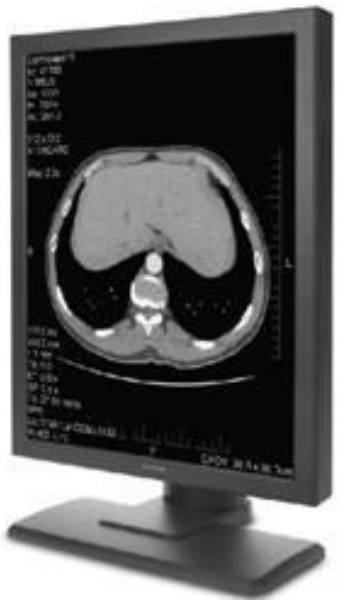


INVESTIGATOR SITE OPERATIONS MANUAL
Astellas Pharma Global Development, Inc. 2693-CL-0302

Project:	Astellas Pharma Global Development, Inc. 2693-CL-0302
Document File Name:	242903 Investigator Site Operations Manual V1.0.doc
Document Revision:	v1.0
Version Date:	09-May-2019
Author's Name	Kate Francis

Copyright Page

REVISION HISTORY

Date	Author	Version	Description of Revision
09-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 Study Background

This Investigator Site Operations Manual provides instructions for the imaging component of the Astellas Pharma Global Development, Inc. 2693-CL-0302 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 Astellas Pharma Global Development, Inc.. 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, as well as listed in the table below:

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.

Cases will be prepared for independent review upon notification of study completion and receipt of complete imaging data.

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.

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 Astellas Pharma Global Development, Inc. (or designee) at a specified time.

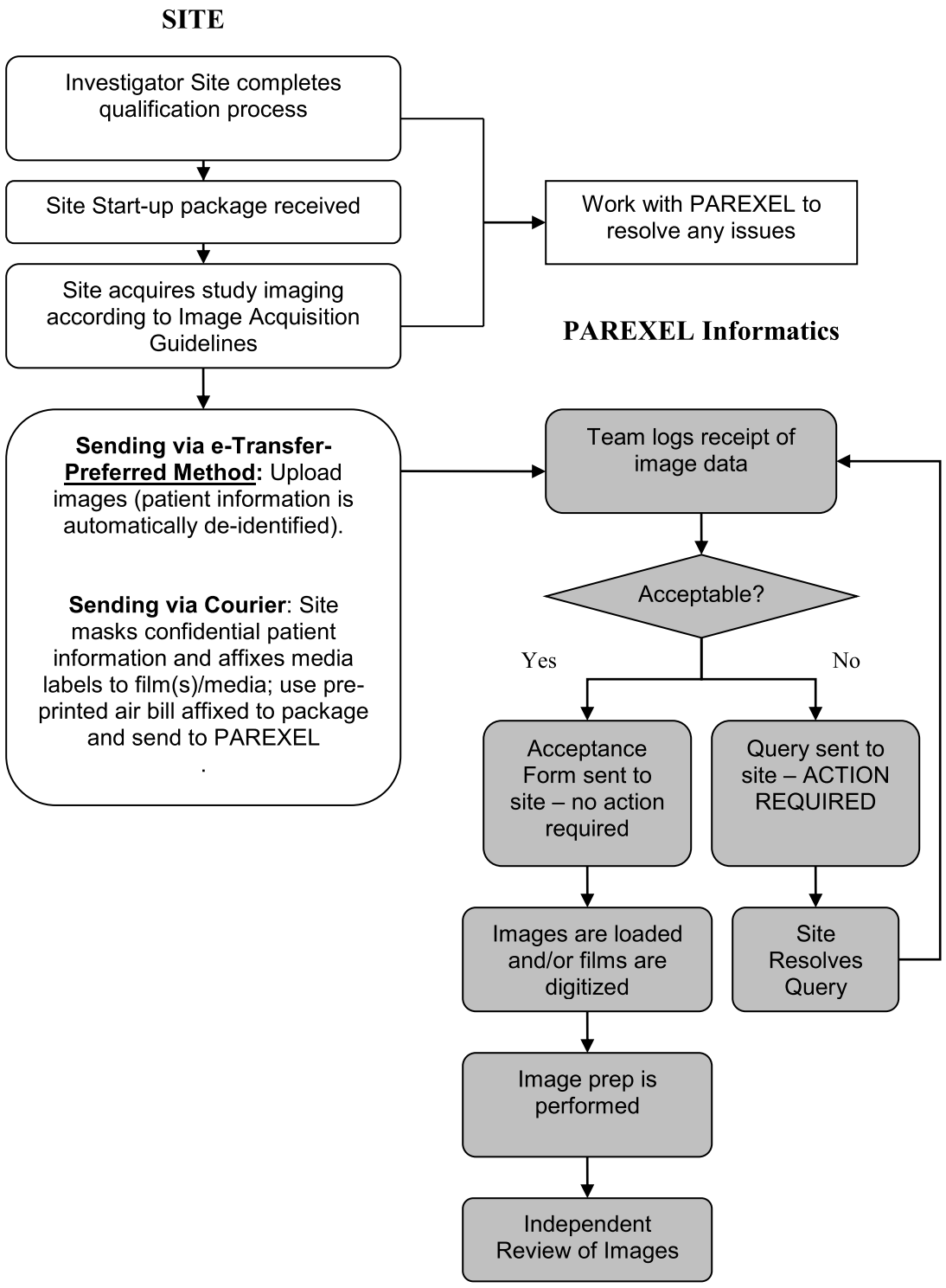
The **Investigator Sites** are responsible for enrolling patients and obtaining imaging per Image Acquisition Guidelines and study protocol. The Investigator Site is also responsible for managing image scheduling and for preparing and forwarding image data to the CIL within 48 hours of acquisition. Any 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

242903-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:	Radiology 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 uncompressed, DICOM format images 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

5. If the images are being saved to hardcopy films, please print two original copies, one remains at the site and the other is sent to PAREXEL.

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)

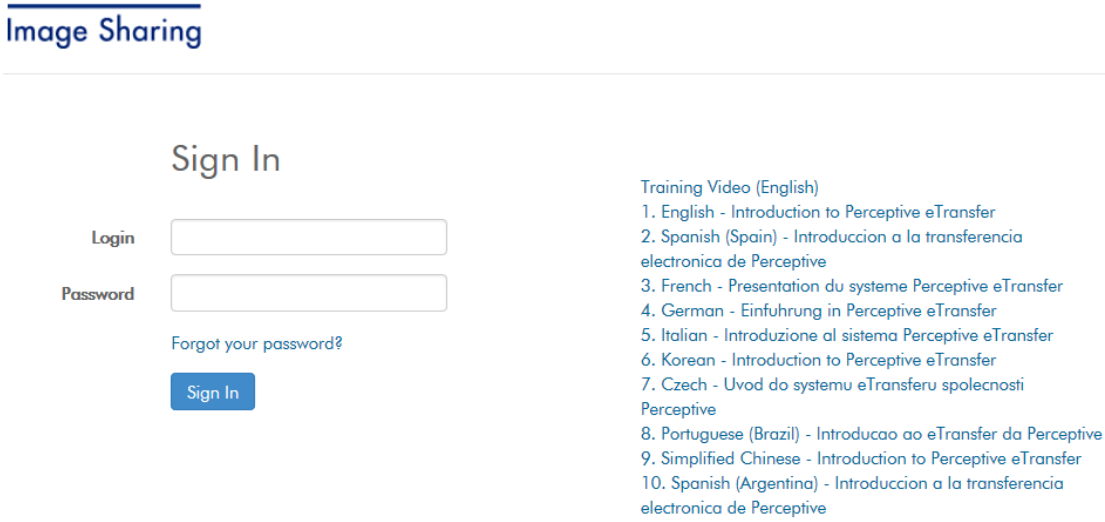
If JAVA is not installed, the Perceptive eTransfer system will guide the user through the Java installation process. If installing the Java plug-in is blocked the user will need to contact the Information Technology Administrator at their facility.

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:

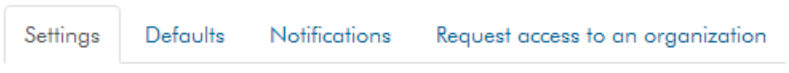
https://parexel.ambrahealth.com/index.html



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



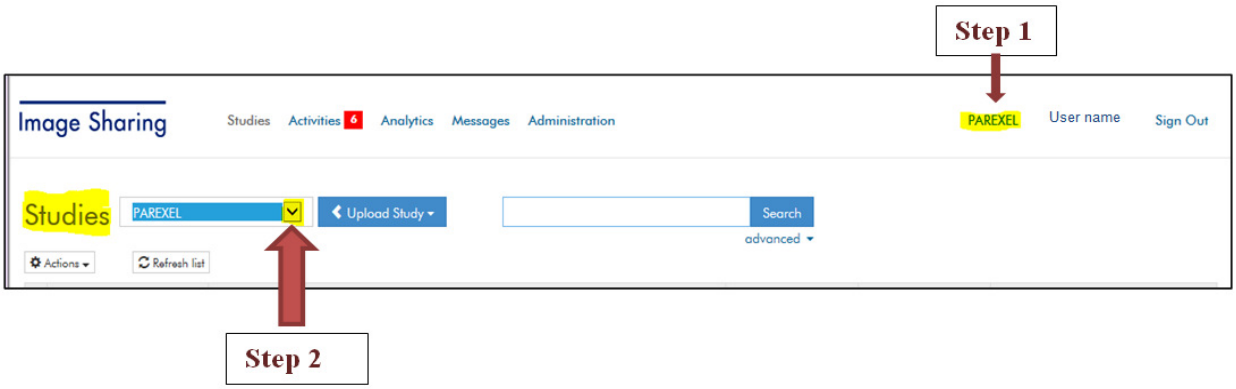
2. To edit notification preferences, the user will select the "Notifications" tab. To receive email notifications. Select "On Upload".

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

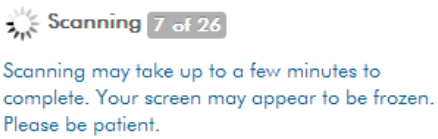
Step 2 - Use the **down-arrow** to the right of the **STUDIES** to select the correct study and site number for the image upload. **– Click** –**Upload Study** and then **Upload Studies**



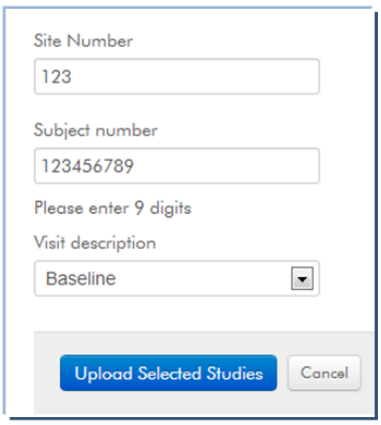
NOTE: If uploading a non-DICOM file (i.e. JPEG, AVI, DXA/IQC files) the user must check the "Select files for DICOM wrapping"

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.

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 Radiology Department and verifies:
   - Images stored on digital media are in **uncompressed DICOM format**
   - No lesion markers or measurements are present
   - Confidential patient information is de-identified.
2. The Study Coordinator will contact the site's Radiology 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 Astellas Pharma Global Development, Inc. of the issue.

2.6 MyQueries Portal

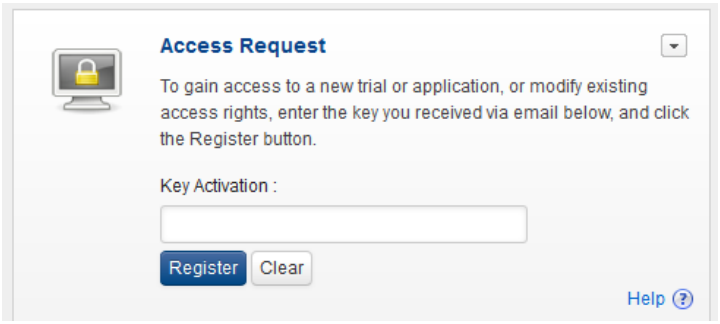
Performed by: Study Coordinator or Designee
Scope: This procedure describes the process for responding to queries sent from PAREXEL via MyQueries

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

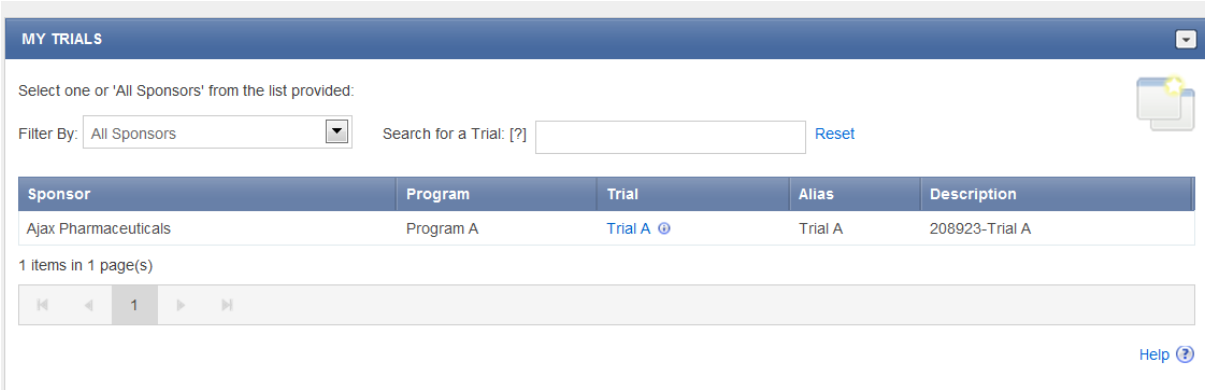
1. Contact the PAREXEL team and request an account for MyTrials.
2. An email will be sent from Perceptive Customer Care with the following email address: do-not-reply@perceptive.com , with an activation code.
3. Login to MyTrials @ WWW.MYTRIALS.COM.

- 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**

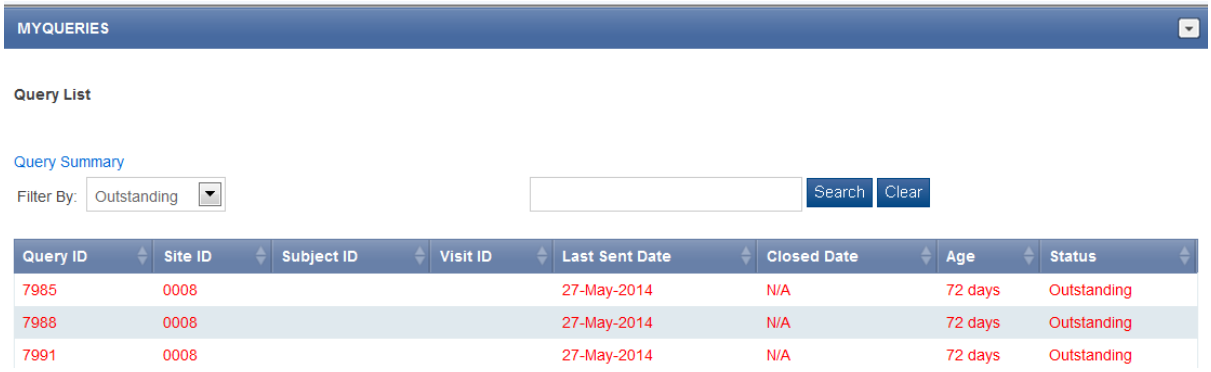


5. All trials that you have access to will appear upon login. Select the desired project.



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:

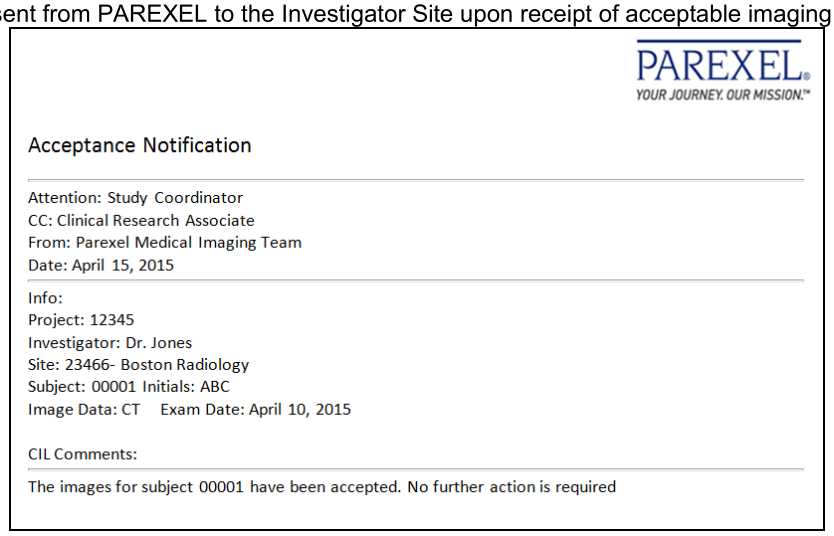
- **Query Comments** - The most recent communication is displayed in this section.
- **Query History** - Click "Show" to see the query history. All communications between PAREXEL and site / monitor users are included.

- **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 Forms

3.1 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

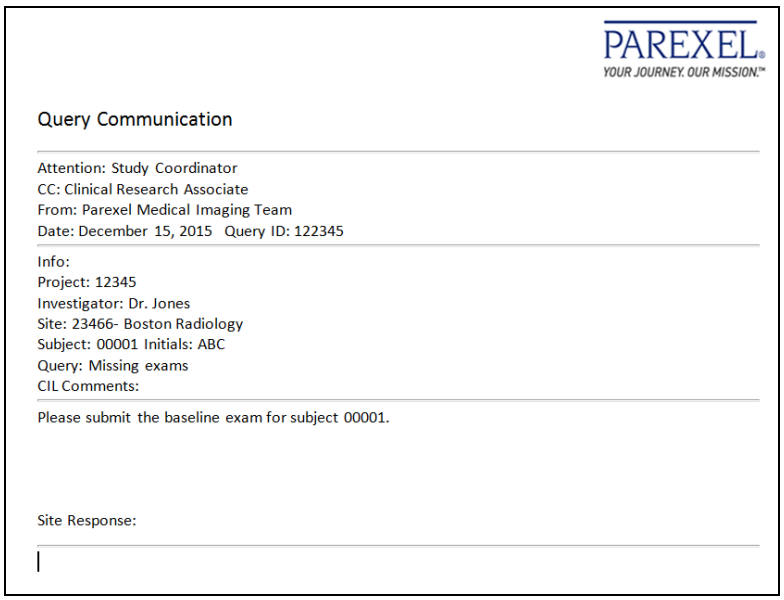
Info:
Project: 12345
Investigator: Dr. Jones
Site: 23466- Boston Radiology
Subject: 00001 Initials: ABC
Image Data: CT Exam Date: April 10, 2015

CIL Comments:

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

3.2 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
YOUR JOURNEY. OUR MISSION.™

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:

3.3 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.

242903 – 2693-CL-0302
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:

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

7 DMAY 2019
Date

Ingrid Gagains
Clinical Study Manager
Astellas Pharma Global Development, Inc.

23MAY 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, 12:35 PM GMT Standard Time
Meaning: Document contents approved.
==========