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# Radiographic Imaging Manual for Examinations of the Knee

Galapagos & Servier
Protocol **CL2-201086-002/GLPG1972-CL-201**
Bioclinica Project Code 10004976

Roccella

Prepared by: Bioclinica Medical Imaging, 7707 Gateway Blvd., 3rd Floor, Newark, CA 94560, +1-415-817-8900

# Galapagos/Servier
# Protocol CL2-201086-002/GLPG1972-CL-201

**Efficacy and safety of 3 doses of S201086/GLPG1972 administered orally once daily in patients with knee osteoarthritis. A 52-week international, multi-regional, multi-center, randomized, double-blind, placebo-controlled, dose-ranging study.**

Version 1.0
28-Jun-2018
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# 1 LIST OF ABBREVIATIONS AND ACRONYMS

| | |
|---|---|
| AWB | Air waybills |
| CD-ROM | Compact Disk – Read Only Memory |
| CRO | Contract Research Organization |
| DCF | Data Clarification Form |
| DICOM | Digital Imaging and Communication in Medicine |
| EC | Ethics Committee |
| FTP | File Transfer Protocol |
| GCP | Good Clinical Practice |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonization |
| IR | Image Receptor |
| PA | Posterior/anterior |
| PACS | Picture archiving and communication system |
| PI | Principal Investigator |
| QRG | Quick Reference Guide |
| TF | Transmittal Form |
| UDF | Universal Disk Format |
| UPS | United Parcel Service |

# 2 INTRODUCTION

The purpose of this manual is to standardize the imaging acquisition procedures among the sites participating in the GALAPAGOS NV & I.R.I.S. Protocol CL2-201086-002/GLPG1972-CL-201, " Efficacy and safety of 3 doses of S201086/GLPG1972 administered orally once daily in patients with knee osteoarthritis. A 52-week international, multi-regional, multi-center, randomized, double-blind, placebo-controlled, dose-ranging study." 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. 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 GALAPAGOS NV & I.R.I.S. CL2-201086-002/GLPG1972-CL-201 study. The procedure manual is designed for the study coordinator and X-ray technologists involved in this project. A Quick Reference Guide for X-ray 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 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, X-ray techniques should be directed to:

Primary Contact:

Galapagos (10004976) Study Team
Bioclinica, Inc.
7707 Gateway Blvd, Third Floor
Newark, CA 94560 USA
Email: 10004976Support@bioclinica.com
Newark Office Number: +1-415-817-8900
Fax: +1-415-817-8999

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

International: +1-484-928-6076

For a listing of all Toll Free numbers please click the link below

http://www.bioclinica.com/sites/default/files/u1/Bioclinica_Toll_Free_Numbers.pdf

# 3 General Study Information

## 3.1 Protocol Synopsis

This is a multi-center, randomized, placebo-controlled, double-blind trial in male and female adult subjects diagnosed with osteoarthritis (OA) of the knee with Kellgren and Lawrence grade 2 and 3, and an OARSI score of 1 or 2 conducted at approximately 110 global sites. The study will enroll approximately 852 randomized subjects to assess the safety and efficacy of at least 1 dose (among 3 doses) of S201086/GLPG1972 administered orally compared to placebo in subjects diagnosed with knee OA.

Bioclinica's role in this study is to support primary outcome measures of the study, specifically, cartilage loss at Screening (ASSE) and Week 52, as assessed from knee radiographs by an independent radiographic reviewer. Both knees are scanned at ASSE followed by confirmation of a target knee for the next visit. JSW measurements of the lateral and medial compartments of the target knee joint will be performed by Bioclinica technicians with Central Reader oversight.

## 3.2 Expected Radiographic Views

Radiographs of the knee will be performed in the following manner:

- Radiographs of both knees (unilateral acquisition) will be captured at screening (ASSE) in the posterioanterior (PA) projection using the standing, 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.
- At followup time-point, the target knee (left or right, as judged by eligibility assessment) will be acquired in the posterioanterior (PA) projection using the standing, fixed-flexion method of positioning. 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.

## 3.3 Imaging Time Points

The required X-ray images obtained for subjects enrolled in the CL2-201086-002/GLPG1972-CL-201 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**

| Study Week | Baseline ASSE | W052 | Premature Withdrawal WD |
|---|---|---|---|
| Both knees | X | | |
| Target knee **ONLY** | | X | X* |

*To be performed only if the previous X-Ray (W000) is done more than 9 months before the premature withdrawal

## 3.4 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 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 |
| ❑ | **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 |
| ❑ | Review the supply package contents to ensure receipt of all study materials. | The supplies enclosed are as follows:<br>• SynaFlexer ™ Knee positioner<br>• X-ray Imaging Manual<br>• X-ray Quick Reference Guide<br>• Pre-Printed airway bill (AWB)<br>• Transmittal Forms for X-ray |
| ❑ | Please ensure that all applicable study personnel read this Procedure Manual and Quick Reference Guide (QRG). | |
| ❑ | Complete the study specific training for X-ray image acquisition provided by Bioclincia in the SMART Portal. | It is expected that at least one lead technologist involved in the study will complete training prior to authorization. |

# 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 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 subject is eligible and can be included in the study, what is the target knee, and is ultimately responsible for the safety of the subjects in the study.

The PI's responsibilities include the following:

- Ensure the subject 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 subject meets all criteria for the X-ray
- Refer the subject to the cooperating imaging facility with all necessary documents, including those provided by the sponsor, to allow correct subject 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, 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 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 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 one (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 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 subjects and across visits for a given subject
- Verify that subject 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 GALAPAGOS NV & I.R.I.S.
- The facility is considered authorized to conduct the imaging of the first subject-visit after the Primary Technologist completes the WebEx training and prints and files the certificate.

| | |
|---|---|
|  | **Acquisition of radiographs of acceptable quality is an important responsibility of the imaging facility.**<br><br>**If you change your equipment during the course of the study, please contact Bioclinica before you do so. Scanner consistency should be maintained through out the study.We need to evaluate the new equipment to make sure it meets the requirements of this study.** |

## 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 image acquisition according to procedures and protocols outlined in this manual
- Check incoming packages for completeness and correctness
- Inform the X-ray 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 subject-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
- 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 subject treatment. Clinical management is the sole responsibility of study subject's locally licensed physicians**. |

## 4.5 Study Supplies

Bioclinica supplies clinical sites with the following study materials:

- Synaflexer™ knee positioning device for X-ray
- X-ray Imaging Manual: one copy each for the radiology/clinical imaging facility or facilities
- X-ray QRG: a laminated guideline that summarizes the most important acquisition parameters and data shipment information.
- X-ray 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 will be provided,envelopes can also be ordered from the courier when scheduling a pick-up or by contacting the study email.

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

### 4.6.1 Imaging Facility Training

Remote online training will be completed by all technologists acquiring radiographs working on this protocol. 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 and the site monitor of the change, confirm that training was completed, and provide a signed training roster for the new technologist, so that Bioclinica can notify Galapagos and Servier teams.

### 4.6.2 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 remote online training again.

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

# 5 X-ray 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 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.
- 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 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,the site is notified of their qualification.It is required that the same equipment 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 subject 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 Subject Exams in Electronic Header

The examination description should include "Galapagos/Servier Protocol CL2-201086-002/GLPG1972-CL-201".

To preserve subject anonymity and protect subject 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 subject identifiers are the Site Number, Subject 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):

- "**Subject Information**" enter 4 digit Site Number and 5 digit Subject Number

  Example: 1234-12345

- "**Date of Birth**" enter **01-JAN-YYYY*.** The day and month for each subject should be entered as 01-Jan followed by the true birth year of a patient.

  Example: 0-JAN-1945

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

  Example: W052, Left

The possible entries for Visit identification:
ASSE
W052
WD [PrematureWithdrawal]

# 6 Procedures and Techniques for X-ray

In this section the specific requirements for the radiographic examination are presented. The quality criteria for radiographs in a clinical trial are stricter than in standard clinical practice. The most reliable evaluations of the radiographs require adherence to uniform acquisition and quality standards by all study sites involved.

Conventional radiographic equipment with exposure of radiographic film or digital radiographic equipment may be used if it satisfies the requirements of the procedures described in this manual. Study centers that plan to use digital X-ray equipment may be contacted by Bioclinica to arrange for a test run of data submission if equipment approval cannot be provided based on site's responses on the Bioclinica Pre-trial Questionnaire. Radiographic equipment used in this study should be in good working order and undergo a quality assurance program that includes regular checks to ensure the equipment is performing properly and safely.

It is preferred that each study center use a single X-ray unit for each acquisition protocol for the duration of the study. Changing equipment can add unnecessary variability to the data. If it becomes necessary to change equipment at some time during the study, please contact Bioclinica as soon as possible before this change occurs.

Please follow standard radiation protection practices. Appropriate collimation of the X-ray beam and use of a lead apron to shield the gonads should minimize radiation dose to the subject.

Before each radiographic examination, prepare the following:

- Have positioning aids present in the procedure room
- Explain the examination procedure to the subject
- Have the Transmittal Form(s) ready to fill in
- Have study supplies ready to label the radiographs immediately
- **IMPORTANT:** To ensure subject confidentiality and HIPPA compliance, the biographical information flashed onto the cassette or entered into the digital image header should include the subject study identifier(Subject number,Visit name , Visit date ) **not the subject's name.**

## 6.1 Radiographic Supplies and Forms

Listed below are radiographic supplies and forms for use for radiographic examinations:

- "SynaFlexer" plexiglass positioning frame for reproducible foot fixation and knee flexion will be supplied by Bioclinica.
- **The X-ray Transmittal Form (TF)** (see Appendix III) must be completed for each subject visit in which X-rays are taken. The majority of images will be submitted to Bioclinica using a web-based portal. If submitting data via courier on disc and using paper TFs, please keep the pink copy of this form and send the white and yellow pages along with the images to Bioclinica.

## 6.2 Unilateral PA Fixed-Flexion Knee Radiograph

Radiographs of both knees will be acquired at Screening using this protocol for all subjects. Each knee at the screening visit needs to be imaged separately. For all radiographs, please concentrate on image quality and optimum positioning of the subject to facilitate grading.

**Please only obtain and submit images of the target knee at Week 52 (W052) and premature withdrawal (WD) visits.**

**Figure 1** A-Proper subject positioning and beam angulation for radiography of the knee. Images shows proper positioning against a Bucky.

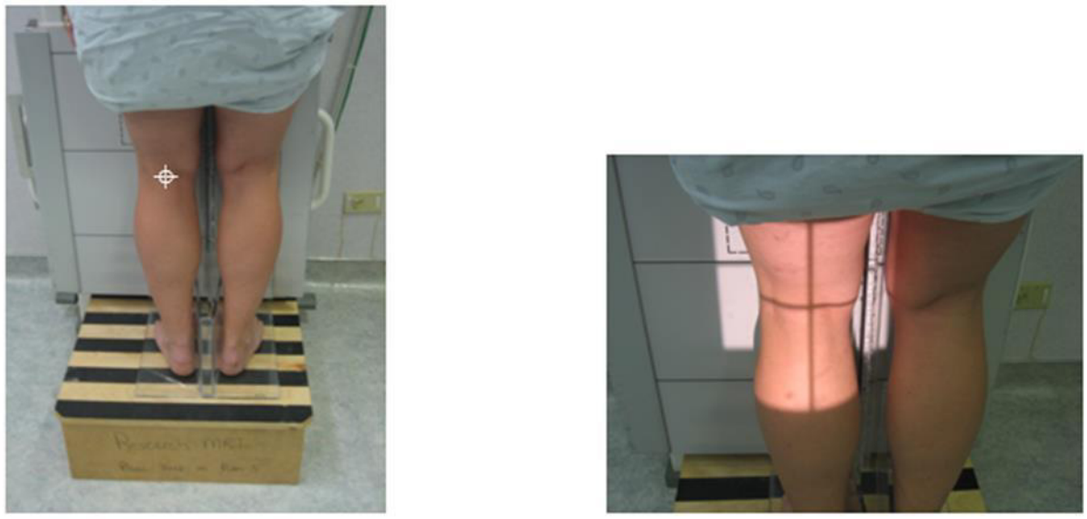


**Figure 2** Please note: if the Bucky is unable to go down to the floor, a platform may be used(not provided by Bioclinica) to better align, elevate, and center the subject as pictured above.

## 6.3 Unilateral PA Fixed-Flexion Knee Radiographic Exposure Technique:

| Imaging System | Bucky | Recommended |
|---|---|---|
| Source to Image Distance (SID); Focus-Film Distance (FFD) | 101.6 cm (40 inches) | **Required** |
| Film Size | 10”x12” (24 x 30 cm) | **Required** |
| mAs | Dependent on Film/Screen system | |
| KVp Range | 70-76 kVp | *Recommended* |
| Focal Spot | Small | **Required** |
| Other | Use Right/Left Lead Markers | **Required** |
| Beam Angle | 10 degrees caudal to start for initial subject X-ray, if it is not the correct angle (tibial plateau not flat and IMD > 1.5mm) use 8 and/or 12 degrees: Please note: the optimal angle for flat medial tibial plateau varies among subjects and angle adjustments should be made to minimize the IMD. If, for example, adjusting to either 8 and/or 12 degrees is an improvement but IMD is still large, please continue to a lower/higher angle as needed. | **Required** |

## 6.4 Examination Procedure:

### 6.4.1 Positioning the Subject

**Prior to Exam:**

Subject must be bare foot and in a gown or shorts to have the knees exposed.

- The anterior wall of the SynaFlexer positioning frame (provided by Bioclinica) must be in direct contact with the Bucky, the device will be placed off-center relative to the Bucky’s vertical center line, position the 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 cassette will be at the level of the subject’s tibiofemoral joint line.
- Please note if Bucky is unable to go down to the floor a platform(not provided by Bioclinica) may be used to better align and center the subject as pictured above.
- The subject should be in a PA standing position on the Synaflexer positioning frame (facing the Bucky, image receptor (IR) or reclining table top).
- Center the knee to be imaged on the IR and center the beam on the knee to be imaged (not on the column of beads). Ensure two columns of beads are visible on the image.
- Collimate to include 10cm (length of 5 beads) above and below the knee joint to be imaged.
- The great toes (or longest toes) of both feet are placed in contact with the anterior wall of the Synaflexer positioning frame.

- The subject should be positioned with their feet hip width apart and the foot of the knee being imaged pressed against the V-shaped plate. The other foot does not have to touch the wedge however the toes need to be in contact with the anterior wall of the SynaFlexer.
- Both knees are flexed until they touch the anterior wall of the frame. This fixes the angulation of the tibias.
- With the toes and knees still touching the anterior wall, both thighs are also pressed directly against the wall to fix the angulation of the femurs. It is important that the knees remain in contact with the Bucky when pushing the thighs against the wall of the Bucky.
- Gently guide the subject forward with your hand in the small of the back to ensure firm contact of both thighs with the wall of the frame. **IMPORTANT**: To ensure proper centering of the patella being imaged, subject should be facing forward with hips and shoulders squared to avoid rotation, 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 radiographs. It is important that the subject does not lift their heels of the frame when flexing.
- Body weight is distributed equally between the two legs.
- Shield the subject's gonads with a half apron.

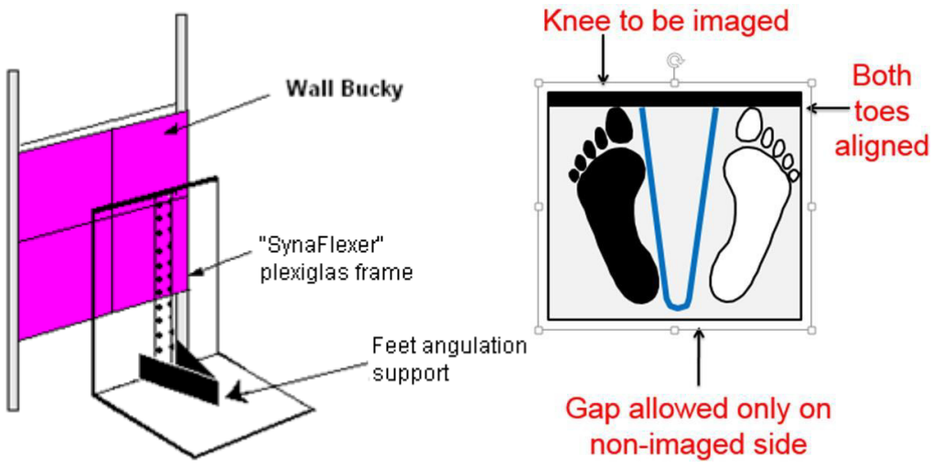



**Figure 3** SynaFlexer for reproducible feet fixation and knee flexion. The frame is positioned off-center with its anterior wall in direct contact with the Bucky, IR or reclining table top such that the target knee is centered on the Bucky/IR With the longest toes touching the anterior wall of the frame, the target knee is 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.

### 6.4.2 Positioning the X-ray Tube and Film Comments

- Center at the level of the joint line in the popliteal space (back of the knee) with a starting tube angle of 10° caudal . Upon reviewing the image, if the tibial plateau is not flat and IMD is > 1.5 mm, adjust the tube angle to 8° and/or 12°. If needed, additional angles may be acquired to obtain an optimal IMD.
- Do not move the Bucky when changing the tube angle. When the tube angle is changed adjust the tube up or down to have the central ray centered to the Bucky (IR).
- Beam centering above or below the knee crease will alter the projection of the tibial rims and the joint space on the radiograph. Precise beam centering and angulation is critical to the success of the study.
- Collimate to the size of the cassette. 10cm (length of 5 beads) above and below the knee joint should be visualized.
- Use a lead (R or L) marker and place it PA on the Bucky(IR) on the lateral aspect of the knee where it will not obscure the knee anatomy Properly collimated images will include the entire femoral and tibial metaphysis and the head of the fibula.
- Expose the target knee using a **10”x12” (24 x 30 cm)** cassette.

### 6.4.3 Special Remarks

If a subject was difficult to position or has a special consideration, please relay that information to Bioclinica, Inc. in the “comments” section of the Transmittal Form. Bioclinica, Inc. may decline to request a repeat if the subject’s knee posed a difficult positioning situation that would most likely not be corrected with another attempt.
To assist with subject confidentiality, the biographical information flashed onto the cassette or entered into the digital image header should include subject study identifiers only, **not the subject’s name**. The flash region may be covered with the self-adhesive study label, but do not apply multiple layers of labels. Please refer to Appendix II for further detail on film labeling.

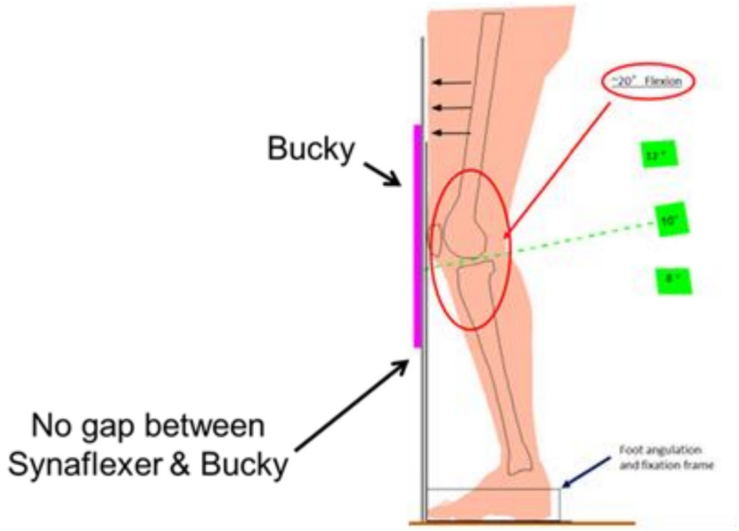



**Figure 4** Proper subject positioning and beam angulation for radiography of the knee.

Pressing the thigh against the anterior wall of the Synaflexer and gently guiding the subject 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 Synaflexer positioning frame. Position the tube so that the X-ray beam is centered on the joint line in the popliteal space (back of the knee) with a starting tube angle of 10° caudal.

**Figure 5** Criteria for Assessing Quality of Unilateral PA Fixed Flexion Knee Radiographs

### 6.4.4 Criteria of good quality knee radiographs

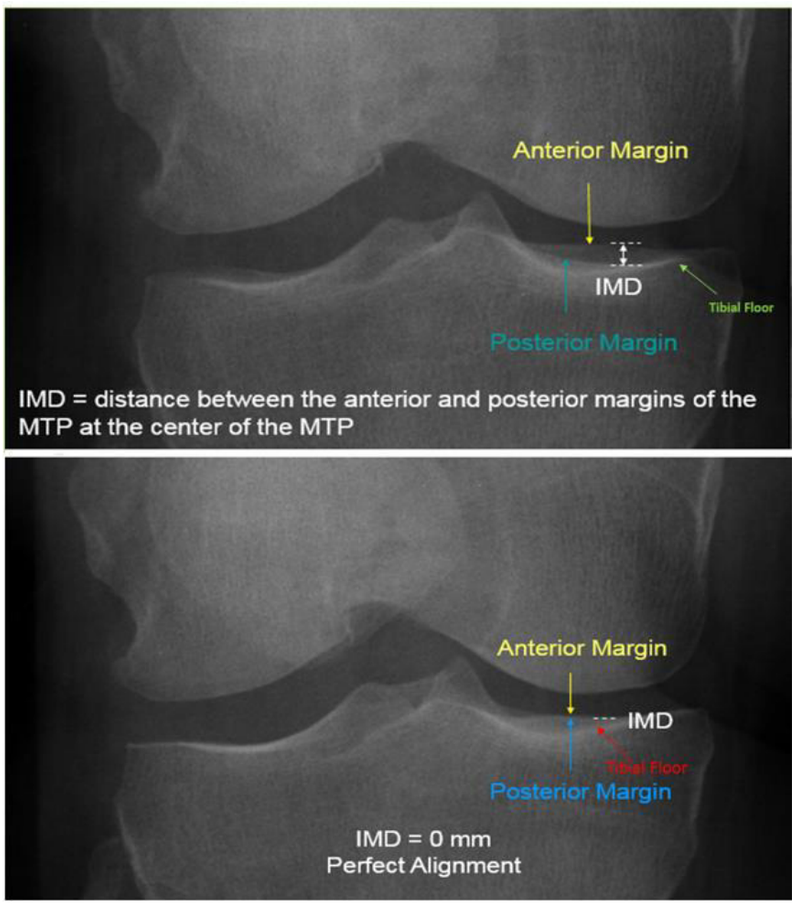
- Complete coverage of the knee anatomy, this includes the femoral and tibial metaphysis as well as the proximal fibula.
- Optimal exposure to visualize the medial and lateral sides of the knee joint, including bone margins, and soft tissue should be clearly visible without the use of a high intensity light.
- The joint space must be open.
- Medial tibial plateau should be flat (horizontal).
- The long axis of the tibia must be parallel to the vertical margins of the cassette.
- The knee must appear centered to the cassette.
- Review the image(s) to ensure the Inter-Margin Distance (IMD) of the medial tibial plateau is < or equal to 1.5 mm.
- 10 cm (length of 5 beads) above and below the knee joint and both columns of beads should be clearly visible on the image.
- The applicable left/right marker must be on the image.
- Digital annotation of tube angle must be visualized.
- The image should not be underexposed or overexposed.

### 6.4.5 Common Mistakes

- Two columns of beads not included on image.
- Incorrect exposure technique may cause over/underexposure of the image.
- Laterality marker not visualized on the image.
- Lead markers obscuring anatomy.

**BEST ALIGNMENT OF THE MEDIAL TIBIAL PLATEAU DETERMINED BY THE IMD (Acceptable IMD = 0-1.5mm)**

## 6.4.6



## Examples of Unilateral PA Fixed-Flexion Knee Projection

For examples of acceptable and unacceptable quality posterioanterior knee radiographs, see the following pages.

### PA Fixed-Flexion Knee – Acceptable

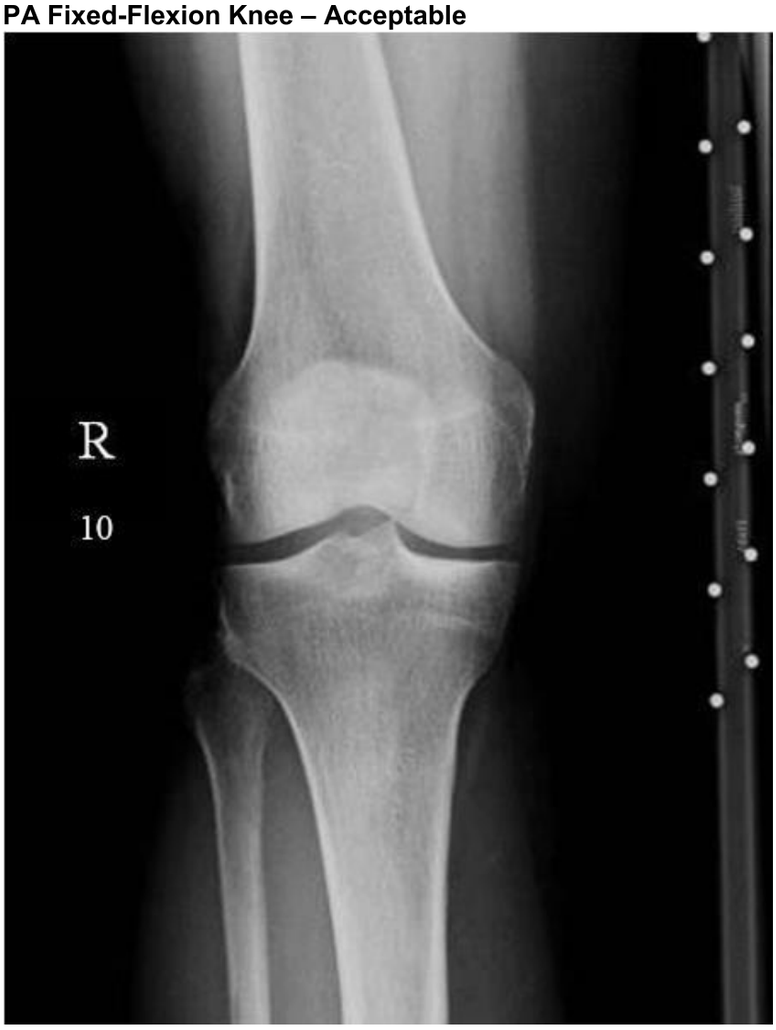



**Figure 6** Example of Good Quality

- Medial tibial plateau flat, good positioning and correct angulation of the tube
- Both columns of the Synaflexer positioning frame beads are visible at the medial margin of the image (medial of the knee)
- Laterality marker properly positioned
- Digital Tube angle annotation visible
- Collimation to the size of the cassette (frame beads not obscured)

## PA Fixed-Flexion Knee – Unacceptable

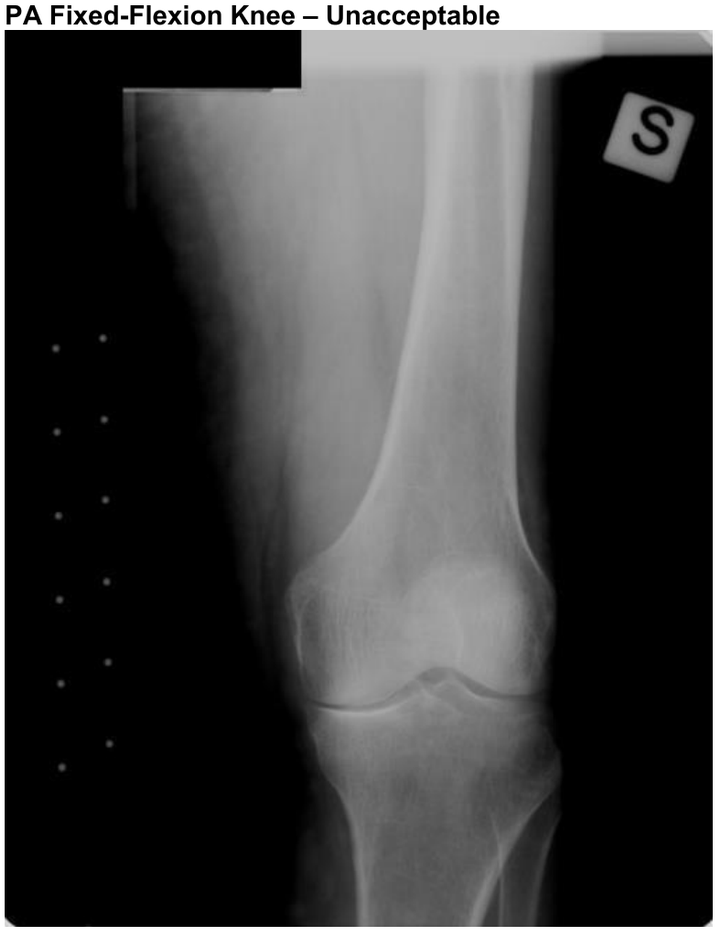



**Figure 7** Inappropriate Positioning

- External rotation (position of the patella)
- Tibial plateau is not flat and cortical rims poorly aligned
- Incorrect centering (joint space of the knee is not in the middle of the cassette)
- Image is overexposed
- Tube angle digital annotation not visible

## PA Fixed Flexion Knee – Unacceptable

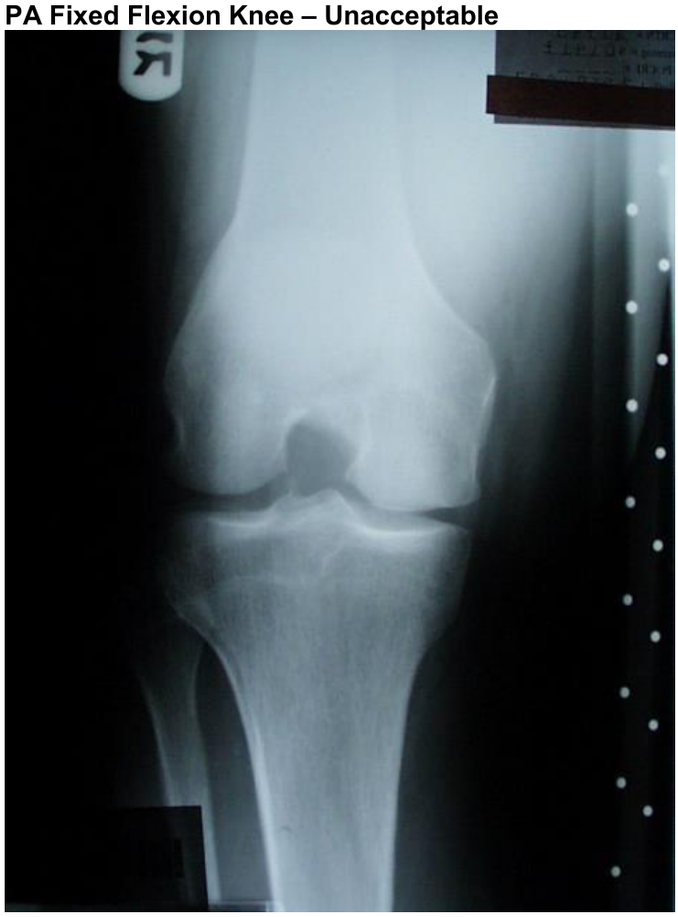


**Figure 8** Inappropriate Positioning

- Internal rotation
- Medial tibial plateau is not perfectly flat (Incorrect beam angle)
- Tube angledigital annotation not visible

**PA Fixed Flexion Knee – Unacceptable**

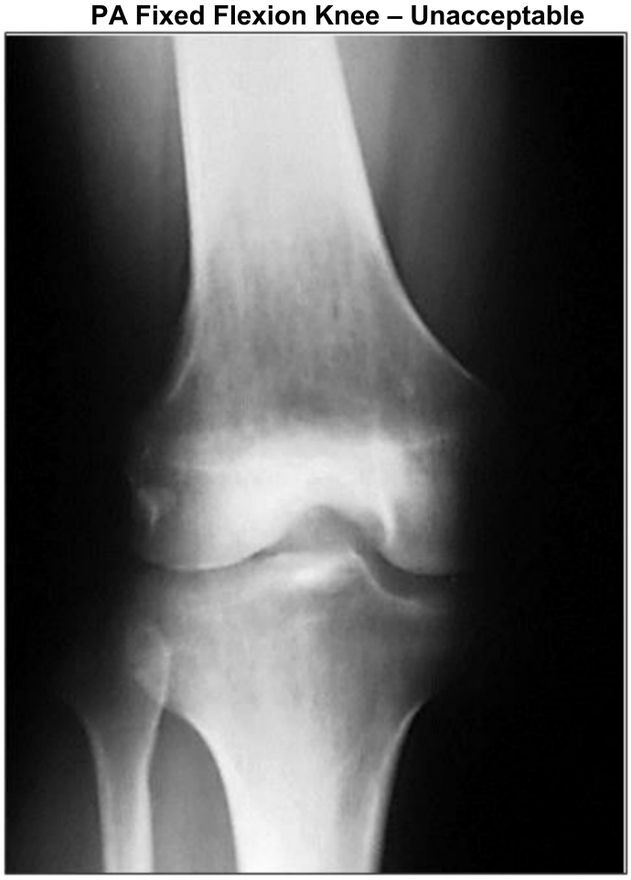


**Figure 9** Beam Centering

- Incorrect centering of X-ray beam
- Medial tibial plateau is not flat
- Synaflexer positioning frame not used therefore both columns of beads are not visualized at the medial margin of the image/medial side of the knee
- Laterality marker is missing
- Tube angle digital annotation not visible
- Over-exposure of medial & lateral aspect

## PA Fixed Flexion Knee – Unacceptable

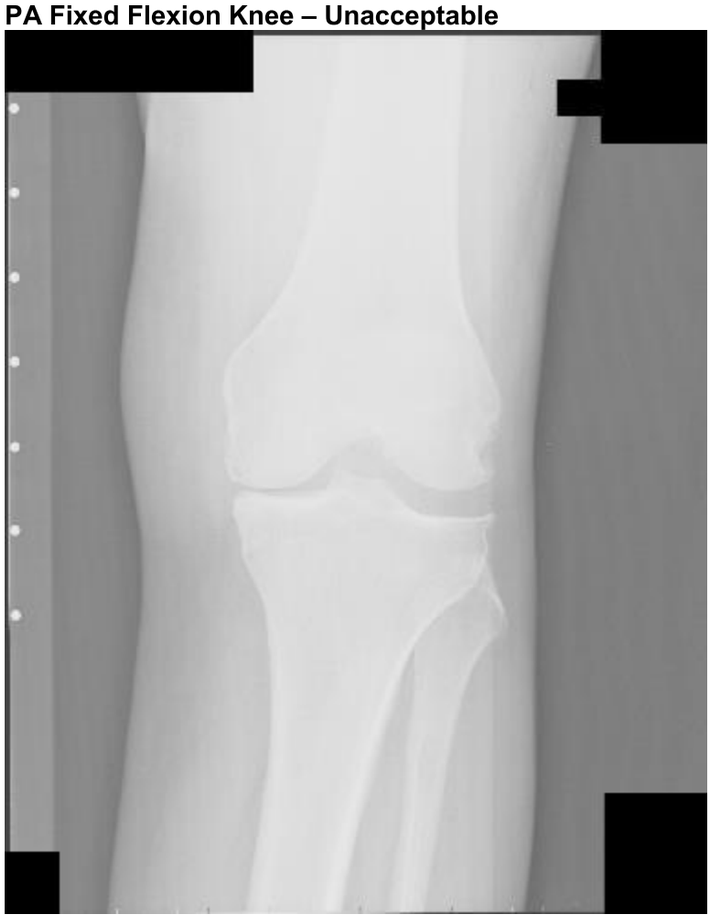


**Figure 10** Incomplete depiction of the frame beads

- Only one line of the frame beads is depicted (both bead columns must be visible)
- Image is underexposed
- Laterality marker is missing

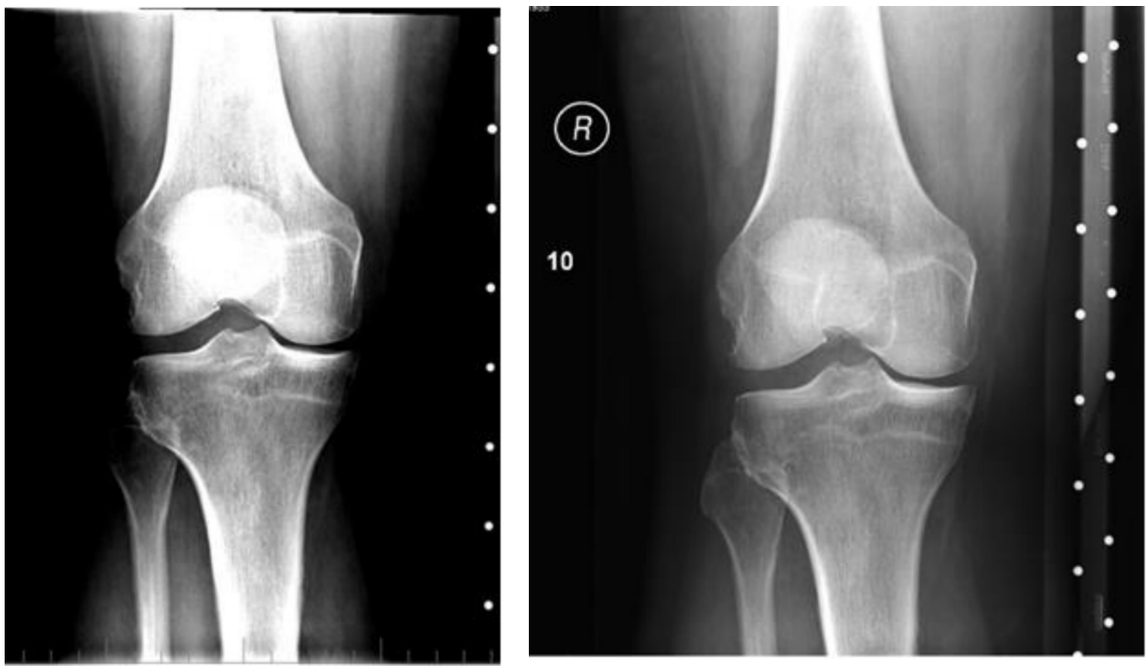



**Figure 11** (Left) Large IMD/Missing marker and (Right) repeat examination

**UNACCEPTABLE *Repeat Requested***

- Only one line of the frame beads is depicted (both lines must be visible)
- IMD greater than 1.5 mm.
- Missing laterality marker
- Under exposure
- Tube angle marker not visible

**ACCEPTABLE *Repeated Image***

- Both columns of beads are visible
- Medial plateau is flat
- Laterality marker on the image
- Adequate exposure
- Tube angle visible

### 6.5 Repeat Examinations

Bioclinica's imaging technologist and/or the imaging physicist, and radiologist will evaluate the quality of each X-ray study. A Quality Assessment 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 DCF to the site's Study Coordinator, 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 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:

- Subject 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 subject 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 or designee, the Lead X-ray 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 (2) 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 File Transfer Protocol (FTP) website (i.e., SMART submit) – the preferred method of data submission (refer to Appendix V for detailed description).
- Using courier will delay image receipt from sites that and is generally not preferred unless no other option is available.Send via United Parcel Service courier (UPS)` ( designated) unless specified courier requested in the PTQ.

Both of these options are described below.

## 7.1 Electronic Transfer (FTP via SMART Submit) - PREFERRED

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 subject-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 Pre-Trial Questionnaire will each be sent an e-mail listing their username, password, and instructions for logging into https://smartsubmit.bioclinica.com/ and navigating the interface.

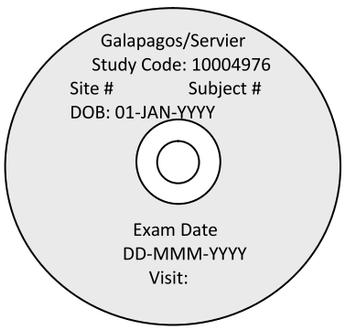
Access may also be requested at any time during the study by emailing the study support team at : 10004976Support@bioclinica.com

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

## 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 subject specific details on the CD. These are:

- Study Protocol Number: Galapagos/Servier CL2-201086-002/GLPG1972-CL-201 (Study Code: 10004976)
- Subject Identifiers (Site number and Subject Number)
- X-ray Exam Date (DD-MMM-YYYY format)
- Visit Name
- Date of Birth (DOB 01-JAN-YYYY format)



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 subject visit!**<br><br>**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 subject data should be accompanied with properly filled (paper) Transmittal form.** Data for multiple subjects may be sent in one shipment. A complete package for one subject 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 AWBs that will include Bioclinica's address on them.Please specify requested AWB's for DHL,Fedex or other couriers requested.

## 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.

- 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).

# 8 Appendix I – X-ray Transmittal Form

BIOCLINICA®

Galapagos and Servier study protocol:
CL2-201086-002 / GLPG-1972-CL-201
Transmittal Form for X-Ray of the Knee

**Site, Subject, and Visit Information** — **To be completed at study site**

Site Number : ☐☐☐☐

Randomization Number: ☐☐☐☐☐

Date of Birth: 0 1 / J A N / ☐☐☐☐ (D D / M M M / Y Y Y Y)

Target Knee: ☐ Left ☐ Right ☐ N/A (ASSE visit only)

Visit:
- ☐ ASSE
- ☐ W052
- ☐ Premature Withdrawal

Premature withdrawal visit to be performed only if the previous X-Ray (ASSE) is done more than 9 months before the premature withdrawal

☐ Check here if data is a repeat requested by BioClinica

**Exam Information** — **To be completed at imaging center**

X-Ray exams acquired and submitted
(check the box below, if acquired and submitted)

**Left Knee PA (Posterioranterior)** ☐

**Right Knee PA (Posterioranterior)** ☐

Exam Date: ☐☐ / ☐☐☐ / 2 0 ☐☐ (D D / M M M / Y Y Y Y)

Comments:

Media: (check one box)
- ☐ CD
- ☐ Hardcopy Films — Number of films sent: ☐☐

Technologist Initials: ☐☐☐ (F M L)

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

**Data Receipt** — **To be completed at Bioclinica**

Comments:

RESERVED FOR BIOCLINICA BARCODE

BioClinica Tracking Number 1 0 0 0 4 9 7 6 1 0 2 0 1 8 0 6 0 6

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

# 9 Appendix II – SMART Submit User Guide


# SMART Submit Release 9.4

# User Guide

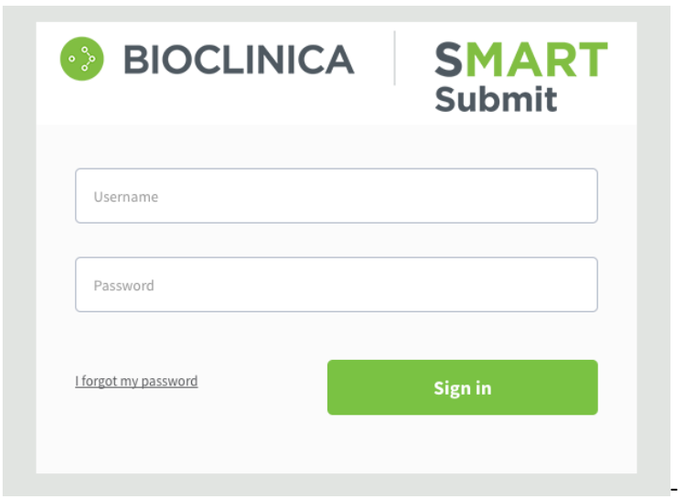
Document Version 1.0

## 9.1 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.**

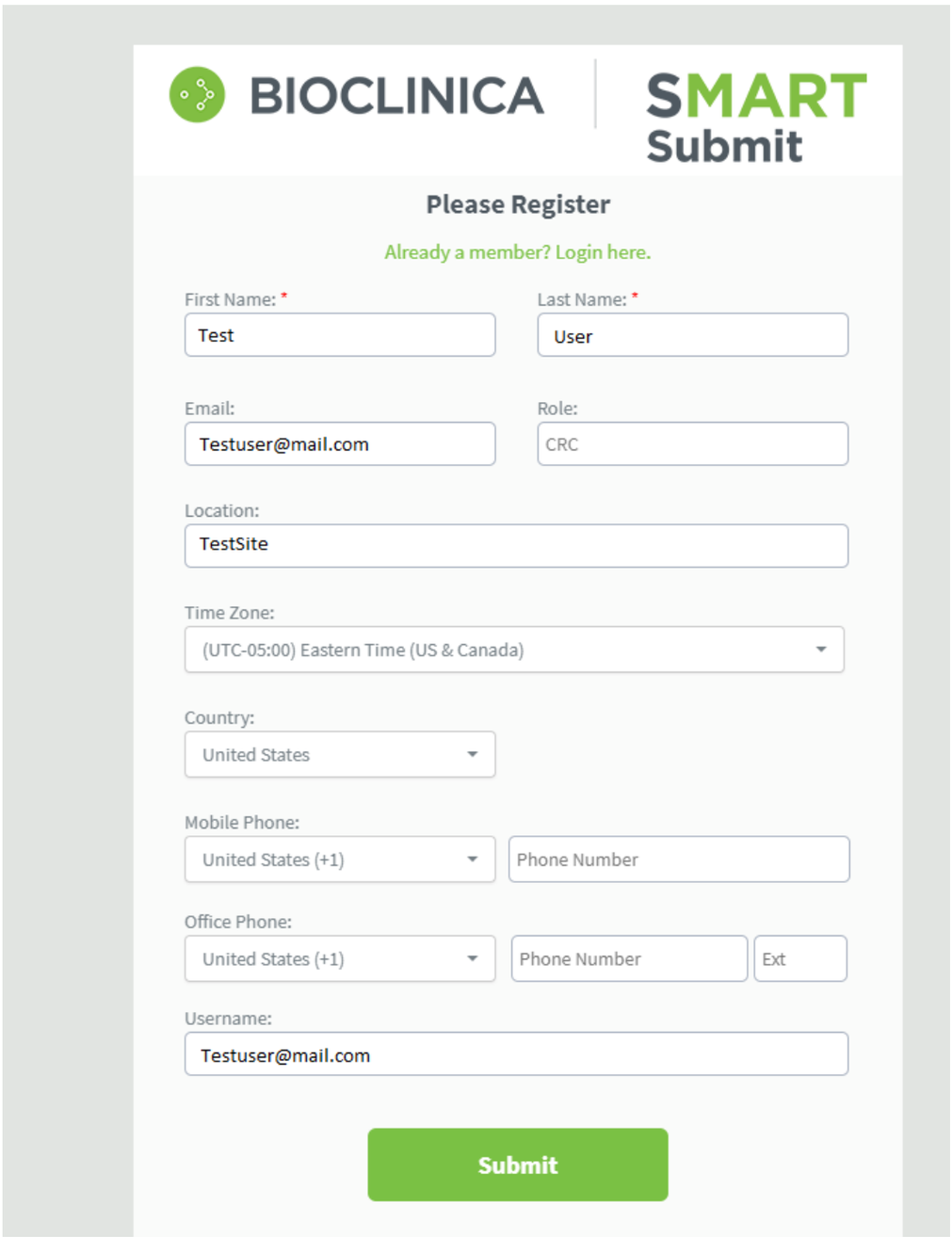
**Logging On**

Once you have received the welcome email, you will be able to log into SMART Submit. Open your browser and open https://smartsubmit.bioclinica.com/. The credentials are valid for 60 days.



## Logging in For the First Time

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



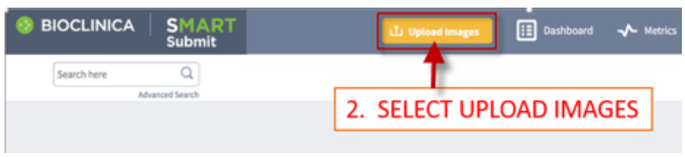
1: Prior to uploading trial images and only at first log in of new users, it will be required to watch a training video.

Note 2: 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 the SMART Submit support team if you don’t have a qualification test image or if you need any help. You can quickly reach out to them by clicking “Q&A” on the right.

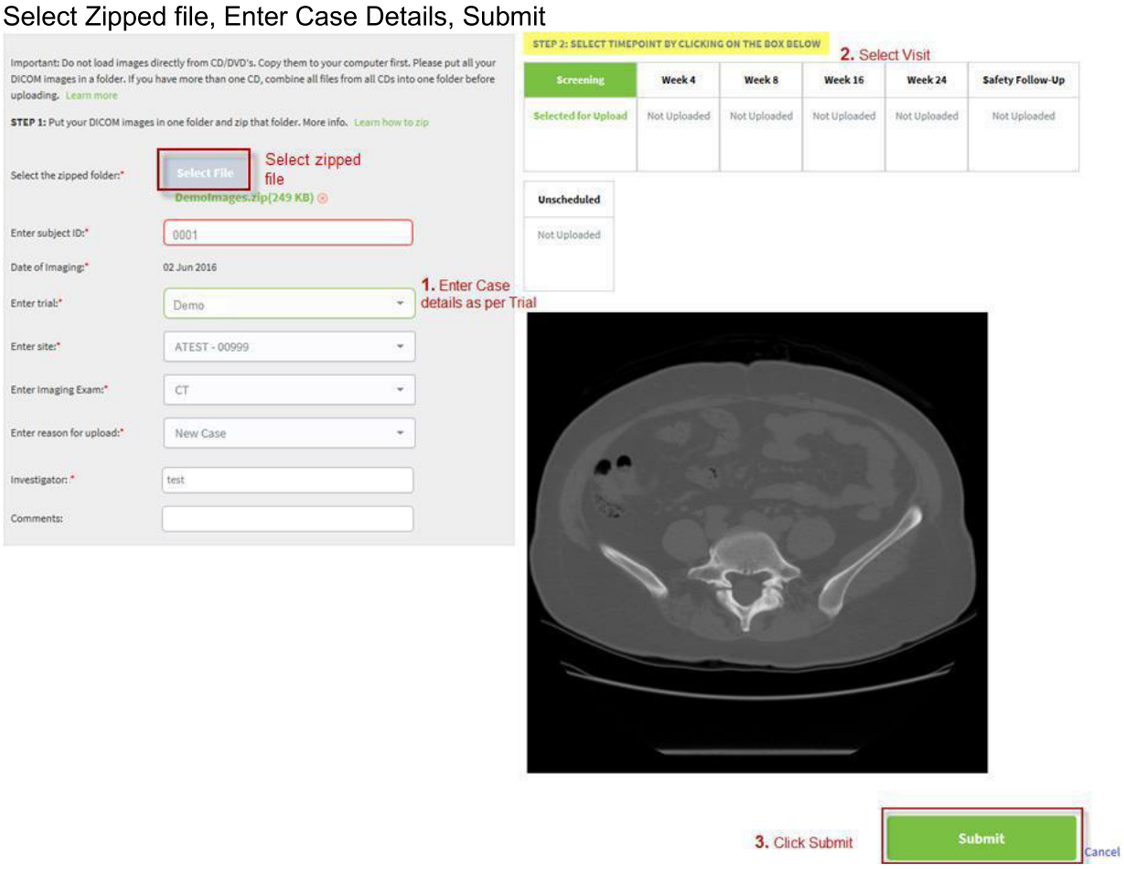
IMPORTANT: There may be additional test data requested by Bioclinica to confirm the correct scanner / equipment setup prior to your site’s authorization.

## 9.2 UPLOADING IMAGES AND DATA

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

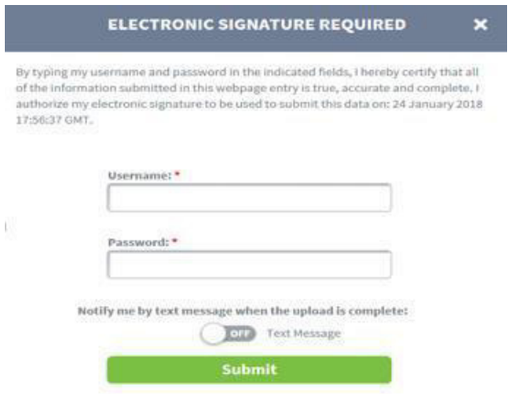


Select Zipped file, Enter Case Details, Submit



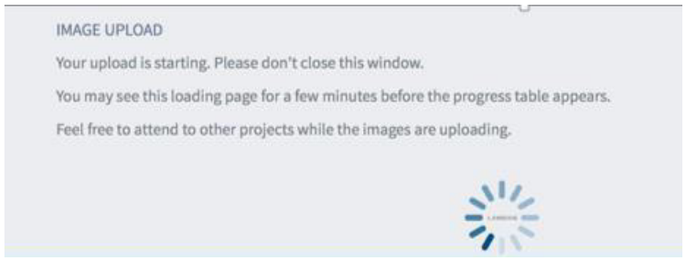

## Electronic Signature

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



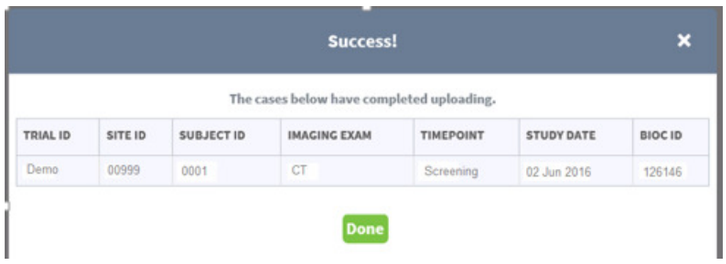

## Image Upload Progress

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.



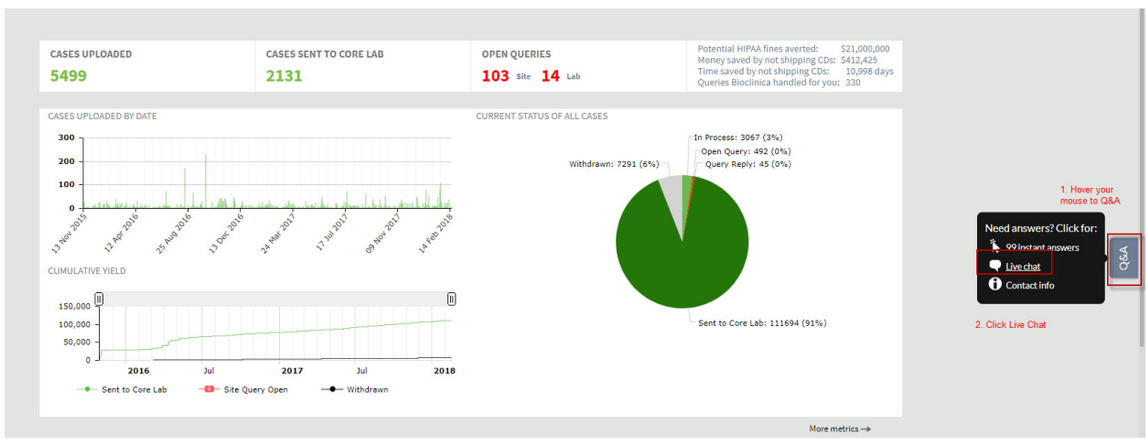

## Image Upload Success

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

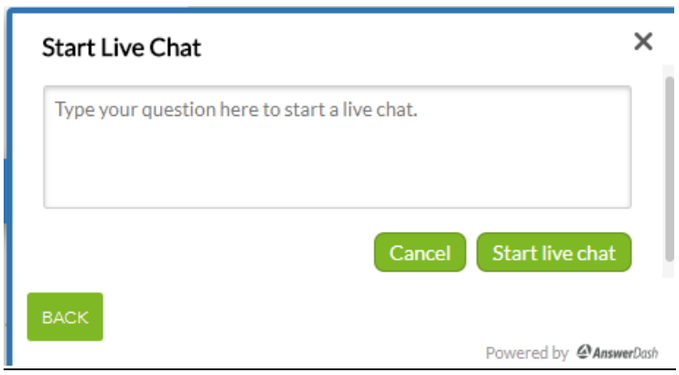



There are many ways you can reach out to support.
1) Live 24/7 chat support:

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



Sites can enter their questions in the Live Chat wndow below.




**Additional Help:**

Call Support Line:
+1 844 612 6640

Email at smart.submit@bioclinica.com

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

http://www.bioclinica.com/sites/default/files/u1/Bioclinica_Toll_Free_Numbers.pdf

## Appendix IV - Pro-Forma Invoice Template

| | |
|---|---|
| **Shipper/Exporter:**<br>*(Complete Name & Address)*<br><br>**Country of Origin:**<br>_____<br><br>**Country of ultimate Destination:**<br>USA | **CONSIGNEE:**<br><br>BIOCLINICA<br>Attn: Galapagos/Servier CL2-201086-002/GLPG1972-CL-201<br>Study Team (Code: 10004976)<br>(complete Bioclinica office address for your site below)<br><br>Bioclinica, Inc.<br>7707 Gateway Blvd., 3rd Floor<br>Newark, CA 94560 USA<br>415.817.8900<br><br>**REASON FOR EXPORT:**<br><br>Data for Clinical Trial.<br>NON COMMERCIAL.<br>FOR RESEARCH PURPOSES ONLY |

| Type of Packaging/ Marks | Detailed Description of Goods | Harmonized Code | Unit Value | Subtotal |
|---|---|---|---|---|
| | | | | |
| *TOTAL : 1* | *TOTAL WEIGHT:*<br>_____ | [redacted] | | $ (Total) |

# Appendix V – Supply Re-Order Form

## Galapagos/Servier CL2-201086-002/GLPG1972-CL-201 Study Supply Order Form

**To order supplies, please email the completed form to:**

**Email:** : 10004976Support@bioclinica.com

**Attention:** Galapagos/Servier CL2-201086-002/GLPG1972-CL-201 Study Team (Code 10004976)

**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) | |

| **General Supply** | **Quantity** |
|---|---|
| Pre-printed Airway Bills | _____ subject exams |
| Envelopes | _____ subject exams |