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Procedure Manual for QCT of the Knee

Samumed Protocol SM04690-OA-06

A Phase 2, 52-Week, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety, Tolerability, and Efficacy of Two Injections of SM04690 Injected in the Target Knee Joint of Moderately to Severely Symptomatic Osteoarthritis Subjects

Project Code: 10005841
Document Version: Final V3.0
Release Date: 10-Oct-2018

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Samumed Protocol SM04690-OA-06

(Bioclinica Study 10005841)

A Phase 2, 52-Week, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety, Tolerability, and Efficacy of Two Injections of SM04690 Injected in the Target Knee Joint of Moderately to Severely Symptomatic Osteoarthritis Subjects

Version 3.0

10 Oct 2018

QCT Manual Sign-Off

Dear Study Coordinator and CT Technologist,

Bioclinica requires that the Study Coordinator(s) and CT Technologist(s) read and fully understand the **QCT Procedure Manual for the Samumed Protocol SM04690-OA-06 study**. This requirement should be completed before imaging any subject for this study.

Please have all applicable study personnel sign and date this form to confirm completion of this requirement. Email a copy of this form to Bioclinica:

To the attention of: Samumed 5841 Study Team

Email: #MI_DEP_MSK.Team.SM04690-OA-06@bioclinica.com and your assigned Samumed Clinical Research Associate

Principal Investigator: _____

Site No.: _____

Who is responsible for submitting image data to Bioclinica? (Please check box)

Study Coordinator ☐ CT Technologist ☐

Study Coordinator(s)			
Printed Name	Signature	Initials	Date
CT Technologist(s)			
Printed Name	Signature	Initials	Date

All new study personnel must comply with this requirement

DO NOT REMOVE THIS PAGE – SEND A PHOTOCOPY ONLY

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1 List of Terms and Abbreviations

Abbreviation/Term/Acronym	Definition
SCREENING	The first clinical trial visit where imaging is acquired, Screening Visit 2, to which all subsequent visits are compared
BDC	Bone Density Calibration Phantom
BMD	Bone Mineral Density
CT	Computed Tomography
DCF	Data Clarification Form (Query)
QC	Quality Control
QCT	Quantitative Computed Tomography
QKP	Knee QC Phantom
QRG	Quick Reference Guide
QRM	Quality Assurance in Radiology and Medicine – Manufacturer of the QKP and BDC
TF	Transmittal Form

2 Introduction

The purpose of this manual is to standardize quantitative computed tomography (QCT) acquisition procedures among the centers participating in the **Samumed Protocol SM04690-OA-06** study:

"A Phase 2, 52-Week, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety, Tolerability, and Efficacy of Two Injections of SM04690 Injected in the Target Knee Joint of Moderately to Severely Symptomatic Osteoarthritis Subjects."

The study protocol, including primary and secondary endpoints and inclusion and exclusion criteria, is described in a separate document. Also, there may be separate documents for other imaging modalities such as DXA if these are also used in the study.

IMPORTANT ►	It is imperative that all centers adhere to the quality/process guidelines contained in this document to ensure data is collected in a comparable and standard manner for all subjects. The standardization requirements are mandated to ensure data reviewability and accessibility from a regulatory perspective. Both Bioclinica and Samumed appreciate that participating centers will have valid local practices which are different from those defined in this guidance document. However, we must stress that for this clinical trial the processes contained in this document must be used for image acquisition.

All radiologists and technologists contributing to this study are expected to have had appropriate theoretical and practical training in QCT. Study personnel should also satisfy all local requirements for radiology licensing and registration. Qualified radiology personnel are the first step toward the successful use of QCT in the Samumed Protocol SM04690-OA-06 study. The procedure manual is designed for the study coordinator, the CT technologists and the radiologists involved in this study. However, this manual, taken alone, should not be considered as sufficient training in the proper technique for acquiring QCT of the Knee. The goal of this manual is to define (a) a standard approach that produces QCT images of sufficient quality for achieving the study goals and (b) a standard approach for submitting QCT data to Bioclinica.

Questions regarding logistics and technique should be directed to:

Samumed 5841 Study Team
Email: #MI_DEP_MSK.Team.SM04690-OA-06@bioclinica.com and your assigned Samumed Clinical Research Associate

In case of Bioclinica employee absences, please send all e-mails to the support email above and we will respond as soon as possible.

3 Study Summary

3.1 Summary of Responsibilities

The roles and responsibilities of the clinical site (study coordinator) will be to:

- Identify exactly one lead CT technologist who will be responsible for the QCT acquisition and who will assure that all technologists performing examinations for this study are sufficiently trained on the study specific QCT acquisition techniques outlined in this manual.
- Identify a person responsible for submitting the QCT exams to Bioclinica. This should be either the study coordinator or the lead CT technologist.
- Assure that the appropriate study supplies are distributed to the responsible CT facility.
- Assure that all CT technologists performing QCT acquisitions for this study participate in the pre-study training.
- Assure that the manual sign-off page (see page 3) is signed by the Study Coordinator and the CT technologists and emailed to Bioclinica before a QCT exam of the first subject is performed.
- Establish a joint process with the QCT 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 (1) business day. Some sites may delegate the imaging technologist to submit QCT images.
- Maintain all study records in compliance with sponsor and regulatory requirements.
- Inform Bioclinica immediately of any technical problems of the CT equipment that may impair image quality of the subject or phantom measurements of this study.
- Inform Bioclinica at least three weeks prior to change of CT equipment.

The roles and responsibilities of the CT facility (CT Technologists) will be to:

- Read the QCT technical manual.
- Sign the QCT technical manual sign off page (see page 3).
- Perform and submit phantom test(s) as requested by Bioclinica.
- Participate in the pre-study site training.
- Perform subject QCT examinations according to procedures detailed in this manual.
- Locally review quality of QCT images.
- Save reconstructed QCT images on CD for submission to Bioclinica or submit QCT images via Bioclinica's web-portal, SMART Submit, and locally store a copy of the data at the site. It is

important to store a **digital copy** of the data at the site. In case of damage of the data submitted to Bioclinica a data resubmission will be requested.

- Save raw data of the acquired CT scans until the Quality assessment report will have been received from Bioclinica.
- Submit QCT images in **DICOM 3 format** via upload to SMART Submit (preferred), or via courier on digital media, together with corresponding transmittal form(s) within one (1) business day of the examination and verify completeness of packages to be submitted to Bioclinica.

The roles and responsibilities of Bioclinica will be to:

- Train at least the lead CT technologist performing QCT examinations for the study on the QCT acquisition techniques described in this manual.
- Provide study coordinator with all necessary supplies and study manuals for distribution to the CT facilities.
- Collect all QCT phantom and subject QCT examinations.
- Verify that the QCT acquisition and reconstruction parameters used are in agreement with the protocol described in this manual.
- Check QCT images for adequate anatomical coverage, signal-to-noise ratio and absence of artifacts.
- Review the quality of all QCT data and, if necessary, provide suggestions for improvement to the CT facility.
- Perform centralized analysis of the QCT data.
- Acknowledge any quality issues within 3 working days of receipt to site. It is expected that the majority of examinations received will be of acceptable quality. **Acquisition of QCT exams with acceptable quality is the responsibility of the CT facility.**

3.2 Study Start-up

Start-Up Requirements

In order to be registered with Bioclinica, sites will need to do the following, described in further detail below:

- Complete a QCT Site Questionnaire.
- Use adequate CT equipment.
- Register QCT technologists.
- Participate in an on-site training. If a site has recently been QCT certified by Bioclinica, the on-site may be replaced by a WebEx training.
- Provide the QCT Manual Sign-Off.
- Bioclinica provides CT supplies to sites.

Site Questionnaires

Before study start up QCT Site Questionnaires will be collected from each CT facility to provide Bioclinica with information about the CT technologist (contact information, experience) and the CT equipment (manufacturer and model, software version, image archiving and transfer capabilities, etc.).

CT Equipment

The CT equipment must fulfill the following requirements:

CT Equipment Requirements
Spiral CT scanner with at least 4 detector rows
Ability to send DICOM 3.0 data to Bioclinica
Ability to archive CT raw data for at least 2 weeks
No hardware or software upgrades during the study period affecting the quality of the subject or phantom images acquired for this study
Ability to perform the QCT acquisition and reconstruction protocol summarized in the Technical Parameter section of the Quick Reference Guide (see Appendix I: Quick Reference Guide)

Technologist Registration

Each CT technologist who performs scanning procedures for this study must read this procedure manual and sign and fax the signature page of this manual to Bioclinica prior to working on the study.

IMPORTANT ►	The CT facility must designate one lead QCT technologist for the study. It is highly recommended that the lead QCT technologist acquires all study images; at most one back-up QCT technologist is allowed. It is expected that the lead QCT technologist will participate in the training performed by Bioclinica personnel. The responsibility of the lead technologist is to ensure that the imaging protocol described in this manual is followed and that the back-up CT technologist (if any) acquiring images for this study have read and understood the procedures detailed in this manual.

On-Site Training

For all sites an on-site training is performed by Bioclinica personnel.

The lead QCT technologist **must** participate in the training. Back-up technologist (if any) performing examinations for the study should participate in the training. The following topics will be covered:

- Overview of study protocol
- Introduction and discussion of difference between QCT and CT examinations

- Introduction and discussion of the study specific QCT subject and phantom examinations
- Establish scanner specific acquisition and reconstruction protocols.
- Execute initial phantom scans (see section 5.6)
- Communication procedures (e.g. for submitting data to Bioclinica, obtaining reports from Bioclinica)

QCT Manual Sign-Off

Each Study Coordinator and technologist assigned to the study must sign, initial and date the QCT Manual Sign-Off Sheet (see page 3).

QCT Supplies

QCT measurements require the use of special materials and supplies not provided with your CT scanner. They will be provided to you for use during this study. The special QCT materials include:

- QRM Knee QC Phantom
- QRM bone density calibration phantom (BDC)

These particular materials are manufactured by QRM™ (Möhrendorf, Germany) and must not be substituted by other materials not provided by Bioclinica.

4 Differences between QCT and CT

Quantitative Computed Tomography is a specialized form of CT scanning that is used to measure bone mineral density (BMD). This is possible because of a linear relation between CT number and physical density of bone. The QCT acquisition procedure differs from a normal CT acquisition in three important aspects:

1. In order to convert the measured CT values into BMD values, a QCT calibration phantom has to be measured with the subject.
2. A fixed predetermined table height has to be used for all subjects and phantoms, see section 5.6 - Determination of table height - for further details
3. Phantom scans have to be performed on a regular basis to monitor stability of the scanner.

In addition, in this multi-center study, cross calibration procedures will be performed to ensure the comparability of different CT scanners. These will be discussed in detail in section 5.6 -Phantom Examinations.

IMPORTANT ►	Quantitative CT measurements such as BMD are more susceptible to CT scanner stability and a variety of technical characteristics of your scanner. It is not possible to do an accurate or precise QCT study without taking potential variations into account. By following quality assurance procedures described in this manual you can ensure that reliable measurements of BMD are made with your CT scanner.

4.1 QCT Calibration Phantom

The CT scanner reports physical density in Hounsfield units (HU). These values must be converted to BMD. For this purpose, a QCT Calibration Phantom is measured simultaneously with the subject. In this study, the QRM™ Bone density calibration phantom (BDC) (Fig. 4-1) will be used. It is composed of rods enclosed in a durable plastic material to protect them from damage. The rods are made of a standard material with known density that has X-ray attenuation properties similar to bone. This allows establishment of a mathematical relations between CT number and BMD. Further details, in particular on how it is used during the CT acquisition, are described in Section 5.4 -QCT Subject Examination Procedures - Preparations.

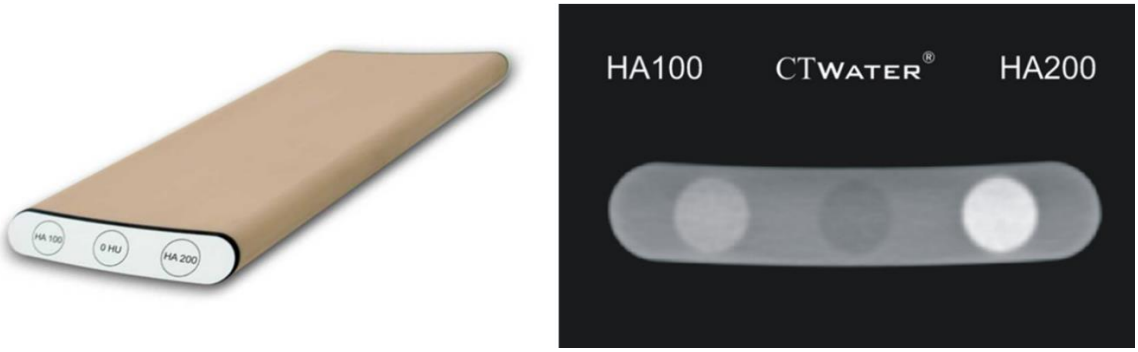


Fig. 4-1: QRM™ BDC Phantom

4.2 QCT Scanner Quality Assurance (QA)

IMPORTANT ►	The quality control of your CT scanner is primarily your responsibility. To ensure your CT scanner is functioning properly please continue your standard quality control procedures and maintenance schedule. In addition to these standard procedures the special quality control tests described in the section must be performed for this study.

In this study, the QRM™ Knee QC Phantom (QKP) will be used for the QA purposes. It should always be scanned on top of the BDC Phantom (see Fig. 4-2).

Two different entities of the phantom combination will be used. One will be available at your site and will be used to monitor and to potentially correct for scanner instabilities. Normally, CT scanner calibrations change slowly, even for QCT. However, BMD calibration can be affected by aging of the X-ray tube or other components, hardware upgrades or repairs, software upgrades, etc. The QKP scans will be analyzed by Bioclinica. If the scanner drifts out of specifications, adjustments will be made at Bioclinica to ensure consistent and reliable measurements. Note, the BDC will also be used for the subject scans.

Fig. 4-2: Left: QRM™ Knee QC phantom and BDC, Right: setup in CT scanner; the red line indicates how the knee phantom should be positioned in the gantry to determine the table height

A second QKP/BDC combination called cross calibration phantom, will be used to 'characterize' field inhomogeneities of all scanners used in the study. For this purpose, the same cross calibration phantom must be scanned twice on each scanner. Depending on the availability of cross calibration phantom, the scans may will be scheduled during the study:

- You will be contacted to determine a time that the cross calibration phantom will arrive at your CT facility.
- The cross calibration phantom will be sent to your CT facility on a strict schedule.
- You will perform the required scans of the cross calibration phantom and send electronic copies of the scans to Bioclinica for analysis.

The scan protocols for the cross-calibration phantom and the QKP phantoms are identical and will be will be discussed in section 5.6 - Phantom Examinations.

5 Schedule of QCT Examinations

The flow of events is shown in table below

Before first QCT subject visit	
Pre-trial questionnaire	Assessment of CT equipment

Before first QCT subject visit	
On-site or telephone training	Determine details of subject and phantom scan acquisition protocols Determine table height to be used for all scans using the QKP phantom shipped to your site
Ongoing subject visits	Perform subject examinations Perform scans of QKP phantom: Scan QKP phantom within ± 7 days of a subject scan but at least once a month
Repeat QCT subject examinations	see section 5.3 - Repeat of Subject Examinations
Scanner Cross Calibration	Perform scans of cross calibration phantom during training or at a later time during the study
Change of CT equipment **(remember: a change of CT equipment is strongly discouraged during the course of the study)**	Notify Bioclinica at least 3 weeks ahead of change Perform scans of cross calibration phantom before and after scanner change

5.1 Subject Visits

Shortly after site set-up subject visits normally begin. Subjects participating in the study should have QCT exams scheduled at the following visits:

QCT	Screening Visit 2	Week 12	Week 24	Week 36	Week 52 EOS/ET
Knee	X	X	X	X	X

The reconstructed data must be sent to Bioclinica as soon as possible, preferably within 24 hours after data acquisition. Bioclinica will review the image quality and the acquisition and reconstruction parameters and will send a quality report to the site. The site must store the raw data of all subject scans until receipt of this report.

5.2 Radiation Exposure

CT is an X-ray based diagnostic technique, which is associated with radiation exposure to the patient. The QCT technique developed for this study was specifically developed to reduce radiation exposure at acceptable image quality. The protocol has been used in other QCT studies. The radiation exposure expressed as equivalent dose is approximately 0.2 to 0.3 mSv per scan, which has to be compared to an average natural background radiation of about 1.5 mSv. Thus, in order avoid unnecessary exposure the CT protocol described in this manual should be strictly adhered to, to avoid repeat scans. However, in case of unacceptable image quality, such as a missing calibration phantom, repeat scan may be requested. Repeat scans are restricted to a maximum of one scan per patient for all visits.

5.3 Repeat of Subject Examinations

After review of the QCT quality at Bioclinica scans may be rejected due to poor image quality, inadequate anatomical coverage, missing calibration phantom, wrong acquisition or reconstruction parameters or due to other reasons. If incorrect reconstruction parameters were used, Bioclinica will request a new reconstruction. In this case the subject does not need to be rescanned; instead the correct reconstruction has to be obtained from the raw data of the examination in question. Therefore, it is important for the site to keep the raw data until Bioclinica's QA report will have arrived.

If a scan has been rejected by Bioclinica, a repeat examination of the subject may be requested. In this case you will receive a written request. It is then important to reschedule the repeat examination within (five) 5 calendar days for the SV2 image, and within (fourteen) 14 calendar days for all other QCTs.

5.4 QCT Subject Examination Procedures - Preparations

This section describes in detail electronic header labeling, subject positioning, and the acquisition and reconstruction parameters for all QCT examinations to be performed in the study. The scheduling of the exams has been described in section 5.1 - Subject Visits.

The quality criteria for QCT in a clinical trial are stricter than in standard clinical practice. An accurate and precise analysis of these QCT exams requires strict adherence to uniform acquisition protocol and quality standards. Closely follow the instructions provided below.

Labeling Subject Exams in the Electronic Header

The information below should be entered into the electronic CT header when acquiring subject examinations. This information is stored in the DICOM header of the CT images and is essential for Bioclinica to identify a scan.

- In the "**Patient Name**" field, enter the [**3 digit Site ID then "6" then the 3 digit Subject ID**] Here is an example of how the Patient Name field should appear:

Patient Name: **1236001**

- In the "**Date of Birth**" field, add the date of birth as 01 Jan YYYY according to the format supported by your scanner
- In the "**Patient Comment**" field, enter: **Visit: xx** where xx can take one of the following entries: Screening Visit 2, Week 12, Week 24, Week 36, Week 52, ET, Unscheduled
- Here is an example of how the Patient History field should appear. This is a possible entry for the Visit identification:

Visit: **Week 12**

Subject Positioning and Setup for QCT Knee Scans

- Ask the subject to remove any metal objects from the area of the scan field.
- Whenever possible, have the subject remove her street clothes and dress her in a hospital gown.
- Position the patient in a supine position on the CT-table.
- Both knees are as straight as possible (Fig. 5-1)
- A small internal rotation of the legs should be applied to position the patellas at the zenith. The feet should be fixed in that position (not shown in Fig. 5-1).
- Both hands are placed flat on the CT-table next to the pelvis/legs or across the chest
- The index knee of the subject must be scanned on top of the QRM™ BDC Calibration Phantom (Fig. 5-1).
- If necessary, use gel pads or equivalent material for comfortable patient positioning
- If an air gap is present between BMD calibration phantom and knee use a gel pad to prevent any air gap between BMD calibration phantom and knee
- Both legs are scanned. Scanning length is 150mm, centered in z-direction on femoro-tibial articular space.
- Set the table height as determined for your system.
- It is important to use an identical set-up for every scan.

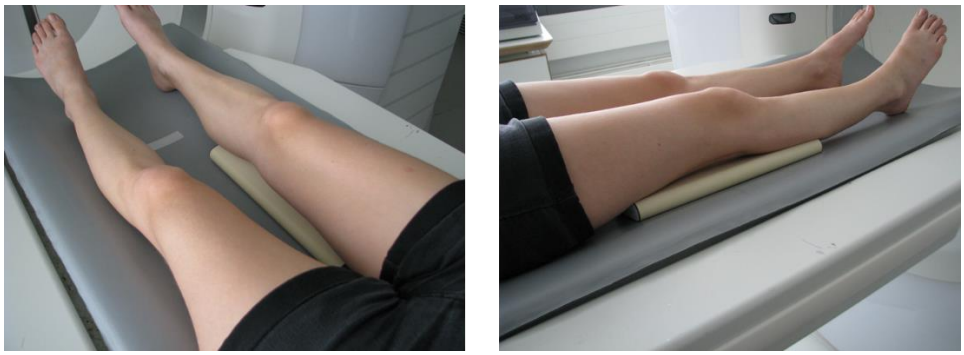


Fig. 5-1: Position of the BDC during the knee scans. BDC is positioned below the index knee. In addition (not shown in the Fig.) a small internal rotation of the legs should be applied to position the patellas at the zenith. The feet should be fixed in that position

The scan acquisition and reconstruction procedures for QCT knee examinations are described in the next sections.

5.5 Subject Examination Procedures - QCT of the Knee

QCT Knee Scan AP: Localizer

- Obtain an AP preview scan or scout scan from about 10 cm above to 10 cm below the femorotibial articular space.
- Use a low dose technique for the localizer that provides sufficient image quality to identify the relevant skeletal landmarks.

- **Please also submit the image of the localizer to Bioclinica.**

QCT Knee Scan: Acquisition

IMPORTANT ►	**Select the acquisition parameters specified for your scanner during site initiation.** These are listed in the Quick Reference Guide. It is critical to use these acquisition parameters for every subject at every visit. Whenever possible, pre-program the scan acquisition protocol by storing it in your CT scanner software.

- Ask the subject to breathe normally during the scanning.
- Typical acquisition parameters are listed in the table; these may vary slightly for your scanner, for which the specific parameters are listed in the quick reference guide.

	GE	Philips	Siemens	Toshiba
kV	120			
mAs	220			
collimation [mm]	0.5 x number of detector rows			
Pitch	0.8	0.8	0.8	0.8
Gantry angle [°]	0			
Table Height*	will be determined with the QKP (see section 5.6 -Determination of table height)			
AEC	off			
Coverage	Scan bilateral knees, 10 cm above the femorotibial articular space to 10 cm below femorotibial articular space			

Knee QCT Scan: Reconstruction

IMPORTANT ►	**Select the reconstruction parameters specified for your scanner during site initiation**. These are listed in the Quick Reference Guide. It is critical to use these reconstruction parameters for every subject at every visit. Whenever possible, pre-program the scan reconstruction protocol by storing it in your CT scanner software.

IMPORTANT ►	**Three reconstructions are required for the QCT knee scan:** **1. Index Knee:** a. **Large (200 mm) reconstruction field of view**: This will completely encompass **the index knee** and the BDC Calibration Phantom. Neither the knee anatomy nor the phantom should be cut off. (Fig. 5-2 left) **b. Small (130 mm) reconstruction field of view** centered on **the index knee,** the BDC Calibration Phantom may or may not be fully or partly visible on this reconstruction. (Fig. 5-2 right) **2. Contralateral Knee:** **a. Small (130 mm) reconstruction field of view** centered on the contralateral knee.

The typical reconstruction parameters are listed in the table; these may vary slightly for your scanner, for which the specific parameters are listed in the quick reference guide.

	GE	Philips	Siemens	Toshiba
Index Knee - large FOV	200 mm			
kernel	standard	C	B40s	FC13
slice thickness [mm]	0.7			
reconstruction increment [mm]	0.5			
Matrix	512 x 512			
Index Knee - small FOV	130 mm			
kernel	standard	C	B40s	FC13
slice thickness [mm]	0.7			
Matrix	512 x 512			
reconstruction increment [mm]	0.5			
Contral. Knee - small FOV	130 mm			
kernel	standard	C	B40s	FC13
slice thickness [mm]	0.7			
Matrix	512 x 512			
reconstruction increment [mm]	0.5			

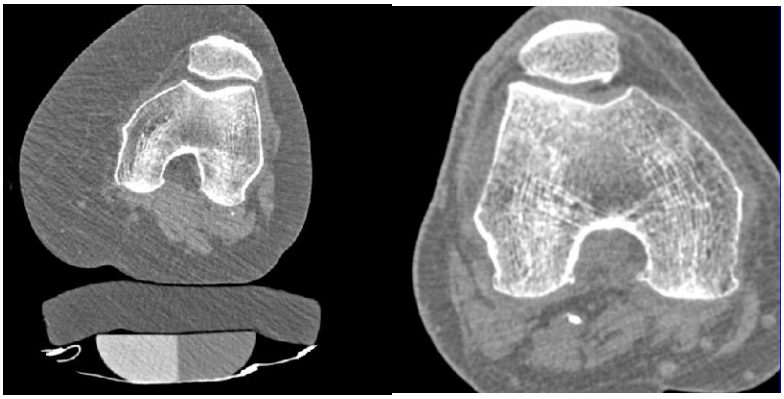


Fig. 5-2: QCT knee scan; left: large FOV (200mm) reconstruction including BDC phantom; right: small FOV (130 mm) reconstruction.

Export the reconstructed images via SMART Submit (preferred), or, if that is not possible, to the media used by your site (CD) in **DICOM 3** format. If you use CDs, please export the data from different subjects to different CDs. That is, each CD should contain data from just one subject.

Please store the data of the different reconstructions in separate folders, i.e. use one folder for the Knee large FOV, one for the Knee small FOV.

The labeling of the electronic media submitted to Bioclinica is described in Section 7.1 -Sending Data on a CD.

5.6 Phantom Examinations

QRM™ Knee QA Phantom (QKP)

As described in Sections 4.2 - QCT Scanner Quality Assurance (QA), the procedures for examinations of the QKP and the cross-calibration phantoms are identical.

Labeling the electronic header for phantom scans

Create a QA protocol for the QKP phantom scan on your CT scanner. This will only need to be done once. It will be done during the site initiation visit. Always use this protocol for future scans of the phantom. This will ensure that the scans are properly identified as Monitoring scans from your site.

For the QKP phantom scan complete the subject biographical information according to the procedures below:

- In the "Patient Name" field, enter the [3-digit SITE code-QKP PHANTOM]
  Here is an example of how the Patient Name field should appear:

Patient Name: **123-QKP PHANTOM**

- In the "**Patient History**" field, enter: **QKP Phantom Scan**
  Here is an example of how the Patient History field should appear. This is a possible entry for the Visit identification:

Visit: **QKP Phantom Scan**

For the cross calibration phantom (the second QA phantom) scan complete the subject biographical information according to the procedures below:

- In the "Patient Name" field, enter the [3-digit SITE code-CrossCal PHANTOM]
  Here is an example of how the Patient Name field should appear:

Patient Name: **123-CrossCal PHANTOM**

- In the "**Patient History**" field, enter: **CrossCal Phantom Scan**
  Here is an example of how the Patient History field should appear. This is a possible entry for the Visit identification:

Visit: **CrossCal Phantom Scan**

QA Phantom Scan Setup

Set up the CT scanner as you would for a subject examination of the knee, placing the BDC Phantom in the usual position on the table. You must position the phantom in the same position on the table as it would be for a subject scan.

Once the BDC Phantom is in position, place the QKP on top of it as shown in Fig. 4-2. Center the QKP lengthwise on the Calibration Phantom.

Determination of table height

Center the phantom combination such that the laser centering lights intersect the insert as shown in Fig. 4-2. Set the table ZERO mark at this point, and note the table height. This is the QCT table height for all QCT scans for your specific scanner. **The table height needs to be determined just once since it will be the same for all subject examinations and for all phantom scans**.

IMPORTANT ►	• If you think there may be a change in your scanner that might affect your QCT table height settings, contact the Bioclinica QCT study team.

	• Replacing the scanner table or the standard table pads on your scanner are both examples of significant changes that require notification to Bioclinica. • A scanner change will require a new determination of table height.

QA Phantom Scan Lateral Localizer

After proper positioning of the Phantom:

- Obtain a lateral localizer scan or scout scan with a length of 30 cm using the center of the Phantom as a landmark
- Obtain axial slices fully covering the QKP phantom plus 5 slices in air on either side. Note full coverage of the BDC phantom is not required.

QA Phantom Scan: Acquisition

IMPORTANT ►	**Select the acquisition parameters specified for your scanner during site initiation.** These are listed in the Quick Reference Guide. It is critical to use these acquisition parameters for every subject at every visit. Whenever possible, pre-program the scan acquisition protocol by storing it in your CT scanner software.

- The typical acquisition parameters are listed in the table; these may vary slightly for your scanner, for which the specific parameters are listed in the quick reference guide.

	GE	Philips	Siemens	Toshiba
kV	120			
mAs	220			
collimation [mm]	0.5 x number of detector rows			
Pitch	0.8	0.8	0.8	0.8
Gantry angle [°]	0			
	GE	Philips	Siemens	Toshiba
kV	120			
AEC	off			
Coverage	Full coverage of the QKP phantom			

QA Phantom Scan: Reconstruction Parameters

IMPORTANT ►	**Select the reconstruction parameters specified for your scanner during site initiation**. These are listed in the Quick Reference Guide. It is critical to use these reconstruction parameters for every subject at every visit. Whenever possible, pre-program the scan reconstruction protocol by storing it in your CT scanner software.

The typical reconstruction parameters are listed in the table; these may vary slightly for your scanner, for which the specific parameters are listed in the quick reference guide. The reconstructions must include the BDC phantom

	GE	Philips	Siemens	Toshiba
FOV	200 mm			
kernel	standard	B	B40s	FC13
slice thickness [mm]	1 or 1.25	1	1	1
Matrix	512 x 512			

6 QCT Scan Quality Review

It is important to check the quality of the QCT scans before dismissing the subject. After reconstruction, please review each axial slice and check for the following:

- **Subject positioning:** Check that the subject is centered in the scan field of view and not rotated.
    - **Correction:** Reposition the subject to correct the problem.
- **Complete coverage of anatomy and calibration phantom:** Check that the axial slices include the entire knee from 10 cm above the femorotibial articular space to 10 cm below femorotibial articular space. Large FOV reconstructions of the target knee must also include the calibration phantom. Small FOV reconstructions do not require the calibration phantom to be visible.
    - **Correction:** Depending on the problem, you might need to a) adjust the relative position of the phantom and subject and rescan the subject; b) rescan the subject without changing the set-up; c) repeat the reconstruction with a different field of view.
- **High density artifacts:** Check that there are no high-density artifacts from metal implants or external objects that create artifacts in the skeletal anatomy or in the calibration phantom.
    - **Correction:** For internal objects, the metal may be avoided by adjusting the scan area. For external objects, remove the object from the scan field and rescan the subject.

7 Data Handling Procedures / Uploading QCT Images

Electronic submission through the SMART web-portal is the preferred method of submission.

QCT images should be submitted to Bioclinica via SMART Submit. See Appendix VI: SMART Submit.

IMPORTANT ►	The Study Coordinator and the Lead QCT Technologist must decide who will be responsible for transmitting the QCT exam data to Bioclinica. This designated person will be responsible for ensuring that the data submitted is complete and accurate.

A DCF will be sent to your site 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. Data Clarification Forms/Incomplete Data Requests must be answered within 1 week, Repeat/Resubmission Request within 2 weeks.

IMPORTANT ►	The study images should be transmitted to Bioclinica within one (1) business day after the exam!

7.1 Sending Data on a CD

When uploading QCT images via SMART Submit is not possible, 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.

IMPORTANT ►	The subject information must be identical between the media label, the DICOM header of the CT images, the QCT transmittal form and the CRF. Subject ID and Date of Birth will be provided by the Study Coordinator. To protect subject confidentiality, no personal identifiers such as names, initials, medical records or social security numbers are to be included in any headers.

For labeling CDs use an indelible marker. The label should contain the following information (see Fig. 7-1):

- **Samumed SM04690-OA-06**
- Site number (3 digits)
- Number "6"
- Subject ID (3 digits)
- Subject's date of birth in **01-JAN-YYYY** format
- Visit ID
- Exam Date in **DD-MMM-YYYY** format

Do not affix any labels to the CD.

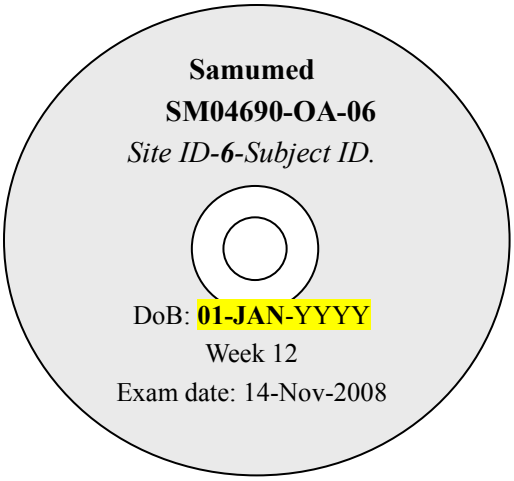


Fig. 7-1: Labeling of CDs

7.2 Data Preparation

All QCT exams for subjects enrolled into the study will be sent to Bioclinica. Complete the Transmittal Form for QCT, retain the pink copy at the clinical site and send white and yellow copies to Bioclinica with the digital media containing the QCT exam data (see Appendix II: Transmittal Form for QCT Subject Examinations and Appendix III: Instructions for Completing the Transmittal Form for QCT Subject Examinations).

7.3 Data Shipping

- Please send exam data with accompanying Transmittal Form to Bioclinica using the specified courier for the study. The courier account number that will be provided is to be used exclusively for sending subject examinations to Bioclinica.
- Complete the sender sections of the provided pre-printed airway bill, keeping a copy for tracking purposes. Place the QCT Transmittal Form and labeled media for each subject into a shipping envelope. Data for more than one subject can be shipping together in one shipping.
- Call the local office for the specified courier to schedule package pick-up, taking into account the latest call and pick-up times. The local office can also provide necessary courier supplies (envelopes for shipping data) when needed.
- Ship labeled media together with a completed Transmittal Form for each subject visit to the Bioclinica QCT study team at the address given in the Introduction.
- Results of Bioclinica's quality assessment will be faxed to the clinical site within 5 working days of receipt of the images. If problems with image quality or protocol adherence are encountered, Bioclinica will interact directly with the imaging center to correct the problem.

7.4 Supplies

In addition to this manual Bioclinica will provide the following supplies to the clinical site:

- Transmittal Form for QCT of Knee
- Transmittal Form for QCT QKP Phantom Scan
- Quick Reference Guide
- Preprinted airway bills
- QRM™ QKP and BDC phantoms Phantom,
- Shipping materials

IMPORTANT ►	To request additional study supplies, please use the Supply Order Form at the back of the manual or send an e-mail to the Bioclinica QCT study team. **#MI_DEP_MSK.Team.SM04690-OA-06@bioclinica.com** and your assigned Samumed Clinical Research Associate Please submit supply requests to allow for 1-week delivery time.

8 Appendix I: Quick Reference Guide

Samumed SM04690-OA-06
Quick Reference Guide for Image Acquisition and Data Handling

QCT of QKP Phantom

Quality Assurance Phantoms need to be scanned at the beginning of the study and once a week when subjects are scanned but at least once a month

Acquisition Parameters for QKP phantom (fill in yellow fields) **Reconstruction Parameters**

Table Height	
mAs	220
Dose reduction	No
kV	120
Slice collimation	
Pitch	
Scan FOV	

Slice thickness	
Reconstruction Increment	
Kernel	
# of slices	Cover complete QKP
Reconstructed FOV	200

QCT of Knee

Visit Schedule

QCT	Screening Visit 2	Week 12	Week 24	Week 36	Week 52 EOS/ET
Knee	X	X	X	X	X

The BDC In-Scan Calibration Phantom for knee must be placed below the target knee.
Scan length: 10 cm above the femorotibial articular space to 10 cm below femorotibial articular space

Technical Parameters (fill in yellow fields)

		Target Knee		**Contralateral Knee**
Acquisition	mAs	220		
	Automated Exposure Control	Off		
	kV	120		
	Slice Collimation			
	Pitch			
	Gantry Angle	0		
	Table Height			
	Coverage	10 cm above the femorotibial articular space to 10 cm below femorotibial articular space		
	Scan FOV			
Reconstruction		**Target Knee**		**Contralateral Knee**
		Large FoV	Small FoV	Small FoV
	Reconstructed FOV	200	130	130
	Slice Thickness			
	Reconstruction Increment			
	Reconstruction Kernel			

Please keep raw data until you have received quality assessment report from Bioclinica.

Samumed SM04690-OA-06
Quick Reference Guide for Image Acquisition and Data Handling

Electronic Data Transfer Using Bioclinica Portal

The Bioclinica Portal (SMART Submit) is the preferred method of data submission. It is a 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. The Transmittal Form (TF) is completed and submitted electronically as well.

IN ORDER TO ENSURE SUBJECT CONFIDENTIALITY, PLEASE ENTER THE FOLLOWING INFORMATION INTO THE ELECTRONIC CT HEADER:

- "Patient Name" enter: **[3 digit Site ID, "6", and 3 digit Subject ID number]** EXAMPLE: **Patient Name: 1236456**
- "Date of Birth" enter: As required per scanner use 01-JAN-YYYY (e.g. 01-JAN-1947) format on all written documents
- "Comment field" enter: [Visit] EXAMPLE: **Screening, Week 12, Week 24, Week 36, Week 52/ET/EOS, Unscheduled**

Labeling CD Media

- Please do not affix self-adhesive labels directly to the CD. This may harm the disk drives and cause read errors.
- Please use an indelible marker to write study and subject specific details on the CD.

These are:

- Protocol Number SM04690-OA-06
- **3 digit Site ID, "6", 3 digit Subject ID (e.g. 1226555)**
- DOB **01-JAN-YYYY**
- Visit Name
- Exam Date

Data Shipping

The data to be sent from the imaging site should contain both the imaging study and the transmittal form. There are two options for sending data to Bioclinica:

- SMART Submit - the preferred method of submission
- Postal mail/courier service.

Sending Data Using Courier Service

- The complete package should contain a CD with imaging data and the completed TF
- Export the data to the CD in uncompressed DICOM 3 format.
- Use an indelible marker to label directly on the CD (See Labeling CD Media above for required information)

SMART Submit: https://smartsubmit.bioclinica.com/

- **SMART Submit is Bioclinica's web-based system for clinical trial uploads. Using SMART Submit sites can fill in required case details as per transmittal form, upload images, authorize, and submit trial cases to Bioclinica. Please refer to the SMART Submit User Guide.**

Sending a Package to Bioclinica

- Complete the sender sections of the air waybill, keeping a copy for tracking purposes.
- Place the white and yellow copies of the TF and the CD for each patient into a shipping envelope. Please keep pink copy at site.
- Call courier to schedule package pick-up

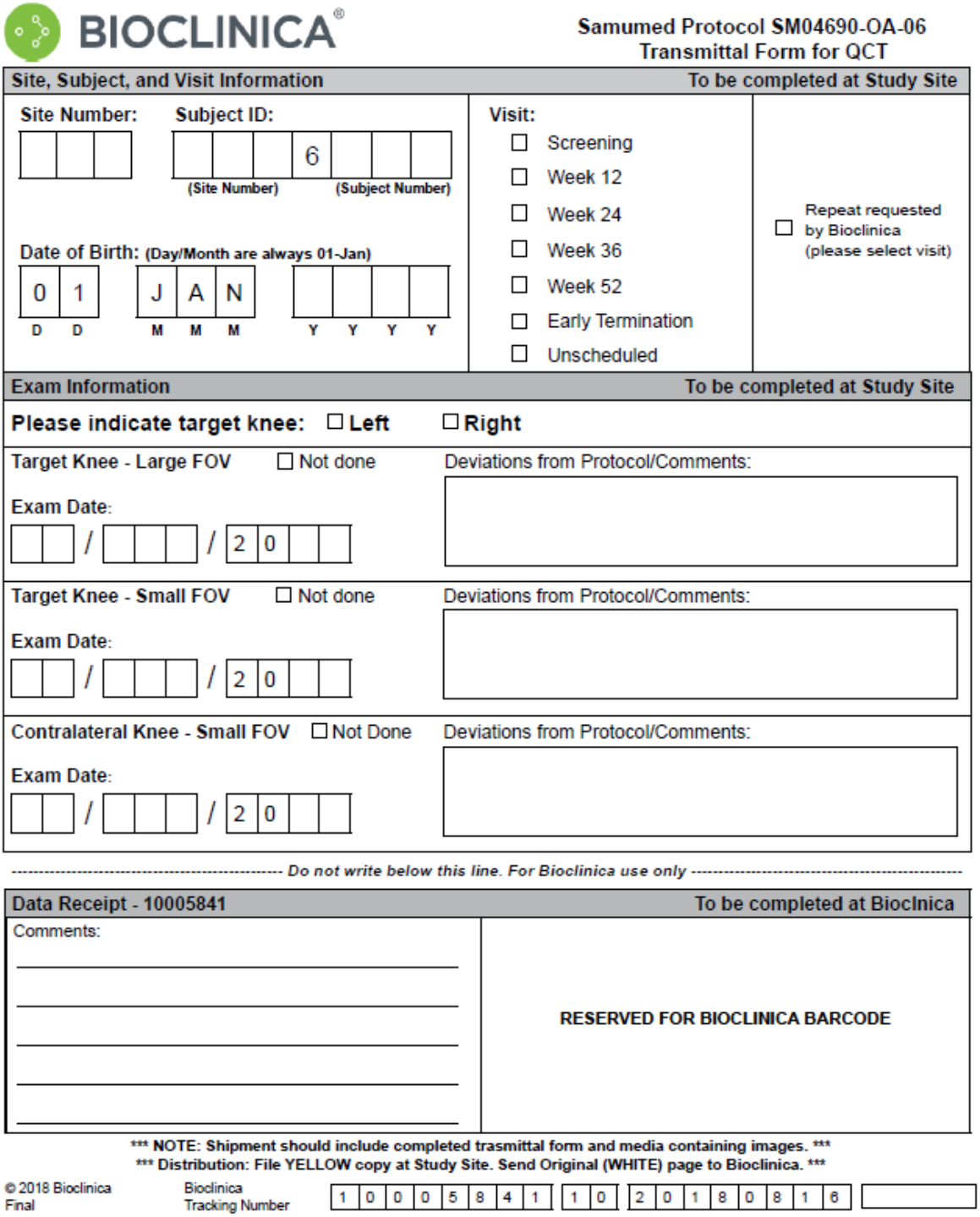
Ship data to:
Bioclinica
Samumed SM04690-OA-06 (10005841) Team
7707 Gateway Blvd., 3rd Floor
Newark, CA 94560, USA

Please contact the Samumed SM04690-OA-06 Study Team if you have any questions. To order additional supplies, please fax a completed copy of the Supply Reorder Form found in the QCT Procedure Manual.

Phone: +1 (415) 817 8900 Fax: +1 (415) 817 8999

Email: #MI_DEP_MSK.Team.SM04690-OA-06@bioclinica.com

9 Appendix II: Transmittal Form for QCT Subject Examinations



BIOCLINICA®

Samumed Protocol SM04690-OA-06
Transmittal Form for QCT

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

Site Number: ☐☐☐

Subject ID: ☐☐☐6☐☐☐
(Site Number) (Subject Number)

Date of Birth: (Day/Month are always 01-Jan)
0 1 (D D) J A N (M M M) ☐☐☐☐ (Y Y Y Y)

Visit:
- ☐ Screening
- ☐ Week 12
- ☐ Week 24
- ☐ Week 36
- ☐ Week 52
- ☐ Early Termination
- ☐ Unscheduled

☐ Repeat requested by Bioclinica (please select visit)

Exam Information — **To be completed at Study Site**

Please indicate target knee: ☐ **Left** ☐ **Right**

Target Knee - Large FOV ☐ Not done
Exam Date: ☐☐ / ☐☐☐ / 20☐☐
Deviations from Protocol/Comments:

Target Knee - Small FOV ☐ Not done
Exam Date: ☐☐ / ☐☐☐ / 20☐☐
Deviations from Protocol/Comments:

Contralateral Knee - Small FOV ☐ Not Done
Exam Date: ☐☐ / ☐☐☐ / 20☐☐
Deviations from Protocol/Comments:

Do not write below this line. For Bioclinica use only

Data Receipt - 10005841 — **To be completed at Bioclnica**

Comments:

RESERVED FOR BIOCLINICA BARCODE

*** NOTE: Shipment should include completed trasmittal form and media containing images. ***
*** Distribution: File YELLOW copy at Study Site. Send Original (WHITE) page to Bioclinica. ***

Final

Bioclinica Tracking Number: 1 0 0 0 5 8 4 1 | 1 0 | 2 0 1 8 0 8 1 6 | ☐☐☐☐

10 Appendix III: Instructions for Completing the Transmittal Form for QCT Subject Examinations

Site, Subject, and Visit Information
• Complete the subject demographic information including Site Number, Baseline Number, Allocation Number, and Date of Birth in **English**. When entering Date of Birth, use the date format: 01/JAN/YYYY (e.g., 01/JAN/1946).
Exam Information
For each scan type: • Check appropriate anatomical locations. • Complete date of QCT exam. Enter the dates using English and the date format: DD/MMM/YYYY (e.g., 11/JAN/2003 for January 11, 2003). See above for abbreviations of months in English. • Enter any parameter that deviated from the protocol. • Enter the table height in mm. • Document any relevant comments (these may include positioning or scheduling issues).
Data Shipment to Bioclinica
• Initial and date the form after checking completeness and correctness. • Record the airway bill number. • Keep the pink clinical site copy for your records.

IMPORTANT ►	**Please include a transmittal form (white and yellow pages) with every submission of a subject exam.** Print **clearly** – all writing needs to be legible. **Use black ink.** Do not use white-out (make corrections according to Good Clinical Practice). COMPLETE the first section of the form – missing information here slows the processing of the subject data and may require the data to be returned to the site for completion.

11 Appendix IV: Transmittal Form for QCT QKP Phantom Scan

BIOCLINICA®

Samumed Protocol SM04690-OA-06
Transmittal Form for QCT QA Phantom Scan

Site and Phantom Information — **To be completed at study site**

Site Number: ☐☐☐

Serial Number listed on QRM Knee Phantom used for scan: ☐☐☐

Serial Number listed on QRM BDC Phantom used for scan: ☐☐☐☐

Please make sure that only a QRM Knee Phantom is used for this Phantom QA scan

Phantom Scan Information — **To be completed at study site**

☐ Longitudinal QC

Scan Date: ☐☐ / ☐☐☐ / 20☐☐ (D D / M M M / Y Y Y Y)

☐ Cross-sectional QC

Scan Date: ☐☐ / ☐☐☐ / 20☐☐ (D D / M M M / Y Y Y Y)

Initials of QCT Technologist Acquiring Scans: ☐☐☐ (F M L)

Deviations from Protocol/Comments: _____

_____

_____

_____

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

Data Receipt Bioclinica Study Code 10005841 — **To be completed at Bioclinica**

Comments: _____

_____

_____

_____

_____

_____

RESERVED FOR BIOCLINICA BARCODE

Final

Bioclinica Tracking Number: 1 0 0 0 5 8 4 1 | 1 0 | 2 0 1 8 0 8 1 6 | ☐

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

12 Appendix V: QCT Supply Order Form

5841

SM04690-OA-06

DO NOT REMOVE THIS PAGE. SEND A PHOTOCOPY ONLY.

QCT Supply Order Form

Please indicate quantity of each supply needed and email this form to:
#MI_DEP_MSK.Team.SM04690-OA-06@bioclinica.com and your assigned Samumed Clinical Research Associate

Supplies shall be sent to the following location:

Site #: ___ ___ ___

Attn: _____

Address: _____

_____

Town: _____

Country: _____ Postal Code: _____

Phone #: _____

Please send the following supplies (Provide quantity required)

Transmittal Forms for QCT of Knee _____

Transmittal Forms for QCT QKP Phantom Scan _____

Padded Mailers _____

Pre-printed Airway bills _____

Signature: _____ **Date: __ __ / __ __ __/ __ __ __ __**

13 Appendix VI: SMART Submit

SMART Submit Release 1.0 User Guide

Document Version 1.0

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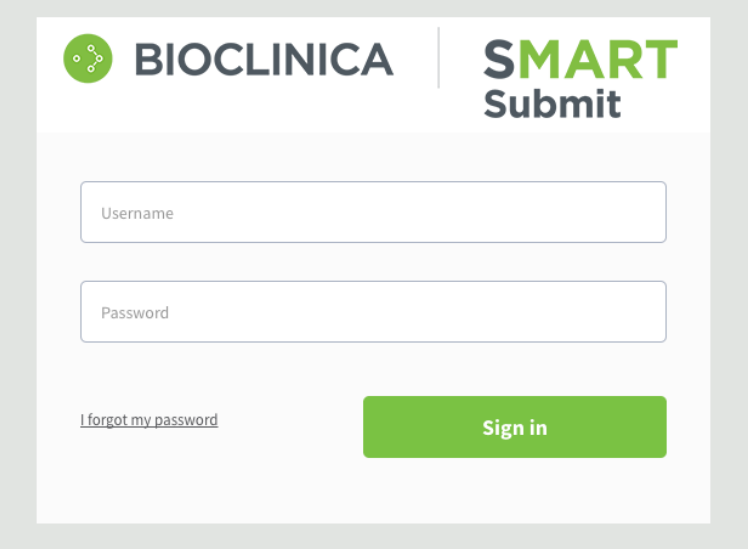
Getting Started

SMART Submit is Bioclinica's web-based system for clinical trial uploads. Using SMART Submit sites can fill in required case details as per transmittal form, upload images, authorize, and submit trial cases to BIOCLINICA.

1. Login

Once you have received the welcome email, click the link to set your password and other important information like your time zone and phone number. Once done, log into SMART Submit at: https://smartsubmit.bioclinica.com/.

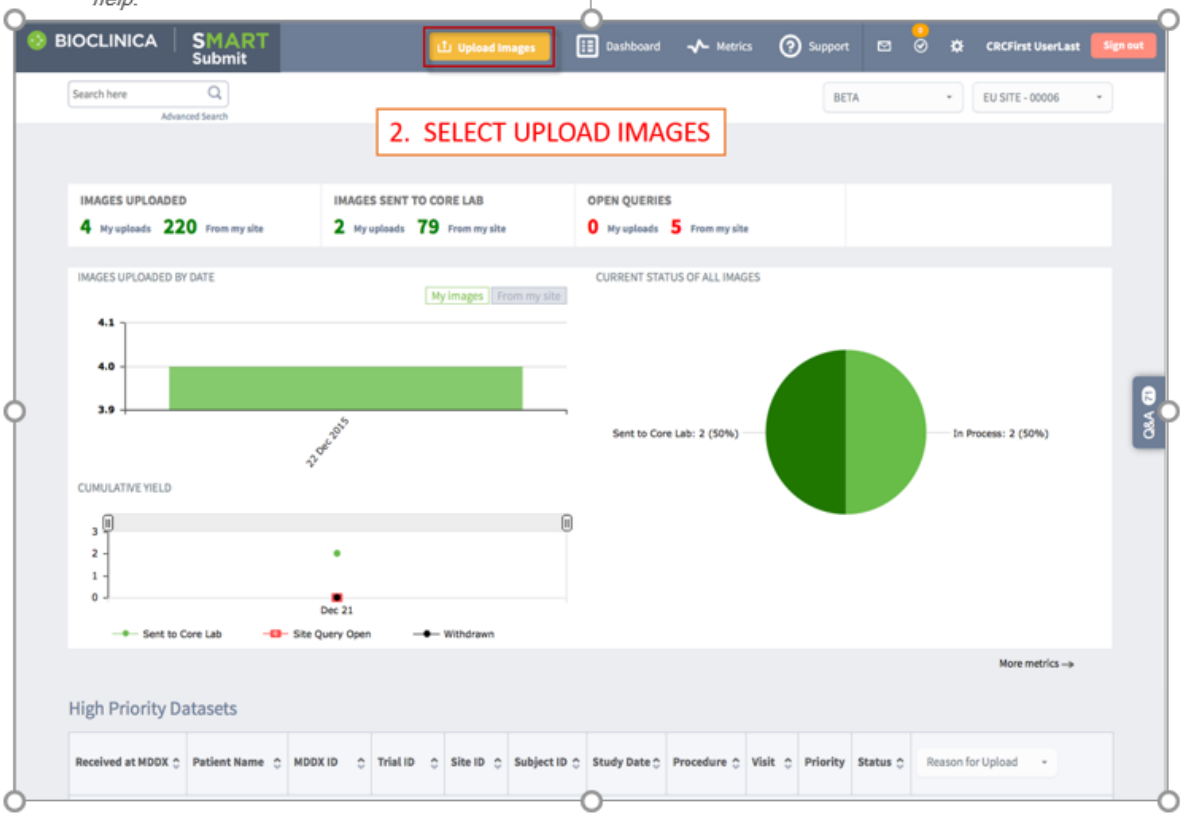


1. Your Username is your email address, and you set your password during account setup.
2. **Click** Sign In.

2. Upload Images

Once you have logged in you will presented with SMART Submit dashboard. Please click "Upload Images" on top middle screen as shown.

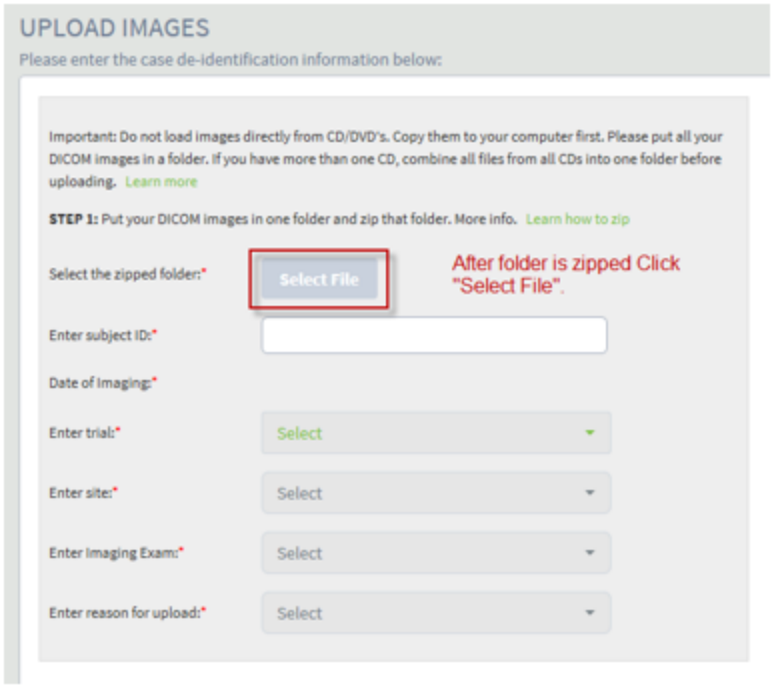
Note: Prior to uploading trial images, all new users will be required to watch a training video and upload a "User Qualification" upload.. . The "User Qualification" upload can be any zipped file containing DICOM files. The purpose of the User Qualification upload is to confirm you have access to DICOM, and have acceptable internet speed. The images will not be sent to BIOCLINICA. Please contact SMARTSubmit support team if you need any help.



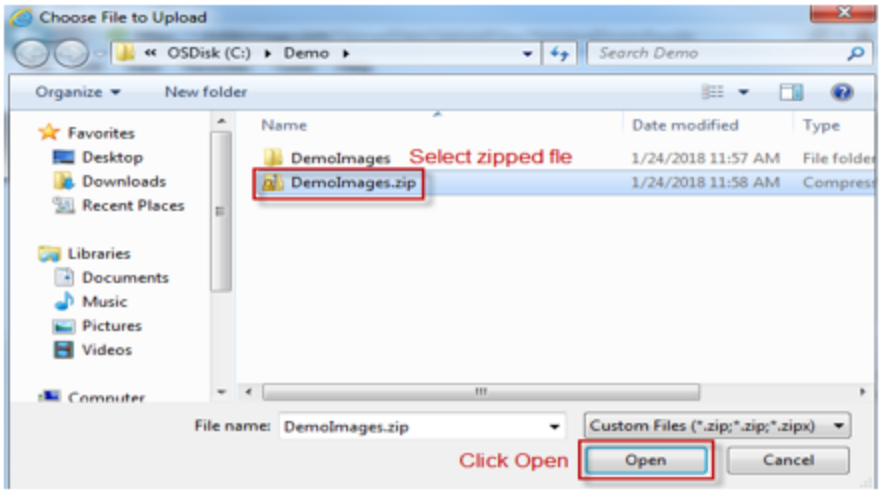
3. ZIP the folder with your images on your Computer and upload it

You will be presented with Upload form as shown.

1. Please zip the folder containing images that needs uploaded
2. Click "Select File"



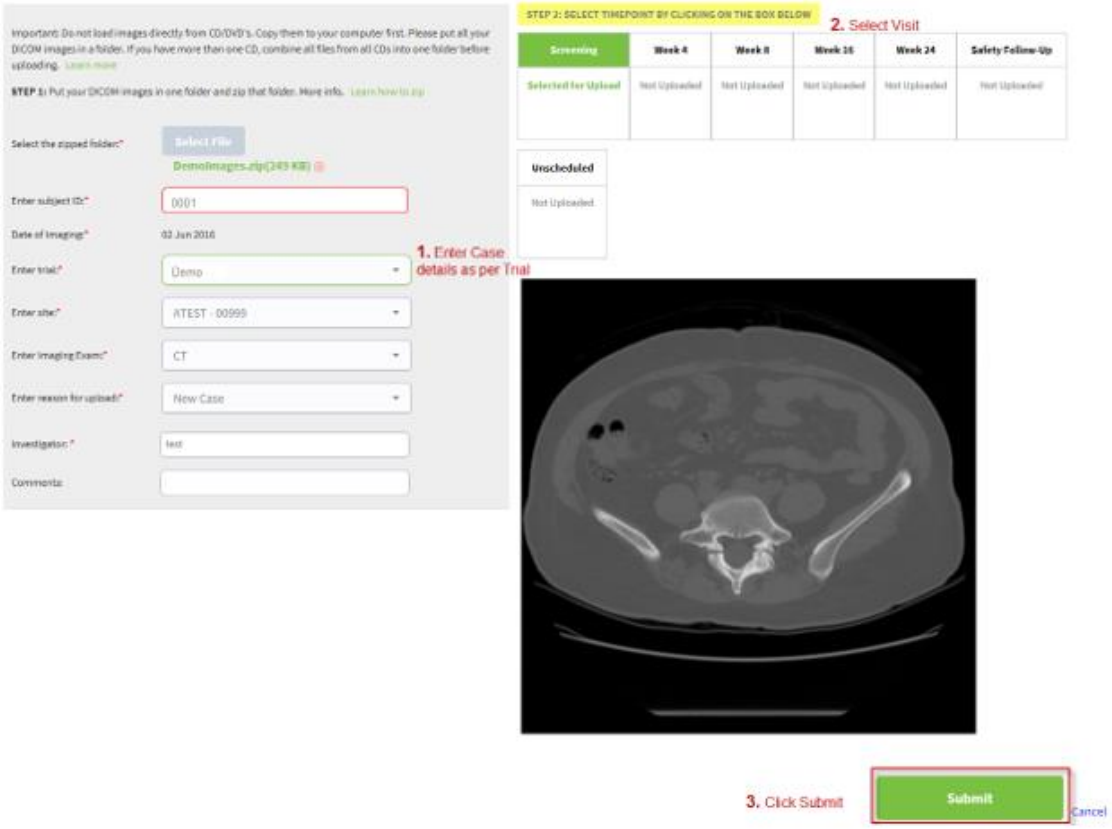
3. Locate the zipped folder and click "Open" button.



You can zip a folder using any utility you have on your computer. The below example shows how to zip a folder

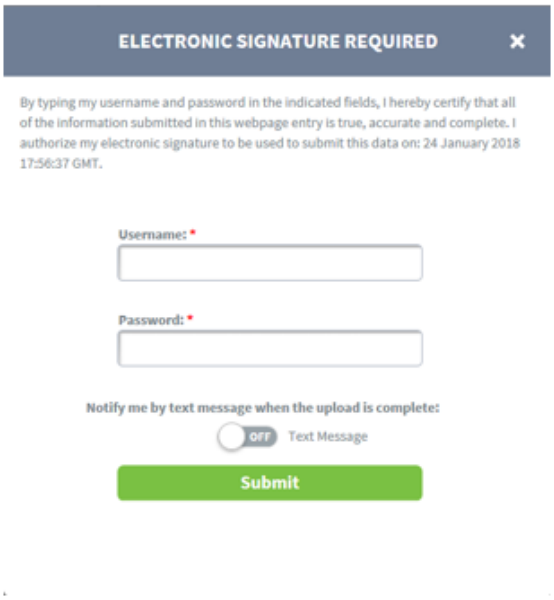
4. Enter Case Details

Please fill in the Case Details (i.e. Subject ID,Trial Name, Reason for Upload, Timepoint. Answer any questions as per Trial requirements) and click "Submit" button.



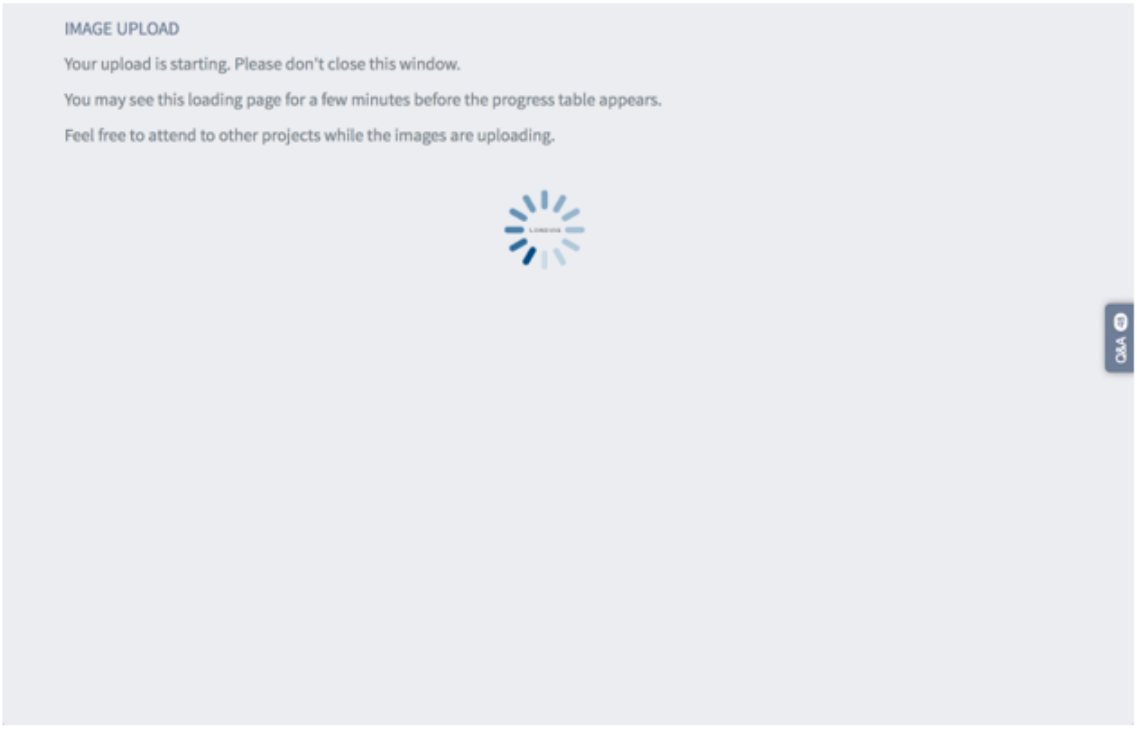
5. Electronic Signature

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



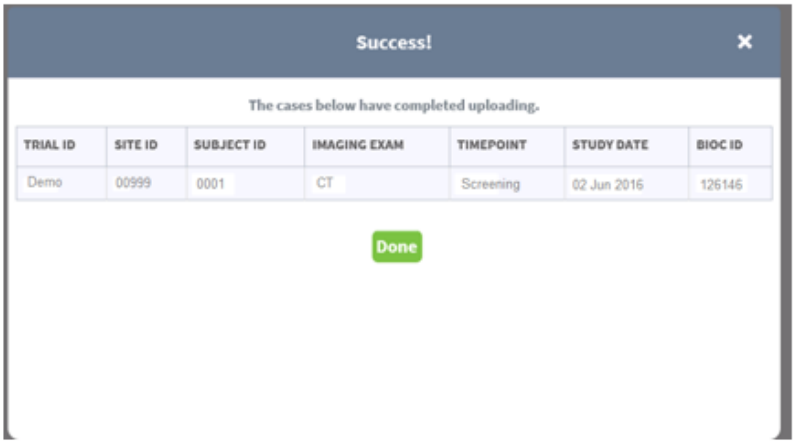
6. Image Upload Progress

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.

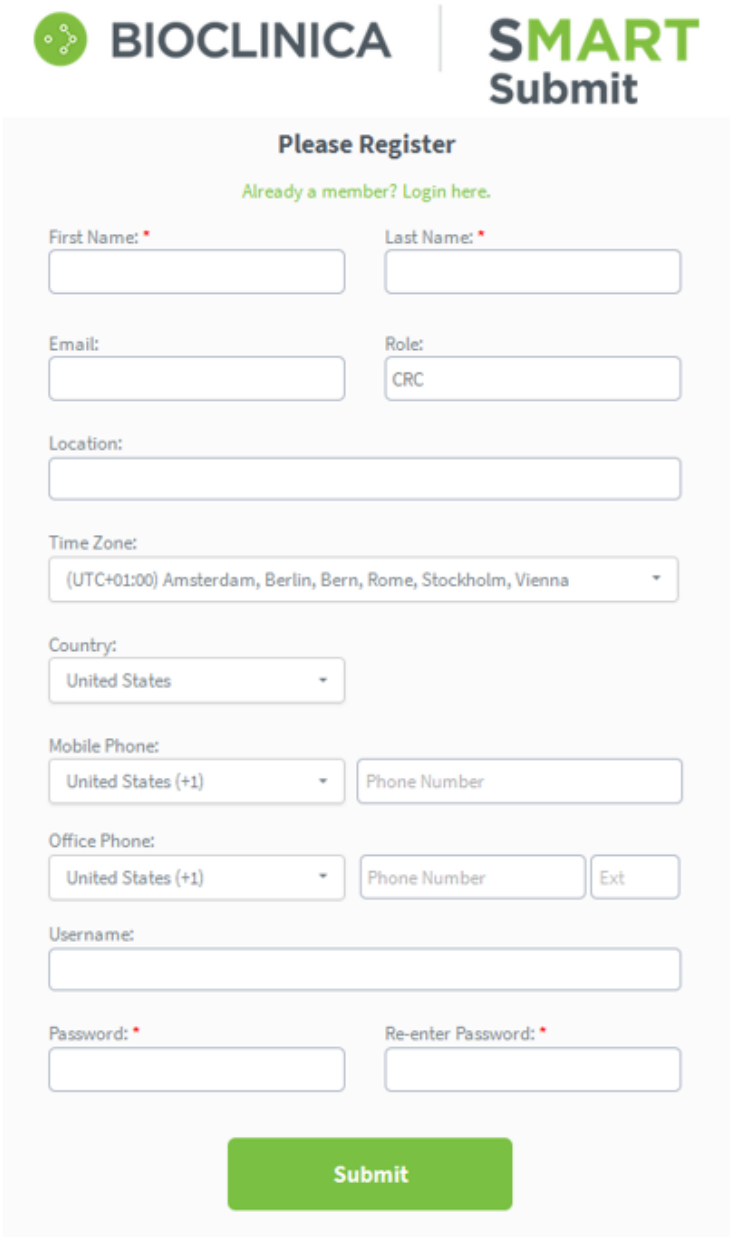


7. Image Upload Success

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.



Logging in For the First Time



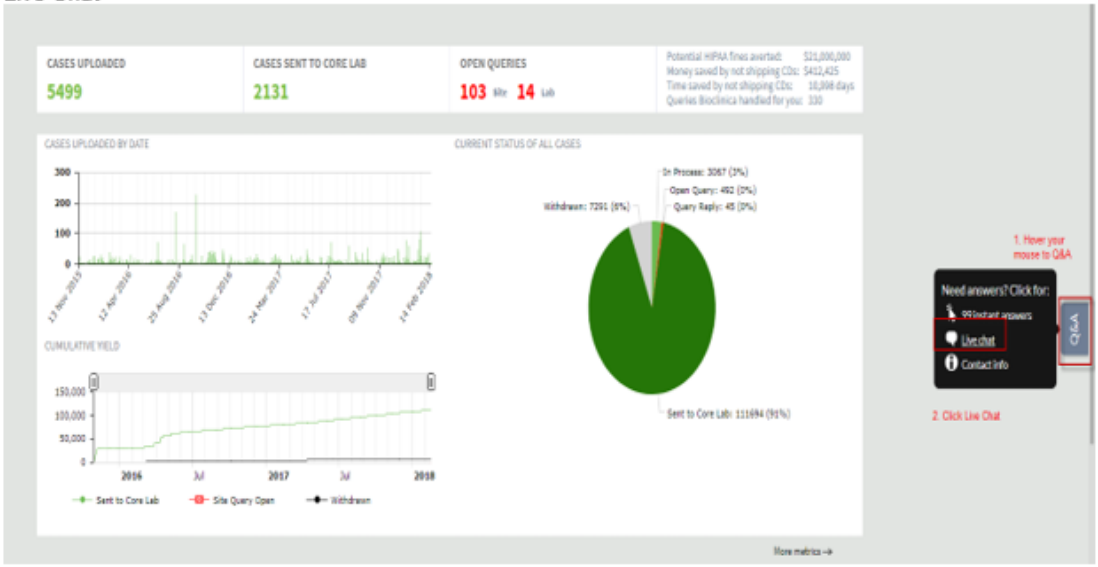
1. **Confirm** your First Name, Last Name, Email, Role, Location, Time Zone, Country, Mobile Phone, Office Phone, and Username.
2. **Enter** a new password. The password must be at least 8 characters long and must contain at least three of the following: an upper-case letter, a lower-case letter, a number, and a symbol.
3. **Re-enter** the new password in the Confirm Password field.
4. **Click** Submit.

SMART Submit Support

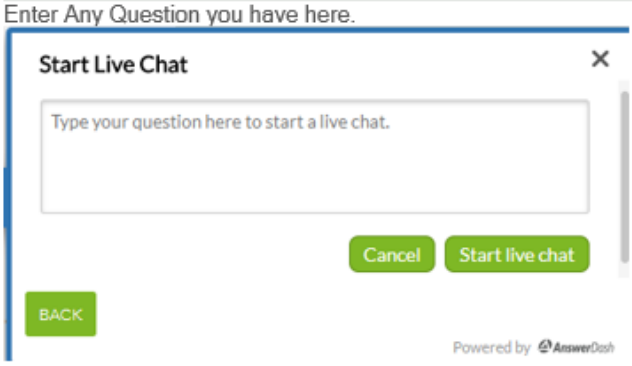
There are many ways you can reach out to support.

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