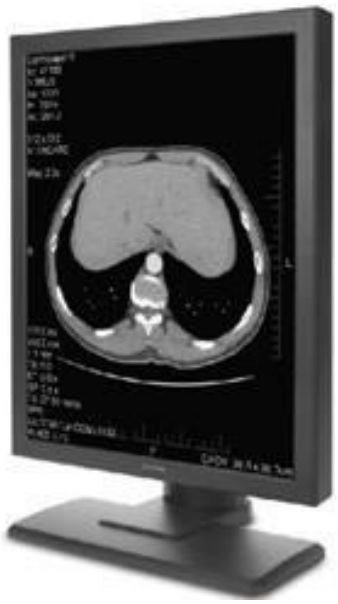

INVESTIGATOR SITE OPERATIONS MANUAL
Astellas Pharma Global Development, Inc. 2693-CL-0304

Project:	Astellas Pharma Global Development, Inc. 2693-CL-0304
Document File Name:	242902 Investigator Site Operations Manual V1.0.doc
Document Revision:	1.0
Version Date:	24-May-2019
Author's Name	Kate Francis

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REVISION HISTORY

Date	Author	Version	Description of Revision
24-May-2019	K.Francis	1.0	Initial Release of Document

Table of Contents

Abbreviations and Acronyms

CIL	Core Imaging Laboratory
DICOM	Digital Imaging and Communications in Medicine
QC	Quality Check

1 Introduction

1.1 PAREXEL Scope

This Investigator Site Operations Manual provides instructions for the imaging component of the study. This document is specifically related to the management of imaging data acquisition, including shipment, tracking, and quality control.

All imaging scans will be acquired in a standardized manner, following pre-established Image Acquisition Guidelines (IAG) developed by PAREXEL Informatics and approved by sponsor. Images will be submitted to PAREXEL for processing and independent analysis. Imaging data for all patients will be acquired according to the imaging schedule outlined in the protocol.

All images will be submitted to PAREXEL within 48 hours of acquisition (2 business days).

Images received at PAREXEL **MAY NOT CONTAIN** any markings, assessments or confidential patient information.

You must remove from the images the names of the patient and investigator site and any other information that can be used to identify the patient or investigator site.

Independent Reviewer findings are independent assessments and will not be communicated to the sites. All patient care decisions are made at the site by the Primary Investigator(s) including whether the patient should continue on the study.

Independent Reviewer(s) will remain blinded to the assessments made at the Investigator Sites.

1.2 Purpose of this Manual

The purpose of this manual is to provide:

- Contact information for additional assistance
- Description of operating procedures for Investigator sites
- Sample forms

1.3 Start Up Package Components

PAREXEL Informatics will provide the Investigator Site with the necessary materials listed below to perform the functions associated with this Investigator Site Operations Manual.

- The **Image Acquisition Guidelines (IAG)** are generated by PAREXEL in an effort to standardize all imaging associated with the clinical trial across multiple Investigator Sites, patients and timepoints. The standardized guidelines are distributed to each Investigator Site participating in this study. Please note that there are separate guidelines for acquiring each involved region, varying scanner types and modalities.
- The **Image Acceptance Notification** is sent from PAREXEL to the Investigator Site when acceptable imaging data is received.
- The **Query Notification** is sent from PAREXEL to the Investigator Site upon receipt of unacceptable imaging data at PAREXEL. The notification will describe the query and indicate the action(s) required to be taken towards submission of acceptable imaging data.
- The **Site Acceptance Form** is sent from PAREXEL to the Investigator Site when all qualification requirements have been met. This notification informs the site that they have been approved for submission

of imaging to Parexel as required to participate in the study. The form may also contain recommendations and/or feedback regarding any test transfer data.

- **DXA IQC Spine Phantom Maintenance Form** is used to capture information regarding any service or maintenance performed on the scanner.

1.4 Responsibilities

The **Core Imaging Laboratory (CIL)** is the centralized facility at PAREXEL Informatics, for all processes associated with image data collection and review by Independent Reviewers. PAREXEL is responsible for the receipt, tracking, processing, Quality Control (QC), archiving of the image data. Data generated by the reviewer are maintained at the CIL and will be transferred to the sponsor (or designee) at a specified time.

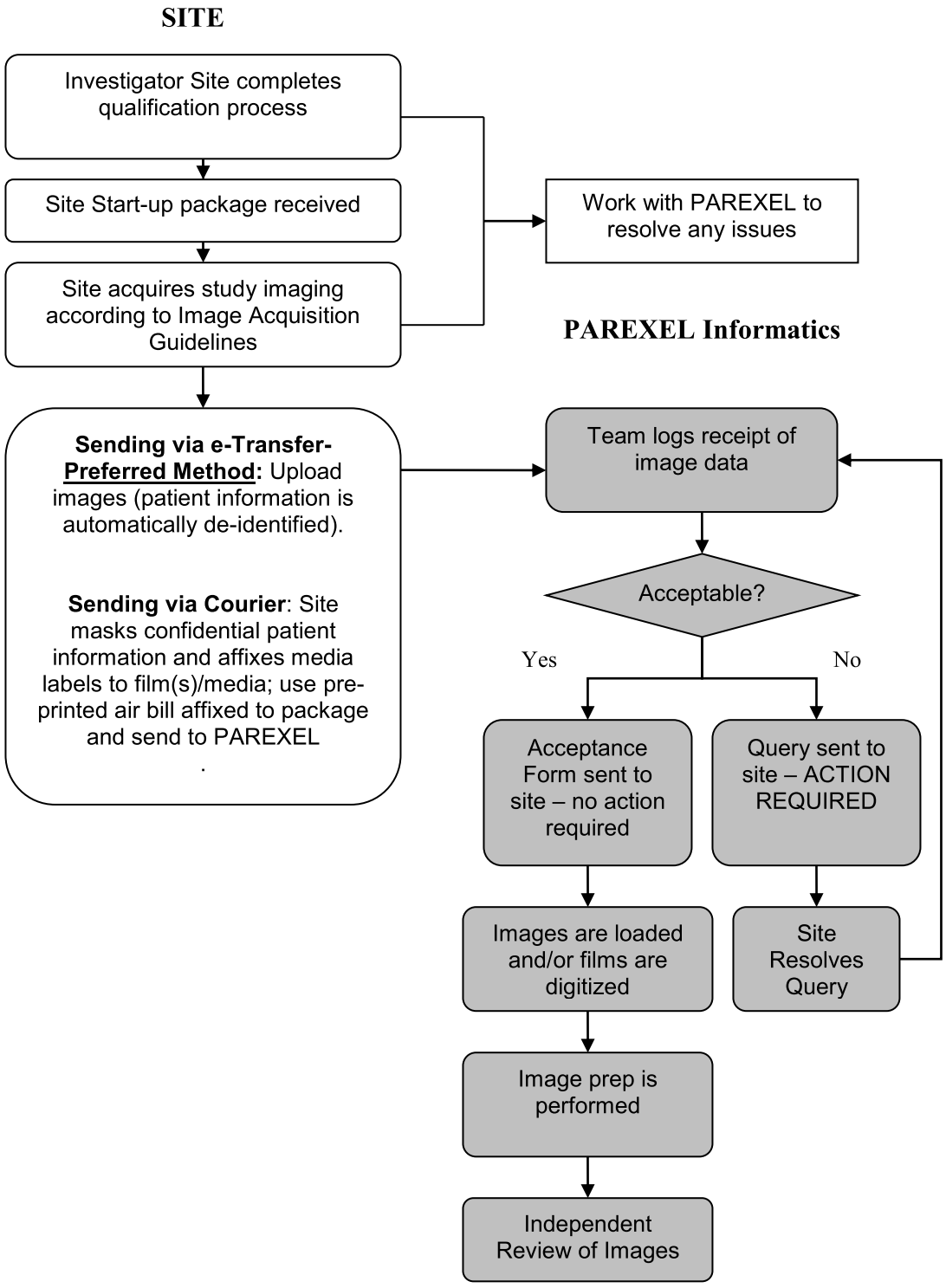
The **Investigator Sites** are responsible for enrolling patients and obtaining imaging per Image Acquisition Guidelines and study protocol. The Investigator Site is also responsible for managing image scheduling and for preparing and forwarding image data to the CIL within 48 hours of acquisition. Any changes in staff must be communicated to PAREXEL in a timely manner so that access to applicable applications/ portals) is removed.

An IRB approved informed consent must be signed prior to acquiring images of healthy volunteers and study subjects.

1.5 PAREXEL Contact Information

242902-Imaging@parexel.com

1.6 **Study Flowchart**



2 Image Processing Procedures

This section details the image acquisition, collection and data transfer procedures for the Investigator Sites participating in this clinical trial. Please notify the radiology staff in advance of a study patient and include the Image Acquisition Guidelines with the image requisition.

2.1 Image Acquisition

Performed by:	Technician, designee
Scope:	This procedure describes the steps necessary to acquire study images and to provide PAREXEL with the necessary patient and visit information. Please refer to the Image Acquisition Guidelines for the specific parameters to be used for image acquisition.

1. The respective technician will acquire the images according to the IAG. The technician will upload image data without markings or measurements to the Perceptive e Transfer portal.

2. If eTransfer is not being used the technician must de-identify patient name and investigator site name and any other information that can be used to identify the patient or investigator site contained in the DICOM Header. Imaging data that has been masked and contains no markings or measurements are placed on the media (CD, film, DVD). A copy of the exam is maintained at the facility.

   Note: If you need to de-identify electronic data, and your IT department is unable to help, you may wish to consider whether DicomEditor is appropriate. For more information about this free software, please visit: http://mircwiki.rsna.org/index.php?title=DicomEditor. DicomEditor is not a PAREXEL product. We do not endorse it, do not make any representations about its performance, and do not supply any training or support for the software. If you have not done so already, we suggest you try DicomEditor prior to using it for study images so that you are sure there are no issues with it.

3. The technician must verify the names of the patient and investigator site and any other information that can be used to identify the patient or investigator site has been completely masked.
4. Confidential patient information is defined as individually identifiable information including but not limited to:
   - name (full name or first name and last initial or first initial and last name)
   - full Date of Birth
   - social security number
   - home address
   - phone number
   - medical record number
   - For photo images, full face or tattoos on body

2.2 Image Data Transfer via Perceptive eTransfer -Preferred Method of Image submission

Performed by:	Study Coordinator or designee
Scope:	This procedure describes the steps used to send images from the Investigator Site to PAREXEL via eTransfer

This web-based electronic transfer solution allows investigator sites to transfer de-identified study images to PAREXEL through an internet browser. The eTransfer website is HIPAA and 21CFR Part 11 compliant. This method provides a chain of custody and de identification of protected patient information.

There are only two requirements to use eTransfer:

1. A computer with internet access
2. JAVA plug-in (already installed on most computers)

Recommended internet browser: Google Chrome (no JAVA plug-in required).
Other compatible internet browsers: Internet Explorer (7, 8, 9 or 10), Safari, or Firefox (all require JAVA for upload)

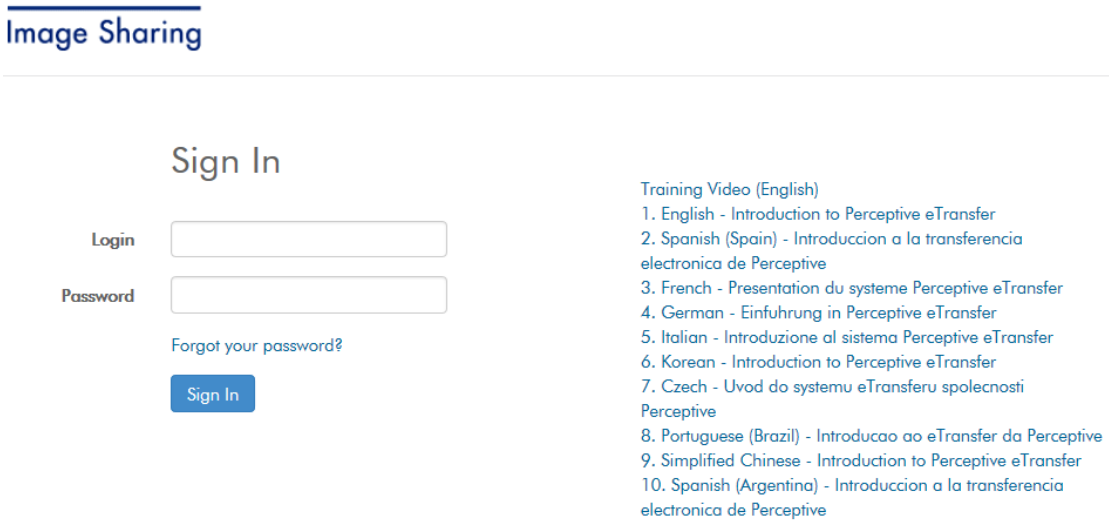
If JAVA is not installed, the Perceptive eTransfer system will guide the user through the Java installation process. If installing the Java plug-in is blocked the user will need to contact the Information Technology Administrator at their facility.

If internet browser or Java issues a desktop study uploader can be used. The link below is used to download the desktop version.
https://access.ambrahealth.com/download/cdupload/publish.htm

User Access

1. The PAREXEL study team will create an account using the email address provided by the sponsor as the user log in ID. The site user will then receive an email notification
    i. New users will receive a link to accept the study, their user ID (email address) and a link to create a password.
    ii. Existing users will receive a link to accept the study. (Existing users should use this current credentials)
2. Additional user accounts can be requested by emailing the PAREXEL team
3. Navigate to the system log in page and select the training link to view a 10 minute training clip.
4. Log into the system and the home page appears:

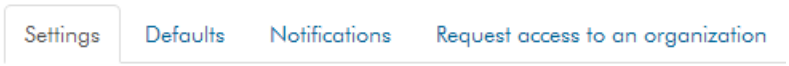
https://parexel.ambrahealth.com/index.html



5. If login is not successful please check the credentials again and/or contact the PAREXEL team.

User Settings

1. The user's name appears in the top right menu of the homepage. Select this to edit:
    - First and/or last name
    - Reset the password
    - Set email notifications



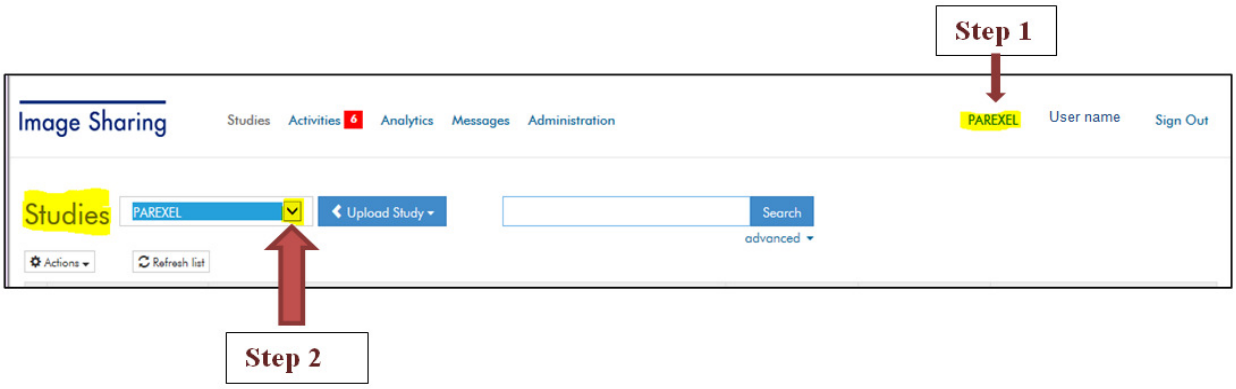
2. To edit notification preferences, the user will select the "Notifications" tab. To receive email notifications. Select "On Upload".

Uploading Images

Once logged in please complete the following steps:

Step 1 - Select the study in the upper right-hand corner by your name and the sign out button

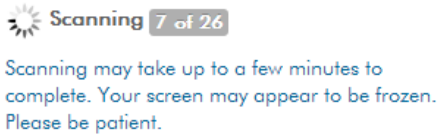
Step 2 - Use the **down-arrow** to the right of the **STUDIES** to select the correct study and site number for the image upload. **– Click** –**Upload Study** and then **Upload Studies**



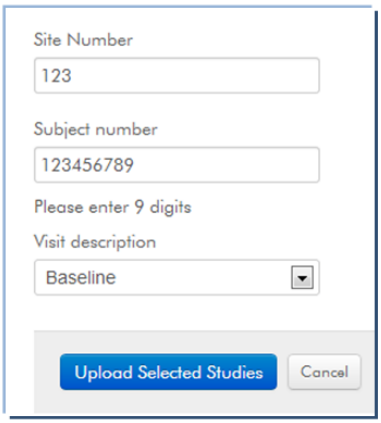
NOTE: If uploading a non-DICOM file (i.e. JPEG, AVI, DXA/IQC files) the user must check the "Select files for DICOM wrapping"

Step 3 - Select " choose file" and a browsing window will appear. The user will select the folder where the study images are stored and select "open".

Step 4 - The "scanning" symbol will appear when a folder has been selected.



Step 5 - The user will complete the trial/subject required information.



The user will select "upload Selected Studies". As the images upload, a status bar will appear. Do not navigate away from the webpage while the upload is in progress. Open another eTransfer webpage to upload another scan concurrently. Upon successful upload the following message will be displayed:

If the image upload notification feature is on, the user will receive an email within minutes of a successful upload from Perceptive eTransfer.

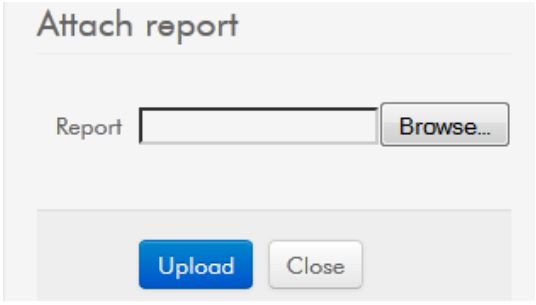
Note: It is critical that the image data is uploaded using the correct subject and visit description. All other identifiers are removed by the system. The site number, subject number and visit description must be correct as these are the only subject identifiers available to PAREXEL. Please help PAREXEL provide quality services by ensuring the correct image data is uploaded.

Uploading IQC data:

If the user selects IQC data from the modality list, a set of IQC specific questions will appear. The user will need to enter the scanner ID as well as any maintenance/service comments and reports.

Uploading Reports and/or Documents

1. A user can upload specific reports or documents associated with an image exam or Monthly IQC submission. The user will navigate to the timepoints list and select the report button for the subject/timepoint after the necessary images have finished uploading.
2. The window below will appear, the user will select the document, and click upload.



Viewing Images in the Image Viewer

1. Once uploaded, images can be viewed through the browser using the "View study in viewer" button:  NOTE: the viewer works best with Google Chrome or Mozilla Firefox.
2. The user can use the scroll on the bottom of the viewer to go through all images.

Technical Support for e Transfer

For technical support contact the Ambra Health Technical support team by phone at 1-888-315-0790 or (321) 339-5348 (available 24/7) or by email at support@ambrahealth.com

2.3 Image Transfer via Courier

Performed by: Study Coordinator or Designee
Scope: This procedure describes the methods used to prepare images for transfer from the Investigator Site to PAREXEL. Study shipments are to be sent within 48 hours of acquisition.

Due to strict data protection laws the preferred method of data transfer is e transfer. Data that is submitted through e transfer is automatically anonymized and has a visible chain of custody. However, if e transfer is not possible, data may be submitted via courier if the following requirements are met:

- Only use pre-printed media labels supplied by PAREXEL. These are completed and placed on all media shipped to PAREXEL.
- Only one exam per subject is placed on each CD that is submitted to PAREXEL. Please do not batch exams.

Non-compliance may cause delays in image acceptance, subject enrollment, subject, image and visit information errors, data reconciliation issues and the wrong subject imaging being entered into the system. Please help PAREXEL provide quality services by complying with these instructions.

1. The study coordinator receives the imaging data from the Imaging Department and verifies:

   - Images stored on digital media are in **uncompressed DICOM format or for DXA, the scanner proprietary format**
   - No lesion markers or measurements are present
   - Confidential patient information is de-identified.

2. The Study Coordinator will contact the site's Imaging Department if any problems are noted.
3. The Study Coordinator will complete and affix media labels directly onto the media, CD / DVD (label includes site number, subject number, visit description, exam date)
4. If hard copy films are sent, each film must have a media label attached in a manner that does not obstruct anatomy.
5. The Study Coordinator is responsible for maintaining patient confidentiality by ensuring the imaging technicians de-identify confidential patient information on all exams being submitted on digital media.

Note: Please ship imaging data to PAREXEL within 48 hours of acquisition (do not wait for a patient to be randomized or wait to collect multiple timepoints).

2.4 Acceptance Process

Performed by: Study Coordinator or Designee
Scope: This procedure outlines the actions required of the Study Coordinator upon receipt of an Acceptance Notification. The notification will be sent from PAREXEL in a timely manner upon receipt of acceptable image data.

1. PAREXEL will perform a quality assurance check on the imaging data received.
2. An Acceptance Notification is sent from PAREXEL to the Investigator Site upon receipt of image data informing the site that the imaging for the timepoint is complete and of acceptable quality.
3. This notification may also contain feedback or recommendations for follow up visits.
4. The Acceptance Notification also serves as documented resolution to a Query.
5. File the Acceptance Notification in the study file. No further action is required.

2.5 Query Process

Performed by: Study Coordinator or Designee
Scope: This procedure outlines the actions required by the Study Coordinator upon receipt of a Query from PAREXEL. A query will be sent from PAREXEL in a timely manner.

The study coordinator may complete and return a query notification, respond via email/phone or login to the MyQueries portal to resolve the query.

1. A Query is sent from PAREXEL to the Investigator Site upon receipt of unacceptable image data. The query will describe the issue and indicate the action(s) required to resolve the issue(s).
2. The study coordinator is required to respond within 10 business days of query receipt.
3. If a written response on the query notification is being sent to PAREXEL, the study coordinator is required to maintain a copy of the query response in the study file.
4. Do not include any confidential patient information in the query response. Only the subject number should be used to identify a subject.
5. If resolution of the query cannot be completed, the site is required to notify PAREXEL within the 10 business day timeframe. This notification must include a definitive date for query resolution.
6. If the site is unable to successfully resolve the query, PAREXEL may request the assistance of the contracted CRO monitors and notify the sponsor of the issue.

2.6 MyQueries Portal

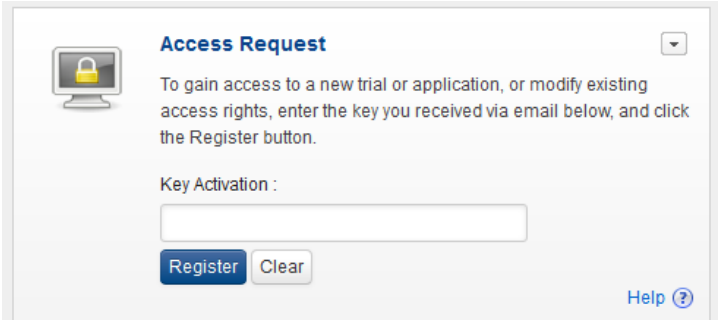
Performed by: Study Coordinator or Designee
Scope: This procedure describes the process for responding to queries sent from PAREXEL via MyQueries

MyQueries is a web-based service for investigator sites, to receive, view, track, and respond to queries from any computer with web access.

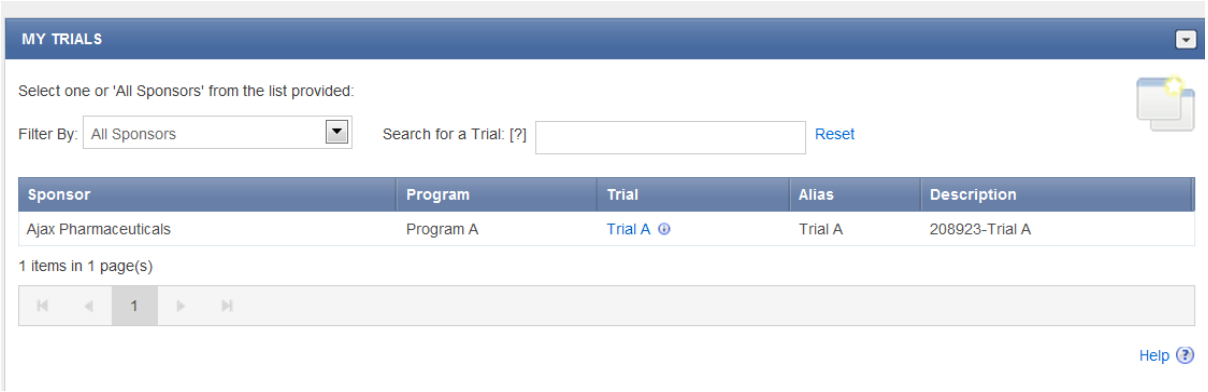
1. Contact the PAREXEL team and request an account for MyTrials.
2. An email will be sent from Perceptive Customer Care with the following email address: do-not-reply@perceptive.com , with an activation code.

3. Login to MyTrials @ WWW.MYTRIALS.COM.
   - If you already have an account log on with your User Name and Password.
   - If you are using MyTrials for the first time, select “register new account” in the “Join MyTrials” box.

4. After logging in to the system or creating a new account; enter the activation key(s) that you have received via email. **Please note you may receive more than one key and will need to enter all keys received for full access**

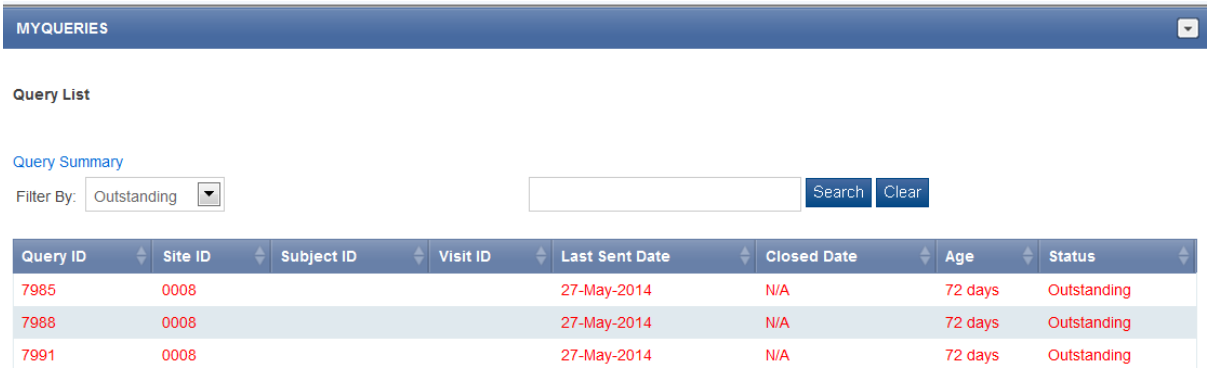


5. All trials that you have access to will appear upon login. Select the desired project.



6. Listed under the MyQueries tab are the new and outstanding queries for the project.

7. Click the links to view queries.



Query List (Queries can be filtered by any column header)

- **Subject ID** - If the query is regarding a site issue, this field may be blank.
- **Query ID** - A query with a number after the query ID (e.g.1234-3) represents the number of times the query was resent

- **Site ID** - If the query is regarding a site issue, the subject field may be blank.
- **Visit ID** -The visit description. If a query is not associated to a visit, this field may be blank.
- **Last Sent Date** -The date the query was sent, or resent from the PAREXEL. The Last Sent Date is updated with every response from the team, but may not be the latest date in the query history.
- **Age** -The number of days since the query was created.

Status

- **New** - Queries that have not been opened/viewed by the site user. Queries can be new to one user and outstanding to another.
- **Outstanding** - Queries that have not been closed by PAREXEL (only PAREXEL can change the status to 'closed'). Outstanding queries may be filtered by "overdue" and "responded".
  - **Overdue** – A query that has not been responded to within 10 business days. The status remains "outstanding" and will be displayed in red text.
  - **Responded** – A query that a site responded to (the status remains "outstanding").
- **Closed** - Queries that have been closed by the PAREXEL team.

Search for Queries

- A user can search for queries, including specific text from the query comments section.
- All fields in the query record are included in the search. The search text must be in English.

View Query Details

Select a query from the Query List to view details or to respond. The following information is displayed:

- **Query Comments** - The most recent communication is displayed in this section.
- **Query History** - Click "Show" to see the query history. All communications between PAREXEL and site / monitor users are included.
- **Query Response** - If the selected query is outstanding and the user has the appropriate permissions, the user will be able to send a query response to PAREXEL. The response must be in English. Enter the response into the query response field and select "send".
- To navigate between queries in the list, click Next or Previous at the bottom of the Query Detail Page.

3 DXA Instrument QC (IQC) Spine Phantom Scanning

Performed by: DXA Technologist

Scope: The following procedures outline the steps required to acquire and submit IQC data for the duration of the study

IQC data is used to monitor the scanners functionality over time so we can see any shifts or drifts in the calibration. Should a scanner shift or drift in calibration at any time, we are able to apply the IQC data to the subject data to correct the shift or drift seen.

3.1 IQC Requirements:

1. Baseline IQC data, Monthly IQC data, and Final IQC data is required to be submitted over the course of a study
2. Subject scanning cannot begin until the BL IQC has been deemed acceptable by PAREXEL.
3. The same QC Spine phantom must be used throughout the duration of the trial and be acquired and analysed in a consistent manner using the same scan mode and Region of Interest.
4. The QC Spine phantom results must be reviewed to ensure the total BMD is within the QC Limits (High and Low Range) calculated at Baseline.
5. Please be sure to analyze these scans consistently and repeat any scan that exceeds the allowable range (set at Baseline) for your scanner. If two sequential BMD's exceed the allowable range, please report to PAREXEL as soon as possible and do not scan study subjects until the issue is resolved. Contact the scanner manufacturer to discuss and resolve the problem. Please see Documenting DXA Software Upgrades or Mechanical Problems section for further details.

6. Please keep an archive of your QC Spine Phantom scans for the duration of this trial, do not delete the scan files.
7. Submission of IQC data is to be managed in the same way as patient imaging and should be submitted via eTransfer.

3.2 Baseline IQC Activities (Preceding 1st Subject Scan):

1. Prior to first subject enrollment, sites are required to scan their local spine phantom (used for routine daily calibration and provided with your equipment) ten (10) consecutive times, without altering the scanner settings or re-positioning the phantom. Please do not use block phantoms that do not contain bone equivalency. If you do not have a spine phantom, please contact the sponsor.
    - PAREXEL will be using the Baseline IQC to determine the Baseline Mean BMD and monitoring that the mean BMD is within ±1.5%.
    - We recommend calculating your site's Baseline mean BMD and allowable range of ±1.5%. This is used to monitor the thresholds for the duration of the study.
2. Submit the current IQC phantom database with the 10 phantom measurements on the provided media or by electronic transfer.

3. Once BL IQC has been submitted and accepted, regular Monthly IQC Data Submissions (see below) must commence, even if subjects are not being scanned.

   GE Lunar: If you currently don't have an IQC Spine Phantom database, don't currently acquire a daily QC Spine Phantom, or are unsure on how to copy the IQC Spine Phantom database please refer to the DXA IQC User Guide or contact PAREXEL if further assistance is needed.

3.3 Monthly IQC Activities:

1. The local spine phantom (likely used for routine daily calibration and provided with your equipment) must be scanned at **least three times a week** and in optimal conditions every day during the course of the trial, even if no subjects will be scanned that week. Please do not use block phantoms or ESP phantoms.

2. A copy of the QC database must be sent to PAREXEL once monthly and should be sent during the first week of the month. These submissions are critical for central monitoring of the scanner's calibration and for accurate reporting of study subject's change in BMD at subsequent visits. Cumulative digital QC database files that are required for central review are as follows:

3. You may receive queries for overdue submissions or IQC database issues from PAREXEL.

4. **If working with PAREXEL on more than one DXA trial, only one monthly submission is required, and your IQC data will be valid for all DXA trials.**

5. **Please note:** Acceptance notifications are not sent for monthly IQC data.

3.4 Final IQC Activities (End of Study):

Acquisition of the QC Spine phantom must continue until ten (10) days of scans have been acquired following site's last subject's last visit or after the cross-calibration phantom is scanned, whichever is later, then a Final QC phantom database must be sent to PAREXEL.

3.5 DXA Equipment Service and Maintenance

- DXA equipment or software should not be replaced or updated during the course of the study. If replacing the equipment or upgrading the software is absolutely necessary, PAREXEL Informatics should be notified immediately, and study subjects should not be scanned until the new equipment or software is approved by PAREXEL.
- It is the site's responsibility to make sure the DXA Equipment is appropriately serviced and maintained.
- Software upgrades to DXA equipment should be approved in advance by PAREXEL.
- As part of the monthly IQC submission to PAREXEL, please submit any Maintenance Reports for that particular month.

- All maintenance and service (including preventative maintenance, software upgrades, etc.) should be noted on the Service Record Form along with a copy of the service report (when applicable) and submitted to PAREXEL.
- **Please use the same machine during the study and try to avoid hardware or software changes unless necessary.** If hardware or software changes must occur, please inform PAREXEL prior to the upgrade.

Important:

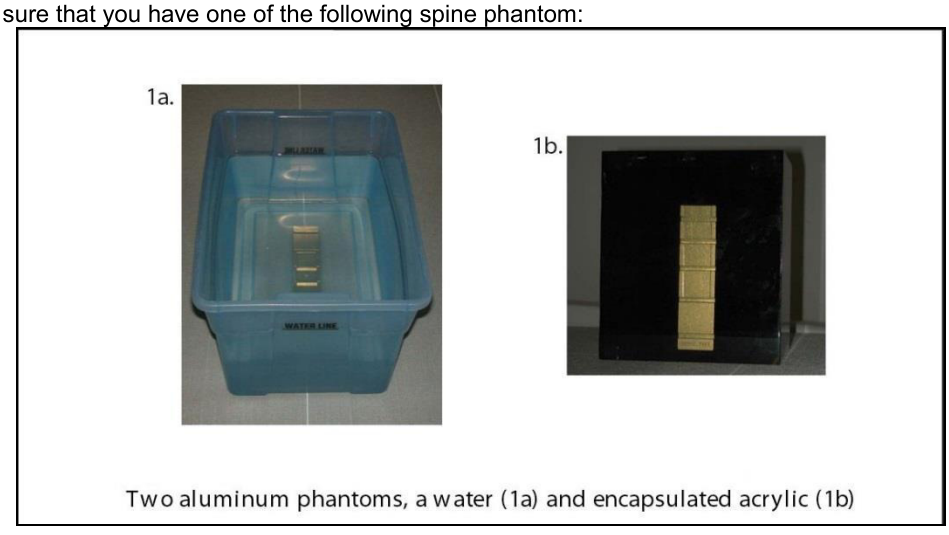
- If any quality control measurement falls outside the manufacturer specified limits, contact your service engineer and notify PAREXEL Informatics' staff immediately.
- IQC Phantom acquisitions should **always** be performed using the same scan mode.
- The monthly DXA IQC must be submitted on a monthly basis, even if no maintenance was performed.

The following DXA scanners are NOT supported by PAREXEL:

Manufacturer	Model
GE Lunar	DPX, DPX Pro, DPX Bravo, DPX Duo, DPX NT, DPX MD, DPX MD+, DPX IQ, DPX L, DPX Alpha, DPX A
GE Lunar	Prodigy 1-4
GE Lunar	Expert XL
Hologic	Explorer Series
Hologic	Delphi A, W, Wi
Hologic	QDR 4500 A, QDR 4500 C, QDR 4500 SL, QDR 4500 W, QDR 4000, QDR 2000, QDR 2000plus, QDR 1500, QDR 1000 W, QDR 1000 Classic, QDR 1000plus
Norland	All Models

4 GE Lunar IQC Information

Please make sure that you have one of the following spine phantom:



Two aluminum phantoms, a water (1a) and encapsulated acrylic (1b)

4.1 Creating a GE Lunar Database

It is required to keep your IQC data in a **separate database** from your patient data. If you do not already have an IQC database separate from your patient database, please follow the instructions below to create one.

1. From the Directory Screen in the Lunar software, click on **'New Database'**
2. A New Database window will appear, in the Name field, type **'IQC Spine Phantom'**
   - In the same New Database window, the location of the working folder is indicated, make a note where the Working Folder is located (this is where the saved database will be found).
   - Keep default settings for Archive from this workstation and Allow Backup from this workstation (see above screen shot) and click "OK"

Note: It will now be **required to select** the Clinic Database that is used for patient imaging when scanning patients or the IQC Database that is used for scanning IQC data depending on what you are scanning.

4.2 GE Lunar Spine Phantom Biography

Enter the information in the Biography section as listed below.

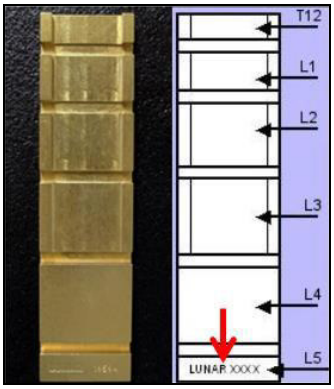
First Name: IQC Spine
Last Name: Phantom
Birth Date: Enter the current date minus 40 years. For example, if today's date were January 1, 2017, then you would enter 01/01/77. Please do not change this for future phantom scans.
Height: 67 inches or 170 centimeters
Weight: 154 pounds or 70 kilograms
Sex: Female
Ethnic: White
Facility ID (Secondary Tab): Record the phantom number given on the L5 region of the spine phantom

Note: This same biography will be used during the study for ongoing IQC phantom scans and is not expected to change.

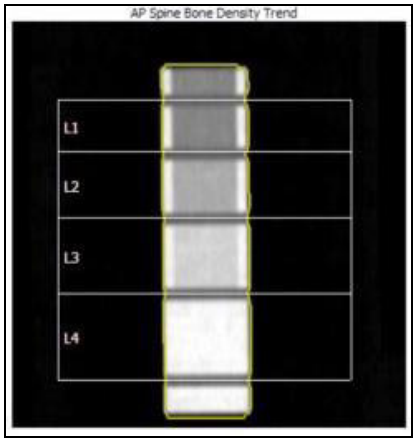
4.3 GE Lunar IQC Spine Phantom Acquisition

- To establish **Baseline IQC**, scan the Aluminum Spine Phantom ten consecutive times (10) in one day only following steps 1-9 as seen below **(wait until all 10 scans are acquired before completing steps 8 and 9)**.
- To establish **Monthly IQC**, please scan the Aluminum Spine Phantom at least 3 times per week following steps 1-9 as seen below.
- To establish **Final IQC** (after all patient and XCAL imaging has been submitted), please scan the Aluminum Spine Phantom 1 time per day for 10 days following steps 1-9 as seen below.

1. Position the phantom centered on the table so that L5 is toward the foot of the scanner
2. From the Main screen, select **"Measure (F2)"**
3. Select **"Position"** from the toolbar
4. Position the laser cross-hair on the letter **"R"** in the word "LUNAR" on the L5 vertebral body of the phantom:



5. Use **"Standard"** mode to scan the phantom, use this scan mode every time you scan the phantom
6. Watch the scan on the computer screen as it is acquired, when approximately half of T12 is imaged, select **"Abort"** from the toolbar
7. Choose **"Save measurement"** from the Save dialog box and select **"OK"** if the measurement was performed correctly (if it was now performed correctly, start over from step 1)
8. Analyze the Spine Phantom scan from L1 to L4 and consistently use the same Regions of Interest (ROIs) by using the copy function and copy the ROIs from the first analyzed scan to all follow-up IQC scans in the order in which they were acquired
9. Select **"Save"** to save analyzed results



(The analyzed scans should look like this example)

4.4 GE Lunar: Locating your IQC Database

1. Open the GE Lunar enCORE Software and go to **"Directory"**
2. Go to the list of **"All Databases"** located on the left side of the screen and click on the database you are using to collect your IQC Spine Phantom scans in
3. Go to the list of **"Active Database"**, locate the **"Working Folder"** and hover over the folder location to see the full text in order to ensure accuracy—note down this information as you will need it in the next steps
4. Next completely close out of the enCORE software without shutting down the computer **(This is a very important step, if you do not do this the Lunar.mdb file will not copy correctly)**
5. Navigate to the location on your computer found in step 3 (open the file browser and enter the folder location from step 3 into the Address field of the file browser and search)
6. Once you have navigated to this location, find the Lunar.mdb file
7. The Lunar.mdb file is the required file for all IQC submissions, this .mdb database should be submitted to PAREXEL as described in the IQC submission section of this guide

4.5 For GE Lunar enCORE Version 15 and higher

It is not possible to export your IQC data as lunar.mdb file as described above for version 15 and higher. Therefore, you will have to submit the analyzed scan files of the IQC spine phantom to the study team via eTransfer.

1. Go to the Desktop and create a new folder by right clicking your mouse and go to New → Folder
2. Name the new folder "PAREXEL"
3. Open GE Lunar software. Go to your original IQC database, where the Spine Phantom scans are located. Highlight all the Spine Phantom scans that need to be copied.
4. On the **Menu**, go to **Directory**, select **Send Exam File To**, and click on **Disk**
5. Compress Options will launch. Make sure the **only check mark is for "Compress File"** and click **"OK"**
6. Browse for the folder created in the Desktop.
7. **Click "OK"**
8. Open the newly created PAREXEL folder to verify that the DXA files are there. Those DXA files are the appropriate Spine Phantom scans that are needed to be copied for submission to PAREXEL

5 Hologic IQC Information

Please make sure that you have one of the following spine phantom:

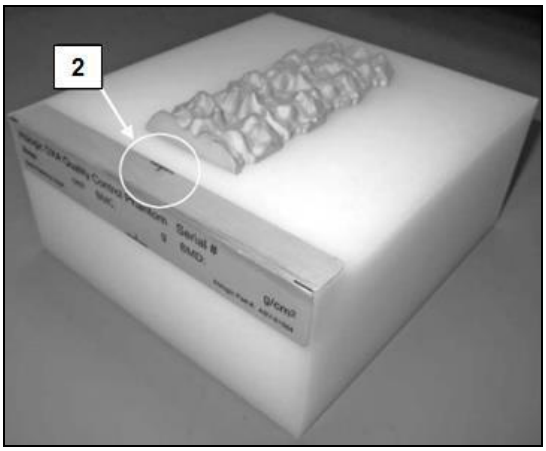
5.1 **Hologic Spine Phantom Biography**

- The spine phantom biography for Hologic scanners does not need to be edited or updated. Please use the current biography that was set up by the Hologic Technician likely when the scanner was installed.

5.2 **Hologic IQC Phantom Acquisition and Analysis**

- To establish **Baseline IQC**, please scan the Hologic QC Spine Phantom ten consecutive times (10) in one day only following steps 1-5 as seen below.
- To establish **Monthly IQC**, please scan the Hologic QC Spine Phantom at least 3 times per week following steps 1-5 as seen below.
- To establish **Final IQC** (after all patient and XCAL imaging has been submitted), please scan the Hologic QC Spine Phantom 1 time per day for 10 days following steps 1-5 as seen below.

1. Position the Hologic Spine Phantom so it is centered on the table
2. Position the laser cross-hair near the foot of the phantom at the indicator pictured below



3. Select the **"Daily QC"** button on the Main Screen to acquire the IQC scan
4. Software will automatically analyze L1-L4
5. Use the **PLOT** feature to verify that the BMD and the BMC of your scanner is within normal limits
6. If the most recent scan falls outside the limits, reposition the phantom and repeat the scan, if the second scan also falls outside the limits, contact both Hologic and Parexel
7. If the CV exceeds 0.5% contact both Parexel and Hologic to initiate appropriate action

5.3 **Exporting the Hologic IQC database**

If Scans are archived follow these steps:

1. Open the Hologic Software

2. Before exporting the data, the scans will need to be restored. There are two ways to perform this action.
    - Click **"Locate Scans"** > click on the **Patient Name** that corresponds to your phantom > click **"Locate"** > click **"Restore"**
    - Or Click **"Archive"** from the task bar at the top of the screen > select **"Restore scans"** and map to the folder where the scans are archived

5.4 How to Export the IQC Database

1. Open the Hologic Software
2. Select the "Utilities" menu at the top of the screen, then scroll down to "Database Tools", then scroll over to "Export" and click on it
3. A new window will pop up called "Export"
4. Make sure that "Patient Data" is unchecked, "IQC Data" is checked, and "All the Data" is selected. After these options are set click on "Export"
5. A "Save As" window will pop up. Give the database a name and save it to your computer
6. The database that you save is the required file for all IQC submissions. This .mdb database should be submitted to PAREXEL

6 Managing the Cross CALIBRATION Phantom

Performed by: DXA Technologist

Scope: The following procedures provides instructions for managing the Cross Calibration Phantom

The Cross Calibration (XCAL) data is different than IQC data in that it is calculated with XCAL data from all other scanners and is then applied to all subject data for the trial. This data ensures that scanners across sites for a trial operate within a certain range thus allowing for the data of subjects from different scanners to be comparable in the larger data set. This helps also to establish scanner equivalency in case a scanner breaks and requires a subject to be scanned on a different scanner.

Start Procedure

1. Carefully read this instruction manual prior to scanning the phantom. If you have any questions or if you are not sure on how to acquire the phantom scans, please contact PAREXEL.
2. You are required to scan the European Spine Phantom (ESP) once during this study. This requires that you scan the ESP 10 times in a row without repositioning and send the scan files to PAREXEL.
3. *We request that you scan the phantom within 2 days of arrival at your facility. If for any reason you are not able to acquire the scans during your scheduled time, please contact PAREXEL immediately.*
4. Carefully remove the phantom from the shipping container. Inspect the phantom to make sure it was not damaged in shipment. If the phantom is damaged, **please contact PAREXEL immediately as scanning a damaged phantom could potentially impact the results acquired.**
5. Upon receiving the phantom, please allow 3-4 hours for the Phantom to reach approximately 70ºF prior to scanning.

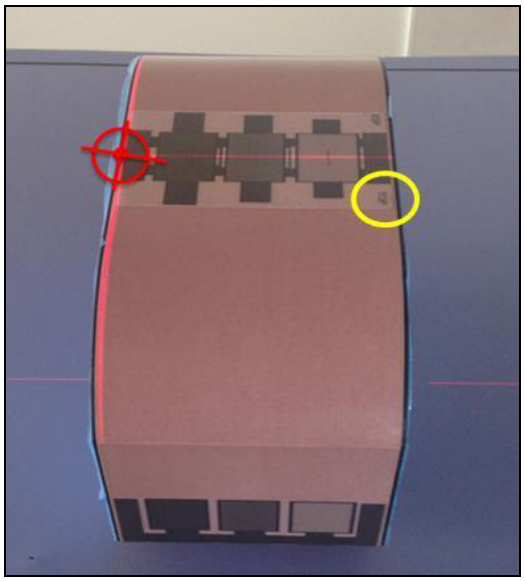
6.1 Creating the Cross Calibration Patient Biography

Please create one new QC Spine Phantom Patient for the European Spine Phantom with the following Patient Biography information **(if a field is not listed below, please leave it blank)**:

Lunar Prodigy Machines	Hologic for Windows
Last Name: Enter "CROSS CAL - SPINE" **Birth Date:** Exactly 40 years ago **Height:** Enter 66.9 inches (170 cm) **Weight:** Enter 154.3pounds (70kg) **Sex:** Female **Ethnic:** Use default choice for White **Facility ID:** Enter in the Phantom Serial Number "ESP-XX-XXX"	**Last Name:** Enter "CROSS CAL - SPINE" **Ethnicity:** Use Default **Sex:** Female **Birth Date:** Exactly 40 years ago **Identifier 2:** Enter in the Phantom Serial Number "ESP-XX-XXX" **Weight:** Enter 154.3pounds (70kg) **Height:** Enter 66.9 inches (170 cm)

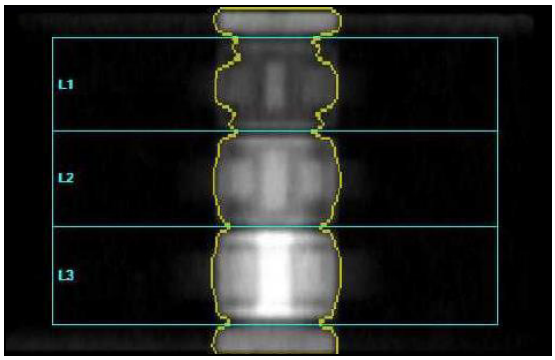
6.2 **Positioning and acquiring the Cross Calibration scans**

1. Place the phantom on the center of the table and aligning the label “ESP” and “TOP” (seen on the phantom) in the direction where the patient’s head would be placed for a scan.
2. Align the laser cross-hair on the bottom edge of the acrylic (as seen below).



Acquisition

1. Use the “AP Spine” scan function to acquire the scan. **DO NOT USE THE “PHANTOM” SCAN FUNCTION.**
2. Select the Standard (Lunar) or Array (Hologic) scan mode.
3. Ensure that the entire phantom anatomy is within the scan field.
   - If the scan appears to be completely black, you might have placed the phantom in the wrong direction and you are just scanning the table.
4. Ensure that the scan doesn’t include any air artifacts at the top, bottom or sides of the scan. This may require manually stopping the scan **(watch the screen as the scan is acquired and manually stop once the entire phantom is seen)**.
5. Acquire 10 scans in one sitting without repositioning the ESP Phantom.
6. Please do NOT analyze these scans. Send the scan files to PAREXEL **UNANALYZED**.
7. The end result of the scan should look something like this:



6.3 **SHIPPING Cross CALIBRATION Phantom to the next site**

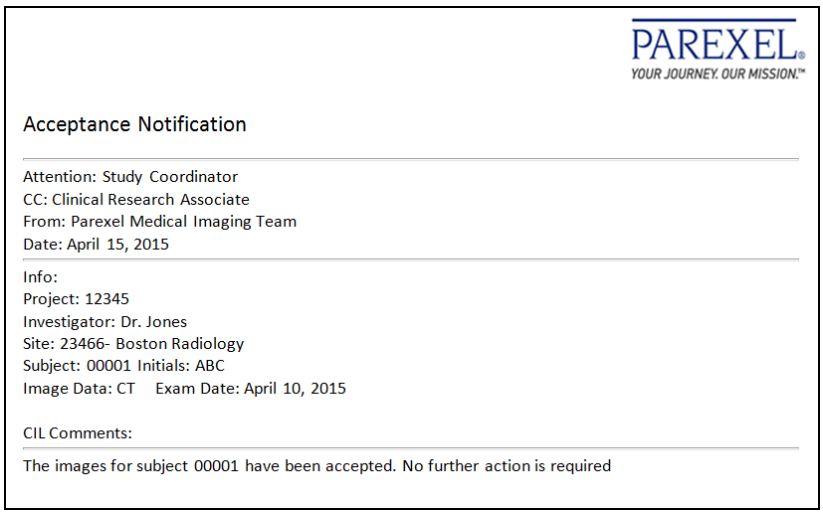
1. Inform PAREXEL upon completion and submission of Cross Calibration scan files.
2. Carefully re-pack the phantom into the shipping container and ensure that the latches are firmly closed.

3. PAREXEL will arrange the pickup with you.
4. If you need to **change your scheduled** pick up day or the phantom is **not picked** up on the scheduled day, please contact PAREXEL.

7 Forms

7.1 Acceptance Notification

This notification is sent from PAREXEL to the Investigator Site upon receipt of acceptable imaging data at PAREXEL.



PAREXEL
YOUR JOURNEY. OUR MISSION.™

Acceptance Notification

Attention: Study Coordinator
CC: Clinical Research Associate
From: Parexel Medical Imaging Team
Date: April 15, 2015

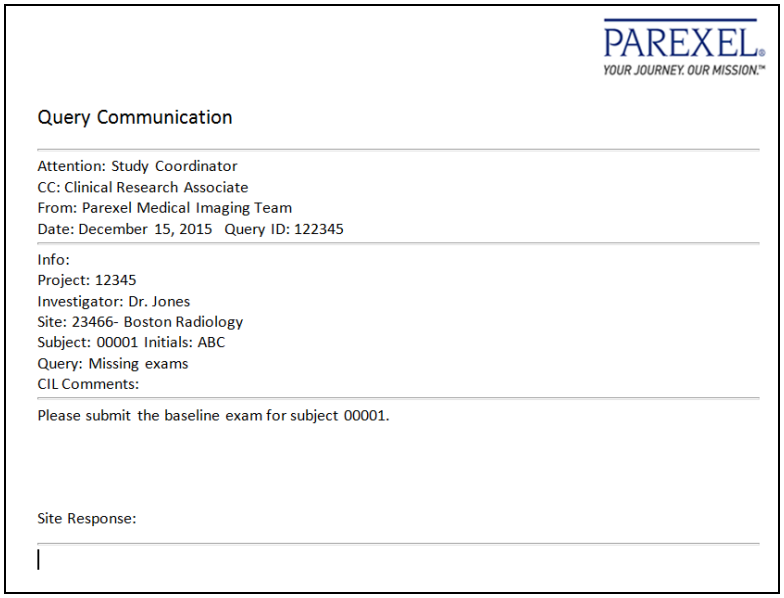
Info:
Project: 12345
Investigator: Dr. Jones
Site: 23466- Boston Radiology
Subject: 00001 Initials: ABC
Image Data: CT Exam Date: April 10, 2015

CIL Comments:

The images for subject 00001 have been accepted. No further action is required

7.2 Query Notification

This notification is sent from PAREXEL to the Investigator Site when unacceptable imaging data is submitted to PAREXEL. The notification will describe the issue of concern, such as, missing data, or deviations from the Image Acquisition Guidelines. The notification will indicate the action required.



PAREXEL
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Query Communication

Attention: Study Coordinator
CC: Clinical Research Associate
From: Parexel Medical Imaging Team
Date: December 15, 2015 Query ID: 122345

Info:
Project: 12345
Investigator: Dr. Jones
Site: 23466- Boston Radiology
Subject: 00001 Initials: ABC
Query: Missing exams
CIL Comments:

Please submit the baseline exam for subject 00001.

Site Response:

7.3 DXA IQC Spine Phantom Maintenance Form

PAREXEL INFORMATICS DXA IQC SPINE PHANTOM MAINTENANCE FORM

DXA IQC - SPINE PHANTOM MAINTENANCE FORM

This form is to be completed for monthly submissions of Instrument Quality Control (IQC) data where maintenance has taken place and for the final IQC submission during this trial. Please include the according report of any DXA machine maintenance or upgrades.

To be completed by the DXA technologist:

DXA Machine Scanner ID: _____ Month/Year of IQC submission: __ __ __/__ __ __ __

(MON / YYYY)

QC Spine Phantom Serial Number:_____

QC Phantom Type: ☐ Hologic Spine ☐ Lunar Spine ☐ European Spine (ESP) ☐ Bona Fide (BFP)

Please verify you have included a digital copy of your cumulative QC database in this shipment:
☐ QC Database (**Prodigy:** Lunar.mdb or **Hologic**: IQC.mdb)

Mean BMD: _____g/cm^2 **High BMD (+1.5%):** _____ g/cm^2 **Low BMD (-1.5%):**_____g/cm^2

Note: Mean BMD and acceptable limits should be calculated at baseline. All subsequent submissions should use these values as the mean and limits throughout the trial.

DXA MACHINE MAINTENANCE:

☐ No, none this month.

☐ Yes; ☐ Preventative Maintenance ☐ Software Upgrade ☐ Hardware changes

☐ Other _____

If applicable, please provide a copy of the report from the engineer who performed the service.

Comments:

7.4 Media Labels

The media labels are completed with applicable patient and visit information. The label is placed on each individual film or media (CD, DVD, film) being sent to PAREXEL. When affixed, the label must not obstruct any anatomy on the films.

242902 – 2693-CL-0304
Site # __ __ __ __ __
Subject # __ __ __ __ __ - __ __ __ __ __
Visit: Screen V15/WK52 Early Withdrawal
Unscheduled (circle one)
Scan date __ __/__ __ __/__ __ (dd/mon/yy)

Signature Approval Page

This document has completed a review and is understood and accepted by the following:

Sharon Kennedy
Senior Clinical Study Manager
Astellas Pharma Global Development, Inc.

28 May 2019
Date

Christopher Lademacher, MD, PhD
Executive Medical Director, Medical & Development
Astellas Pharma Global Development, Inc.

28 May 2019
Date

Signatures of the appropriate PAREXEL team members are captured electronically and appended to the last page of this document.

PAREXEL International Electronic Signature Page

This page is the manifestation of the electronic signature(s) used in compliance with PAREXEL International's electronic signature policies and procedures and in compliance with applicable regulations.

UserName: Francis, Kathryn (francik)
Title: Senior Project Manager, MEDICAL IMAGING
Date: Thursday, 30 May 2019, 12:55 PM GMT Standard Time
Meaning: Document contents approved.
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