Procedure Manual for Radiographic Examinations of the Hands/Wrists and Feet

Horizon Pharma Rheumatology LLC
Protocol HZNP-KRY-202

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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
❑	The Pre-Trial Questionnaire (PTQ) will be collected from each facility participating in the study prior to the beginning of the trial.	The completed PTQ should be sent to Bioclinica by fax or email within 5 business days of receipt.
❑	**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 PTQ
❑	Review the supply package contents to ensure receipt of all study materials.	The supplies enclosed are as follows: • Radiographic Procedure Manual • Quick Reference Guide (QRG) • Transmittal Forms • Pre-printed air waybills • SYN-X-RA hand/foot positioning device • Blank CDs • USB drives
❑	Please have all applicable study personnel read this Procedure Manual and the Quick Reference Guides (QRG).	
❑	Complete the study specific online training for X-ray acquisition. An email invitation to complete the self-directed online training will be sent to the lead technician as indicated on the Pre-Trial Questionnaire.	It is required that a lead technologist (as indicated on the PTQ) in the study will complete the online training for X-ray acquisition before any subjects are imaged at the site.
❑	After completion of the training, print and file a copy of the completion certificate for documentation of training per your local regulatory and study requirements.	For X-ray, after the lead X-ray technologist certifies that he or she has completed training, the imaging facility is considered ready to scan the first subject and the site will be considered qualified on the first subject scan passing QC.

Horizon Pharma Rheumatology LLC

Protocol HZNP-KRY-202

A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Efficacy and Safety Study of Methotrexate to Increase Response Rates in Patients with Uncontrolled GOut Receiving KRYSTEXXA® (pegloticase) (MIRROR Randomized Controlled Trial [RCT])

Short Title: MIRROR RCT

Procedure Manual for Radiographic Examinations of the Hands and Feet

Version 1.0
26-Jun-2019

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Terms and Acronyms

Abbreviation	Description
ACR	American College of Rheumatology
CD	Compact Disk
CRF	Case Report Form
DCF	Data Clarification Form
DICOM	Digital Imaging and Communications in Medicine
FTP	File Transfer Protocol
ID	Identifier
JRE	Java Runtime Environment
kV	kiloVolts
mAs	milliAmpere second
MTX	Methotrexate
PTQ	Pre-Trial Questionnaire
QC	Quality Control
QRG	Quick Reference Guide
SMART Submit	Bioclinica's web-based system for clinical trial image uploads and related communication management
UDF	Universal Disk Format

1 Introduction

The purpose of this manual is to standardize the X-ray acquisition procedures among the sites participating in the Horizon Pharma Rheumatology LLC ("Horizon") protocol HZNP-KRY-202. The latest version of the protocol should be consulted for overall inclusion/exclusion criteria and other study details.

All radiologists and technologists contributing to these studies are required to have had appropriate theoretical and practical training in X-ray. 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 X-ray in the Horizon HZNP-KRY-202 study. The procedure manual is designed for the study coordinator and X-ray technologists involved in this project. All new personnel, who join the study after site initiation, are also required to 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 images. The goal of this manual is to define a standard approach to performing X-ray that produces images of sufficient quality for achieving the study goals.

Questions regarding this manual or imaging techniques should be directed to:

Primary Contact:

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

Bioclinica Helpdesk:

Toll Free from the US and Canada: 1-888-ASK-BIO2 (1-888-275-2462)
International: +1-484-928-6076
Email: helpdesk@bioclinica.com

SMART Portal Live 24/7 Chat Support (See Appendix III)

2 General Study Information

The detailed description of the study rationale, design, objectives, investigational methods, eligibility criteria, evaluation criteria, and analysis approach is presented in the final version of the Horizon HZNP-KRY-202 study protocol.

Protocol HZNP-KRY-202 is a Phase 4, multicenter, randomized, double-blind, placebo-controlled, parallel-group, efficacy and safety study of pegloticase with methotrexate (MTX) vs. pegloticase with placebo for MTX in adult subjects with uncontrolled gout. The study design will include: 1) a Screening Period (screening should be completed within 4 weeks prior to Week -6); 2) a 2-week MTX Tolerability Assessment Period consisting of 2 weeks oral MTX for all subjects; 3) a Run-In Period consisting of randomization followed by 4 weeks of blinded oral MTX or placebo for MTX; 4) a 52-week Pegloticase + IMM Period; 5) a Safety Follow-up (Phone/Email/Site Visit) and 6) a 3 and 6 month Post Treatment Follow-up.

The overall objective of this study is to assess the potential for pegloticase with MTX to increase the response rate seen with pegloticase alone, and to characterize the safety, tolerability and pharmacokinetics of the concomitant use of pegloticase with MTX, by comparing pegloticase co-administered with MTX to pegloticase co-administered with placebo for MTX in adults with uncontrolled gout.

Imaging of the hands and feet will contribute to exploratory objectives of HZNP-KRY-202 through evaluation of mean change from baseline in bone erosions due to gout based on X-rays of the hands and feet.

Approximately 135 patients from approximately 65 sites are expected to be enrolled into this study.

2.1 Visit Schedule for Imaging Exams

X-ray examinations should be conducted according to the following visit schedule per protocol:

Day 1

Week 24

Week 52

Early Termination

End of Pegloticase Infusion Visit (if applicable)*

Unscheduled

* Subjects who end pegloticase infusions prior to Week 52 should follow the scheduled timepoints but avoid a repeat X-ray exam within 3 months of a prior exam.

A total of four (4) images should be acquired at each visit:

Left Hand/Wrist

Right hand/Wrist

Left Foot

Right Foot

2.2 Repeat Scans

Acquisition of scans of acceptable quality is an important responsibility of the imaging facility. In particular, it is critical to have a high-quality data for the baseline visit. If the imaging data are of substandard quality (Section 6.5), Bioclinica may request that the sequences failing quality control be repeated.

	**Repeats should be implemented as quickly as possible.**

3 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. An overview of roles and responsibilities as handled by the various parties follows. Note that the Principal Investigator, Study Coordinator, and X-ray Center technologist should agree in advance on their workflow.

3.1 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 their consent to participate
- Refer the patient to the cooperating imaging facility with all necessary documents, including those provided by the sponsor, to allow correct patient identification, include site ID, subject ID (screening # and subject #) and year of birth (per Country requirements)
- 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 (e.g. technologist)
    - A sub-investigator
    - The study coordinator
- The signed queries should be returned to Bioclinica within 5 business days. These queries are initially emailed from Bioclinica to the study coordinator in the form of a Data Clarification Form (DCF).
- The PI, or designee, is responsible for ensuring that the quality standards as outlined in this manual are followed.

3.2 Study Coordinator or Designee

In general terms the Study Coordinator's role is to facilitate communication among Principal Investigator, X-ray imaging facility, Bioclinica, and 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

- 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 imaging facility and ensure that a Transmittal Form with demographic and visit information is available at the X-ray imaging facility at the time of the exam
- Establish a joint process with the X-ray 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 exams 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 five (5) 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

3.3 X-ray Imaging Facility Personnel

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

- Perform X-ray exams as indicated in this manual, ensuring consistency (i.e. anatomical coverage, etc.) across subjects and across visits for a given subject
- Verify that subject demographic information (per country requirements) and exam information captured on the Transmittal Form are entered completely and correctly on the electronic image file headers
- Verify that the initials of the technologist who actually acquired data for a given subject's visit are correctly noted on the Transmittal Form
- Retain a complete archive of the acquired imaging exams at the facility
- Document and report to the PI and Bioclinica any adverse events or reactions that happen during subject preparation and/or imaging sessions
- Establish with the study coordinator a joint process for sending data to Bioclinica
- Submit acquired data to Bioclinica 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 should designate a single Lead Technologist to work on this study. The responsibility of the Lead Technologist is to ensure that the imaging protocol is followed and other technologists working on this study are qualified to perform imaging for it

	**Acquisition of radiographs of acceptable quality is an important responsibility of the imaging facility.**

3.4 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 image acquisition according to procedures and protocols outlined in this manual
- Check incoming packages for completeness and correctness
- Inform the X-ray imaging facility about any issues related to data within five (5) 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 for each patient-visit within three (3) business days of receipt of a complete package
- Should any images be of unacceptable quality, the center will be instructed how to obtain a second image/data set
- Archive images and associated study information
- Perform central imaging analysis of X-ray data

	**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**.

4 Inclusion and Exclusion Criteria

Please refer to Inclusion Criteria and Exclusion Criteria of the latest versions of the applicable Horizon HZNP-KRY-202 study protocols.

5 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 Questionnaire (PTQ) within 5 business days of receipt. 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 capable X-ray device
- Digital images generated should be of DICOM format
- Digital archival capabilities at the imaging center

5.2 Technologist Training

The lead assigned X-ray technologist logs into https://bioclinica-imaging.csod.com and completes the web training online. All usernames and passwords will be provided by Bioclinica within 2 business days from Bioclinica receiving the completed PTQ. Please print out the SMART Start training completion confirmation and file this in the study site files. After the lead imaging technologists certifies that he or she has completed training, the imaging facility is considered ready to scan the first subject per the imaging protocol, and the site will be considered qualified once the first subject scan passes quality control. If the first subject scan fails quality control then the subject will need a repeat scan and this scan will need to be sent to Bioclinica for quality control. Once the site is qualified, other screening subjects at the site can be scanned.

The Study Coordinator may send Bioclinica the name and email addresses of any back-up technologists to take part in the training as well. If at any time the site would like additional technologists to be invited to do the online training due to absences or staffing changes, the Study Coordinator should inform Bioclinica.

5.3 Digital Equipment

Digital equipment (computed radiography or digital radiography) will 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 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 the electronic image upload system (see Appendix III)
- If the electronic image upload system can't be used then deidentified data may be sent on CD-ROM or film
- The digital acquired data must be submitted as DICOM files. In the rare case that you are unable to do this, please contact Bioclinica

5.4 First Subject Test Image

The first subject submitted from each site will be reviewed for site qualification purposes to ensure image quality meets study requirements. Further subjects are not to be scheduled until the first subject passes image QC. A QC report listing results of quality review will be e-mailed to the site within three (3) business days from receipt of data. The site will be fully authorized to screen study subjects upon receiving quality confirmation from Bioclinica regarding the first subject.

	**Bioclinica will review first subject submitted for site qualification purposes to ensure image quality meets study requirements. Do not schedule further subjects until the first subject passes Bioclinica image QC.**

6 Procedures and Techniques for X-ray

In this section the specific requirements are presented for X-ray examination of the hands/wrists and feet. 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.

6.1 Labeling Patient Exams in Electronic Header

The examination description should include protocol information "Horizon HZNP-KRY-202".

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 10-digit Subject Number [Site Number (US-XXX) hyphen (-) 3-digits 2XX)]

  Example: US-001-201

- "**Date of Birth**" enter 01-JUL-19YY (enter subject's year of birth only, along with 01-Jul

  Example: 01-Jul-1945

- "**Patient History**" enter: **Visit Name**

  Example: Day 1

6.2 Exposure Technique for Hand/Wrist Radiographs

Expose to optimally depict trabeculae and joints.

Radiographic Table	Central ray perpendicular to the plane of the film	Required
FFD	40" (100 cm)	Required
Focal Point	Small	Required
Collimation	Full size of the film (24 x 30 cm) including Syn-X-RA™ scale	Required
Digital	100 – 150 µm or 0.1-0.15 mm or 7-10 line pairs/mm	Required
Positioner	Syn-X-RA™ for hands and feet *(provided)*	Required

6.3 Hand/Wrist Positioning using the Syn-X-RA™

- Remove all rings and jewelry from the hand and wrist. Place the subject comfortably in a chair next to the table. The surface of the table should be slightly lower than the subject's shoulder: approximately the level of the axilla (Fig.1).
- The elbow should be flexed approximately 90° (Fig. 1).
- The entire forearm should be flat against the X-ray table (i.e., the wrist should not be extended). A sandbag may be placed across the forearm to help stabilize it.
- Center the transparent template, Syn-X-RA positioning device (Fig. 2) on the cassette and rest one of the subject's hands on it **(right and left hands must be filmed separately on different films)**.
- Center the hand on the film with the metacarpophalangeal joints mid-line and the forearm parallel to the long axis of the cassette. Make sure the entire wrist is included.
- Position the hand in slight ulnar deviation so that the index finger falls along a straight line through the radius (Fig. 3).
- Spread the fingers slightly apart, as on Syn-X-RA positioning device.
- The palm and wrist should be kept firmly in contact with the film. This usually requires conscious effort on the part of the subject as there is a natural tendency to supinate the forearm and flex the knuckles lifting the radial side of the hand and wrist off the cassette. **Therefore, please tell the subject to make an effort to keep the hand flat.** (Fig. 4, 5).

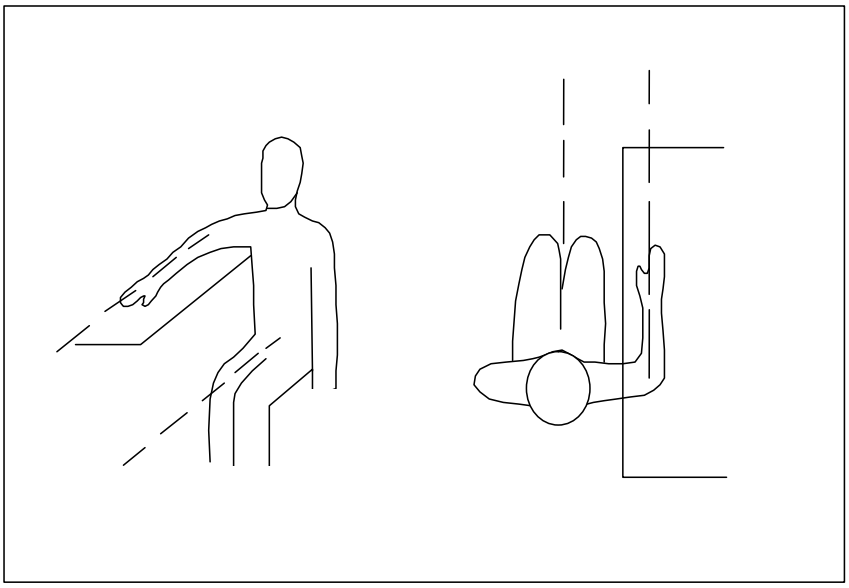


Figure 1: Proper Subject Positioning

The subject is seated beside a table at the level of the axilla with the arm resting on the table, the elbow bent 90°, and the forearm parallel to the thigh.

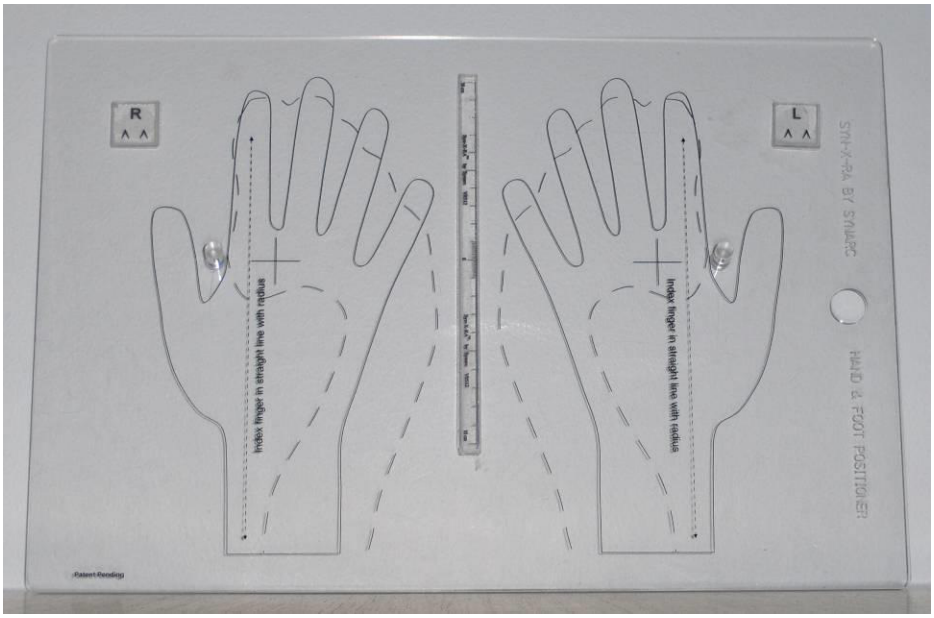


Figure 2: Syn-X-RA™ Positioning device

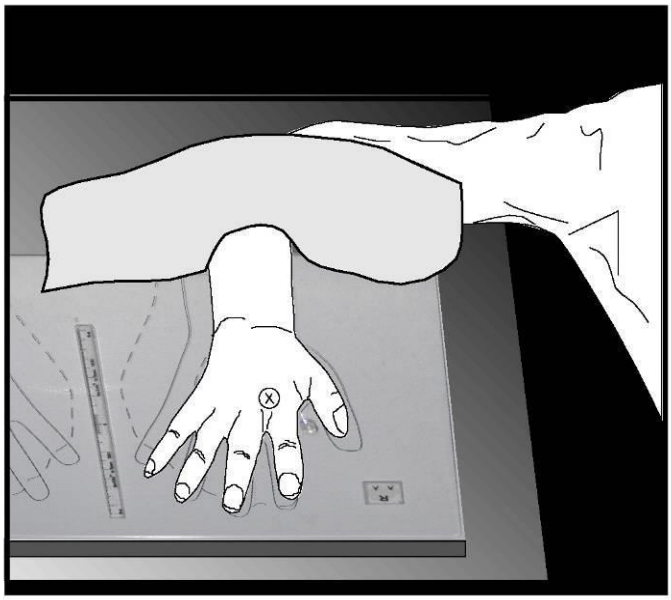


Figure 3: Proper Positioning of the Hand and Wrist

The Syn-X-RA™ is positioned on top of the film, and the hand is placed on the outline with the peg between the thumb and index finger. The palm and forearm should be pressed firmly against the Syn-X-RA™ and the fingers spread slightly. The X-ray beam should be centered between the 2nd and 3rd knuckles (⊗). A sandbag across the forearm helps stabilize the arm.

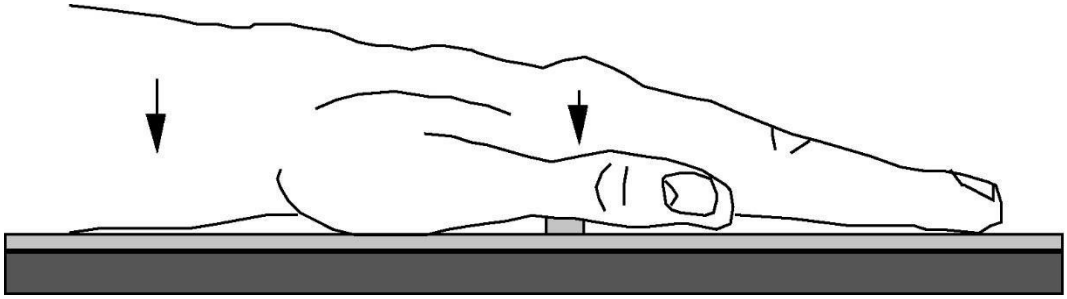


Figure 4: Proper Positioning of the Hand and Wrist

Ensure firm contact between the Syn-X-RA™ and the subject's hand and wrist. This requires mild effort by the subject; however, the subject should not press so hard as to cause trembling.

If the subject has difficulty maintaining this position, you can place a sandbag across the forearm to help prevent movement. Make sure the sandbag is not on the film. If you use tape to immobilize the hand or straighten arthritic fingers, please use paper tape as other tapes may show up on the film.

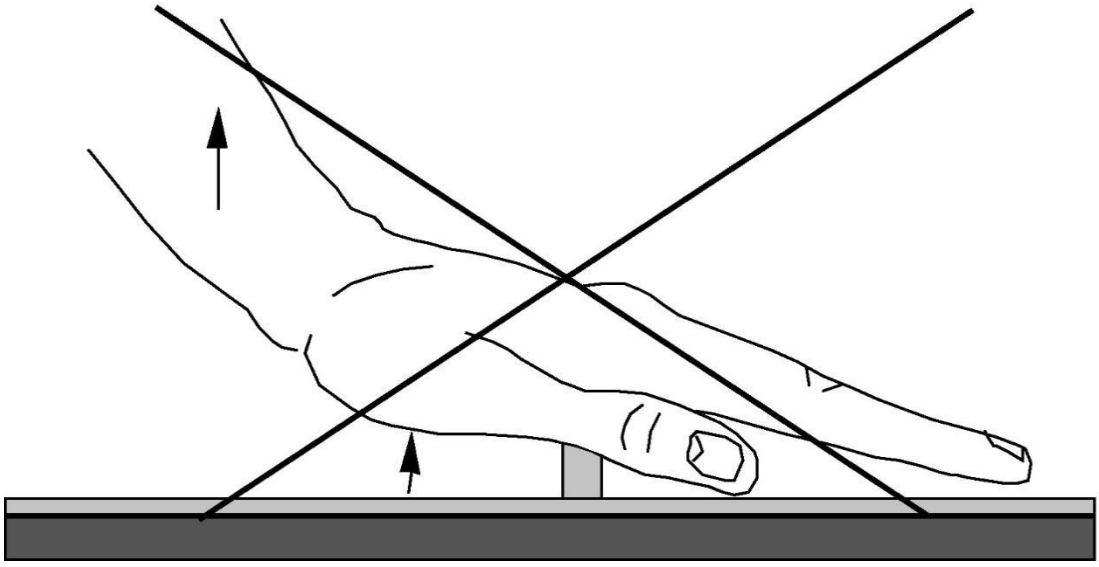


Figure 5: Improper Positioning of the Hand and Wrist

If the table level is not high enough (arm is insufficiently abducted) or if the subject does not consciously press hand and wrist against the cassette, the wrist will tend to rise off the Syn-X-RA™. This leads to image blurring, geometric magnification and superimposition of anatomy.

6.4 Positioning the X-ray Tube for Hand/Wrist Radiographs

6.4.1 Beam Centering

- Position the X-ray tube so that the beam is centered between the 2nd and 3rd metacarpophalangeal joints (knuckles) (Syn-X-RA Fig. 1). The central ray should be at 90 degrees to the plane of the film (Fig. 6).

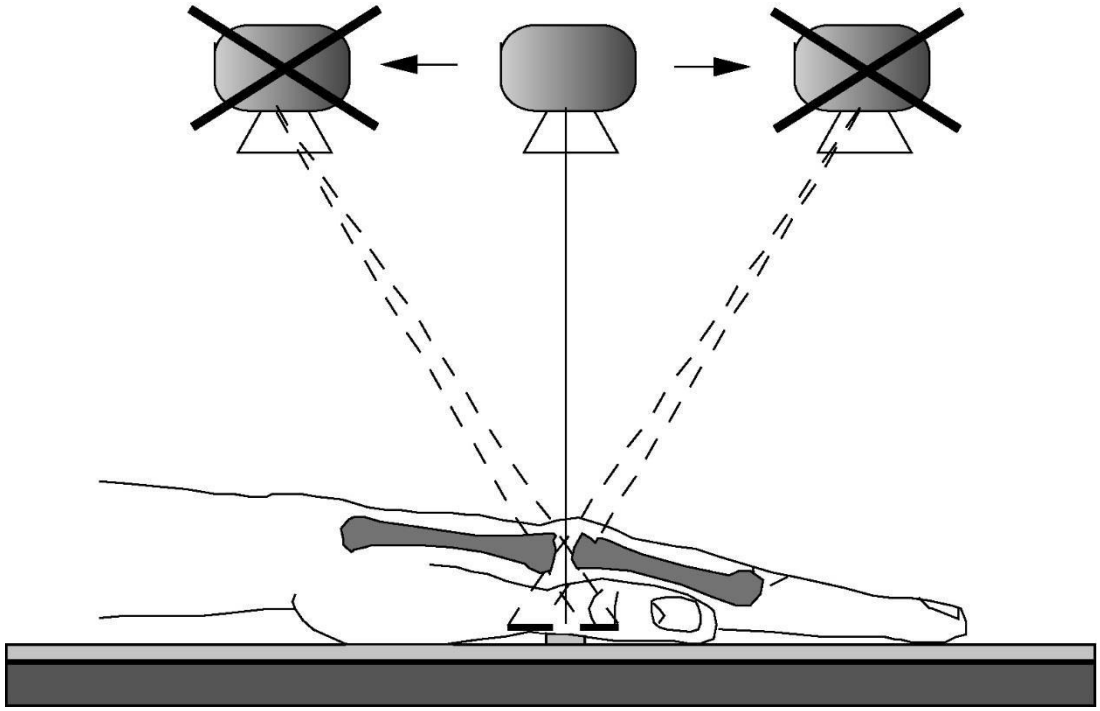


Figure 6: Beam Centering of the Hand and Wrist

The X-ray beam should be centered between the 2nd and 3rd metacarpophalangeal joints and angled at 90° to the film surface. This will image the joints tangentially. Improper beam centering will result in overlapping joint margins.

6.4.2 Collimation

Collimate to the size of the film. In order to optimize the radiologist's ability to identify subtle pathological changes, the entire film must be exposed to produce a black background against which to view the anatomy. There should be no white margins on the films and the Syn-X-RA scale must be included.

6.5 Criteria of Good Quality Hand/Wrist Radiographs

- Exposure should be appropriate for evaluation of all joints of interest, being neither too dark (overexposure) nor too light (underexposure). Expose to optimally depict the trabeculae and joints.
- Correct beam centering. The X-ray beam should be centered exactly between the 2nd and the 3rd metacarpophalangeal joints with no angulation. This will image the joints tangentially. Improper beam centering will result in overlapping joint margins in a hand otherwise properly positioned.
- Correct subject preparation and positioning. Jewelry (rings, watches, bracelets, etc.) should be removed if possible. The hand should be positioned on the Syn-X-RA and centered on the film with the index finger aligned with the radius along the long axis of the cassette. The fingers should be slightly spread apart and the thumb slightly extended. Proper projection of the ulnar styloid (without superimposition) will indicate the wrist was kept flat.
- Complete depiction. Complete anatomical coverage of the entire hand is required, including the distal radius and ulna and the radiocarpal joint. Both hands on one film are not acceptable.

6.5.1 Examples of Hand / Wrist Projection

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

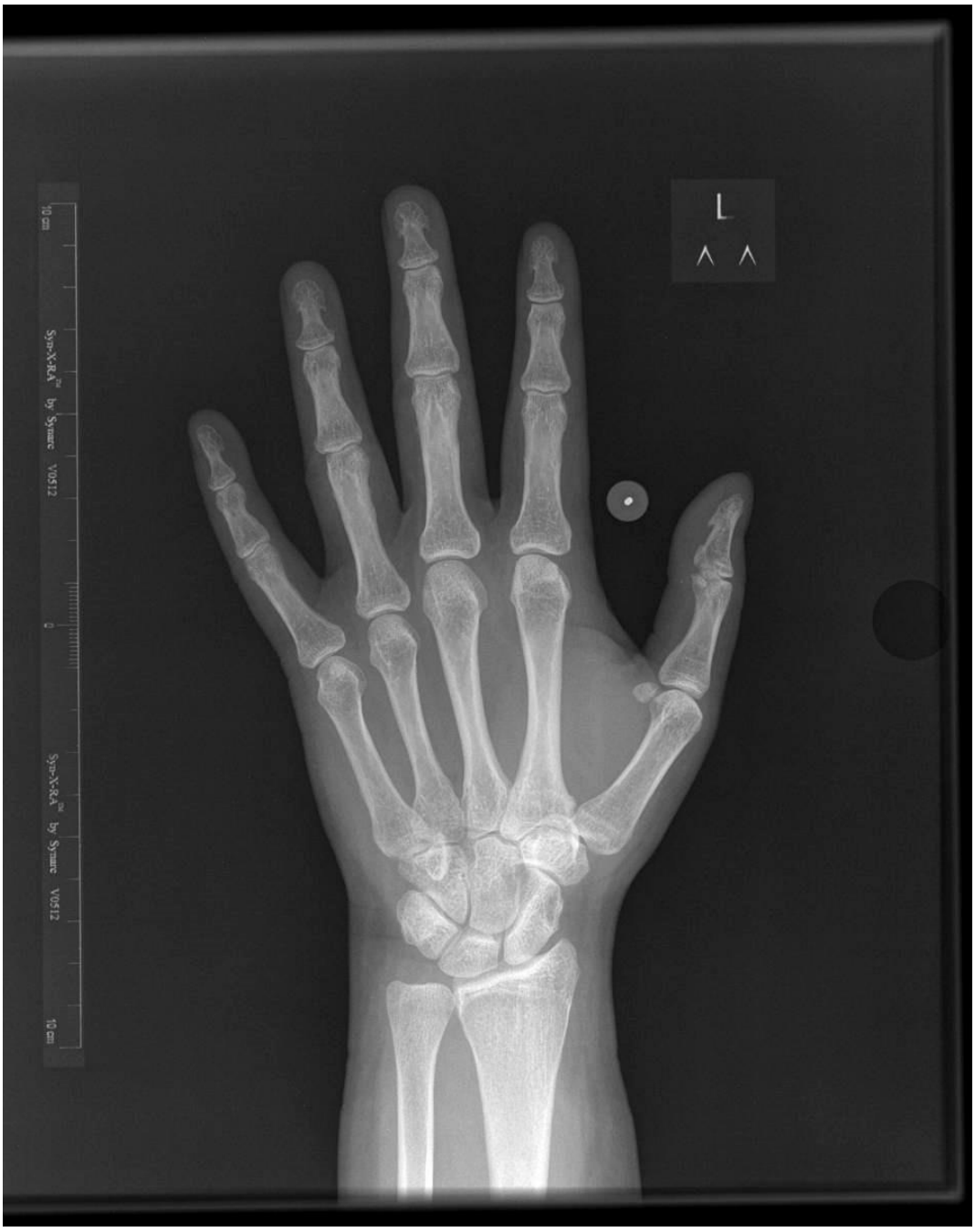


Figure 7: Good exposure of the Hand and Wrist

Includes entire hand and wrist; Fingers and thumb are well separated; The index finger is aligned with the radius; No overlapping of contours of the MCP's (indicating proper beam centering); Correct orientation of the ulnar styloid (indicates that the wrist is flat).

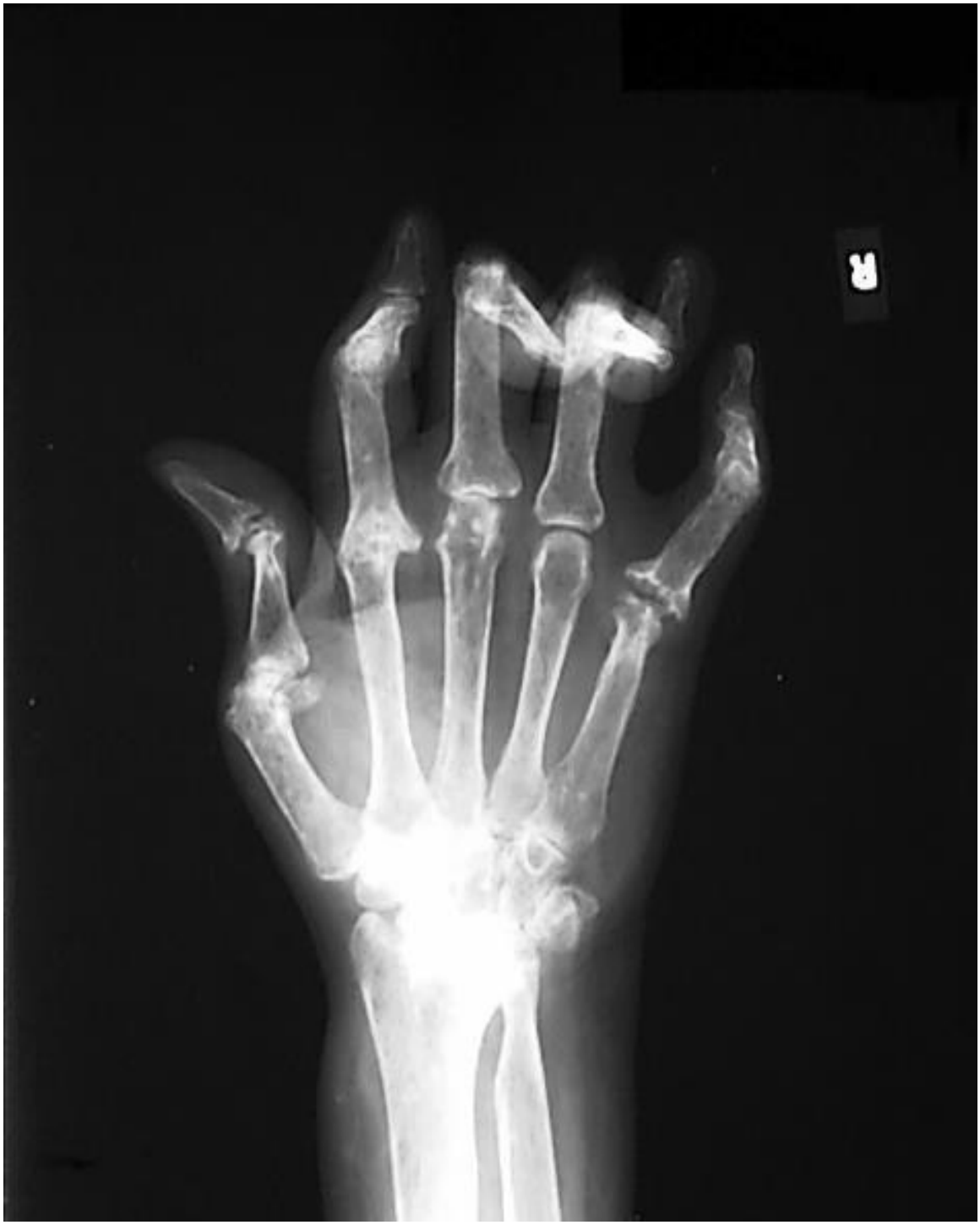


Figure 8: Finger deformities

In mild cases: please try to improve the alignment by taping the fingers (use only paper tape); in severe cases when it is impossible to correct (as the one above), please include a comment on the Transmittal Form.

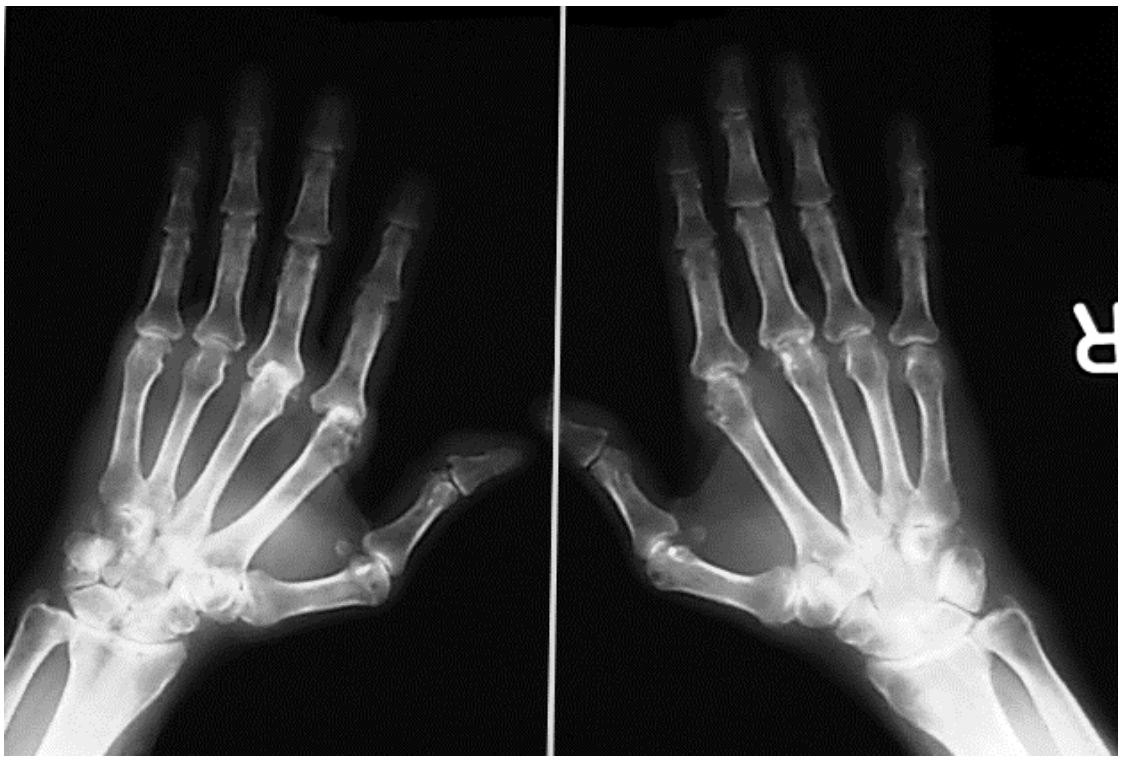


Figure 9: Both hands on one film on the Syn-X-RA™

This is an unacceptable image. Each hand must be imag**ed separately.**

6.6 Exposure Technique for Foot Radiographs

The aim of foot radiography is to evaluate the forefoot joints, particularly the five metatarsophalangeal joints and the interphalangeal joint of the great toe. Correct exposure settings and radiographic technique, as well as proper positioning, ensure adequate radiological evaluation of these joints.

Expose to optimally image the trabeculae and joints of the forefoot. This typically requires underexposure of the midfoot and ankle. A properly exposed radiograph of the forefoot may thus appear esthetically unpleasant when taken as a whole. It must be remembered, however, that it is the quality of the forefoot images that is the only true concern.

Table Top	**Central ray perpendicular to the plane of the film with 5° cephalad angulation**	**Required**
FFD	**40" (100 cm)**	**Required**
Focal Point	**Small**	**Required**
Collimation	**Full size of the film (24 x 30 cm) including Syn-X-RA scale**	**Required**
Digital	**100 – 150 µm or 0.1-0.15 mm or 7-10 line pairs/mm**	**Required**
Positioner	**Syn-X-RA™ for FEET** **Follow dotted lines on positioner**	**Required**

6.7 Foot Positioning using the Syn-X-RA™

- The subject must remove socks or nylons.
- Place the subject in the supine position. A table pad may be used for the comfort of the subject.
- Flex the knee enough to have the plantar surface of the foot flat on the table.
- Center the correct side of the Syn-X-RA™, (Figure 10) on the cassette and rest one of the subject's feet on it (right and left foot must be filmed separately). The Syn-X-RA™ is one of the study supplies and will be provided by Bioclinica.
- The long axis of the foot should be parallel to the long axis of the film.
- Tell the subject not to let the knee fall to the side, as this will elevate the medial side of the foot off the film.
- If the subject has difficulty with this position, an ankle sponge can be placed under the film to decrease the eversion strain on the ankle. If an ankle sponge is used, adjust the beam to maintain 5° cephalad angle relative to cassette. If you use tape to immobilize the foot, use only paper tape as any other tapes may show up on the film.

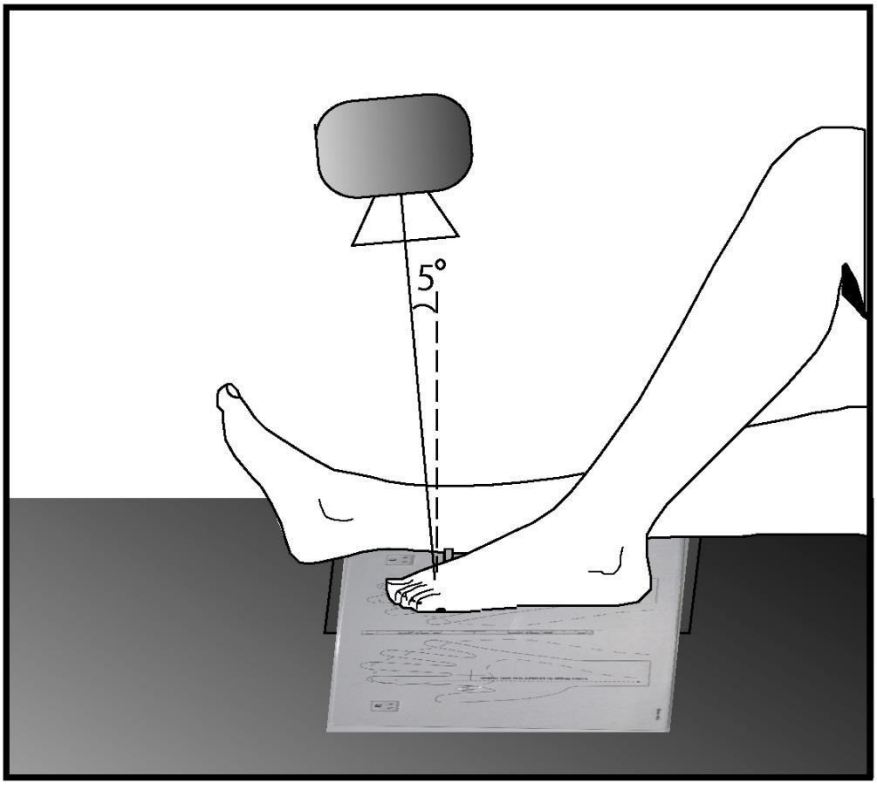


Figure 10: Proper Foot Positioning

The foot is centered flat on the cassette and the X-ray beam centered on the forefoot with 5° angulation cephalad.

6.8 Positioning the X-ray Tube for Foot

6.8.1 Beam centering and angulation

Center the X-ray beam vertically between the 2nd and 3rd metatarsophalangeal joints. The central ray should be angled 5° cephalad. For the assessment of subtle radiological signs (i.e., measurement of joint spaces and erosions), a consistent tube angulation is an absolute requirement.

6.9 Criteria of Good Quality Foot Radiographs

- Exposure should be appropriate for evaluation of the forefoot, being neither too dark (overexposure) nor too light (underexposure). The film should be exposed to optimally depict the trabeculae and joints.
- Correct beam centering and angulation. The X-ray beam should be centered exactly between the 2nd and the 3rd metatarsophalangeal joints with 5° cephalad angulation. This will image the joints tangentially. Improper beam centering or failure to angulate the tube will result in overlapping joint margins in a foot otherwise properly positioned.
- Correct subject positioning using the Syn-X-RA™. The foot should be centered on the film with its long axis parallel to that of the film. Proper projection of the metatarsophalangeal joints

without overlapping of the metatarsal bones will indicate the plantar surface of the foot was kept flat.

- Complete depiction. Complete anatomical coverage of the entire forefoot is required. The right and left foot must be filmed separately. Some collimation is required.

6.10 Examples of Foot Projection

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

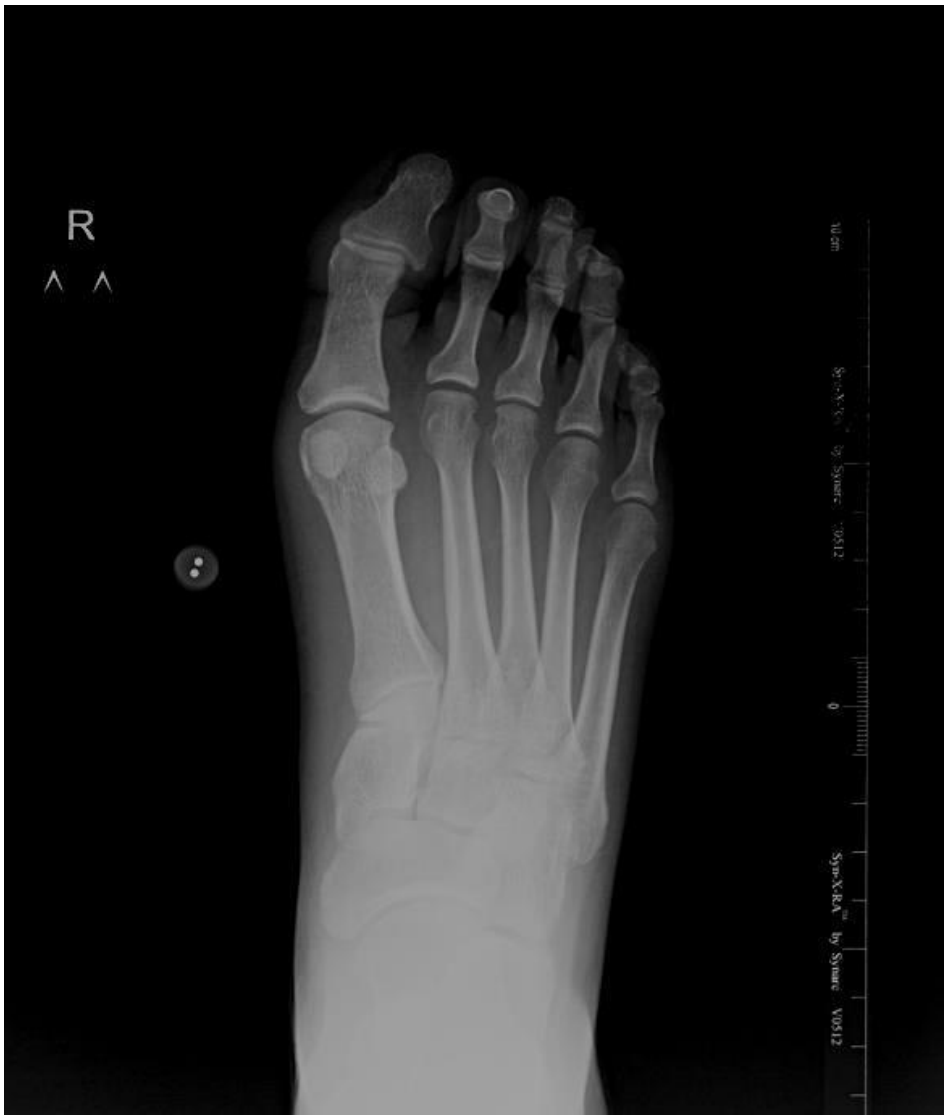


Figure 11: Good Exposure of the Foot

X-ray beam centered between the 2nd & 3rd MTPs with 5° cephalad angulation. Good positioning: foot centered on the film with long axis parallel to film; Proper projection of MTP joints; complete depiction of forefoot.

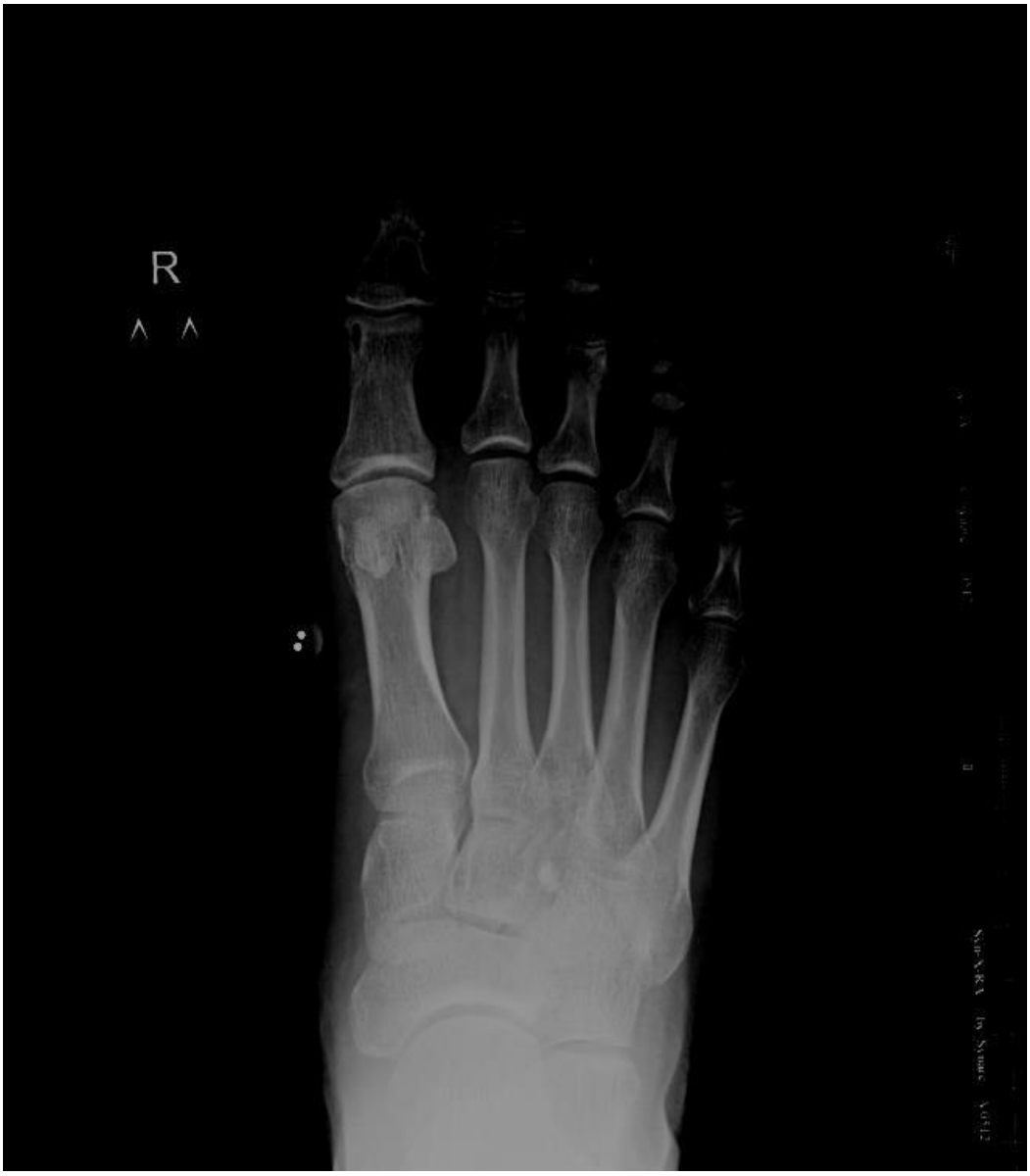


Figure 12: Overexposure of the Foot

Forefoot too dark. Proper exposure of forefoot requires underexposure of the midfoot and ankle

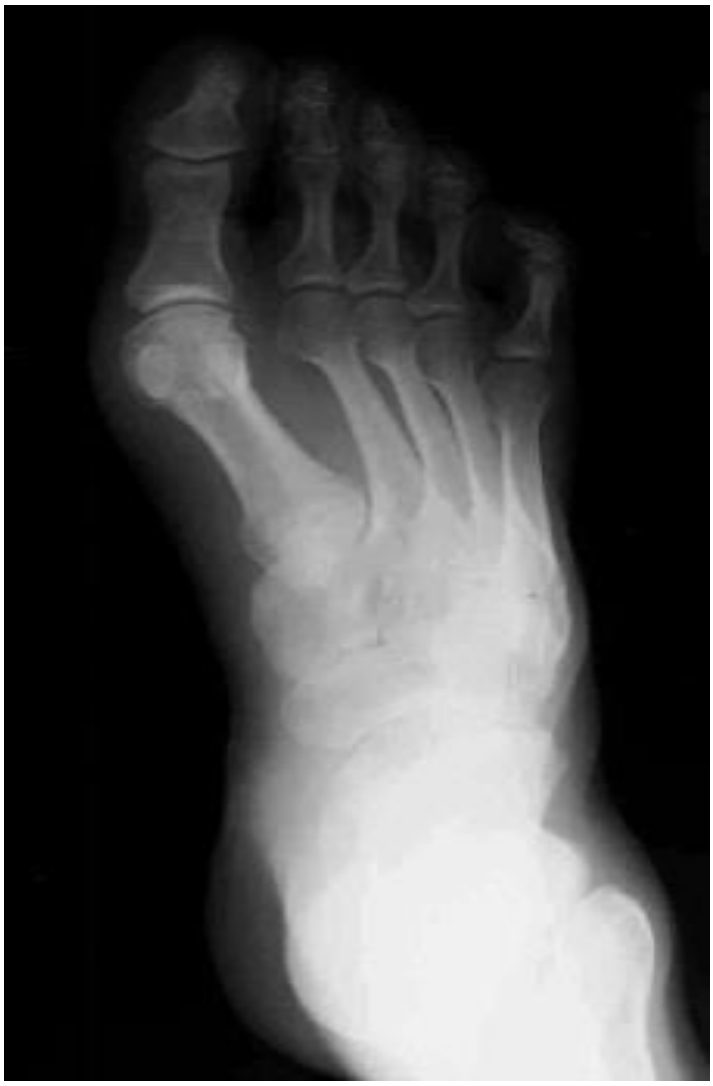


Figure 13: Incorrect positioning of the foot

The knee was allowed to fall to the side lifting the medial plantar surface of the foot off the cassette. Syn-X-RA was not used.

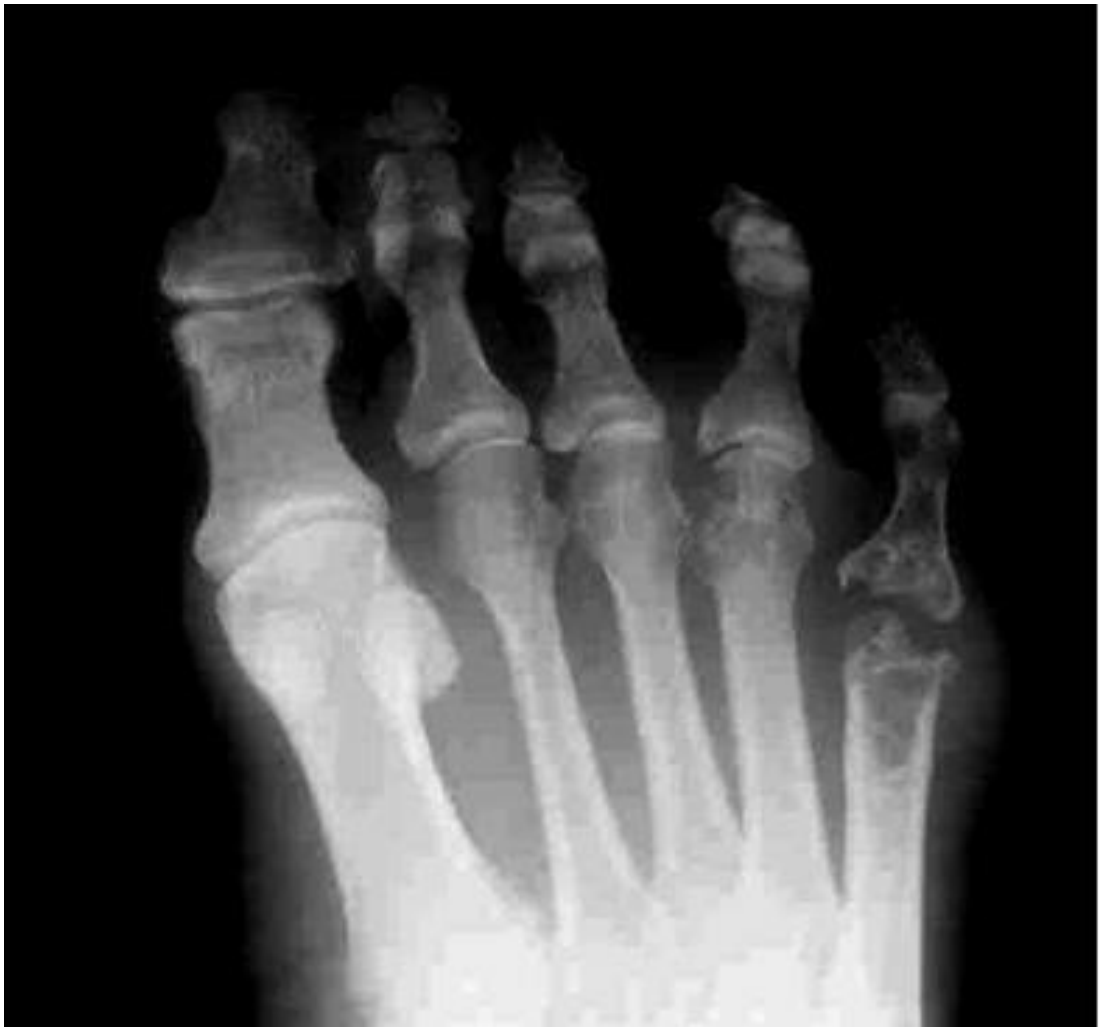


Figure 14: Incorrect beam centering of the foot
Incorrect beam centering or failure to angulate the tube: Nontangential projection of the MTP joints. Syn-X-RA was not used.

6.11 Repeat Examinations

Bioclinica's imaging technologist and/or the imaging physicist, and radiologist will evaluate the quality of each X-ray study. **A QC report listing results of quality review will be e-mailed to the clinical site within five (5) 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 and the X-ray 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 Baseline is still a Baseline exam – the repeated status will be marked on the radiographic transmittal form)

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

- Patient positioning and use of Syn-X-RA™ 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

7 Data Handling Procedures

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

	**The Study Coordinator and the Lead X-ray Technologist must decide who will be responsible for shipping or uploading the X-ray 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 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.

	**The imaging study should be sent to Bioclinica within one (1) business days 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 Portal) – the preferred method of data submission (refer to Appendix III for detailed description).
- Sending out via courier (UPS)

Both of these options are described below.

7.1 Electronic Transfer (FTP via SMART Portal)

SMART Portal 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 should contain:

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

The following is needed to run SMART Portal:

- Internet access with standard web browser (Microsoft Internet Explorer 6.1 and above or Mozilla Firefox 2.0 and above are preferred)
- Sun Java Runtime Environment (JRE) on computer. If your computer does not have it, you can download it for free from Sun's website
- Java applet for SMART Portal.

Sites interested in using this portal must fill out the SMART Portal: Use of Digital Image Upload Capability section included in the questionnaire packet. The personnel listed on this form will each be sent an e-mail listing their username, password, and instructions for logging into and navigating the interface.

Please refer to Appendix III for detailed instructions on using SMART Portal.

7.2 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 (Horizon HZNP-KRY-202)
- Patient Identifiers (Subject Number if available)
- Exam Date (DD-MMM-YYYY format)
- Visit Name (as specified in section 2.1)

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 airway bills (AWBs) that will include Bioclinica's address on them.

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

7.3 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.

	**Please do not use the left side of the radiographs to affix the label, because Bioclinica needs to place the internal barcode here.**

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).

Do not attach other labels to the film.

Do not mark the film.

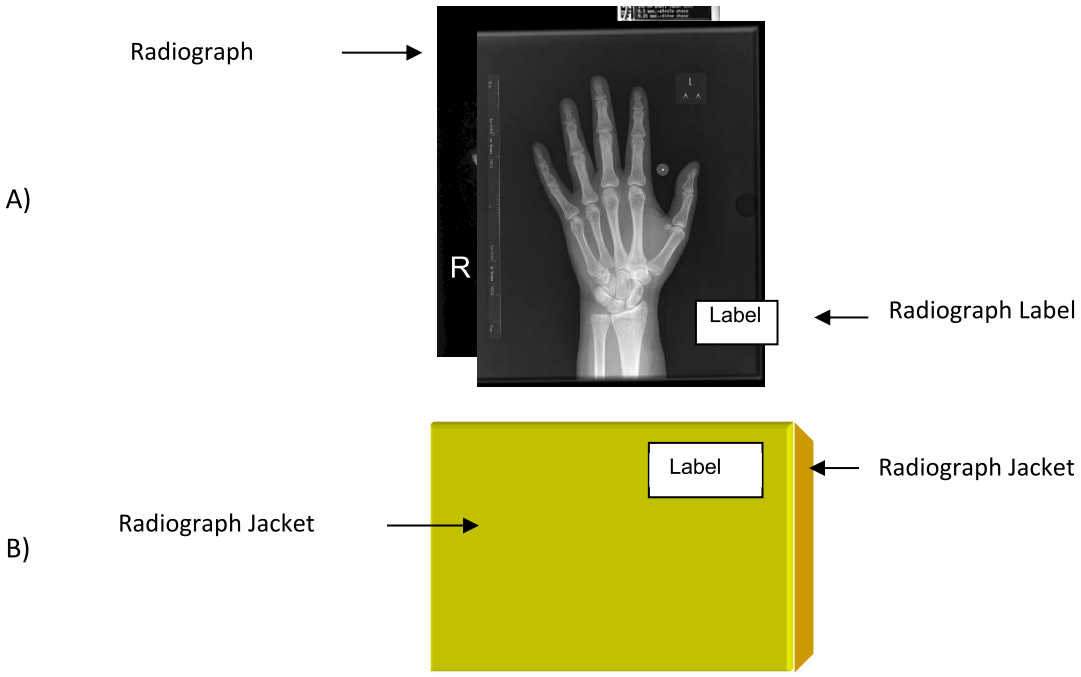


Figure 15: Labeling of the films (A) and the radiograph jacket (B)

- All hand and foot radiographs should be placed in the same radiograph jacket (one patient 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.

8 Supplies Provided by Bioclinica

Bioclinica Newark will be providing the following supplies to the imaging Site:

- Syn-X-RA™ hand/foot positioning device
- Radiographic Procedure Manual: one copy each for the radiology/clinical imaging facility
- Quick Reference Guide (QRG): a laminated guideline that summarizes the most important acquisition parameters and data shipment information
- Transmittal Forms: This form must be sent to Bioclinica per subject per visit if sending images via courier.
- Pre-printed air waybills
- High Resolution film and cassette (for analog sites)

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 the manual and email or fax it to Bioclinica. Supplies will be sent as soon as possible. Please plan ahead for imaging material needs.

Appendix I – Quick Reference Guide

THIS IS AVAILABLE AS A SEPARATE DOCUMENT

Appendix II – X-ray Transmittal Form

BIOCLINICA®

Horizon HZNP-KRY-202
Transmittal Form for X-Ray

Site, Subject, and Visit Information — To be completed at Study Site

Site ID: U S - [ ][ ][ ] (US) (-) (3 digit site ID)

Subject ID: U S - [ ][ ][ ] - 2 [ ][ ] (US) (-) (3 digit site ID) (-) (3 digit subject ID 2XX)

Year of Birth: [ ][ ][ ][ ] Y Y Y Y

Visit
- ☐ Day 1
- ☐ Week 24
- ☐ Week 52
- ☐ Early Termination
- ☐ End of Pegloticase Infusion Visit (if applicable)
- ☐ Unscheduled

Please select if:
- ☐ Repeat Submission

X-Ray Information — To be completed at Imaging Center

X-Ray Exams
- ☐ Left Hand / Wrist
- ☐ Right Hand / Wrist
- ☐ Left Foot
- ☐ Right Foot

X-Ray Date: [ ][ ] / [ ][ ][ ] / 2 0 [ ][ ] (D D / M M M / Y Y Y Y)

Comments

Do not write below this line. For Bioclinica use only.

Data Receipt — To be completed at Bioclinica

RESERVED FOR BIOCLINICA BARCODE

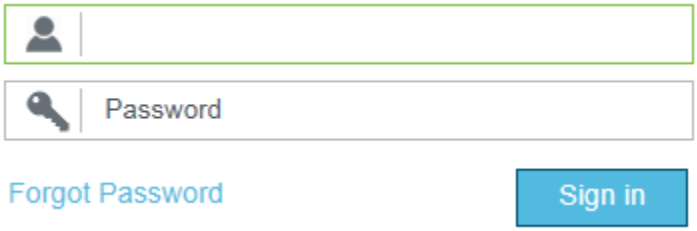
Comments

Bioclinica Tracking Number: 1 0 0 0 7 0 3 2 | 0 2 | 2 0 1 9 0 5 1 0

*** Distribution: File PINK copy at Study Site. Send Original (WHITE) and YELLOW pages to Bioclinica. ***

Appendix III - SMART Submit Quick Reference Guide

1. Login to https://smart.bioclinica.com



1. Your Username is your email address, password is SMART Portal password.
2. **Click** Sign In.

Note: Prior to uploading trial images and only at first log in of new users it will be required to watch a training video.

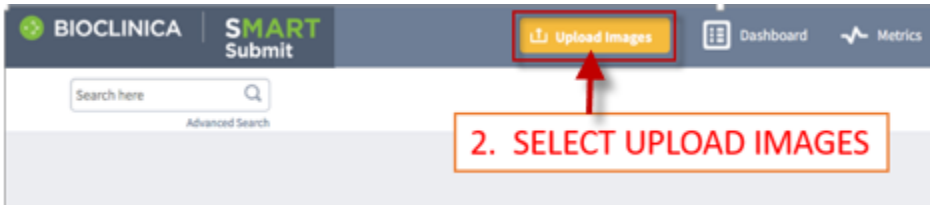
Note: After completing the training video and only at first log in of new users it will be required to upload a "User Qualification" upload. The "User Qualification" upload can be any zipped file containing DICOM files. The purpose of the User Qualification upload is to confirm you have access to DICOM, and have acceptable internet speed. The images will not be sent to BIOCLINICA. Please contact SMART Submit support team if you don't have qualification test image or need any help. You can quickly reach out to them by clicking "Q&A" on the right.

IMPORTANT: There may be additional test data requested by Bioclinica to confirm the correct scanner / equipment setup prior to your site's authorization.

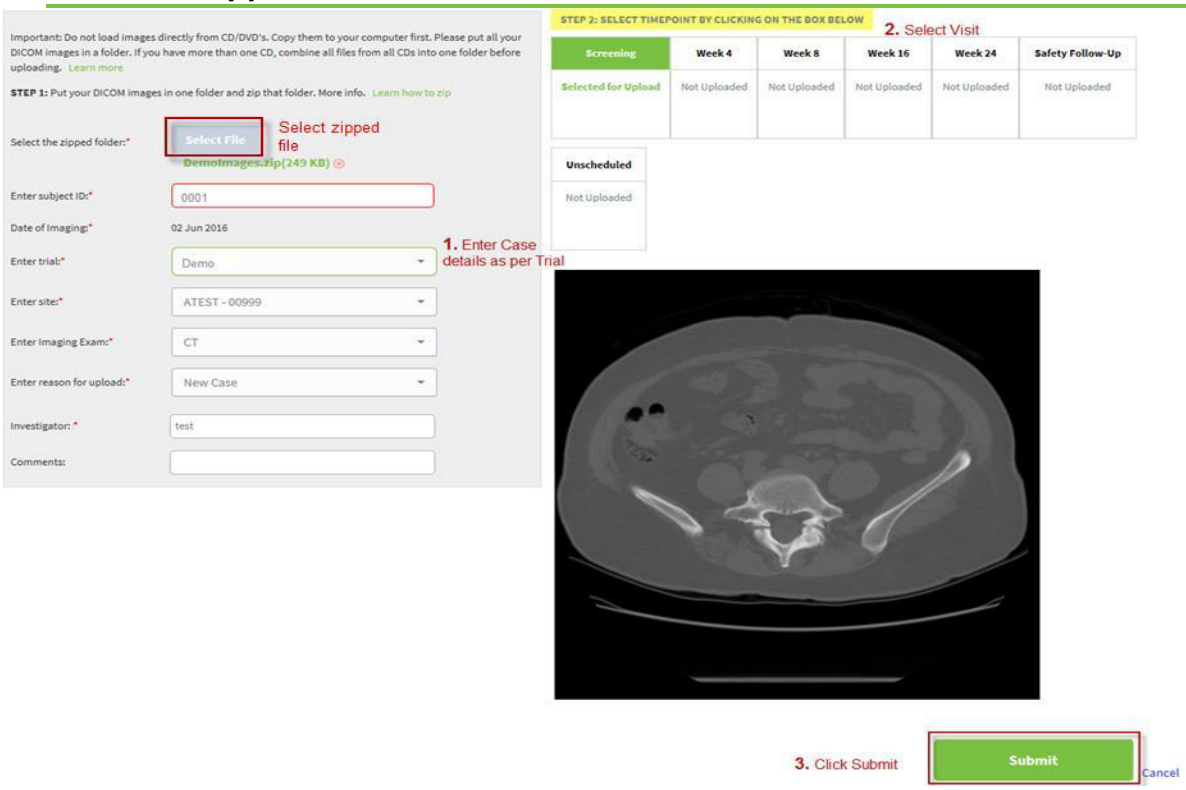
Click Image Submission Link with appropriate trial and Site.

2. Upload Images

You will be presented with SMART Submit dashboard. Please click "Upload Images" on top middle screen as shown.

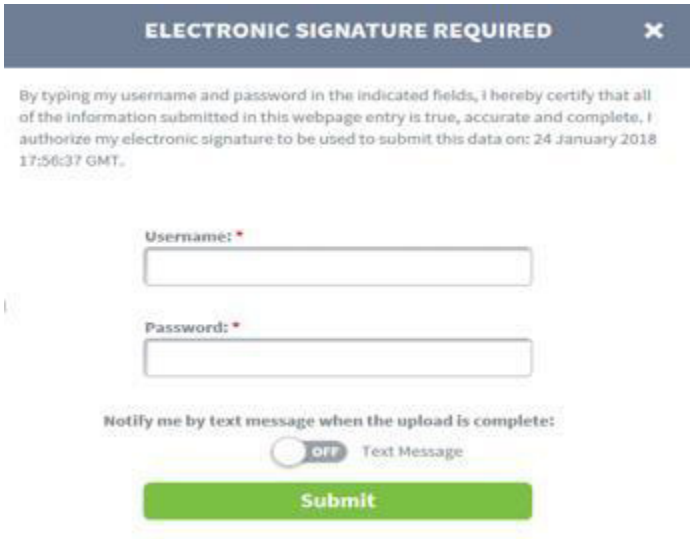


3. Select Zipped File, Enter Case Details, Submit



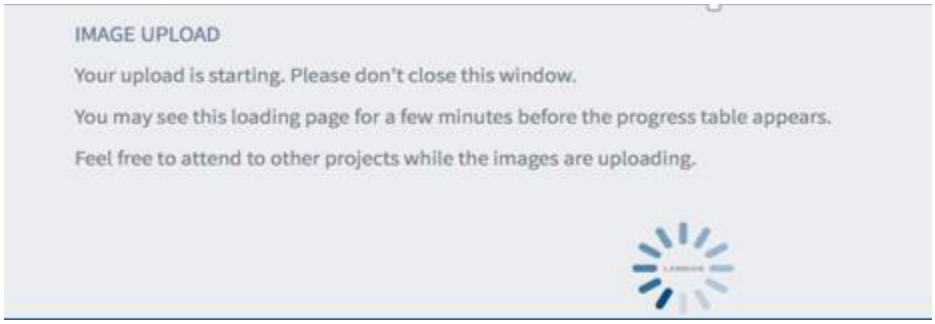
4. Electronic Signature

Please enter your username and password to sign and authorize the upload.



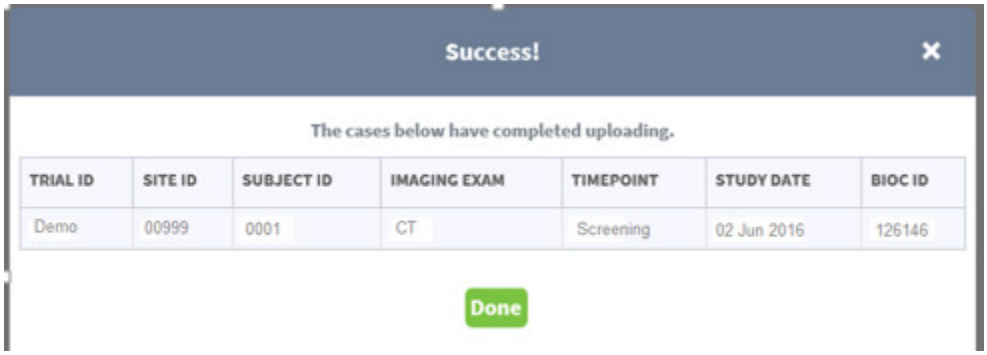
5. Image Upload Progress

After you click Submit button you will be directed to Image Upload Progress. At this point you can leave the computer Unattended while the images are uploaded.

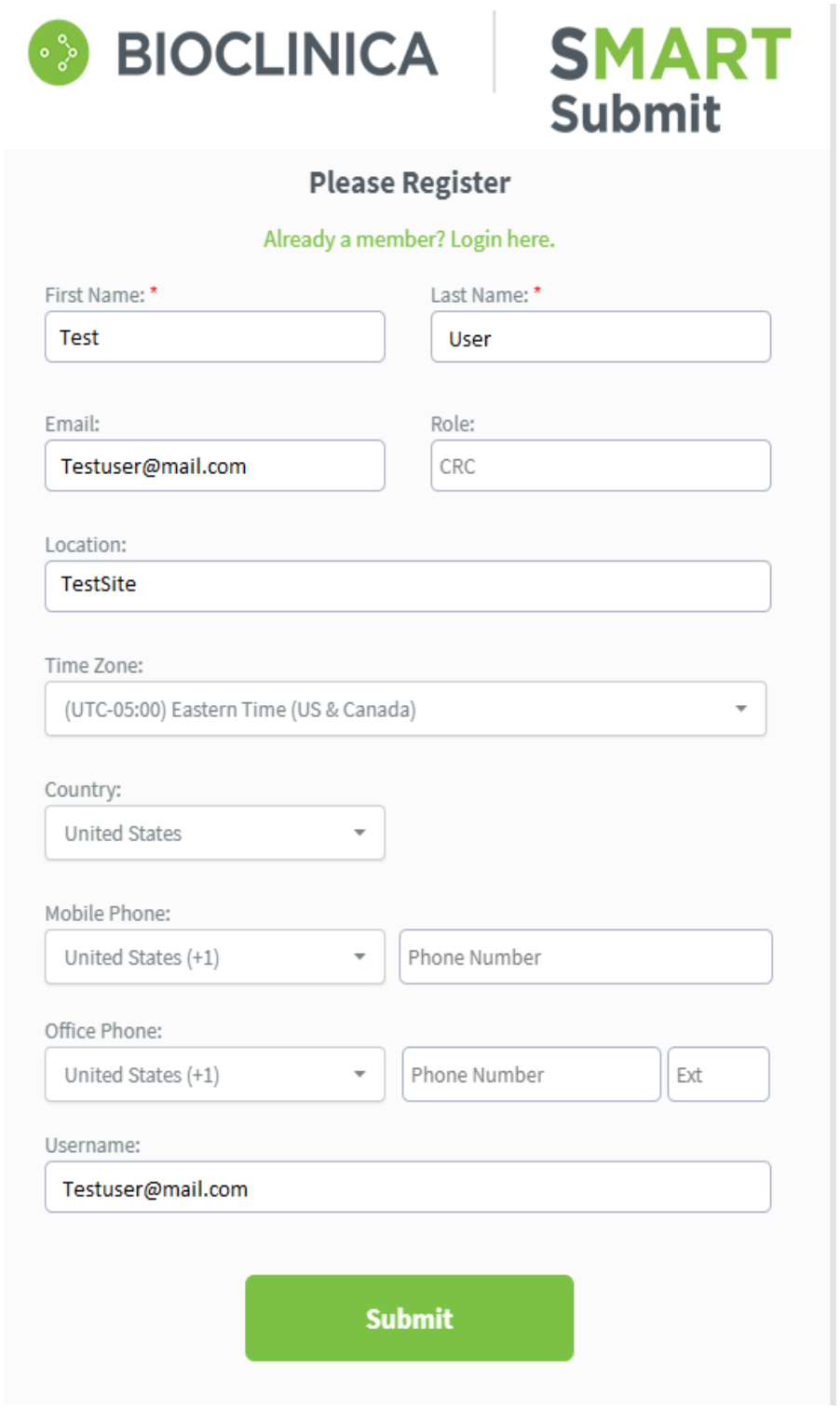


6. Image Upload Success

Once the image upload is completed you will be presented with Success! Message. Please click “Done” and you will be directed back to the SMART Submit dashboard.



Logging in For the First Time



1. **Confirm** your First Name, Last Name, Email, Role, Location, Time Zone, Country, Mobile Phone, Office Phone, and Username.

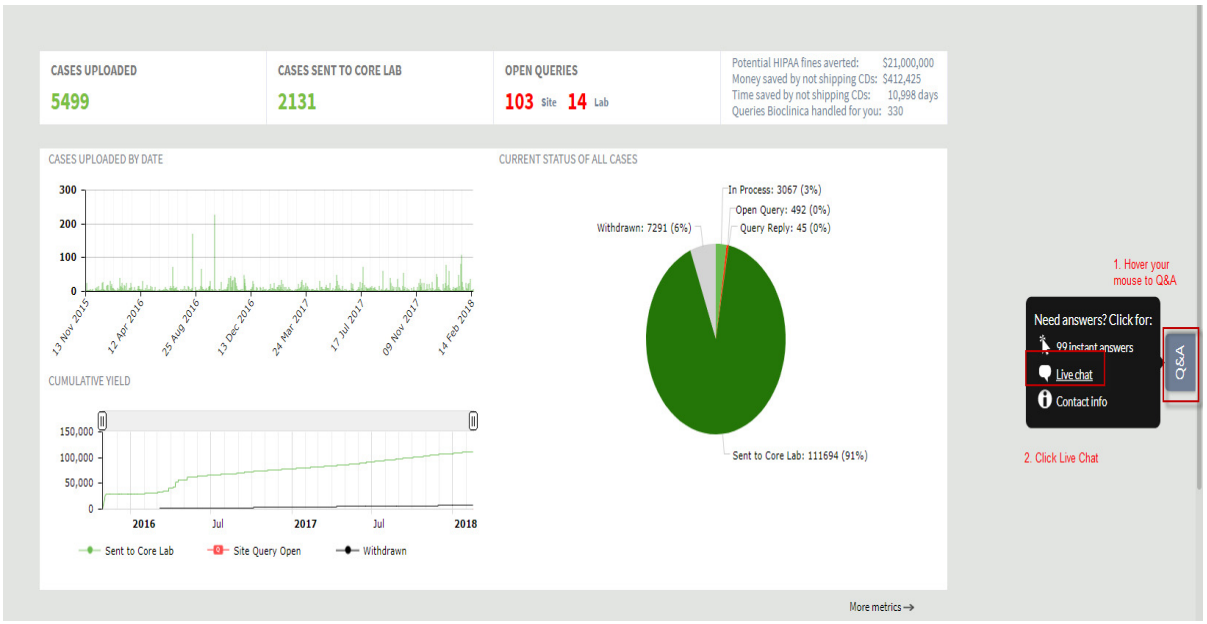
2. **Click** Submit.

SMART Submit Support

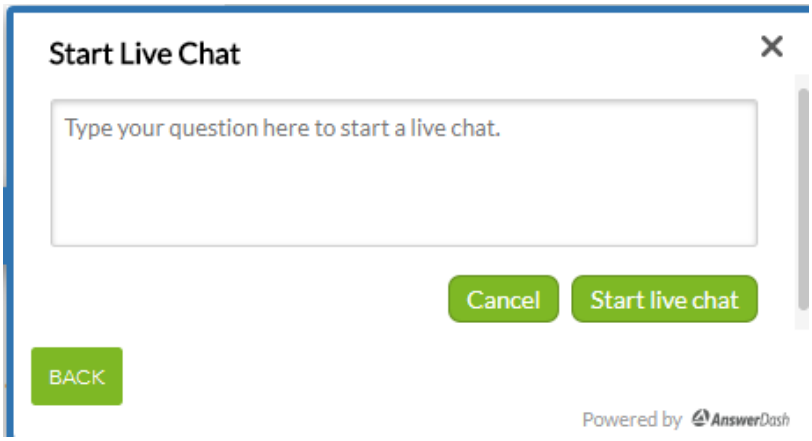
There are many ways you can reach out to support.

1) Live 24/7 chat support:

After logging on to SMART Submit on right side of screen you can hover your mouse over Q&A and Click Live Chat



Enter Any Question you have here.



2) Call Support Line:
+1 844 612 6640

3) Email at smart.submit@bioclinica.com