during shipment. Presented below is an example for how the CD should be labeled. Please use an **indelible marker** to write study and patient specific details on the CD. These are:

- Study Protocol Number: REGENERON R475-OA-1611 (Study Code: 5288)
- Patient Identifiers (**Site number and Subject Number**)
- X-RAY or MRI Exam Date (DD-MMM-YYYY format)
- Visit Name
- Date of Birth (DOB DD-MMM-YYYY format)

**Please enter the date of birth as indicated. If regulations prohibit your site from entering the day and month of the date of birth please enter 01 JAN and the correct Year of Birth for the subject. The Year of Birth must be the actual year for the subject*



Please do not affix any self-adhesive labels directly to the CD. This may harm the disc drives and cause read errors!



A new blank CD should be used for every patient visit!

Make sure to finalize the recording session when writing a CD. Do not use Universal Disk Format (UDF) or packet writing without finalization.

Each CD with patient data should be accompanied with properly filled (paper) Transmittal form. Data for multiple patients may be sent in one shipment. A complete package for one patient visit shipped via courier should contain:

- One (1) correctly labeled CD placed in a padded envelope for protection
- White and yellow copies of the Transmittal Form (the pink copy should be retained at the site).

UPS is the designated courier for this study. Bioclinica will provide pre-printed air waybills (AWBs) that will include Bioclinica's address on them.



When calling UPS to schedule a pick-up, remember to order courier envelopes.

8.3 Radiograph labeling

One label must be affixed to the bottom or top **right** corner (when radiograph is in portrait orientation) on the front of each radiograph submitted. Be sure you do not obscure any anatomy when attaching the label.

- The flash region may be covered by the study label, but do not apply multiple layers of labels or labels on the back of the film.
- Do not wrap label around the edge of the film (this hinders digitization of the film at Bioclinica).
- Do not attach other labels to the film.
- Do not mark the film.
- All radiographs should be placed in the same radiograph jacket (one subject per jacket). The radiograph jacket should be labeled with the same adhesive label used for the radiographs. Complete this label with the same information as on the radiographs.
- All radiographs should be labeled using the pre-printed adhesive labels provided by Bioclinica.

Each radiograph submission should be accompanied with properly filled (paper) Transmittal form.

White and yellow copies of the Transmittal Form (the pink copy should be retained at the site).

UPS is the designated courier for this study. Bioclinica will provide pre-printed air waybills (AWBs) that will include Bioclinica's address on them.

Appendix I – X-RAY QRG

THIS IS AVAILABLE AS A SEPARATE DOCUMENT

Appendix II – MRI QRG (1.5T and 3T)


THESE ARE AVAILABLE AS SEPARATE DOCUMENTS

Appendix III – X-RAY Transmittal Form

BIOCLINICA®		Regeneron Protocol R475-OA-1611 Transmittal Form for X-Ray	
Site, Subject, and Visit Information		To be completed at study site	
Country Code/Site Number: <table border="1" style="display: inline-table; width: 100px; height: 20px;"></table>		Subject ID: <table border="1" style="display: inline-table; width: 100px; height: 20px;"></table> <small>Country Code Site Number Randomization Number</small>	
Date of Birth*: <table border="1" style="display: inline-table; width: 30px; height: 20px;"></table> / <table border="1" style="display: inline-table; width: 30px; height: 20px;"></table> / <table border="1" style="display: inline-table; width: 30px; height: 20px;"></table> <small>D D M M M Y Y Y Y</small>		Visit: <input type="checkbox"/> Screening <input type="checkbox"/> Week 16 <input type="checkbox"/> Week 52 <input type="checkbox"/> Week 72 <input type="checkbox"/> Early Termination <input type="checkbox"/> JR Pre-Operative <input type="checkbox"/> Post-Op Week 20 <input type="checkbox"/> Unscheduled <input type="checkbox"/> Event Driven	
<small>*If regulations prohibit your site from entering the day and month of the date of birth, please enter "01 JAN" and the correct year of birth for the subject.</small> For imaging done outside of regular study visits, were the images acquired following a report of clinically significant worsening or exacerbation of pain in that joint?		<input type="checkbox"/> Re-screen Subject <small>(Enter previous subject ID in Comment)</small>	
<input type="checkbox"/> If YES, please select EVENT DRIVEN visit		<input type="checkbox"/> If NO, please select UNSCHEDULED visit	
Exam Information		To be completed at imaging center	
X-Ray exams acquired and submitted (check the box below, if acquired and submitted)		Exam Date: <table border="1" style="display: inline-table; width: 30px; height: 20px;"></table> / <table border="1" style="display: inline-table; width: 30px; height: 20px;"></table> / <table border="1" style="display: inline-table; width: 30px; height: 20px;"></table> <small>D D M M M Y Y Y Y</small>	
1. Left Knee (PA) <input type="checkbox"/>		Comments: _____ _____ _____	
2. Right Knee (PA) <input type="checkbox"/>		_____ _____ _____	
3. Left Hip (AP) <input type="checkbox"/>		_____ _____ _____	
4. Right Hip (AP) <input type="checkbox"/>		_____ _____ _____	
5. Left Hip (Frog Leg) <input type="checkbox"/>		_____ _____ _____	
6. Right Hip (Frog Leg) <input type="checkbox"/>		Previous Subject ID: _____	
7. Left Shoulder (AP) <input type="checkbox"/>		Media: <input type="checkbox"/> CD	
8. Right Shoulder (AP) <input type="checkbox"/>		(Check one box) <input type="checkbox"/> Hardcopy Films	
9. Other _____		Number of films sent: <table border="1" style="display: inline-table; width: 30px; height: 20px;"></table>	
Do not write below this line. For Bioclinica use			
Data Receipt		To be completed at Bioclinica	
RESERVED FOR BIOCLINICA BARCODE			
Comments: _____ _____ _____		Received: Initials: <table border="1" style="display: inline-table; width: 30px; height: 20px;"></table> <small>F M L</small>	
		Date: <table border="1" style="display: inline-table; width: 30px; height: 20px;"></table> / <table border="1" style="display: inline-table; width: 30px; height: 20px;"></table> / <table border="1" style="display: inline-table; width: 30px; height: 20px;"></table> <small>D D M M M Y Y Y Y</small>	
Bioclinica Tracking Number <table border="1" style="display: inline-table; width: 100px; height: 20px;"></table>			
*** Distribution: File PINK copy at Study Site. Send Original (WHITE) and YELLOW pages to Bioclinica. ***			

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Appendix IV – MRI Transmittal Form

 BIOCLINICA®		Regeneron Protocol R475-OA-1611 Transmittal Form for MRI	
Site, Subject, and Visit Information		To be completed at study site	
Country Code/Site Number: <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>		Subject ID: <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	
Date of Birth*: <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>		Visit: <input type="checkbox"/> Screening <input type="checkbox"/> JR Pre-Operative	
<small>*If regulations prohibit your site from entering the day and month of the date of birth, please enter "01 JAN" and the correct year of birth for the subject.</small>		<input type="checkbox"/> Post-Op Week 20	
For imaging done outside of regular study visits, were the images acquired following a report of clinically significant worsening or exacerbation of pain in that joint?		<input type="checkbox"/> Event Driven <input type="checkbox"/> Unscheduled	
<input type="checkbox"/> If YES, please select EVENT DRIVEN visit		<input type="checkbox"/> Repeat submission	
<input type="checkbox"/> If NO, please select UNSCHEDULED visit		<input type="checkbox"/> Re-screen Subject <small>(Enter previous subject ID in Comment)</small>	
Exam Information		To be completed at study site	
An MRI must be performed of the index and contralateral joints at screening for all patients. In addition, an MRI must be performed on any knee or hip with a K-L of ≥ 3 .			
Exam Date: <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>		Comments: _____	
		Previous Subject ID: _____	
MRI Sequence Submitted	Right Knee	Left Knee	Bilateral Hips
3-Plane Localizer(s)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Coronal 2D T1-w FSE	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Coronal 2D PD-w FSE fat sat	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Sagittal 2D PD-w FSE fat sat	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Coronal 2D STIR	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Axial PD-w FSE fat sat	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Oblique coronal 2D PD-w FSE	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Oblique coronal 2D PD-w FSE fat sat	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Oblique sagittal 2D PD-w FSE	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Other (indicate the sequence)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Do not write below this line. For Bioclinica use only.			
Data Receipt		To be completed at Bioclinica	
RESERVED FOR BIOCLINICA BARCODE			
Comments: _____		Received: _____	
_____		Initials: <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> Date: <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	
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Bioclinica Tracking Number		5 2 8 8 1 0 2 0 1 7 0 6 0 8	
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Appendix V – SMART Submit User Guide



SMART Submit Release 9.4 User Guide

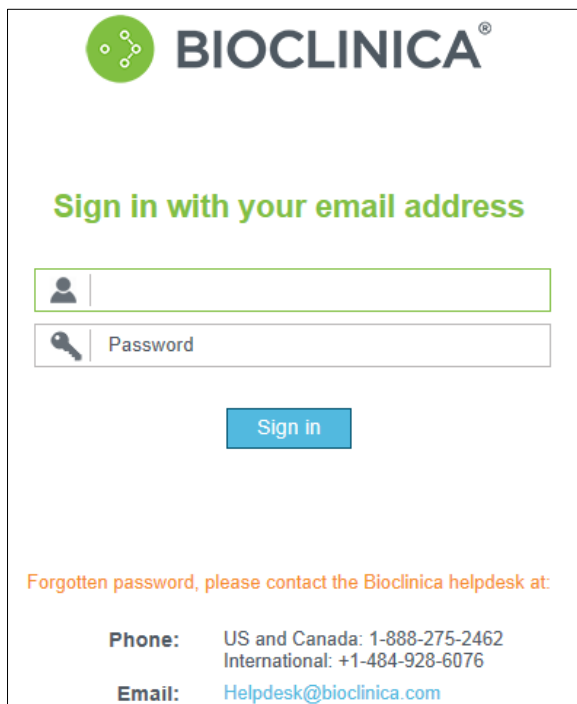
Document Version 1.0

1.1 Getting Started

SMART Submit is Bioclinica's web-based system for clinical trial image uploads and related communication management. Clinical sites use SMART Submit to upload image and transmittal form data to Bioclinica.

Logging On


Once you have received the welcome email, you will be able to log into SMART Submit. Open your browser and open <https://smart.Bioclinica.com> - If needed change your temporary password.

The image shows the login page for the SMART Submit system. At the top is the Bioclinica logo, which consists of a green circle with a white network-like icon and the word "BIOCLINICA" in blue. Below the logo is the text "Sign in with your email address" in green. There are two input fields: the first has a person icon and is for the email address, and the second has a key icon and is labeled "Password". Below these fields is a blue "Sign in" button. At the bottom, there is a link for forgotten passwords and contact information for the Bioclinica helpdesk, including phone numbers for US/Canada and International, and an email address.

1. **Type** your email address and default password.
2. **Click** Sign In.
 - a. *If this is the first time that you are logging on, the Change Password box automatically displays. (See Below)*
 - b. *If you have already changed your password, The main SMART Portal page will display with all your projects listed*





Note: If the project that you want to use is not listed, please contact the Bioclinica helpdesk.


**BIOCLINICA®**


Update Password

You must update your password because your password has expired.

 yourname@company.com

 Old password

 New password

 Confirm new password

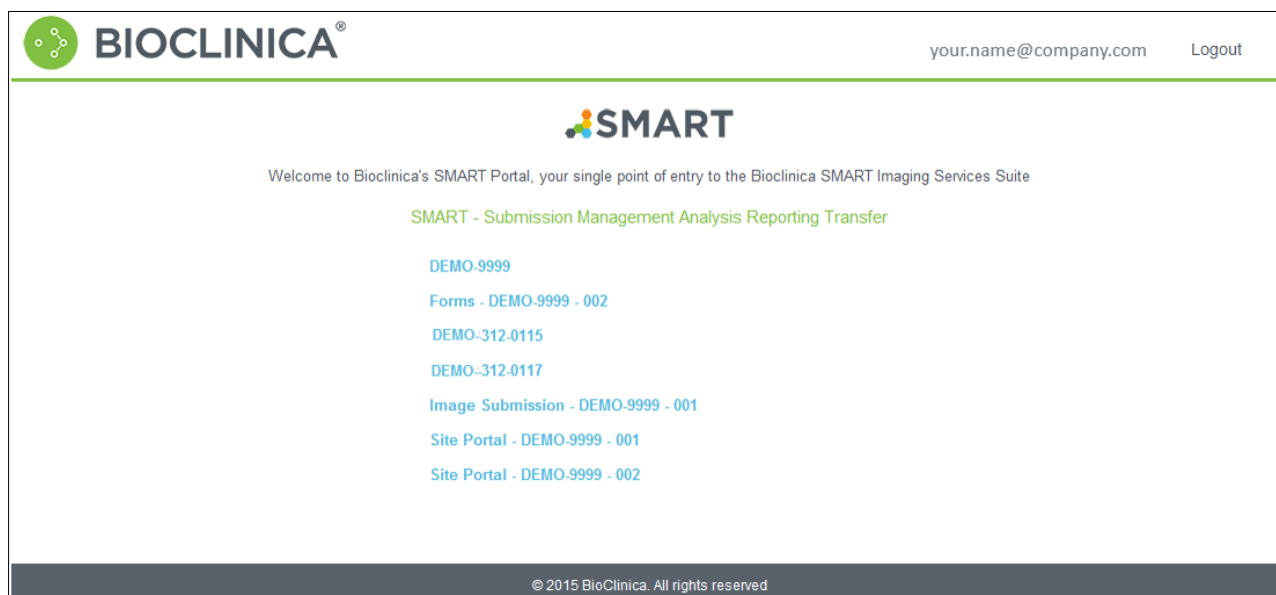
Submit

Cancel

3. **Type** your email address and default password.
4. **Type** a new password.
The password must be at least 8 characters long and must contain at least three of the following: an upper-case letter, a lower-case letter, a number, and a symbol.
5. **Re-enter** the new password in the Confirm Password field.
6. **Click** Submit.

Select Study

If you have access to more than one study, or multiple sites within a study, the System displays a study selection dialog after login:



1. Click the link to the project you wish to work with from the list.

If you select an item beginning with [Image Submissions](#)— the [Site Submission Home](#) page displays.

If you select an item beginning with [Forms](#) – the [Study Forms](#) page display.

If you select an item beginning with [Site Portal](#)— the [Study Portal](#) page display.

Logout

To logout of SMART submit, click **Logout** in the upper right corner of the screen. The system confirms that you have successfully logged out.



1.2 UPLOADING IMAGES AND DATA

After you have selected the project the File Upload Activities Summary page displays. The upper right corner of the page displays your Login ID. You can always return to this page by clicking **Site Submission Home** in the upper right of the page. The center section highlighted below only displays if you don't already have the Aspera Connect Browser Plug-in installed.



Note: You must download and install the Aspera Connect Browser Plug-in before you can upload any files. Please see Aspera Connect Browser Plug-in for more information.



DemoCompany Protocol US-DEM-999

Welcome IQUser1

Help | SMART Portal | Sign Out

Study:US-DEM-999 ([Change Study](#)) Site: 001

Search Criteria

Participant/Phantom No:

Visit: Show All

Results per page: 10

Upload Files

Below you will find a list of all your previous uploads for this study. You may filter this list by providing the desired search criteria and pressing the button labelled 'Filter' to the left. To send new files for this study press the 'Upload Files' button below. Please refer to our [User Guide](#) and/or [Upload Video Tutorial](#) for help (requires a **Flash Player**).

To test whether you can upload files from this location, please click here - [Mock Upload](#). Note: this mock upload will not be saved.

Study Resources

Please click here to access the Site Portal - [Site Portal](#)

We are pleased to announce that SMART now utilizes Aspera's high-performance **asp**™ transport technology for site submissions. This enhancement will provide significantly faster upload times and more reliable transfers.

To send files to BioClinica you will first need to install the Aspera Connect browser plug-in. Please navigate to the following page and download the version for your particular operating system. After installing, you will need to restart your browser and log in to SMART again.

For any questions regarding this upgrade, please send email to websupport@bioclinica.com.

[Download Aspera Connect \(Installation Guide\)](#)

File Uploads

	Upload Date	TF Type	Participant No/Phantom No	Subject Id	Visit	Number of Files DICOM/Total	Size (Kb) DICOM/Total	Status	Upload User	Updated By	Quarantine Folder
<input type="checkbox"/>	04-Jan-2016 15:04	CT/MRI	11	11	Baseline	1/1	640/640	Complete	iqal.user@synarc.com	iqal.user@synarc.com	NWK
<input type="checkbox"/>	17-Dec-2015 18:59	CT/MRI	13	13	Baseline	1/1	640/640	Complete	iqal.user@synarc.com	iqal.user@synarc.com	NWK
<input type="checkbox"/>	17-Dec-2015 18:44	CT/MRI	13	13	Baseline	1/1	640/640	Complete	iqal.user@synarc.com	iqal.user@synarc.com	NWK
<input type="checkbox"/>	17-Dec-2015 15:10	CT/MRI	11	11	Baseline	1/1	109/109	Complete	iqal.user@synarc.com	iqal.user@synarc.com	NWK
<input type="checkbox"/>	17-Dec-2015 15:04	CT/MRI	11	11	Baseline	1/1	640/640	Complete	iqal.user@synarc.com	iqal.user@synarc.com	NWK
<input type="checkbox"/>	17-Dec-2015 13:54	CT/MRI	11	11	Baseline	1/1	640/640	Complete	iqal.user@synarc.com	iqal.user@synarc.com	NWK
<input type="checkbox"/>	17-Dec-2015 12:03	CT/MRI	11	11	Baseline	1/1	640/640	Complete	iqal.user@synarc.com	iqal.user@synarc.com	NWK
<input type="checkbox"/>	17-Dec-2015 11:08	CT/MRI	11	11	Baseline	1/1	640/640	Complete	iqal.user@synarc.com	iqal.user@synarc.com	NWK
<input type="checkbox"/>	17-Dec-2015 10:49	CT/MRI	11	11	Baseline	1/1	109/109	Complete	iqal.user@synarc.com	iqal.user@synarc.com	NWK
<input type="checkbox"/>	16-Dec-2015 13:31	CT/MRI	11	11	Baseline	1/1	640/640	Complete	iqal.user@synarc.com	iqal.user@synarc.com	NWK

☐ Select All

>Showing: 1 - 10 of 1,001 results. Page 1 / 101

Physical Package Submissions

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1.3 Upload Methods: Aspera Connect vs. "Classic SFTP"

SMART Submit supports two methods for uploading files. "Classic SFTP" is a fallback method available to sites where the Aspera Connect plug-in cannot be installed, or network restrictions at a site prevent its use. This uses Unlimitech's web-based file transfer client. It is handy as a back-up solution, but it is slow compared to using Aspera Connect.

You can switch between the Aspera and SFTP methods. On the electronic Transmittal Form data entry page that you are presented with prior to uploading the data (after selecting Upload or Test), there is a link at the bottom of the web page if you are using Classic SFTP:

Currently using Classic SFTP to upload files.

[Use Aspera \(recommended\)](#)

Clicking on the “Use Aspera (recommended)” link switches your session to use the Aspera Connect method. When Aspera is selected, you will see this at the bottom of the electronic TF data entry page:

Currently using 'Aspera' to upload files (no deidentification).

[Use Classic SFTP](#)

If you have not installed the Aspera Connect file transfer software, or if you have it installed for a single user rather than for all users, a warning displays at the top of the electronic Transmittal Form data entry page.

Download Aspera Connect Browser Plug-in

The first time you access SMART Submit, a message on the Site Submission Home Page announcing the Aspera high-performance *fast*TM transport technology that SMART Submit now uses for site submissions displays in the middle of the page.

We are pleased to announce that SMART now utilizes Aspera's high-performance *fast*TM transport technology for site submissions. This enhancement will provide significantly faster upload times and more reliable transfers.

To send files to BioClinica you will first need to install the Aspera Connect browser plug-in. Please navigate to the following page and download the version for your particular operating system. After installing, you will need to restart your browser and log in to SMART again.

For any questions regarding this upgrade, please send email to websupport@bioclinica.com.

[Download Aspera Connect \(Installation Guide\)](#)



Note: You must have local administrator permissions to install this plug-in.

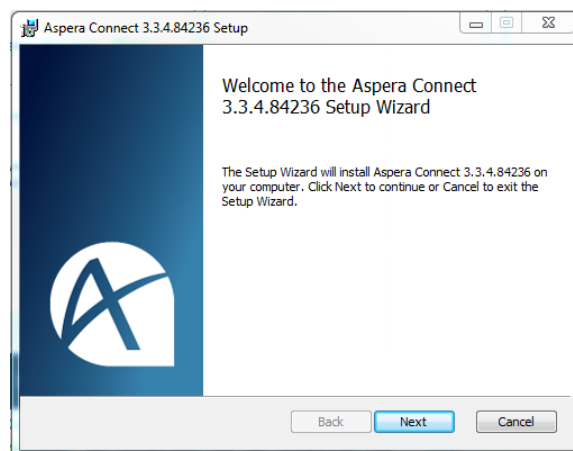
1. **Click Download Aspera Connect.**

The security warning displays at the bottom of the page.



2. **Click Run.**

The Welcome box displays.

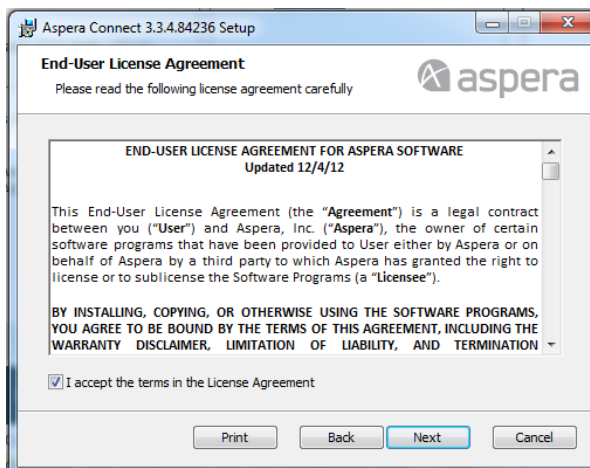


3. **Click Next.**

The License Agreement box displays.

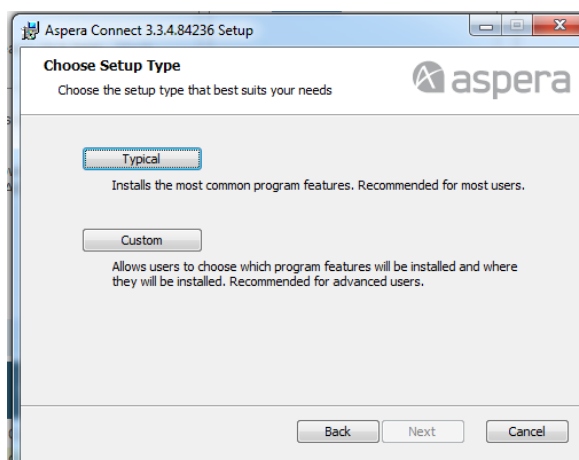
4. **Click** the check box to accept the License Agreement and **click** Next.

The Choose Setup Type box displays.



5. **Click** Custom.

The Installation Scope box displays.



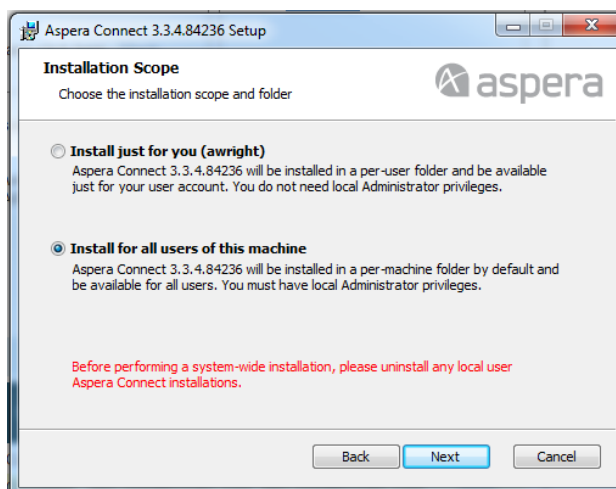
6. **Click** the radio button next to Install for all users on this machine and **click** Next.

The Ready to install box displays.

7. **Click** Install.

After the installation is complete the Complete box displays.

8. **Click** Finish.



Further Information:

Sometimes the Aspera Connect software is not able to communicate with the SMART submit web site from a location where the networking security is blocking its access. Aspera Connect uses two “port numbers” in its communications with Bioclinica. These must be allowed for in your network firewall configuration. If you have trouble after installing the software, be sure your network infrastructure personnel allow for communications on the following two network port numbers:

TCP/7600 UDP/33001

Additional Help:

For additional assistance, contact the Help Desk:

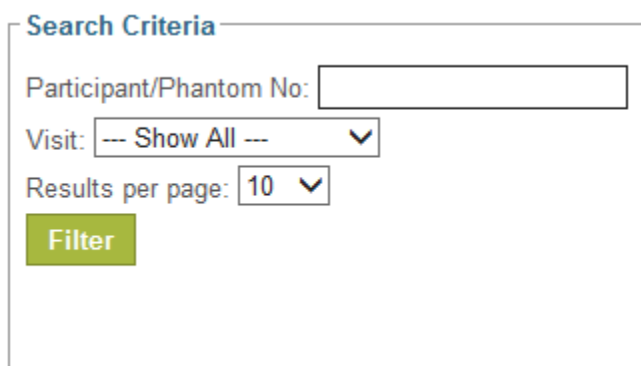
Toll Free from the US and Canada: 1-888-ASK-BIO2 (1-888-275-2462)

International: +1-484-928-6076

Email: helpdesk@Bioclinica.com

1.4 Search Criteria for Files

The **Search Criteria** section allows you to filter and view a history of previously uploaded images.

A screenshot of the 'Search Criteria' form. It has a title 'Search Criteria' in blue. Below the title, there is a text input field for 'Participant/Phantom No:'. Below that is a dropdown menu for 'Visit:' with '--- Show All ---' selected. Below that is another dropdown menu for 'Results per page:' with '10' selected. At the bottom left of the form is a green button labeled 'Filter'.

1. **Define** your filter using one or more of the following criteria:
 - Participant/Phantom Number
 - Visit
2. **Select** the number of Results per Page you wish to display (the default is 10).
3. **Click** the **Filter** button.

The File Upload History section at the bottom on the page displays the results of the filter.

File Upload History

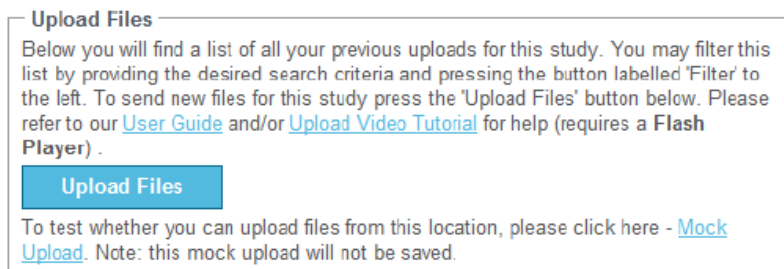
The **File Uploads** section, on the bottom half of the screen, shows the file upload history by the date uploaded. The most recent uploads are listed first. This list includes the Upload Date, Site Number, Participant (or Phantom) Number, Visit, Number of Files, and the file Size of the uploads. The last two fields include the total number of DICOM files and the overall Total (DICOM and non-DICOM), with the values separated by a forward slash.

The upload history displays items up to the number you specified in the Search Criteria, so any items over this amount will show on another page, which can be accessible via the Next and Previous arrow buttons, or by clicking on a particular page number. You can also sort the files by clicking on the column name. All files in the upload history are included in the sort process, not just the files showing on the page.

Uploading Files

The **Upload Files** section includes a button for initiating an upload, a link to test upload functionality, and links to the online help and User Guide.

1. From the Site Submission Home Page, **click Upload Files**.

A screenshot of the 'Upload Files' section. It has a title 'Upload Files' in blue. Below the title is a paragraph of text: 'Below you will find a list of all your previous uploads for this study. You may filter this list by providing the desired search criteria and pressing the button labelled 'Filter' to the left. To send new files for this study press the 'Upload Files' button below. Please refer to our [User Guide](#) and/or [Upload Video Tutorial](#) for help (requires a Flash Player)'. Below the text is a blue button labeled 'Upload Files'. At the bottom is another paragraph: 'To test whether you can upload files from this location, please click here - [Mock Upload](#). Note: this mock upload will not be saved.'

The Select Transmittal Form Type page displays.

Please select a transmittal form type

☐ Phantom PET/CT
☐ CT/MRI
☐ X-ray of RG
☐ X-ray of Hands/Feet

Submit

2. **Select** the transmittal form type and **click Submit**.

The Transmittal Form data page displays.

BIOCLINICA® DemoCompany Protocol US-DEM-999 Welcome IQUser1
Help | SMART Portal | Sign Out

Study: DEMO-9999 Site: 001 [Site Submission Home](#) > Transmittal Form

Transmittal Form For CT/MRI

Site, Patient, and Visit Information

Screening Number: (e.g. 12) *Participant Initials: (F-M L or F-L) *Visit: ☐ Repeat Request

Subject Number: (e.g. 12) *Date Of Birth: (DD-M MM-YYYY) (31-DEC-1906 to 31-DEC-1990) Patient Gender: ☐ Resubmission Request

CT Information

Exam Site (check all that apply):
☐ Chest ☐ Abdomen
☐ Pelvis
 Comments:
 Exam Date: (DD-M MM-YYYY)
 Tech Initials:

MRI Information

Exam Site (check all that apply):
☐ Chest ☐ Abdomen
☐ Pelvis
 Comments:
 Exam Date: (DD-M MM-YYYY)
 Tech Initials:

Submit and Upload

Currently using 'Aspera' to upload files (no deidentification).
[Use Classic SFTP](#)
[Use Aspera + client deidentification \(DICOM files only\)](#)

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3. **Enter** the Site, Patient, and Visit Information fields.
4. If the form is being submitted as a **Repeat Request** or **Resubmission Request**, check the appropriate box.
5. **Check** the Exam Site(s), enter Exam Date, Tech Initials, and any applicable Comments for each modality identified on the transmittal form.
6. **Select** the method of upload you wish to use:
 - a. If you are using Aspera to upload files with no de-identification **Click Submit and Upload**
 - b. If you are using Classic SFTP, **Click Use Classic SFTP** at the bottom of the page and then **click Submit and Upload**
 - c. If you are using Aspera up load files with de-identification, Click **Use Aspera+client deidentification (DICOM files only)** at the bottom of the page and then **click Submit and Upload**

7. Click Submit and Upload.

Your transmittal form data is saved.

Submit and Upload

After the image upload program connects, you will see the File Uploads page. This page shows two panels: a Current Upload Status panel, and an Upload Files panel.

BIOCLINICA® DemoCompany Protocol US-DEM-999 Welcome IQUser1
Help | SMART Portal | Sign Out

Study: DEM O-9999 Site: 001 [SiteSubmission Home](#) > Upload Files

File Uploads

Below you will find a list of all your previous uploads for this study
Select the appropriate files from your local system. Press Upload Files to begin the upload to Synarc.
Note: if possible, you should zip large numbers of files into an archive to reduce upload time.

Current Upload Status
Ready OMB uploaded this session.

Upload Files

1. **Add Files** **Add Folders** 2. **Upload Files/Folders** **Remove Selected** **Remove All Unsent** [Display As per Transfer Manager](#)

Local Folder/File	Status

Signature Required to Upload Files

After you have finished uploading your file(s), you must sign the upload by entering your password again.

Meaning : *** Password :** Authorship
Please enter your password to complete the upload.

Sign and Complete

The Current Upload Status panel always displays the status of the current file upload session, and have values such as “Ready”, “Completed”, etc.

At first the Upload Files panel has two enabled buttons:

Add Files – is used to add individual files to your upload list.

Add Folders – is used to add all the contents of a folder or folders to your upload list

After you select files, the other three buttons are enabled:

Upload Files/Folders – is used to upload the files or folders with the status of “Ready to Upload.”

Remove Selected Files – is used to remove files that have been placed on the upload list in error but not yet uploaded. Click the check the box to the left of the files and click this button to remove the selected files from the list.

Remove All Unsent – is used to remove all the files in the upload list that have a status of “Ready for Upload”. Files already uploaded cannot be removed from the list.

Upload Files/Folders

1. Click either **Add Files** or **Add Folders**.

Current Upload Status
Ready OMB uploaded this session.

Upload Files

1. **Add Files** **Add Folders** 2. **Upload Files/Folders** **Remove Selected** **Remove All Unsent** [Display Aspera Transfer Manager](#)

	Local Folder/File	Status

A pop up a window displays showing your local file system on your computer.

2. **Navigate** to the directory where your file(s) are located using the buttons inside the local system view, select the file(s). – Use SHIFT + Click / CTRL + Click to highlight multiple files -- and click Open.

The File Uploads page displays with the selected files/folders in the upload list.

Current Upload Status
Ready OMB uploaded this session.

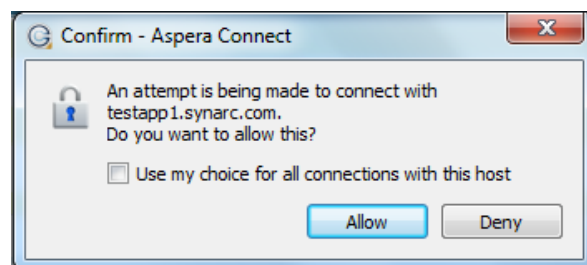
Upload Files

1. **Add Files** **Add Folders** 2. **Upload Files/Folders** **Remove Selected** **Remove All Unsent** [Display Aspera Transfer Manager](#)

	Local Folder/File	Status
<input type="checkbox"/>	IM-0001-0001.dcm	Ready for upload
<input type="checkbox"/>	IM-0001-0002.dcm	Ready for upload
<input type="checkbox"/>	IM-0001-0003.dcm	Ready for upload

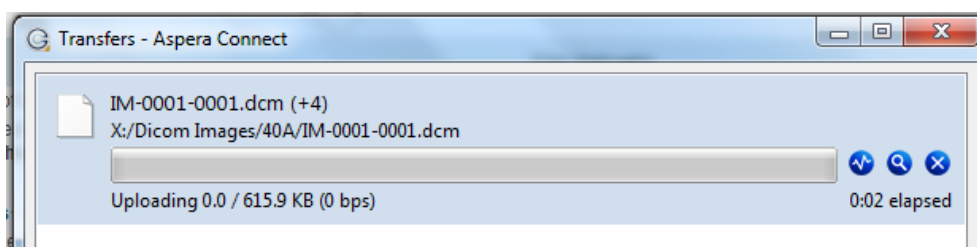
3. Click **Upload Files/Folders**.

An additional popup window alerting you that an attempt is being made to initiate a transfer with the Bioclinica server may display.



4. Click **Allow** to permit the image upload to proceed.

When the file is uploading, the Current Upload Status panel displays the percent and status of upload. In addition, a popup Transfer Manager window displays the status of the transfer.



The first time you attempt to upload files to Bioclinica, you may see a Windows Security Alert regarding the ascp Application. If you do, click **Unblock** to continue with the upload.

When the upload is complete, the Upload Files panel displays the status of each uploaded file.

BIOCLINICA®
DemoCompany Protocol US-DEM-999
Welcome IQUser1

[Help](#) | [SMART Portal](#) | [Sign Out](#)

Study: DEM O-9999 Site: 001
[SiteSubmission Home](#) > Upload Files

File Uploads

Below you will find a list of all your previous uploads for this study
Select the appropriate files from your local system. Press Upload Files to begin the upload to Synarc.
Note: if possible, you should zip large numbers of files into an archive to reduce upload time.

Current Upload Status
Ready 1.8MB uploaded this session.

Upload Files
1. [Add Files](#) [Add Folders](#) 2. [Upload Files/Folders](#) [Remove Selected](#) [Remove All Unsent](#) [Display Aspera Transfer Manager](#)

Local Folder/File	Status
IM-0001-0001.dcm	Complete
IM-0001-0002.dcm	Complete
IM-0001-0003.dcm	Complete

Signature Required to Upload Files
After you have finished uploading your file(s), you must sign the upload by entering your password again.

Meaning : * **Password :** Authorship
Please enter your password to complete the upload.



Note: When all the files have been uploaded, you must sign the session to complete the process.

5. **Enter** your password in the signature box below and click **Sign and Complete**.

If you attempt to sign before the upload is complete, the system prompts you to wait.

After you sign the upload session, a confirmation of your upload is sent. An image verification is run on your uploaded files to check for valid DICOM images. If there was an error with the files, then the system asks if you want to re-upload the files.

If there were no errors encountered by the verification process, then a confirmation displays.


BIOCLINICA[®]

DemoCompany Protocol US-DEM-999
 Welcome IQUser1
[Help](#) | [SMART Portal](#) | [Sign Out](#)

Study: DEM O-9999 Site: 001
 [Site Submission Home](#) > Upload Confirm

Upload Confirmation

Your files have been uploaded. All DICOM image files you have uploaded are currently being verified for format completeness/consistency. A confirmation email will be sent to you shortly listing all files in your upload.

[Home](#)
[Upload More Files](#)

You will also receive a confirmation email with a summary of the uploaded files, including the study, site, participant, and visit the upload was associated to. The email also lists any files that failed the DICOM verification check.



Note: The system continues uploading a file for up to 24 hours. After 24 hours, the system stops loading the file and times out. It is suggested that you segment very large files so they load in the time allowed.


Resubmit Images

If there is an issue with an image, a query may be initiated asking for the image to be resubmitted. In DCF Resolution, a “Resubmit” button displays under Query Status. After uploading the new image, click “Resubmit” to go to Image Submission.

DCF Resolution

Query Detail

Investigator:	Test Test	Visit:	Week 48
Site ID:	001	Modality:	
Participant ID:	18	DCF Type:	Rejected Images -> Resubmission/Repeat Request
Initials:	NAL	Issue:	Images were submitted using the incorrect parameter settings, details below:
Date of Birth:	01-Jan-1980	Additional Comments:	
Query Type:	DCF	Resolution:	Resubmit a new reconstruction using the parameter settings as described. Please do not repeat the image(s).
Query Due Date:	29-Dec-2012	Synarc Comment:	
Exam:		Exam Date:	



Query Status

Status: Pending Response

☐ Prepopulate TF from DCF data

Note: Selecting Resubmit will direct you to Image Submission

Viewing Study Portal

Depending on the permissions granted to you and the study setup, you may be able to view study-specific documents and other information uploaded by Bioclinica. These documents are available through the SMART Portal.



Note: Not all studies utilize this functionality.

If the Site Portal has been enabled for your studies, they display on the SMART Portal page in the format:

[Site Portal - Study/Protocol Number – Site Number](#)

View Site Portal/Study Documents as a Site User

1. **From** the SMART Portal page, **click** the Site Portal link.

The Site Portal Selection page displays.

BIOCLINICA®

Welcome IQ User1
[Study Home](#) | [Help](#) | [SMART Portal](#) | [Sign Out](#)

Welcome to the DemoCompany Protocol US-DEM-999 study
Welcome to SMART for DemoCompany Protocol US-DEM-999: IQA018-StudyEdit-2016010415123003

BioClinica Team for DemoCompany Protocol US-DEM-999 (9999)

Automation3 User
7707 Gateway Boulevard, 3rd Floor
Newark, CA 94560, United States
email: auto3.user@synarc.com

Automation3 User
7707 Gateway Boulevard, 3rd Floor
Newark, CA 94560, United States
email: auto3.user@synarc.com

Automation3 User
7707 Gateway Boulevard, 3rd Floor
Newark, CA 94560, United States
email: auto3.user@synarc.com

Site: 001
View another site:
Select a study

Quick View Menu

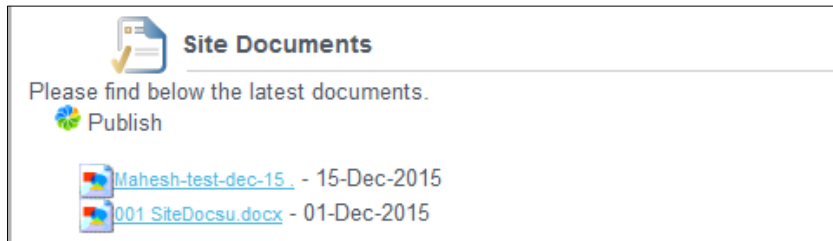
- Study Direct Training
- Study Direct Reports
- DCF Resolution
- Back
- Site Documents
- Contact Information
- Site Submissions
- Site Study Materials
- Operations Manual
- Images

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The options display on the Quick View Menu to the right of the screen.

2. **Click** on Site Documents to list documents for site users within your browser.

The list of Site Documents displays.



3. **Click** the link for the document you wish to view.

A warning similar to the one below displays.



4. **Click** Open or Save to view or save the file.

Appendix VI - Pro-Forma Invoice Template

Shipper/Exporter: (Complete Name & Address)		CONSIGNEE: BIOCLINICA Attn: REGENERON R475-OA-1611 Study Team (Code: 5288) (complete Bioclinica office address for your site below) Bioclinica, Inc. 7707 Gateway Blvd., 3rd Floor Newark, CA 94560 USA 415.817.8900		
Country of Origin: <hr/>		REASON FOR EXPORT: Data for Clinical Trial. NON COMMERCIAL. FOR RESEARCH PURPOSES ONLY		
Country of ultimate Destination: USA				
Type of Packaging/ Marks	Detailed Description of Goods	Harmonized Code	Unit Value	Subtotal
TOTAL : 1	TOTAL WEIGHT: <hr/>			\$ (Total)

Appendix VII – Supply Re-Order Form

REGENERON R475-OA-1611 Study Supply Order Form

To order supplies, please email the completed form to:

Email: Regeneron1611@Bioclinica.com

Attention: Regeneron 1611 Study Team (Code 5288)

Supplies will be sent to the following location:

Please update contact name and address information as needed.

Site #:	
Attn:	
Facility:	
Address:	
Phone #:	

X-ray Supply

Quantity

Film Labels (15 labels per subject exam will be provided) _____ subject exams

X-ray Data Transmittal Form _____ subject exams

X-ray Jackets _____ subject exams

SynaFlexer™ (Only 1 will be provided if the positioner from the first shipment is damaged)

MRI Supply

Quantity

MRI Data Transmittal Form _____ subject exams

General Supply

Quantity

Pre-printed Airway Bills _____ subject exams