PAREXEL Informatics
Medical Imaging and Patient Technology Solutions

Ankylosing Spondylitis
Protocol: CAIN457K2340

Image Acquisition Guidelines

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Author:	**Sally (Sarah) Warner, PhD, Stephanie Mullen**

Document Approvals

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Document Revision History

Version	Date	Author	Description
1.0	25 Sep 2017	Sally Warner, Stephanie Mullen	Initial release of the document
2.0	25 Oct 2017	Sally Warner, Stephanie Mullen	Updated Imaging Schedule
3.0	02 Nov 2018	Sally Warner, Stephanie Mullen	Updated Imaging Schedule

Introduction

PAREXEL Informatics has developed the following **Image Acquisition Guidelines** for standardization of the study imaging components across radiology centers participating in the Novartis CAIN457K2340 clinical trial. Please be sure to review the Imaging Reference Manual and refer to it during the trial as needed.

Provided here are Image Acquisition Guidelines for the following imaging modalities:

CAIN457K2340 Imaging Schedule

Imaging Data	Screening Period	Treatment Period			
	Screening Visit 1 (Week -10 to -4)	Baseline (Day 1)	Week 16	Week 52	Week 104[6]
X-Ray cervical and thoraco-lumbar spine [2]	X[1,3]	X[1,3]		X	X
X-Ray sacroiliac joints (AP view)[2]	X[3,4]				X
MRI[5] Spine and SI joints		X	X	X	X

[1]Spinal x-rays (cervical and thoraco-lumbar) to be collected during the screening period to confirm eligibility for subjects with CRP < 5 mg/L. If additional lateral thoracic spine x-ray is available, it may also be submitted for syndesmophyte eligibility review. Subjects with CRP ≥ 5mg/L and confirmed study eligibility should obtain the spinal x-rays at baseline.

[2]SIJ and spinal x-ray image acquisition must follow the vendor's Image Acquisition Guidelines. The SIJ x-ray will be centrally read for eligibility

[3]Re-screening subjects may utilize previous x-rays if taken within the past 3 months according to the imaging criteria

[4]Subjects may utilize previous obtained SIJ x-rays if taken within the past 3 months according to the imaging criteria

[5]MRI only performed in a sub-population of subjects at selected sites. All subjects at the selected MRI site should be considered for the MRI assessment

[6]For all subjects who discontinue from the study, the investigator should ensure that the subject completes the end of treatment visit (Week 104 assessments) 4 weeks after last study treatment of secukinumab or 2 weeks after last study treatment of GP2017. Every attempt should be made to obtain the scheduled x-ray and MRI images at the final visit, unless the last x-ray and/or MRI were taken within 12 weeks before discontinuation.

Note – All X-Ray Images obtained at Screening will be the Baseline Images for the Efficacy Reads

Important Notes

- Regularly scheduled imaging for this study should be acquired in strict adherence to these guidelines.
- PAREXEL recommends having only one primary experienced and trained technician for each modality (X-ray and MRI) scanning all trial subjects. Sites should have a trained back-up technician for each modality.
- Please ensure the **blinding of all confidential patient/site information** on all images.
- Images sent to PAREXEL should be clear of any marks or annotations determined at the site.
- The imaging for this study should be acquired in strict adherence to these guidelines. If there are any deviations from these parameters please provide explanation in the Comments on the Image Transmittal Form (forms supplied by PAREXEL). **Please use the same technique throughout the course of the study.**
- Once values have been selected, they should remain consistent throughout this examination and follow-up examinations. Please save the protocols on your instrument's system.
- All imaging data must be archived at the site as required by regulatory agencies. PAREXEL may request re-transmittal of the archived images.
- It is required that all images acquired be submitted to PAREXEL.

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

For inquiries regarding these guidelines, please contact:
Project Team 236483
Email: 236483-Imaging@PAREXEL.com

IMAGE TRANSFER METHODS

X-RAY

Digital Images: If images are digitally acquired please submit using a digital transfer method (i.e. CD-ROM, DVD, E-Transfer). Digital images must be in uncompressed DICOM format or proprietary scanner format.

Hardcopy Films: Original X-Rays should be provided to PAREXEL. Please complete and apply subject labels provided by PAREXEL. Use PAREXEL provided shipping supplies for courier shipment to PAREXEL. Original X-rays should be marked as such and will be returned to the site as soon as possible following acceptance at PAREXEL if requested. All copied originals will require approval by PAREXEL to ensure image quality is not lost in copying.

All Screening images are required to be submitted to PAREXEL within 24 hours of acquisition (1 business day).The baseline and all post-baseline visit images should be submitted within 48 hours of acquisition. (2 business days)

MRI

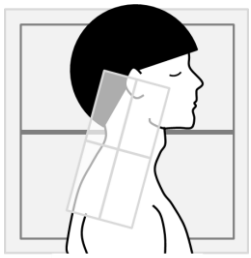
Digital Images Only: It is required that all MRIs be digitally acquired and transmitted on digital media (i.e. CD-ROM, DVD, E-Transfer). Digital images must be in uncompressed DICOM format or proprietary scanner format.

Baseline visit images should be submitted within 24 hours (1 business day) and all post-baseline visit images should be submitted within 48 hours of acquisition. (2 business days)

X-RAY

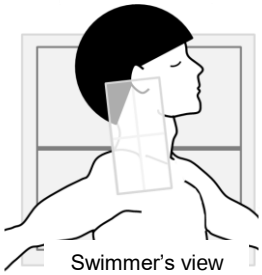
- **Parameters and positioning used during Screening imaging for the patient should be kept consistent for all follow up imaging.**
- **Appropriate shielding of the eyes, thyroid, breast region and gonads should be performed without obscuring the vertebrae of interest.**
- **Please document when left lateral is not possible and the right side was used for lateral spine views. This should be handled consistently for a patient throughout the study.**
- **Complete Image Transmittal Form with all exposure information.**

LATERAL CERVICAL SPINE X-RAY



PATIENT POSITIONING:

1. Position patient standing or sitting in a chair with a horizontal beam (left lateral if possible for consistency). Alternatively, a cross-table lateral film can be obtained with the patient supine. Patient should be instructed to elevate chin slightly to prevent superimposition of the upper C-Spine.



Swimmer's view alternative

2. Place both arms at side in comfortable position: use voluntary or assisted arm traction as necessary to obtain a clear view of the top of T1*. While sitting or standing, assisted traction may be gained by the use of weights or sandbags.

3. If necessary a swimmer's view can be obtained to visualize top of T1.

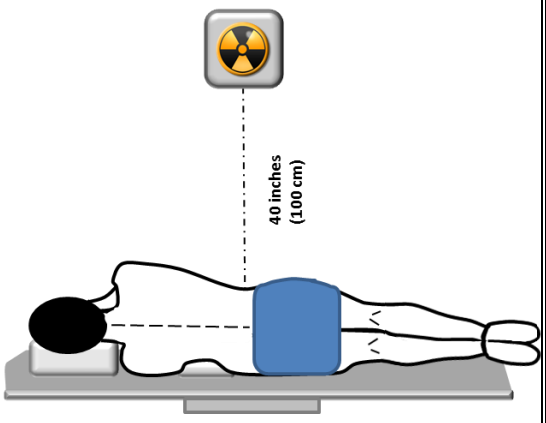
Required Parameters (Please comply with these for all study subjects):

Anatomical Coverage	**Bottom 1/3 of C2 Through Top 1/3 of T1, Inclusive. **Obtaining T1 is very important. Please ensure that T1 is visualized.*** *Use swimmer's view if needed.*
Markers	Metal marker upper right hand corner of the film should be "L" or "Left" and "Lateral"
Central Ray	4th and 5th cervical vertebrae (level of cricothyroid cartilage)
Collimation	Adjust collimation: Direct to the spine to exclude as much unneeded anatomy as possible.

Suggested Parameters (Can use institutional standard, *but must be consistent within patient for study*):

Breathing Instructions	Quiet breathing for exposure and no swallowing.
Imaging System	Bucky (wall) or static grid technique
Scattering Grid	Preferred
Film/Focus distance	79 in (200 cm) *be consistent across timepoints*
Imaging KvP and mAs	75-85 kVp. 10-15 mAs may vary based on body size.
Exposure Time	Breathing technique; approx. 2 second exposure
Film Size	10x12 inches (25x30cm) (May vary based on body size)

LATERAL THORACO-LUMBAR SPINE X-RAY



PATIENT POSITIONING:

1. Place patient on table in lateral position (left lateral if possible for consistency) with legs flexed for comfort and support.
2. Place support under patient's head.
3. Place both arms at right angles to anterior surface of body and flex elbows for comfort.
4. Place supports between knees and ankles and under knee next to table (for support and to aid in maintaining lateral position).
5. Place support under mid lumbar region to position long axis of spine parallel to table.
6. Complete Image Transmittal Form for all exposure information.

Required Parameters (Please comply with these for all study subjects):

Anatomical Coverage	Lumbar: T10 through S1***Obtaining T10 is very important. Please ensure that up to T10 is visualized in this lumbar view.***
Markers	Metal marker upper right hand corner of the film should be "L" or "Left" and "Lateral"
Central Ray	2nd lumbar vertebrae
Collimation	Adjust collimation: Direct to the spine to exclude, as much unneeded anatomy as possible.

Suggested Parameters (Can use institutional standard, *but must be consistent within patient for study*):

Breathing Instructions	Breath hold on exhalation or breathing technique
Imaging System	Bucky (screen) or static grid technique
Film/Focus distance	40 inches (102 cm)
Imaging kVp and mAs	80-90 kVp, 80-100 mAs, may vary based on body size
Exposure Time	Manual < 1.0 second exposure Automated Central photocell
Film Size	14x17 inches (36x43 cm) (May vary based on body size)

X-ray Image quality review:

- Orthogonal view with spine positioned parallel to film
- Anatomical coverage complete and consistent with Screening
- Patient positioning and acquisition parameters consistent with Screening
- Vertebrae visible and unobstructed for assessments of vertebral shape/deformities

AP PELVIS X-RAY

OBJECTIVE: Clear view of sacroiliac joints for assessment of sacroiliitis

PATIENT POSITIONING (see diagram next page)**:**

1. Place the subject on the table in the supine position.
2. Center the mid-sagittal plane of the body to the midline of the grid, and adjust it in a true supine position.
3. Flex the elbows and rest the hands on the upper chest.
4. The heels should be placed 20-25 cm (8 – 10 inches) apart.
5. Medially rotate both feet and lower limbs the same degrees.
6. Immobilize the legs with a sandbag across the ankles, if needed.
7. Check the distance from the anterior superior iliac spine to the table and make sure the pelvis is not rotated.
8. Center the cassette/receptor midway between anterior superior iliac spine and the pubic symphysis. The cassette/receptor will be about 2 inches (5 cm) inferior to the pubic symphysis in average-sized subjects.
9. If the pelvis is deep, palpate for the crest of the ilium and adjust the position of the cassette so that its upper border will project 1 to 1½ inches (2.5 to 3.8 cm) above the crest of the ilium.

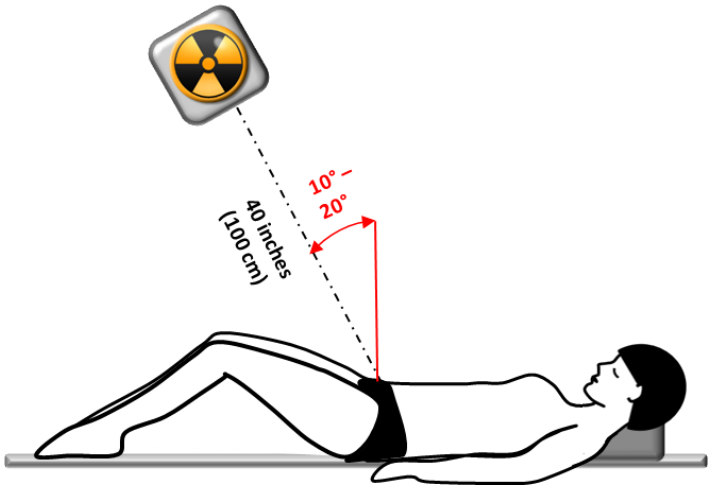
Required Parameters (Please comply with these for all study subjects):

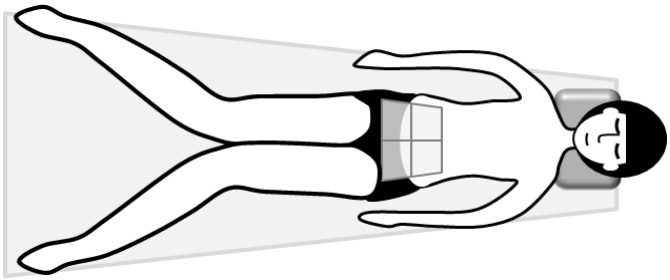
Anatomical Coverage	Pelvis including clear view of both Sacroiliac joints
Markers	Metal marker in the upper right hand corner of the image should be “R” or “Right” and “AP”
Central Ray Direction	Caudo - cranial 10 to 20 degrees (see diagram next page)

Suggested Parameters (Use clinical standard for optimal imaging on your instrument):

Breathing Instructions	Suspend
Imaging System	Bucky screen technique
Film/Focus distance	**40 inches (100 cm)** *see film/focus distance note above*
Imaging kVp	65-85 kVp, may vary based on body size
Exposure Time	**Manual** < 1.0 second exposure **Automated** Central photocell
Central Ray	Perpendicular to the midpoint of the cassette/receptor
Film Size	14x17 inches (35x43 cm)

AP PELVIS X-RAY - POSITIONING





X-ray Image quality review:

- Orthogonal view with beam angled so it is perpendicular to sacrum
- Anatomical coverage complete and consistent with Screening
- Patient positioning and acquisition parameters consistent with Screening
- Sacro-illiac joints visible and unobstructed for assessments of sacro-illitis (sclerosis, erosions, ankylosis)

MRI GUIDELINES

Please closely approximate these sequences with your particular MRI scanner
SCREENING IMAGING PARAMETERS FOR THE PATIENT SHOULD BE KEPT CONSISTENT FOR ALL IMAGES OBTAINED THROUGHOUT THE COURSE OF THE STUDY.

SAGITTAL CERVICAL, THORACIC, AND LUMBAR MRI

Scanner Type	1.5 Tesla or 3.0 Tesla (consistent for subject throughout trial)
Coil	Posterior Spine Coil
Patient Orientation	Standard Supine, knees supported, spine as straight as possible (L-R)
Breathing Instructions	None
Sequences	Scout 3 planes 1) 2D Sagittal T1, TSE or FSE, without fat suppression* 2) 2D Sagittal TSE or FSE STIR
Scan Locations/Coverage:	2 Segments (must include complete coverage with slight overlap)*: Cervical & Upper Thoracic: C2-T10 Lower Thoracic & Lumbar (T8-S1) * For tall patients > 2 segments may be used to ensure complete coverage.
Slice Thickness	3 mm for Cervical & Upper Thoracic 4 mm for Lower Thoracic & Lumbar
Skip/gap (slice spacing)	10%
Percent phase sampling	60 - 80% (or optimal)
FOV	380 mm (or optimal) (Rectangular FOV may be used to reduce scan time)
Contrast	None
Phase encoding direction	Left/Right or Anterior/Posterior (whichever produces less artifact on your system)

***T1**	**TR**	500 - 600 ms (or lowest)	****STIR**	**TR**	4000-5500 ms (or optimal)
	TE	10-20 ms (or lowest)		**TE**	40-60 (or optimal)
	Slice Acquisition	Interleaved		**TI**	150 (220 for 3T) ms
	Averages/NEX	1 (or optimal)		**Averages/NEX**	1 – 2 (or optimal)
	Matrix (FE x PE)	512 x 256 (or optimal)		**Matrix (FE x PE)**	512 x 256 (or optimal)
	Echo Train Length	2 - 4		**Echo Train Length**	7-12 (or optimal)
	Pixel bandwith(Hz/pixel)	150 Hz/Pixel (or optimal)		**Pixel bandwidth (Hz/pixel)**	250 Hz/Pixel (or optimal)
	Concatenations	1 (or optimal)		**Saturation Band**	Anterior saturation slab.

SACROILIAC MRI

Please closely approximate to these sequences with your particular MRI scanner

Scanner Type	1.5 Tesla or 3.0 Tesla (consistent for subject throughout trial)
Coil	Posterior spine coil ONLY
Patient Positioning	Standard Supine, knees supported, spine as straight as possible (L-R)
Breathing Instructions	None
Scout Sequences All are Required **(Please see slice positioning diagrams and examples below)**	1) Scout images in 3 planes, axial scout to include hip joints. 2) Repeat axial if necessary – see required scan locations for study sequences below. 3) True sagittal scout: Centre - S1 vertebral body Angle 1 - from axial scout - perpendicular to line between hip joints Angle 2 - from coronal scout - longitudinal axis of sacrum
Study Sequences	1) 2D T1 oblique Coronal, TSE or FSE, without fat suppression* 2) 2D STIR tilted Coronal, TSE or FSE (see scan details in table below)**
Scan Locations/Coverage for Study Sequences	Coronal sequence tilted forward to parallel the longitudinal axis of the sacrum ("tilted coronal" or "semi-coronal") Centering point of stack – Left/right - midline Head/Foot - At sclerotic scar formed by vestigial disc between S1 and S2 Anterior/Posterior - place posterior edge of stack at posterior border of S2 Angles: a. Perpendicular to above "true sagittal scout" b. Tilt forward until parallel to posterior surface of S2
# of Slices	15 (or optimal to ensure complete coverage)
Scan FOV	300 mm (consistent throughout the study)
Slice Thickness	4 mm
Skip/gap (slice spacing)	10% gap (0.4mm spacing)
Contrast	None
Phase Encoding	Left/Right or Anterior/Posterior (whichever produces less artifact on your system)
Oversampling	100% (or optimal)
Saturation Band	Superior/Inferior saturation slab (if needed)

***T1**	**TR**	500-600 ms (or lowest)	****STIR**	**TR**	4000-5500 ms (or optimal)
	TE	10-20 ms (or lowest)		**TE**	40-60 (or optimal)
	TI	N/A		**TI**	150 (220 for 3T) ms
	# of averages	1 (or optimal)		**# of averages**	1-2 (or optimal)
	Matrix	512 x 256 (or optimal)		**Matrix**	384 x 256 (or optimal)
	Concatenations	1 (or optimal)		**Saturation Band**	Superior/Inferior saturation slab (if needed)

- **Please save the protocol/parameters in your MRI machine so that the same parameters can be used throughout the study with each subject at every time point.**

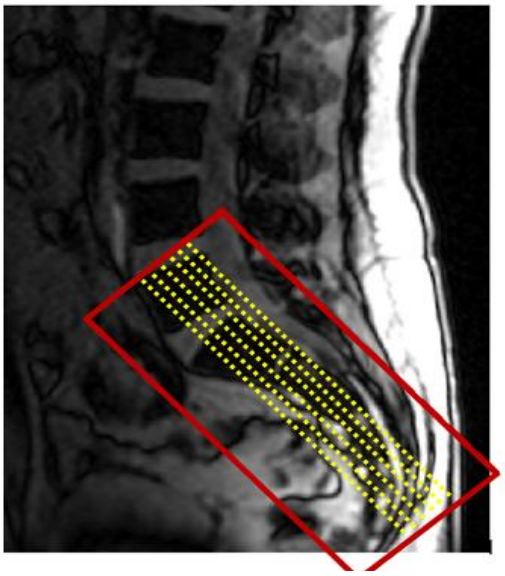
- **Please closely approximate these sequences for optimal image quality with your particular MRI scanner.**

For Sacral imaging sites need to acquire:

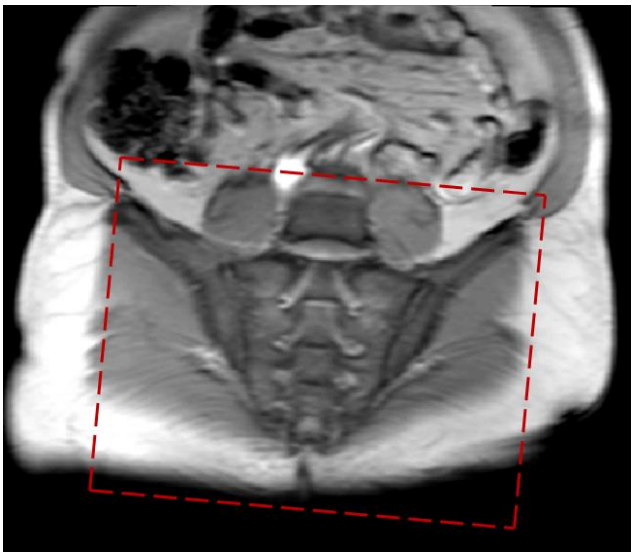
1) Regular 3-plane (axial, coronal and sagittal) scouts
2) Axial scout of hip area – need to see hip joints
3) True Sagittal Scout- see next slide
4) Coronal study images

Sacral coronal study images – planned from True Sagittal Scout

Anatomy diagrams below demonstrate what is required for SI joints to assist with planning for MRI technicians. First acquire a set of true sagittal scouts (first set of diagrams) then use these to plan the tilted coronal views of SI joint



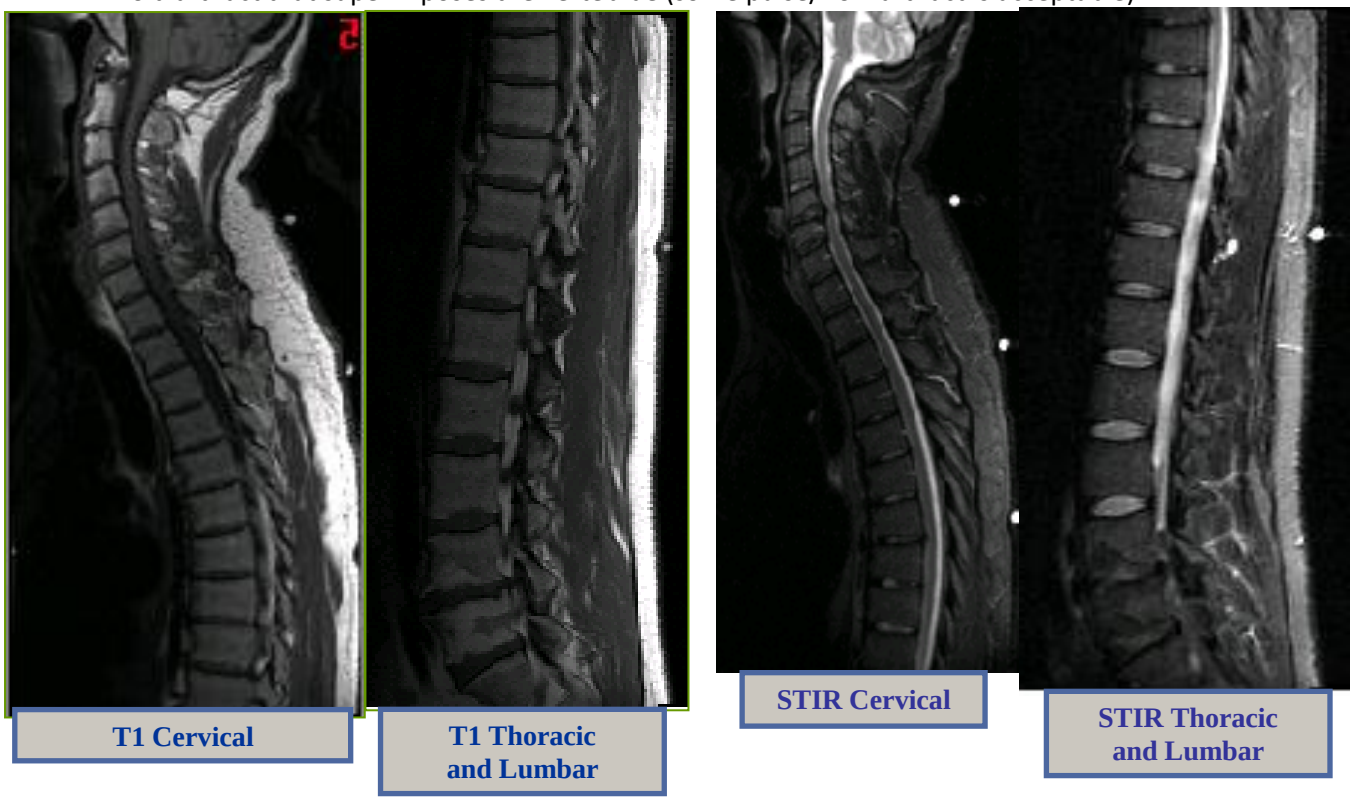
Alignment of Coronal slices tilted forward to parallel the longitudinal axis of the sacrum. Dash yellow lines indicate 6 out of 15+ slices must include SIJ for accurate assessment.

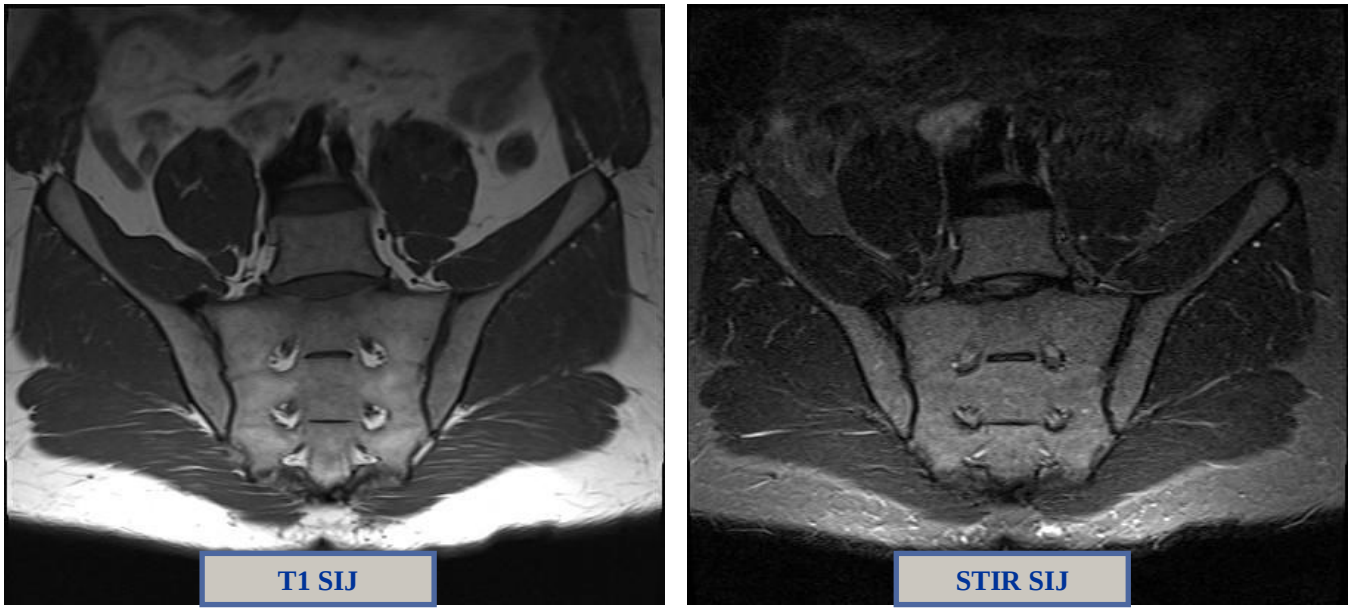


Centering point of stack: Left/right – midline Head/Foot - At sclerotic scar formed by vestigial disc between S1 and S2.

MR Image quality review:

- Anatomical coverage complete and consistent with Screening
- Acquisition parameters consistent with Screening
- Vertebrae visible and unobstructed for assessments of vertebral shape/deformities (spine)
- Avoid artifact that superimposes the vertebrae (some pulse/flow artifact is acceptable)





Example of **Good Quality T1 and STIR**

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.

All Screening X-Ray images are required to be submitted to PAREXEL within 24 hours of acquisition (1 business day). The follow-up images should be submitted within 48 hours of acquisition (2 business days).

Electronic Transfer preferred

- Images shall be raw and uncompressed DICOM
- eTransfer will automatically blind the image header information

Shipment via Courier

- Blank Digital Media 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)

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 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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