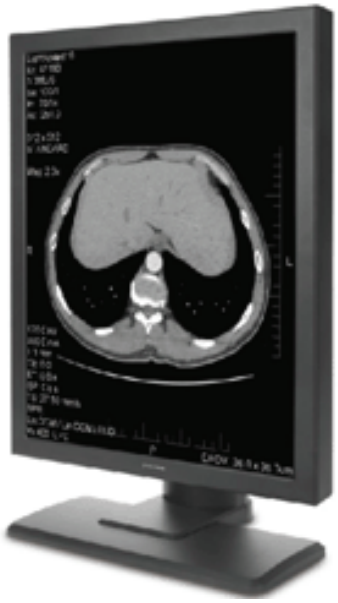


INVESTIGATOR SITE OPERATIONS MANUAL

Pfizer A3921120

Project:	Pfizer A3921120
Document File Name:	A3921120 239961 Investigator Site Operations Manual V4.0.doc
Document Revision:	4.0
Version Date:	26-Sep-2018
Author's Name	Rick Nelson

Copyright Page

REVISION HISTORY

Date	Author	Version	Description of Revision
17-May-2018	Rick Nelson	1.0	Initial Release of Document
16-Jul-2018	Rick Nelson	2.0	Updated Eligibility Form added
29-Aug-2018	Rick Nelson	3.0	Updated the Zip code for the Imaging Team in section 1.5 *PAREXEL Contact Information.*
26-Sep-2018	Rick Nelson	4.0	• Added new contact information for Image Operations Lead in section *1.5 PAREXEL Contact Information* • Updated section *3.4 Example Eligibility Confirmation Form*

Table of Contents

Abbreviations and Acronyms

IAG	Image Acquisition Guidelines
CIL	Core Imaging Laboratory
DICOM	Digital Imaging and Communications in Medicine
QC	Quality Control

1 Introduction

1.1 Study Background

A3921120 is a phase 3, Randomized, Double-blind, Placebo-controlled to study the efficacy and safety of Tofacitinib in subjects with active Ankylosing Spondylitis. For specific study inquiries relating to study design or study objectives, please reference the Study Protocol.

This Investigator Site Operations Manual provides instructions for the imaging component of the Pfizer A3921120 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 Pfizer. Images will be submitted to PAREXEL for processing and independent analysis. Imaging data for all study subjects will be acquired according to the imaging schedule outlined in the protocol, as well as listed in the table below:

X-ray of sacroiliac joints (AP pelvis)	Screening	Acquired during the screening visit or historical[1]
[1]Previous radiographs (up to 2 years old) of the SI joints (ideally AP view of the pelvis) documenting the diagnosis of AS will be acceptable and should be used in lieu of performing screening radiographs if they can be obtained and sent to the central reader for confirmation. If the results are considered unevaluable during the image QC process or by the central reader, the x-ray must be repeated. If a historical radiograph cannot be obtained, x-ray of the AP pelvis view at the screening visit must be obtained to visualize the SI joints.		

The required modality of imaging in this study is X-ray

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 subject information.

You must remove from the images the names of the study subject and investigator site and any other information that can be used to identify the study subject or investigator site. The only information that should be provided is the 8-digit subject ID number, subject year of birth, and the 4-digit site ID number.

Cases will be prepared for independent review upon receipt of complete imaging data and after all queries (if applicable) have been closed.

Independent Reviewer findings are independent assessments and will be communicated to the sites. All study subject care decisions are made at the site by the Primary Investigator(s) including whether the subject should be enrolled in 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 and Image Tracking Log templates

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 and study subjects. The standardized guidelines are distributed to each Investigator Site participating in this study. The IAGs are located in the study binder.
- The **Imaging Study Tracking Log** is used at the Investigator Site to document the shipment status of all images related to the clinical trial. The log is updated with information regarding image acquisition and shipment dates and corresponding shipment tracking numbers.
- The **Media Labels** are completed with study subject/visit information and placed on each individual film or media (CD, DVD), making sure not to obscure anatomy, being sent to PAREXEL. Please place the label on the actual media and not the media case.
- 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 the imaging portion of the study. The form may also contain recommendations and/or feedback regarding any test transfer data.
- **Additional Site Supplies (if needed):** digital media (CD, DVD, bubble mailers, masking pencils, and airbills).

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), and archiving of the image data. Data generated by the reviewer are maintained at the CIL and will be transferred to Pfizer (or designee) at a specified time.

The **Investigator Sites** are responsible for enrolling study subjects 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 (e.g. e transfer portal, FTP accounts) is removed.

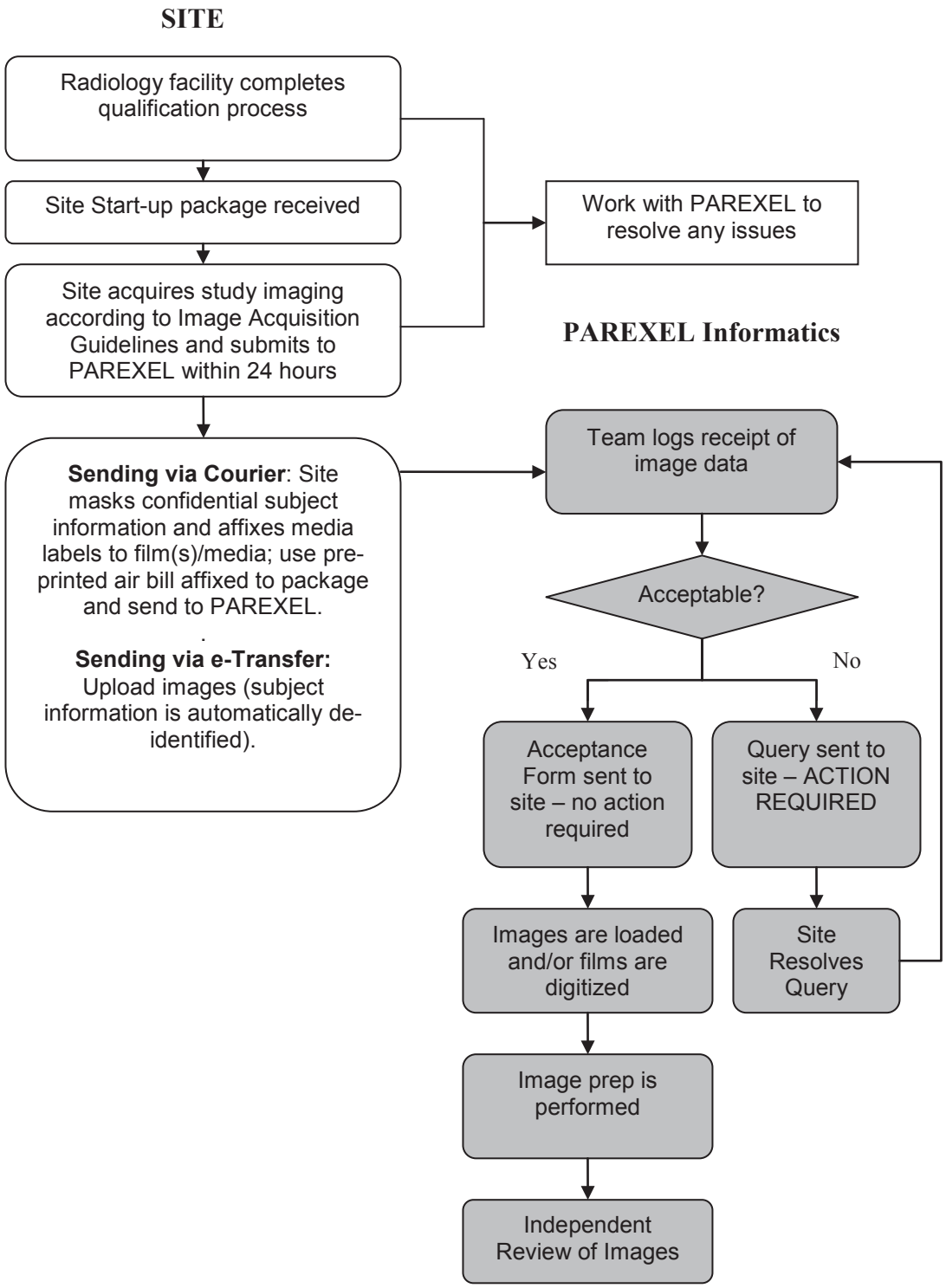
1.5 PAREXEL Contact Information

Name	Title	Contact	Information
Imaging Team	Project Mailbox	**Email:** 239961-Imaging@PAREXEL.com **Fax:** 1-844-377-8209 **Address:** 2 Federal Street, Billerica, MA 01821	• Answering Queries/Questions • Contact Changes • Shipments • Eligibility Results • other
Rick Nelson	Project Manager	**Email:** Richard.nelson@PAREXEL.com **Phone:** 1-978-435-6464	Urgent Requests/Escalations
Matthew Turgiss	Imaging Operations Lead	**Email:** Matthew.Turgiss@parexel.com **Phone:** 1-978-495-8695	Project Manager Backup Urgent Requests/Escalations
e-Transfer Support	e-Transfer Support	**Phone:** 1-888-587-2280	Questions related to uploading

		Email: support@ambrahealth.com	imaging and using e-Transfer. Please note that the Imaging Team can assist as well.
Perceptive Customer Care	Support	**Phone:** 1-877-819-6025 **Email:** CustomerCare@perceptive.com	If the Imaging Team or Project Manager is unavailable, please contact customer care.

Note: Contacts will change during the study. PAREXEL will distribute updated spreadsheets (Contact lists) periodically to keep sites informed of new contact information. Please place these updates in the study binder to keep current with communication needs

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 scheduled study subject visit and include the Image Acquisition Guidelines with the image requisition.

2.1 Image Acquisition

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

1. The radiology or respective technician will acquire the images according to the IAG. The radiology technician will save uncompressed, DICOM format images to the site preferred media (CD, film, DVD) and maintain a copy of the exam at the facility. If eTransfer is not being used the technician must de-identify the study subject name and investigator site name and any other information that can be used to identify the study subject or investigator site contained in the DICOM Header.

   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 haven't 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.

2. The study coordinator must verify the names of the study subject and investigator site and any other information that can be used to identify the study subject or investigator site has been completely masked.
3. Confidential subject 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

4. 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 Preparation and Tracking of Images

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

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 subject 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.
4. If hard copy films are sent, each film must have a media label attached in a manner that does not obstruct anatomy.
5. Submitting imaging data containing confidential subject information is not permitted.

6. The Study Coordinator is responsible for maintaining subject confidentiality by ensuring the imaging technicians de-identify confidential subject information on all exams being submitted on digital media.
7. Hardcopy films may be masked using the specialized masking pencils. Please contact PAREXEL to request masking pencils.

2.3 Image Transfer via Courier

Performed by: Study Coordinator
References: Imaging Study Tracking Log, Airbill
Scope: This procedure describes the steps used to send images from the Investigator Site to PAREXEL.

1. The Study Coordinator will use the pre-printed airbills that are provided by PAREXEL for this study.
   Note: Additional airbills must be requested directly from PAREXEL
2. The Study Coordinator will place the hard copy films or digital media in the package for shipment.
3. If hardcopy films are being sent, these will be placed in the padded envelopes that can be provided by PAREXEL. Taping around the edges of the envelope will help to secure the images. Shipping boxes can also be obtained free of charge from the appropriate Courier.
4. The date of shipment and airbill tracking number will be recorded on the Imaging Study Tracking Log.
   ***Note*:** Please ship imaging data to PAREXEL within 48 hours of acquisition.

2.4 Image Data Transfer via Perceptive eTransfer

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 Informatics through an internet browser. The eTransfer website is HIPAA and 21CFR Part 11 compliant

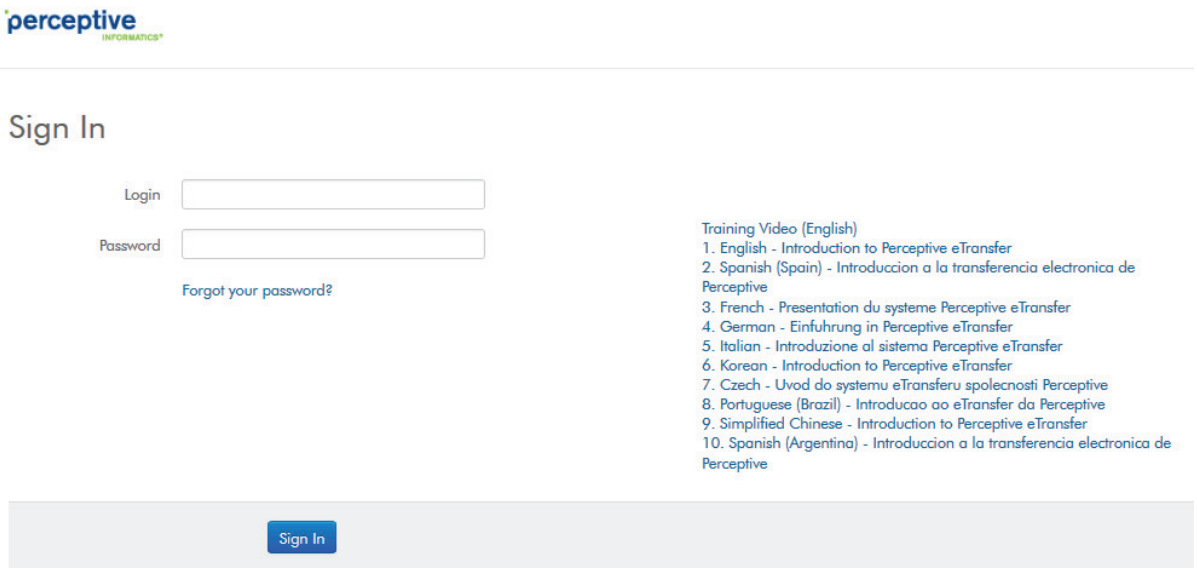
There are only two requirements to use eTransfer:
1. A computer with internet access
2. JAVA plug-in (already installed on most computers)

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 contact the Information Technology Administrator at the site.

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 containing the account credentials and login instructions.
2. Additional user accounts can be requested by emailing the PAREXEL team at 239961-Imaging@PAREXEL.com
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:

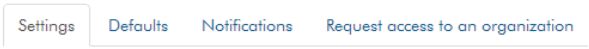
https://Perceptive.dicomgrid.com/



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

User Settings

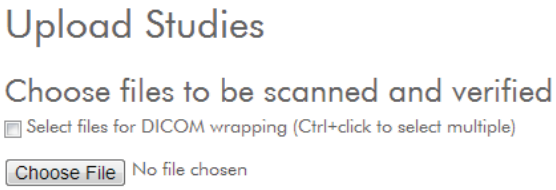
1. The user's name appears in the top right menu of the homepage. Select this to edit:
   - First and/or last name
   - Reset the password
   - Set email notifications



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

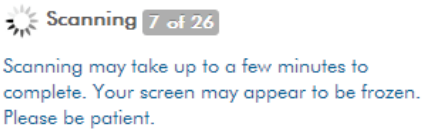
Uploading Images

1. Select the trial/site from the dropdown list. Returning users will see the list of all previously transmitted images for the trial.
2. To upload images, the user will select the trial and site from the "Studies" dropdown list then select "upload Studies".

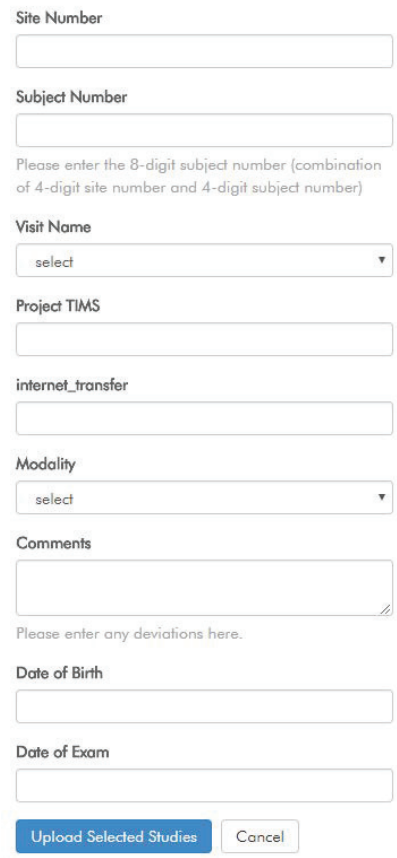


NOTE: If uploading a non-DICOM file (i.e. JPEG, AVI, DXA/IQC files) the user must check the "Select files for DICOM wrapping"

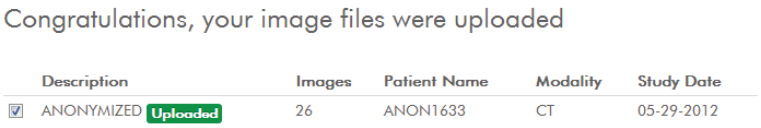
3. Select " choose file" and a browsing window will appear. The user will select the folder where the study images are stored and select "open".
4. The "scanning" symbol will appear when a folder has been selected.



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



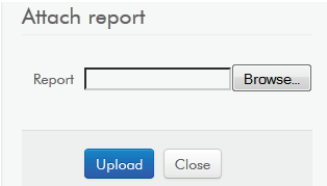
6. The user will select "upload Selected Studies". As the images upload, a status bar will appear. Do not navigate away from the webpage while the upload is in progress. Open another eTransfer webpage to upload another scan concurrently. Upon successful upload the following message will be displayed:



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

Uploading Reports and/or Documents

1. A user can upload specific reports or documents associated with an image exam. 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 is only available is using Google Chrome or Mozilla Firefox.
2. The user can use the scroll on the bottom of the viewer to go through all images.

For technical support contact the DicomGrid support team by phone at 1-888-315-0790 (available 24/7) or by email at support@dicomgrid.com

2.5 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.

2.6 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 2 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 subject 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 2 business day timeframe..
6. If the site is unable to successfully resolve the query, PAREXEL may request the assistance of the contracted CRO monitors and notify Pfizer of the issue.

2.7 MyQueries Portal

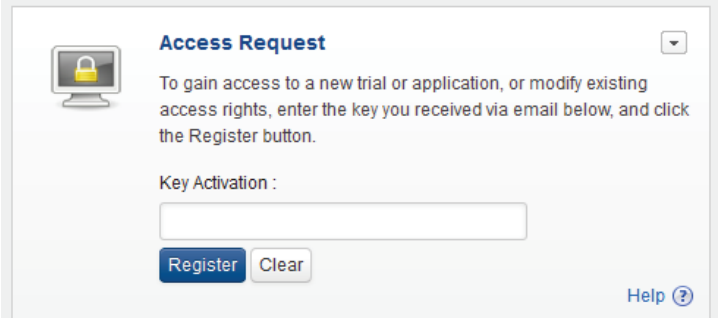
Performed by: Study Coordinator or Designee
Scope: This procedure describes the process for responding to queries sent from PAREXEL via MyQueries

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

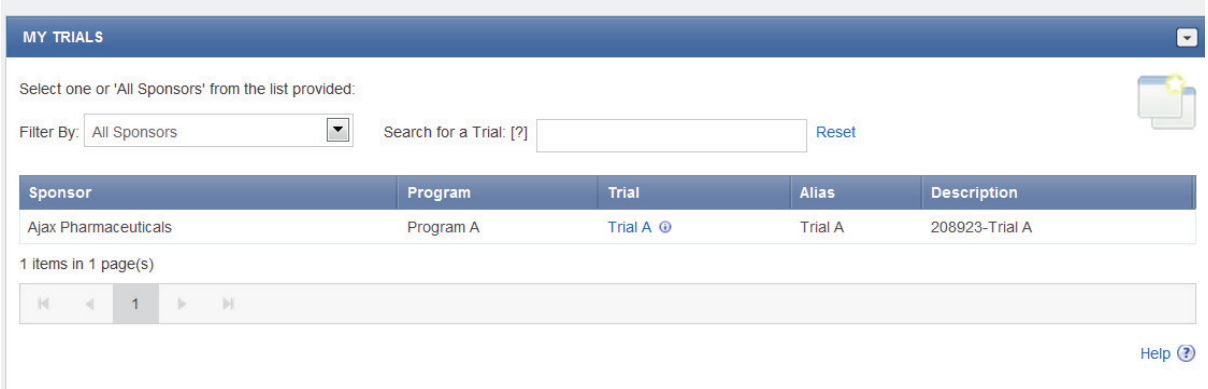
1. Contact the PAREXEL team and request an account for MyTrials.
2. An email will be sent from Perceptive Customer Care with the following email address: do-not-reply@perceptive.com , with an activation code.
3. Login to MyTrials @ WWW.MYTRIALS.COM.

- 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.

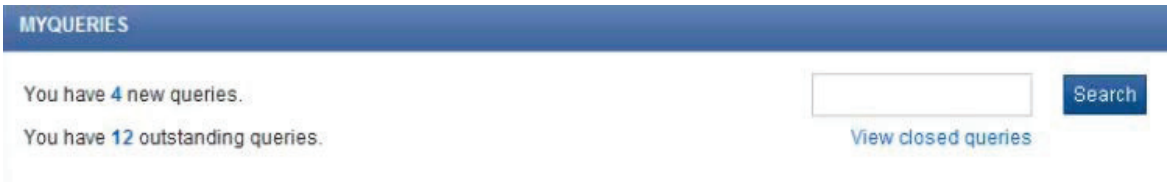
4. After logging in to the system or creating a new account; enter the activation key(s) that you have received via email. **Please note you may receive more than one key**



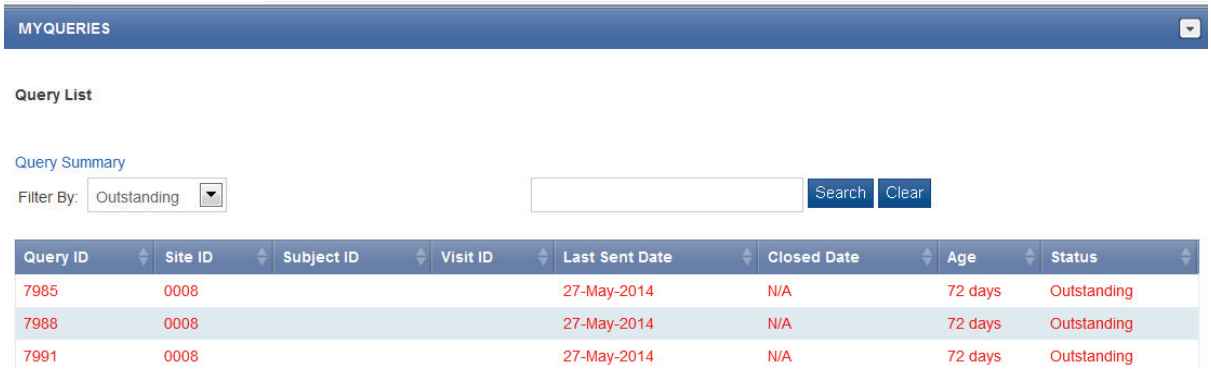
5. All trials that you have access to will appear upon login. Select the desired project.



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



7. Click the links to view queries.



Query ID	Site ID	Subject ID	Visit ID	Last Sent Date	Closed Date	Age	Status
7985	0008			27-May-2014	N/A	72 days	Outstanding
7988	0008			27-May-2014	N/A	72 days	Outstanding
7991	0008			27-May-2014	N/A	72 days	Outstanding

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 2 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 Receiving Eligibility Read Results from PAREXEL

Within ***three (3) business days*** of receiving images PAREXEL will contact the investigator with central read results, declaring the study subject either eligible or not eligible per modified New York x-ray criteria. In the event that images do not meet the QC requirements of the study, a query will be issued and the three business day turn-around-time

will be restarted following query closure. Upon receipt of protocol required imaging, all screening images are assigned for Independent Review – the investigator site does not have to request the Eligibility read.

The Eligibility read results will be sent from PAREXEL to the Investigator via email. The following individuals will be included on the distribution list for delivery of Eligibility results:

- Investigator
- Study Coordinator
- Assistant Study Coordinator (if applicable)
- CRO Site Monitor
- Regional Study Team
- Sponsor Team

Below is the text for all expedited Eligibility read communications, which will also include a PDF file attachment with results:

Dear Investigator,

PAREXEL Informatics has completed an independent assessment for your subject to determine Eligibility for the A3921120 clinical trial.

Please find the attached results and file the results with the subject's source documents. Please do not hesitate to contact your study monitor with any questions or concerns.

Kind regards,
The PAREXEL Informatics team
239961-Imaging@PAREXEL.com

3.4 **Example Eligibility Confirmation Form:**

PAREXEL®
YOUR JOURNEY. OUR MISSION.™

Pfizer A3921120
Subject Eligibility Assessment

PAREXEL has completed the central imaging read that was requested for your Pfizer A3921120 subject. Please find the results below and file with the subject's source documents. Please do not hesitate to contact your study monitor with any questions or concerns.

PAREXEL is responsible to perform the independent subject eligibility assessment as per protocol. Sponsor acknowledges that the subject eligibility assessment is based only on the image data, made available to PAREXEL, does not constitute medical advice, and may not be used for patient care. All responsibility for patient care and the final decision whether a patient should be enrolled in the study rests with the principal investigator and not with PAREXEL or its independent readers. Sponsor shall ensure that any site receiving information about eligibility confirmation has agreed to an acknowledgement that is substantially similar to the acknowledgement in the preceding sentences.

Site ID	XXXX
Subject ID	XXXXXXXX
Latest Timepoint Read	Screening
Right SIJ Sacroiliitis Grade	
Left SIJ Sacroiliitis Grade	
Modified New York Criteria Assessment	
Is subject eligible?	
Date of Report Generation	DD-MMM-YYY

3.5 **Imaging Study Tracking Log**

The Imaging Study Tracking Log is used to document the shipping status of study data.

Study Tracking Log

Investigator Name: _____ **Site Number:** _____

PFIZER | PROTOCOL A3921120

Subject Number	Exam Date dd/mmn/yyyy	Date Shipped to PAREXEL dd/mmn/yyyy	# of Films / Media Sent (CD, Perceptive eTransfer)	Air bill Number	Sent by (initials)

3.6 Media Labels

The media labels are completed with applicable subject 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.

A3921120 PAREXEL International

Subject ID: __ __ __ __ __ __ __ __

Exam Date: __ __/__ __ __ __/__ __ __ __
d d mmm y y y y

Visit: _____

Signature Approval Page

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

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02-Oct-2018

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Meaning: Document contents approved.
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