

** Chest X RAY PA & Lateral
with (B) hands & (B) feet*

MEDICAL IMAGING SERVICES

AbbVie

Protocol M14-465

M13-542

A Phase 3, Randomized, Double-Blind Study Comparing ABT-494 to Placebo and to Adalimumab in Subjects with Moderately to Severely Active Rheumatoid Arthritis Who are on a Stable Background of Methotrexate (MTX) and Who Have an Inadequate Response to MTX Alone (MTX-IR)

Image Acquisition Guideline

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AbbVie – 226452 Image Acquisition Guideline

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Document Approvals

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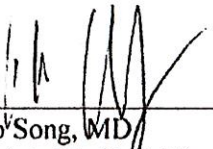
PAREXEL internal signatures will be captured electronically through the PMED system.

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Version	Date	Author	Description
1.0	28-Sep-2015	Farhan Syed/Sally Warner/Marlon Green	Initial release of the document
2.0	15-Jan-2016	Farhan Syed/Sally Warner/Marlon Green	Revised Imaging Schedule

Introduction

PAREXEL Informatics has developed the following acquisition guidelines for standardization of the study imaging components across radiology centers participating in the AbbVie M14-465 clinical trial. Provided here are image acquisition guidelines for the following imaging modalities:

- Bilateral Hands and Feet X-ray

Important Notes

- Regularly scheduled imaging for this study should be acquired in **strict adherence to these guidelines**.
- **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.**
- Images sent to PAREXEL should be clear of any tumor marks or annotations determined at the site.

IMPORTANT: Imaging modality, patient positioning and anatomical coverage should remain consistent across all imaging visits for any given study subject.

IMAGING SCHEDULE

Imaging Modality	Imaged Anatomy	Imaging Schedule
X-ray	Bilateral Hands (PA View) and Feet (AP view)	Period 1: Screening/Baseline, Week 14*, Week 26, Week 48/Premature Discontinuation (PD; Period 1) Period 2: Week 96 and Week 192/PD (Period 2)

*Week 14 X-ray is done only for non-responders

- X-rays of hands and feet must be performed during the screening process in compliance with the imaging acquisition guidelines (IAG) and image quality acceptability must be confirmed via central QC by PAREXEL.
- A screening x-ray of hands and feet must be performed only in subjects who have been deemed eligible based on clinical and laboratory inclusion criteria.
- Subjects who do not meet the clinical and laboratory inclusion criteria or meet one of the exclusion criteria, must not undergo a screening x-ray examination of hands and feet to avoid unnecessary radiation exposure.
- Screening x-rays of hands and feet will serve as baseline x-rays for central Van der Heijde's modified Sharp scoring.
- Digitalized images may be acceptable provided that they meet the specifications outlined the IAG and Site Operations Manual.
- X-rays not meeting the quality requirements must be repeated within the 35 day screening window.
- Subjects can only receive first dose of study drug if the screening x-rays have been determined to be of sufficient quality.
- Subjects will be deemed eligible if ≥ 3 bone erosions on x-ray OR ≥ 1 bone erosion and a positive rheumatoid factor OR ≥ 1 bone erosion and a positive anti-cyclic citrullinated peptide autoantibody titers are determined at screening.

In cases of premature discontinuation (PD) from the study during Period 1, the following imaging rules apply:

1. PD before Week 12: No X-ray required
2. PD \geq Week 12 and $<$ Week 26: New X-ray required except if Week 14 X-rays already done
3. PD $>$ Week 26 and $<$ Week 36 : No X-ray required

4. PD \geq Week 36 and < Week 48 : New X-ray required

In cases of premature discontinuation (PD) from the study during Period 2, the following imaging rules apply:
Period 2:

1. Subjects who prematurely discontinue will NOT require X-ray of hands and feet if the previous X-ray was performed according to guidelines outlined and was performed within the 24 weeks prior to the PD time point.

***** Patient safety in relation to image acquisition is the responsibility of the Investigator sites. *****

For inquiries regarding these guidelines, please contact the study mailbox:

Email: 226452-imaging@parexel.com

Thank you for your participation and cooperation in this clinical study.

Image Acquisition Guidelines for X-Ray Assessments M14 465

PAREXEL has developed the following **Image Acquisition Guidelines (IAGs)** for standardization of the study imaging components across radiology centers participating in the M14-465 clinical trial. This IAG will provide high level requirements for the imaging required in this study. Provided here are IAGs for 1) X-Ray of hands including wrists and 2) X-Ray of feet.

IMAGE RESOLUTION REQUIREMENTS

Digital Images: Images **MUST** be acquired with high resolution. A digital resolution of 100 microns (digital pixel spacing 0.10 x 0.10 mm) is preferred. If your instrument is not capable of 100 micron resolution, then PAREXEL may still be able to qualify your instrument at a different resolution (85 to 175 microns). This will be determined as part of site qualification. Instruments with resolution outside of the 85 to 175 micron range will be approved for use on a case by-case basis by Abbvie. ***Please use this optimal digital resolution for which your instrument was qualified for all study imaging during this trial.***

Hardcopy Films: Sites with conventional scanners **MUST** acquire using **high resolution, single emulsion or mammography** grade film and compatible cassette. Hardcopy films should be 11"x14". In order to ensure compliance for this study, PAREXEL will provide these films and cassettes to all conventional sites. Please be sure to use these specific supplies for all study imaging.

IMAGE TRANSFER METHOD

Digital Images: If images are digitally acquired PAREXEL expects a digital transfer method (i.e. eTransfer is preferred or CD-ROM, DVD) to be used. Digital images cannot be printed on film for submission to PAREXEL. Digital images must be in uncompressed DICOM format or proprietary scanner format.

Hardcopy Films: Original high resolution X-Rays should be provided to PAREXEL on **single emulsion or mammography grade film**. PAREXEL will provide these films and cassettes to all conventional sites. Please be sure to use these specific supplies for all study imaging. Please complete and apply subject labels provided by PAREXEL. Use PAREXEL provided shipping supplies for courier shipment to PAREXEL. Original X-rays should be clearly marked as such and will be returned to the site, per the site's request, as soon as possible following acceptance at PAREXEL.

POSITIONING TEMPLATES

For all M14-465 subject imaging (irrespective of instrument type), please remember to use the PAREXEL positioning templates. Place the correct template (Left or Right accordingly) on the cassette/receptor then position each hand/foot on top of the positioning template aligned with the hand/foot outline. If unable to align the hand to the positioning template as requested please use positioning descriptions to best orient anatomy as described.

IMPORTANT: Imaging modality, resolution requirements and anatomical coverage should remain consistent across all imaging visits for any given study subject. Always use the positioning templates provided.

Confidentiality: Please ensure the **blinding of all confidential patient/site information** on all images (including marks or annotations determined at the investigator site).

Archival: All imaging data must be archived at the site as required by regulatory agencies. PAREXEL may request re-transmittal of the archived images.

Deviations: The imaging for this study should be acquired in strict adherence to these guidelines. If there are any deviations from these parameters please contact PAREXEL immediately.

For inquiries regarding these guidelines, please contact:

Email: 226452-imaging@PAREXEL.com

HAND X-RAYS (Postero-Anterior view)

Goal: Consistent, high quality images with good bone detail for assessment of joint space narrowing & erosions

Important Reminders:

- Parameters and positioning used during Baseline imaging for the patient should be kept consistent for all follow up imaging.
- Always use the PAREXEL positioning template.
- Each hand must be imaged one at a time using one film/capture for each extremity.
- Remove jewelry where possible (if not, shift so does not obscure any joint). Please adhere to institutional policies and procedures for shielding.

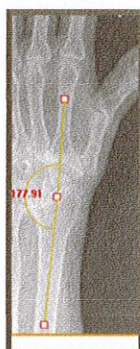


Fig. 2 Good Alignment



Fig. 3 Good Image Quality

Patient Positioning: Patient must be seated next to the imaging table with the **elbow flexed 90 degrees**. The **elbow should be at the same level as the shoulder**.

1. With the correct positioning template (Left or Right accordingly) on the cassette/receptor, position the hand/wrist (palm down) on the template according to the hand outline (Fig. 1).
2. Fingers straightened, if possible, and only slightly separated. Fingers should not be strained far apart.
3. Hand and wrist flat on the template (and cassette/receptor) to avoid joint magnification.
4. **Align 2nd metacarpal in a straight line with the radius (180 degrees, Fig. 2). Use a sandbag placed across the forearm just above the wrist to avoid motion.**

Parameters:

- **Film/Resolution:** Conventional X-ray: **high resolution, single emulsion** film. Digital: optimal and consistent digital resolution (100 micron pixel size preferred). Be consistent with the resolution accepted for your instrument during site qualification.
- **Film Focus Distance (FFD): 40 inches** (102 cm)
- **Beam centering:** on the 3rd MCP joint, perpendicular to the plane of the film (Fig. 1).
- **Exposure settings:** Suggest 60kVp and 3 mAs. Optimize for sharp bone detail.
- **Collimate** to film.

Anatomical Coverage and Image Quality Control Checks:

- Ensure inclusion of the entire hand and wrist, including at least 1 inch of forearm.
- Ensure optimal visualization of the wrist, MCP, PIP & DIP joints (Fig. 3).
- PA view with left/right markers visible and accurate to anatomy. *Oblique views are not required.*
- Ensure that follow up visits are consistent with baseline: X-ray instrument, patient positioning, acquisition parameters (mAs, kV, FFD, focal spot, film and cassette type or digital resolution).
- Please inform PAREXEL if your methods or results deviate from these guidelines or from those used at Baseline for each patient.

FOOT X-RAYS (Antero-Posterior view)

Goal: Consistent, high quality images with good bone detail for assessment of joint space narrowing & erosions

Important Reminders:

- **Parameters and positioning used during Baseline imaging for the patient should be kept consistent for all follow up imaging.**
- Always use the PAREXEL positioning template.
- Each foot must be imaged one at a time using one film/capture for each extremity.
- Please adhere to institutional policies and procedures for shielding.
- Remove jewelry where possible (if not, shift the jewelry so it does not obscure any joint).

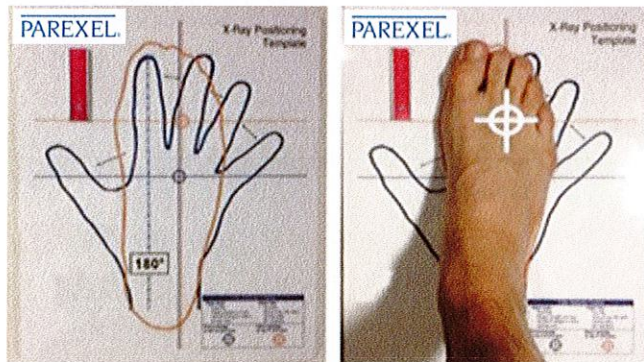


Fig. 1 Positioning Template (Right)



Fig. 2 Good Image Quality

Patient Positioning: The patient should be **lying supine on the imaging table** with the **knee flexed** and the plantar surface of the foot centered flat on the cassette/panel with the long axis of the foot parallel to the midline of the film/receptor.

1. Align the **knee with the ankle** (no internal or external rotation).
2. Ensure that the **foot is placed flat on the template and cassette/receptor** to avoid magnification of joints (Fig. 1).
3. If possible, toes should be flat and not compressed by tight socks.

Parameters: Film/Resolution: Conventional X-ray: **high resolution, single emulsion** film. Digital: optimal and consistent digital resolution (100 micron pixel size preferred). Be consistent with the resolution accepted for your instrument during site qualification.

- **Film Focus Distance (FFD): 40 inches** (102 cm)
- **Beam centering:** **between the 2nd and 3rd MTP joints**, angled 10 degrees towards the head (Fig. 1).
- **Exposure settings:** Suggest 60kVp and 3 mAs. Optimize for sharp bone detail.
- **Collimate** to film.

Anatomical Coverage and Image Quality Control Checks:

- **Ensure inclusion of the entire foot and ankle** including at least 2 inches of distal tibia (Fig.1).
- Ensure **optimal visualization** of the **forefoot** (Fig. 2).
- **AP view with left/right markers visible and accurate to anatomy.**
Be Consistent: For follow-up timepoints use the same x-ray instrument, patient positioning, acquisition parameters (mAs, kV, FFD, focal spot, film and cassette type or digital resolution) as that used for Baseline.

Please contact PAREXEL immediately if your methods or results deviate from these guidelines or from those used at Baseline for each patient.

For inquiries regarding these guidelines, please contact:	Email: 226452-imaging@PAREXEL.com
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IMAGE ACQUISITION GUIDELINES – ADDITIONAL NOTES

SENDING IMAGING TO PAREXEL

Patient confidentiality is the responsibility of the sites and all imaging should be sent in free of patient identifiers.

PLEASE SUBMIT EXAMS WITHIN 48 HOURS OF ACQUISITION

Electronic Transfer preferred

- For X-rays acquire using digital X-ray instruments only (DR, DX, CR, etc.), not conventional.
- Images shall be raw and uncompressed DICOM
- eTransfer will automatically blind the image header information

Shipment via Courier

- For original hard copy films from conventional radiography instruments OR digitally acquired X-ray when not using eTransfer (preferred)
- Blank Digital Media and all shipping supplies can be provided by PAREXEL
- If using optical disc, submission shall be limited to 2 studies per disc at a maximum (1 patient / study on each disc side)

Hardcopy Film: only for conventional instruments

- Original hard copy films must be sent to PAREXEL. To ensure a back-up copy is available on site, a duplicate original (laser-printed) hard copies films should be obtained.
- All X-rays should be appropriately labelled for the right (R) and left side (L) for all both hands and feet.

Guidelines

- **Keep all parameters constant for subsequent imaging performed during the study.**
- **Keep imaging data (including raw/original data if possible) digitally archived until PAREXEL has provided feedback regarding the quality of the images.**
- **Send ALL images acquired for the study to PAREXEL until instructed otherwise.**
- **Images sent to PAREXEL shall be clear of any marks, writings, measurements or annotations.**
- **All confidential patient information must be de-identified prior to sending the data to PAREXEL.**

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