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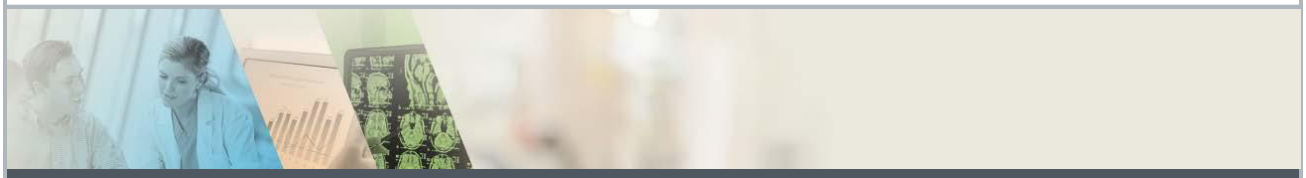
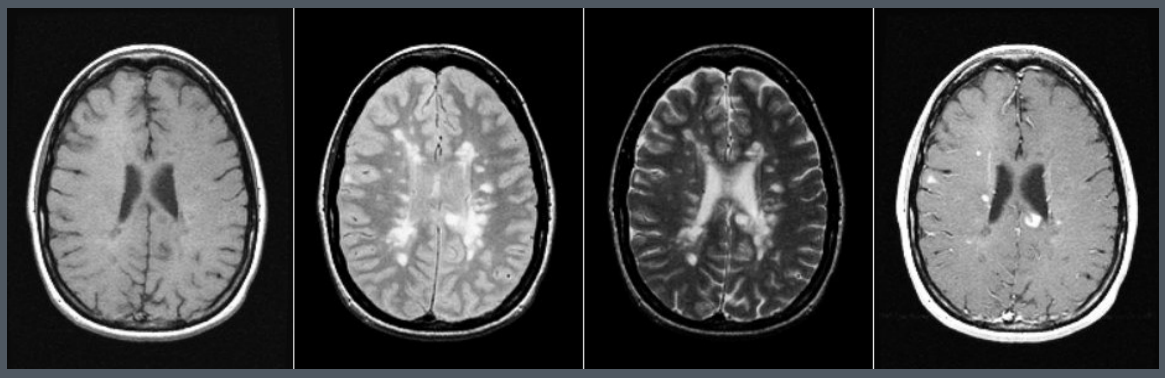


Procedure Manual for MRI of the Brain and Cervical Spine

AbbVie Protocol M14-397



Prepared for:

abbvie

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AbbVie M14-397 Protocol

A Randomized, Double-Blind, Placebo-Controlled, Multiple Dose Study to Assess the Safety and Efficacy of Elezanumab when Added to Standard of Care in Progressive Forms of Multiple Sclerosis

Bioclinica Code: 10005789

Document Revision History:

Date	Version #	Reason for Change	Authored by
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Glossary and Abbreviations

Abbreviation	Definition
AWB	Airway Bill
CD	Compact Disk
CSF	Cerebro Spinal Fluid
DICOM	Digital Imaging and Communications in Medicine
DOB	Date Of Birth
FOV	Field Of View
Gd	Gadolinium
GRAPPA	Generalized Autocalibrating Partially Parallel Acquisition
iPat	Integrated Parallel Acquisition Techniques
MEDIC	Multi-Echo Data Image Combination
MERGE	Multiple Echo Recombined Gradient Echo
mFFE	Merged Fast Field Echo
MP-RAGE	Magnetization-Prepared Rapid Acquisition Gradient-Echo
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
MT	Magnetization Transfer
MTC	Magnetization Transfer Contrast
NEX	Number of EXcitations
NSA	Number of Signal Averaged
NSF	Nephrogenic Systemic Fibrosis
PD	Proton Density
PI	Principal Investigator
PMS	Progressive forms of Multiple Sclerosis
QC	Quality Control
QRG	Quick Reference Guide
RF	Radio Frequency
RFOV	Rectangular Field Of View
SENSE	Sensitivity encoding
SNR	Signal-to-Noise Ratio
SPGR	SPoiled Gradient Recalled
SPIR	Spectral Presaturation Inversion Recovery
STIR	Short Tau Inversion Recovery
TF	Transmittal Form
TFE	Turbo Field Echo

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1.0 Introduction

The purpose of this Procedure Manual is to standardize Magnetic Resonance Imaging (MRI) image acquisition procedures between the MRI imaging facilities participating in the AbbVie M14-397 study.

All radiologists and technologists contributing to this study are expected to have had appropriate theoretical and practical training in MRI. Study personnel should also satisfy all local requirements for radiology licensing and registration. For the safety of subjects and technologists alike, an understanding of risks and safety procedures related to MRI scanning is also required. Utilizing qualified radiology personnel is the first step toward the successful use of medical imaging in this study. The Procedure Manual is designed for the study coordinator and the MRI technologists involved in this study. All new personnel who join the study after initiation of the MRI imaging facility are also required to read and understand the manual.

This Procedure Manual, taken alone, should not be considered as sufficient training in the proper technique for acquiring MR images. The goal of the manual is to define a standard procedural approach for acquiring MRIs of sufficient quality for achieving the study goals.

Questions regarding this Procedure Manual for MRI techniques should be directed to:

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2.0 Study Introduction

2.1 Study Overview

MR imaging will be used in the AbbVie M14-397 study to support efficacy and exploratory biomarker measures by evaluating changes in the brain using various volumetric and functional measurements. The primary objective of this study is to evaluate the safety and efficacy of elezanumab in subjects with progressive forms of multiple sclerosis (PMS).

This is a 52-week, Phase 2a, proof-of concept, randomized, double-blinded, parallel-group, placebo-controlled multicenter study. Approximately 90 subjects with PMS (approximately 60 primary progressive MS [PPMS] subjects and approximately 30 secondary progressive MS [SPMS] subjects) will be recruited from approximately 30 sites in the United States and Canada.

Eligible subjects will be randomized at the Week 0 - Baseline Visit to receive either elezanumab 400 mg or 1800 mg as an intravenous (IV) infusion or placebo in a 1:1:1 ratio. Blinded doses will be administered intravenously every 4 weeks for 48 weeks. Subjects will remain on their current immunomodulatory treatment regimen.

2.2 Role of Bioclinica

Primary Responsibilities of Bioclinica

- Qualify MRI imaging facilities into the study. Bioclinica will conduct an initial MRI Instrument Assessment through the evaluation of Pre-Trial Questionnaires, Test scans and First Subject Qualification scans.
- Conduct trainings for MRI Technologists on the MRI acquisition procedures specific to the AbbVie MRI study.
- Provide Procedure Manual and Quick Reference Guides (QRG) for subject scanning.
- Evaluate all subject scans and submit timely quality control reports and MRI queries.
- Evaluate MRI lesion outcome measures for all subjects in study.
- Evaluate additional MRI endpoints (change in brain and spinal cord volume, Magnetization Transfer Ratio, Diffusion Tensor Imaging).

Continued responsibilities of Bioclinica are to:

- Collect and archive exams.
- Verify that the sequence parameters used to acquire test and subject MRI exams are in agreement with the Procedure Manual.
- Review the quality of the subject MRI images for adequate anatomical coverage, signal-to-noise ratio, and the presence of artifacts.
- Provide quality control (QC) reports to the MRI imaging facility detailing any issues regarding image quality found during subject scan QC along with suggestions for improvement.
- Provide ongoing support and feedback to MRI imaging facilities.

Bioclinica personnel will review the quality of all MRI data submitted. It is expected that the majority of examinations received will be of acceptable quality. If any problems are detected related to image

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quality, Bioclinica will notify the MRI imaging facility via email, suggest possible causes of the problem, offer potential solutions and request repeat MRI of specific sequences when feasible. The MRI imaging facility should try to correct these errors and avoid them in future exams. Despite this review, the acquisition of MRI scans of acceptable quality remains the responsibility of the MRI imaging facility.

MRI outcome measures

- Scans obtained during the study will be reviewed centrally by independent radiology reviewers to assess the MRI endpoints defined by the protocol.
- Number and volume of Gadolinium-enhancing T1 lesions and T2 hyperintense lesions will be assessed. Screening results as well as changes from Screening will be assessed, as defined in the protocol.
- Cervical spinal cord (lesions and atrophy) will be assessed using the 3D-T1 weighted brain MRI sequence as well as dedicated spinal cord MRI scans.
- Exploratory measures of MTR and DTI will also be performed.
- These efficacy/exploratory outcome measure results will be sent to AbbVie by batch on an on-going basis but **will not** be shared with the sites**.**

2.3 Responsibilities of Clinical Sites

Primary Responsibilities of Clinical Sites

- Ensure that subjects enrolling in this study do not have any MR contraindications and that subjects are good candidates for tolerating an MRI scan and possible repeat exams
- Schedule subject exams for all visits in collaboration with the MRI technologist.
- During MRI imaging facility initiation, subjects should only be scheduled after the imaging facility has received training from Bioclinica and submitted a passing test scan and a passing first subject scan (see Sections 3.3.1 and 3.3.2 of this manual).
- Provide all subject demographic and exam information to the MRI technologist so that this information is entered completely and correctly on the MRI Transmittal Form that is submitted with the data.
- Ensure that MRI data and corresponding Transmittal Form are submitted to Bioclinica **within 24 hours** of acquisition.

Continued responsibilities of Clinical Sites:

- Confirm receipt of Bioclinica supplies and distribute these supplies to the appropriate study personnel based on defined roles in the data acquisition and submission process.
- Ensure that the MRI personnel have a copy of the "Quick Reference Guide for the Acquisition of MRI Scans."
- Notify Bioclinica when all subjects enrolled in the study have completed all exams
- After the First Subject scan, do not proceed with scanning or scheduling additional subjects for MRI until MRI imaging facility has been approved by Bioclinica.
- Notify Bioclinica about planned or unanticipated software or hardware upgrades at the MRI facility or other issues that might compromise the consistency of MRI scanning over time.

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2.4 Responsibilities of MRI Facilities

Primary Responsibilities of MR imaging facility

- Acquire MR scans for subjects in compliance with Bioclinica's procedures and imaging protocol detailed in the "Procedure Manual for MRI of the Brain and Cervical spine."
    - In particular, ensure that MRI parameters are consistent for each subject at each visit
    - Ensure that for each follow-up visit, the subject is precisely repositioned with respect to the reference point used at Screening
- Verify that all subject demographic and exam information are entered completely and correctly on the MRI Transmittal Form that is submitted with the MRI data.
- Verify that the electronic MRI header is entered completely and correctly and in compliance with privacy laws to ensure and protect the confidentiality of the subject (i.e., no subject names or identifiers).
- Send MRI data and corresponding Transmittal Form to Bioclinica **within 24 hours** of image acquisition (1 business day).
- Submit a test scan as part of the site qualification (as defined in Section 3.3.1 "**Test scan**").

Continued responsibilities of MR imaging facility:

- Confirm that all MRI technologists who will be performing scans for the AbbVie M14-397 protocol are properly trained on the study-specific acquisition parameters and data submission procedures.
- Do not scan First Subject until an approved test scan has been received from Bioclinica.
- Do not scan additional subjects until a passing First Subject Qualification Scan QC report has been received from Bioclinica.
- Review quality of each series during an exam and obtain repeats as necessary.
- Maintain an archive of subject MRI exams.
- Notify Bioclinica immediately as soon as they are aware that a hardware or software upgrade is scheduled. Bioclinica will evaluate the planned upgrade and provide feedback to the imaging facility as to whether this will compromise analysis.

2.5 Contraindications for the MRI Study

Subjects may not undergo MR scans with known MR contraindications. It is the responsibility of the MR imaging technologist and/or local radiologist to check for all contraindications. If a contraindication is found for a subject, the MR imaging facility shall report this finding to the clinical site Study Coordinator.

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3.0 MRI Study Imaging Facility Qualification Process

Bioclinica will assist in identifying and qualifying imaging facilities for participation in the study. To be considered for participation, imaging facilities must meet the requirements listed in the box below:

Preliminary Requirements for Imaging Facilities

- MRI scanner must have a magnetic field strength of 1.5 Tesla or 3 Tesla ONLY.
- MRI scanner, associated equipment and imaging parameters may not be switched during the length of the study without prior sponsor approval.
- MRI scanner must be manufactured by Siemens (SymphonyTIM, Espree, Essenza, Avanto, Aera, Sola, Trio, Verio, Skyra, Prisma, Spectra, Vida or newer), General Electric (Excite HD (Release 12 or above), Discovery, Optima, Brivo, Voyager, Creator, Explorer, Artist, Pioneer, Architect or newer), or Philips (Intera, Achieva, Ingenia or newer). Certain older vendor release levels will not be allowed. Scanners not listed above would require specific approval from the sponsor and may not be allowed.
- MRI imaging facilities will submit images electronically via the SMART Submit in uncompressed DICOM format. In the event of a system issue, the images can be copied to CD and sent to Bioclinica by UPS courier; this is allowed only when necessary.
- Imaging facilities must be able to perform the required MRI scans using the Technical Parameters specified in Appendices I and II of the Procedure Manual for MRI.
- MRI Scanner to be used for the study should not be a mobile MRI scanner or must not be moved during the study.
- Only one MR scanner may be used at an imaging facility and the scanner may not be switched during the length of the study. Sites with multiple MR scanners may submit more than one scanner in the Pre-Trial Questionnaire. However, during evaluation, a Bioclinica scientist will select that best suited scanner and that will be the only scanner the site may use for the study.

MRI imaging facilities that meet the requirements listed above will then advance through subsequent qualification procedures. The complete Site Qualification procedure is described in detail in the following sections and summarized here. **If your site is participating in both trials, you will only need to perform the qualification steps in the M18-918 trial and this will qualify you for the same steps in the M14-397 trial as well.**

1) **Pre-Trial Questionnaire**: MRI imaging facility must complete and submit a Bioclinica Pre-Trial Questionnaire.
2) **Self-Guided Smart START Training:** Primary MR technologists must complete a self-guided training through the Bioclinica Smart START module to ensure comprehension of and adherence to MRI protocol and procedures.
3) **MRI Instrument Assessment**:
   a) **Pre-Study Test Scan** – Upon completion of training, imaging facility will be asked to perform a test scan.
   b) **First Subject Scan** – After receipt of the Authorization Letter, the imaging facility will be authorized to acquire MR imaging on the first study subject.

The MRI imaging facility will be notified of its complete eligibility to participate in the MRI study once Bioclinica has received and reviewed the MRI Instrument assessment data.

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3.1 Pre-Trial Questionnaire (PTQ)

Pre-Trial Questionnaires (PTQs) will be collected from each MRI imaging facility considered for participation in the AbbVie M14-397 study. The PTQ will ask for information about the MRI technologists as well as the MRI equipment. **If your site is participating in both trials, you will only need to perform the qualification steps in the M18-918 trial and this will qualify you for the same steps in the M14-397 trial as well. Therefore, a PTQ for the M18-918 will suffice for the M14-397 as well.**

Although several technologists may work on this study from one imaging facility, the MRI imaging facility must designate one MRI technologist to be the Primary MRI Technologist to work on this study. The responsibility of the Primary Technologist is to ensure that the imaging protocol is followed when acquiring any subject for this study, as well as to ensure that other MRI technologists acquiring images for this study read and understand the procedures detailed in this manual.

IMPORTANT ►	**If the Primary MRI Technologist leaves the MRI imaging facility, it is the responsibility of the MRI imaging facility to ensure that he/she trains the replacement technologist on the protocol provided by this Procedure Manual.** Should the new personnel have any questions, they should contact Bioclinica.

3.2 Web Training for MR Imaging Facilities (Smart START)

Once Bioclinica has received the completed PTQ and has determined that the imaging facility meets the "Preliminary Requirements for Imaging Facilities" (as defined in Section 3.0), the primary technologists at each imaging facility along with clinical site coordinators are required to take a self-paced web training (approximately 30-60 minutes). The goal of this web training is to:

- Instruct imaging facilities on study specific protocols for acquiring acceptable MR images of the brain and test scan.
- Allow for troubleshooting of potential common problems.
- Explain the submission process of MRI data to Bioclinica.

IMPORTANT ►	Imaging facilities should not acquire subject MRI exams until they have completed Bioclinica web training and have submitted an acceptable test scan.

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3.3 MRI Instrument Assessment

The overall purpose of the MRI Instrument Assessment is to detect and reduce measurement noise on one scanner per imaging facility and to minimize scanner differences between imaging facilities, ensuring the most standard and reliable data for volumetric analysis. The Test and First Subject assessments are critical, because each provides unique information about scanner performance that allows the evaluation, optimization and correction of scan parameters.

3.3.1 Test scan

The overall purpose of the test scan is:

1) To confirm correct programming and execution of the imaging sequences as defined in the study Quick Reference Guide (QRG) and as outlined during the site training.
2) To confirm the ability of the site to submit images in DICOM format that is compatible with Bioclinica's systems.

The test scan can be completed on a healthy volunteer, non-study subject or any MR-compatible local phantom. If a phantom is not available, a plastic bottle filled with water can also be used.

This test scan should contain all required sequences using sequence parameters as specified by the protocol (see 6.3 and Quick Reference Guides). Gadolinium injection is not needed.

Please use transmittal procedures described in this document to submit the test scan through Bioclinica's SMART Submit portal to Bioclinica (film copy is not allowed). If this is not available or working, Bioclinica's Helpdesk will troubleshoot to resolve the issue. For backup purposes only, sites may submit via courier. In this instance, make sure a Transmittal form accompanies the CD. Upon receipt, data will be evaluated by a radiologist, scientist, or specially-trained technologist who will assess the images. The results of the evaluation will be sent to the site within 5 business days after receipt of the test scan.

The MRI test scan should be completed and provided to Bioclinica at least 10 business days prior to the first patient's first MRI scan. In case of rejection, the MRI test scan may have to be repeated. Repeat requests will be made by sending a QC Report and Medical Image Repeat Request Notification (MIRRN) to both the study coordinator and MRI facility. The QC Report will state a request for the test data repeat, the reason for the repeat request, and detailed information regarding the image quality and suggestions for improvement. Repeat exams requested by Bioclinica should be performed as quickly as possible.

Alternatively, Bioclinica may also request the site to submit protocol exports (.pdf or .txt files) or screenshots of the sequence parameters to confirm that comments provided in the "Test Scan QC Report" have been implemented accordingly.

If deemed appropriate, a Bioclinica MRI scientist will direct discussions on how to resolve test scan issues.

Upon receipt of a passing Test Scan QC report, an Authorization Letter will be issued, and the site is qualified to proceed to the First Subject Scan.

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IMPORTANT ►	A healthy volunteer, non-study subject or local phantom can be scanned as a test, provided that the MRI requirements are followed. If a phantom is not available, a plastic bottle filled with water can also be used. Test scans should be repeated during the course of the study after any major software/hardware upgrade. Gadolinium injection is not needed on test scans.

3.3.2 First Subject Scan

After an acceptable test scan has been received by Bioclinica, sites can perform the First Subject Scan.

The first subject scan may be the first in-vivo scan for the study, if a phantom was used as a test. In which case, subtle image quality or MRI parameter issues may be detected at this stage. It is requested, when scheduling the first subject scan for the study, not to schedule other subject scans until a passing Subject Quality Assessment Report (QAR) is sent to the MRI imaging facility.

The results of the First Subject Scan will be emailed to the MRI imaging facility and the clinical site within 5 business days after Bioclinica receives the data, as any other data. This report will note any technical deviations from protocol and offer potential suggestions for the improvement of image data. Should quality issues be detected upon QC, a formal repeat request notification form will be sent to the Primary Technologist by email along with the QAR. This repeat must take place as soon as possible after the original scan date and within 15 days.

IMPORTANT ►	**An imaging facility may not proceed in scanning any additional subjects until an acceptable "Subject QC Report" is received from Bioclinica. Once the First Subject Scan requirement is satisfied, the imaging facility can start scheduling additional subjects.**

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4.0 Procedures for Subject MRI Scans

4.1 Subject Scheduling

4.1.1 First Subject Scan

Once an acceptable test scan has been received and the clinical site has obtained complete IRB (or Ethics Committee) approval to scan these clinical research subjects, the imaging facility may schedule and submit a First Subject Scan.

Please allow 5 business days in between the submission of a First Subject Scan to Bioclinica and scanning additional subjects. Scanning of additional subjects for the MRI study may need to be rescheduled or repeated based on the amount of time required to obtain a passing first subject scan. After the first subject scan is accepted, additional subjects may be scheduled and scanned as needed.

IMPORTANT ►	The clinical site Study Coordinator and the MRI Imaging Facility must receive written confirmation from Bioclinica stating acceptance of the First Subject's baseline MRI prior to scanning another subject for the study.

4.1.2 Subject scans

Upon the acceptance of the First Subject Scan, all subjects will have MRIs to monitor for disease activity at the following visit intervals:

- Screening (Screening MRI must be performed prior to first dose.)
- Week 24 (± 7 days)
- Week 52 (± 7 days)

Early Termination and Unscheduled scans may also be performed as needed. The same MRI protocol must be used still.

The Screening MRI scan must be performed prior to the first dose of study drug. Non-scheduled MRIs after Screening will be performed at the discretion of the subject's treating physician or in the case of early subject discontinuation, if it has been more than 4 weeks since the subject's most recent MRI. The site is not allowed to randomize a subject without centralized confirmation of acceptable quality of the scan. In case the Screening MRI scan needs to be repeated, this repeat must take place as soon as possible after the original scan date and within 15 days.

IMPORTANT ►	A subject cannot be randomized in the study and start receiving study treatment prior to confirmation that Screening MRI scan is of acceptable quality.

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4.2 Evaluation of Subject Scans

Once subject MRI data have been properly transferred to Bioclinica, the corresponding Subject Quality Assessment Report is sent to the Study Coordinator and imaging facility within 5 business days after receipt of complete package at Bioclinica.

4.2.1 Requests for Resubmission of Subject Data

If subject data cannot be loaded and viewed on our image viewing stations, or data are apparently incomplete, a Resubmission Request will be made via email to the MRI imaging facility identifying need for resubmission. The data must be resubmitted to Bioclinica within 24 hours.

4.2.2 Requests for Repeat Subject Scans

If subject data are unacceptable for this study due to poor quality, for example, Bioclinica will require a repeat of the scan. The request for the subject MRI repeat exam will be noted in the Subject QAR, the reason for the request detailing information regarding the image quality issues and suggestions for improvement. The MRI Imaging Facility should reply to Bioclinica **within 1 business day** of receiving a Repeat Request to acknowledge receipt and implications.

It is important to note that if Bioclinica requests a repeat scan, it should be repeated at earliest time possible and within 15 days of the protocol-required time point, as per protocol. Good communication between the clinical site Study Coordinator, MRI imaging facility and Bioclinica is critical throughout the study to ensure repeats are performed in a timely manner.

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5.0 Subject MRI Exam Preparation

Preparation for the MRI exam prior to the subject's arrival is critical in order to ensure that all scans can be acquired within the allotted time frame and for accommodation of any unforeseen delays. The total scan time, not including subject positioning, is approximately 40-60 minutes depending on the type of scanner. Make certain that positioning aids are present in the procedure room, have the transmittal form on-hand for completion, and have supplies ready to label the digital media immediately after the MRI exam is complete.

5.1 Subject Safety and Monitoring

Remember to follow all standard subject consent protocols approved by the Institutional Review Board (IRB) or Ethics Committee. Ensure that the subject does not have any of the MRI contraindications and comply with the local requirements outlined at your imaging facility. Prior to having an MRI, each subject is required to complete the imaging center's routine MRI safety screening questionnaire, if any, as per local practice. The imaging facility is responsible for collecting accurate subject's response to pre-scan MR safety questionnaire at each MRI visit and the MRI safety of subjects who are scanned at the imaging facility, all procedures and guidelines for safety consideration should be followed.

Be sure to explain the examination procedure to the subject and caregiver, if applicable. When necessary, the caregiver should be present for MRI exam preparation, and scan acquisition. In some cases, it may be helpful to ask the caregiver to hold the subject's hand and offer reassurance during the MRI exam. If the caregiver will be going into the MRI scanner room during the examination, the caregiver must also complete the MR safety questionnaire if any, as per local practice, and be checked to ensure that they do not have any MRI contraindications. Note: extremely rare cases of small "burns" on the skin resulting from MR have been reported, due to face tattoos, permanent eyeliners or permanent eyebrows. Subjects should report any past adverse reaction to a tattoo. In addition, the use of wet washcloths on tattoos to prevent burns should be noted on the Transmittal Form.

Sedation is not recommended but is allowed. Subjects who might need sedation should discuss this with either the Principal Investigator or the subject's primary care Physician. **If a subject uses sedation, it is important to note the type of sedation on the Transmittal Form for MRI** (as defined in Appendix II, "Transmittal Forms for MRI Scans"). It is also advisable to monitor the subject's pulse, respiration and O2 levels through use of a standard on-site monitoring device during the scan, even if a caregiver is present.

5.2 Subject Positioning

Proper subject positioning is critical for obtaining high quality images. Correct, consistent and comfortable positioning of the subject within the MRI scanner will limit artifacts and maximize the acquisition of good quality images. It is also required that the subject is briefed about the importance of minimizing head motion and its adverse impact on signal quality and the achieving the objectives of the study.

- As part of the normal subject pre-screening routine, make sure all removable dental bridgework or other metallic objects (removable dental plates, jewelry from piercings, necklaces, zippers, etc.) are removed prior to entering the scanner room. The metal (even though not ferromagnetic) may cause artifacts that can affect analysis. Consistency of the

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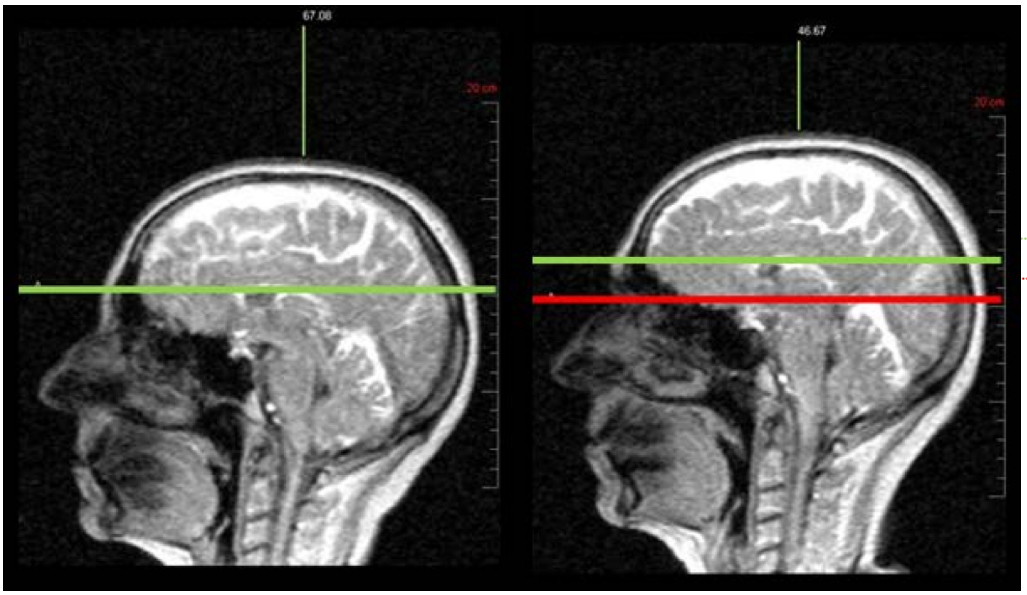
environment (e.g., no metal objects) around the subject is also very important for consistently achieving high scan quality.

- **The subject's head must be placed in a volumetric radio frequency (RF) head coil** (no surface coils are allowed).
- Maximize the subject's comfort in the RF head coil by using soft padding materials between the head and the inner surface of the RF coil.
- Once the subject has been placed into the RF coil and comfort is maximized, ensure that the center of the RF coil to be used for landmarking, is approximately 1 finger width above the eyebrows. Using the laser beams on the scanner, a landmark is set at the level of the glabella while the subject's eyes are closed. The laser beam along the magnet axis should be running straight over the subject's nose.
- The images (from first set of scout images which identify how landmarkings were performed) below show a correct landmarking (left) and an incorrect landmarking (right, red line shows current coil centering, green line shows ideal centering). However, if the subject was landmarked as shown on the right for the Screening, landmarking for a follow up visits must be done identical to the Screening to ensure that the 3D T1 images can be properly co-registered.



Correct Landmarking **Incorrect Landmarking**

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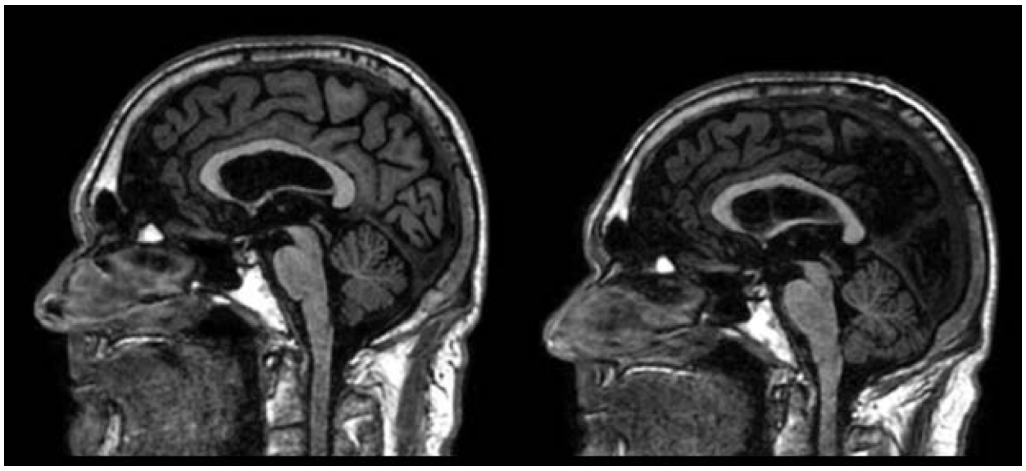
- Ensure consistency of position of the volume of interest and field of view of the scan with respect to the magnet's isocenter.



15 mm from head to top of FOV **45 mm from head to top of FOV**

The issue of consistent positioning of the 3D T1 scans is very important to prevent variations in geometric distortion due to gradient's field non-linearity. One should be careful to be consistent at the time of graphic positioning, to ensure maximum reproducibility. It matters little whether the subjects are positioned like the image on the left or the right, but the imaging facility must be consistent throughout the study for each subject. Having a consistent general plan for how this is done and doing it for all subjects, makes QC simpler when imaging facilities use multiple technologists during the study.

Consistency between the MRI exam taken at the Screening and at all follow-up visits is extremely important. If there are any deviations from these instructions (i.e., positioning, or parameters) to accommodate a subject during the Screening visit, the MRI technologist must note these on the Transmittal Form (as defined in Appendix I).

General guidelines for positioning of the head in the FOV is + 5 mm difference from Screening to all follow ups. For follow up scans, always check the position of the Screening not the last scan.

Maximizing comfort through proper head support will not only help to restrict head movement but will also provide greater compliance in completing the entire exam within the allotted exam time. Proper head support can be achieved through the use of a vacuum-molded head holder, foam wedges or padding at the sides of the head, or a neck brace. Placing a Velcro strap or tape over the forehead can also provide stability and feedback to the subject and decrease movement. It is imperative that the subject's head remains stable during acquisition. Imaging data degradation due to motion artifacts will almost always result in data rejection.

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6.0 Subject MRI Acquisition Technique

Image quality criteria for MRI of the brain in a clinical trial are stricter than in standard clinical practice. The measurements that will be performed on this MRI data depend highly upon the quality of images. Thus, **it is imperative that the acquisition of the MRI data be extremely precise and consistent in order to accurately assess potential changes**. In order to achieve the most reliable evaluations of MRI of the brain, strict adherence to a uniform acquisition protocol and quality standards is required.

6.1 Labeling Digital Header Fields for Subject MRI Scans

In compliance with privacy laws to ensure and protect the confidentiality of the subject, no subject names or identifiers should be entered into the electronic MRI header. The information in the box below should be entered into the electronic MRI header in lieu of subject identifiers.

FIELD	
SUBJECT INFORMATION:	Enter **3-digit Site ID** and **6-digit Subject Number**. (6-digit Subject Number = 1 + 3-digit site # + 2-digit screening #)
DATE OF BIRTH:	**Subject Date of Birth will not be collected for this study and the actual DOB should not be entered into the DICOM headers of the images.** Use 01-Jan-1950 for all subjects instead.
VISIT INFORMATION:	Enter the Visit name (e.g., Screening, Week 24, Week 52, Early Discontinuation, or Unscheduled) Indicate if this is a repeat exam requested by Bioclinica in the Comments.

At the end of the exam, upload MRI images to the SMART Submit website in uncompressed DICOM format. If there are difficulties with using the SMART Submit, contact Bioclinica support (helpdesk@bioclinica.com) who will work with the Imaging Facility to resolve the problem. As a last resort, the digital images can be copied to CD and sent via courier to Bioclinica. MRI images should be submitted to Bioclinica within 24 hours of acquisition. In addition to archiving the data to digital media, the imaging facility will need to locally archive these data.

6.2 Pre-scan Adjustments

All modern MRI scanners provide automated adjustment procedures for RF coil tuning and frequency adjustments after the subject is positioned in the magnet. Follow the adjustment procedures provided by the manufacturer. If the scanner is an older model, then automated adjustments may not be available, in which case the operator will have to include and run the adjustment sequences manually prior to acquisition of any of the protocol defined sequences**. Image quality is usually unacceptable without proper adjustment of the RF coil and the transmit/receive settings.** Furthermore, without frequency adjustment, problems can occur with signal acquisition and proper localization of image FOV and slices.

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6.3 Protocol for MRI of the Brain and Cervical Spine

The following is the list of the MRI sequences recommended for this protocol along with the approximate scan time for each sequence. This protocol is to be complied for all Screening and follow up visits. All scheduled scans for each subject should be performed on the same scanner employing the same parameters used for Screening visit.

This list is organized in the chronological order of acquisition:

Brain MRI protocol:

1. **3D** Sagittal **T1** (3-4 mins)
2. 2D Axial **FLAIR** (4-6 mins)
3. 3D Axial **MT** (7-12 mins)

Contrast agent injection

4. 2D Axial **PD/T2** (4-6 mins)
5. 2D Axial **T1 post Gadolinium** (4-6 mins)
6. 2D Axial **DTI** (5-7 mins) – if available on the MRI scanner

Cervical spine MRI protocol:

1. 2D Sagittal **T1** (2-4 mins)
2. 2D Sagittal **STIR** (2-4 mins)
3. 2D Axial **T2*** (2-4 mins)

The purpose of these sequences is as follows:

Sequence	Primary Role	Specific Function
3DT1	Efficacy/Exploratory	Brain volumetry + Reference before injection and detection of black holes
FLAIR	Efficacy	Detection of T2-weighted lesions
MT	Efficacy	Microstructural analysis and assessment of potential remyelination
PD/T2	Efficacy	Detection of T2-weighted lesions
T1 Gd	Efficacy	Detection of Gd-enhancing lesions and black holes
DTI	Exploratory	Assessment of white matter diffusivity and integrity
Spine T1	Efficacy/Exploratory	Detection of cervical spine cord lesions / Spine volumetry
Spine STIR	Efficacy	Detection of cervical spine cord lesions
Spine T2*	Efficacy	Detection of cervical spine cord lesions

IMPORTANT ► **The order of the sequences is critical!**

At least **5 minutes must pass after Gd injection**, before scanning the post-contrast axial T1 sequence.

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Detailed parameter settings for each sequence can be found in the study QRGs. These parameters have been standardized across MRI manufacturers and field strengths and are designed to allow the comparison of images acquired at different sites. This standardized protocol should be used for all visits. Some general guidelines are listed below:

Brain MRI protocol:

	3DT1	FLAIR	MT	PDT2	T1Gd	DTI
Orientation	Sagittal	Axial	Axial	Axial	Axial	Axial
Slice thickness (mm)	1.2	3	3	3	3	2
Slice gap (distance factor)	0.0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
# of slices	170-176 (1)	46	60	46	46	80
FOV (mm)	240	250	240	250	240	(1)
RFOV (%)	100	75 (2)	75	75	75	100
Phase encoding direction	AP	RL	RL	RL	RL	AP
Acquisition matrix	192×192	256×256	256×256	256×256	256×256	(1)
In-plane resolution (acquisition, in mm)	1.2×1.2	0.98×0.98	0.98×0.98	0.98×0.98	0.98×0.98	2.0×2.0
Number of averages (NSA/NEX)	1	1	1	1	2	1
Parallel imaging	Required	Allowed	Allowed	Allowed	Allowed	Required

1) Depending on manufacturer, see QRGs.
2) For GE scanners, RFOV is fixed ad 100%

Cervical spine MRI protocol:

	T1	STIR	T2*
Slice thickness (mm)	3.0	3.0	4.0
Slice gap (distance factor)	0.3 (10%)	0.3 (10%)	0.4 (10%)
# of slices	13	13	30
FOV (mm)	240	240	200
RFOV (%)	100	100	100
Phase encoding direction	SI	SI	AP
Acquisition matrix	192×256	192×256	256×256
In-plane resolution (acquisition, in mm)	1.25×0.94	1.25×0.94	0.78×0.78
Number of averages (NSA/NEX)	1	2	1
Parallel imaging	Required	Required	Required

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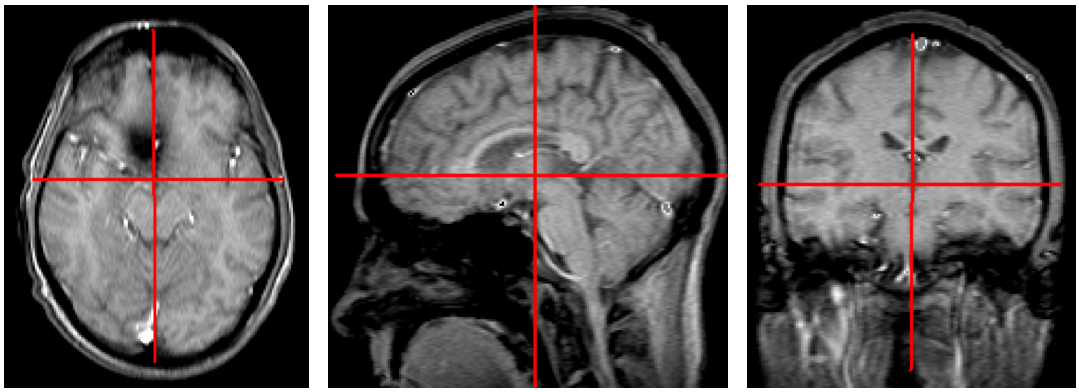
6.3.1 Localizer: 3-Plane Gradient Sequence (Scouts)

Localizer: 3-Plane Gradient echo sequence. This shows a quick acquisition in 3 orthogonal planes for anatomical orientation. Acquire one slice in the middle of each plane (sagittal, coronal, and axial) plus additional slices as needed. Ensure that the subject is positioned properly. The actual localizer FOV may be larger than that shown in the image below [*Figure 1*].

Figure 1. 3-Plane Gradient Sequence



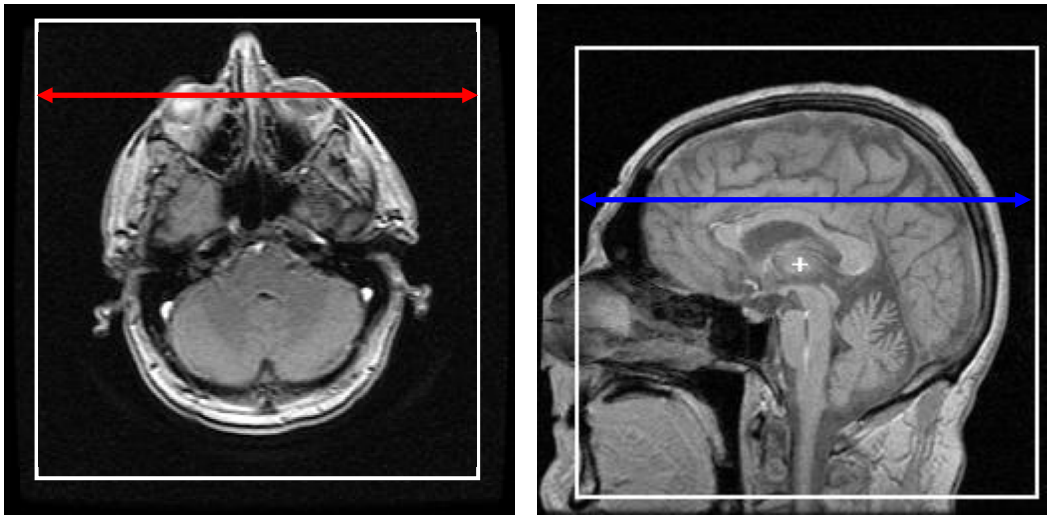
a) Mid-plane axial slice b) Mid-plane sagittal slice c) Mid-plane coronal slice

6.3.2 3D T1 / MP-RAGE / IR-prepped fast SPGR / TFE

a. Pulse sequence: Details on MRI parameters are provided in the QRGs. The following pulse sequence should be used depending on scanner manufacturer:
   - GE: 3D IR-Prep Fast SPGR
   - Philips: 3D TFE
   - Siemens: MP-RAGE

b. Orientation: Use the orthogonal Sagittal plane.

Figure 2. 3D T1 sagittal orientation and positioning



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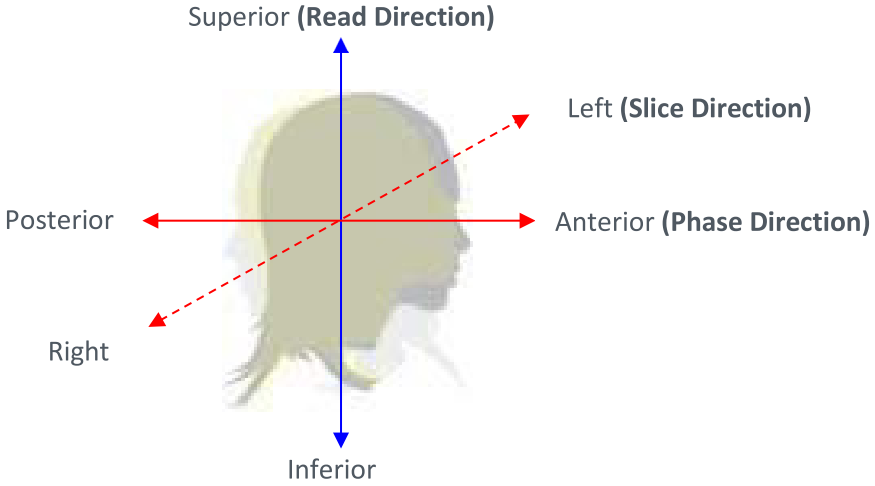
c. Positioning: Use an axial slice that shows the inferior part of the brain and nose as well as mid-sagittal slice to fully define the volume of the 3D acquisition. Since this brain sequence will also be used to measure the upper cervical spinal cord area, please **ensure that the FOV includes the C3/C4 intervertebral disc, provided that there is at least 5 mm left from top of the head to the top of the FOV**. The priority remains full coverage of the brain and skull. **Scans that do not contain the whole brain cannot be processed.** For follow up scans, refer to the Screening for positioning. Consistent positioning is critical to the volumetric analysis of this longitudinal study.

- if the acquisition box does not completely encompass the head from front to back, make sure the posterior brain is included. If the nose extends outside the FOV, it will wrap into the back of the image. Make sure that this does not impinge on the brain.
- If the subject's head is larger than the field of view (FOV), a small amount of oversampling (up to 20%) can be added to eliminate any aliasing. If partial oversampling is not available, ensure that any aliasing does not impact the brain. This can be achieved by slightly increasing the number of slices while keeping the slice thickness intact. If so, please use the same settings across visits.

IMPORTANT ►	**Ensure that the FOV includes the C3/C4 intervertebral disc, but more importantly that the whole brain and skull fit within the FOV.** Nose wrapping is not an issue as long as brain tissue is not impacted. Any deviations from the 3D T1 protocol should be: 1. Documented locally 2. Reported to Bioclinica. This can be noted on the Transmittal Form. 3. Implemented identically for every subsequent scan for the subject.

d. Read and Phase Directions: The read or frequency direction (in blue) must be along the superior-inferior plane to avoid aliasing of neck and shoulder into the FOV. The phase direction (in solid red) should be anterior-posterior.

Figure 3. 3D T1 read and phase directions



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e. 3D Partition: For all Siemens scanners use 176 slices with a slice thickness of 1.2 mm. For all Philips scanners use 170 slices with a slice thickness 1.2 mm. For GE scanners, use approximately 174 "locs per slab" with 1.2 mm slice thickness. This will generate 170 slices as GE throws away the outer 4 slices. You need to fully cover the head from left to right. For a larger head, you may add slices to get complete coverage but do not reduce the number to maintain consistent signal to noise. Note that "air shots" mean nothing as this is a volume acquisition and the total number of slices determine the SNR. Remember, however, adding slices does add scan time. Do not worry that the area covered by the slices extends outside the head. Using a Phase FOV less than 100% will most likely not be an option because of aliasing in the AP direction. If the head is very large, you may add up to 20% oversampling to avoid serious aliasing of the face/nose into the brain. Note this modification on the Transmittal Form. Do NOT change the number of slices as this will affect contrast but not scan time.

f. Parallel imaging: Allowed if available. To be used consistently across MRI timepoints. The following settings must be applied:

General Electric		Philips		Siemens	
Asset		SENSE	yes	PAT mode	GRAPPA
phase acceleration	1.75	P reduction (AP)	1	Accel. factor PE	2
		P os factor	1.2		
		S reduction (RL)	1.8		

Further, in order to optimize image quality and facilitate subsequent image analysis, the following options should be turned off:

General Electric		Philips		Siemens	
CV6 Turbo mode	1 (Faster)	Overcontiguous slices	no	Slice resolution	100%
CV23 Slice resolution	100%	Scan percentage	100%	Phase resolution	100%
ZIP2	Off	Halfscan	no	Slice partial Fourier	Off
ZIP512	Off	Partial echo	no	Phase partial Fourier	Off
3D Geometry Correction	On			Asymmetric echo	Off
				Distortion Correction	On (3D)

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6.3.3 Magnetization Transfer (MT)

MT imaging allows assessing structural integrity of tissues, and therefore global disease activity. This analysis is performed on Magnetization Transfer Ratio (MTR) maps, which are calculated from two sets of MT data, acquired without and with a saturation pulse.

Consequently, you are required to run the MT scan two times – first, one with no MTC pulse selected, then one with MTC pulse selected ('MT off' and 'MT on'). Apart from the 'MTC' option all other parameters and slice position MUST be the same. Do not perform a 'prescan' between the 'MT off' and 'MT on' if this could cause the transmitter and receiver coil values to change - they need to be identical for both sequences.

Note: For Philips scanners, this will result in a single interleaved series. For other manufacturers, 2 separate sequences will be performed and sent.

a. Pulse sequence: Use 3D spoiled gradient-recalled echo must be used, with selective excitation
b. Orientation: 60 oblique axial slices (obtained with 60 partitions of 1 slab) must be acquired, parallel to the subcallosal line, as described on next page (see *Figure 4 left*)
c. Positioning: Stack must be positioned to acquire at least 2-3 blank slices (containing just air) above the top of the head.

IMPORTANT ►	**The MT scan MUST be performed prior to the administration of Gadolinium.** **MT must be performed twice, first with no MTC pulse, then with the MTC pulse.**

6.3.4 Axial 2D Diffusion Tensor Imaging

DTI is required, if available on the MRI scanner. Please see the below requirements.

a. Pulse sequence: Use single-shot Echo Planar Imaging (EPI).
b. Resolution: Isotropic voxel size of 2.0x2.0x2.0 mm^3. See QRGs for exact manufacturer settings.
c. Number of directions and b values:
    - Two b values should be used, b = 0 and 1000 s/mm^2.
    - For b=1000, ~30 directions should be used. The same gradient scheme must be used for every participant and visit.
d. Orientation: Use the same subcallosal orientation, as described on next page (see *Figure 4 left*).
e. Datasets to export: The following datasets must be exported to Bioclinica
    - Native images (b_0 images and all b_{1000} directional images)
    - Trace and ADC maps
      Note: On Siemens scanners, the use of Mosaic mode is recommended in order to minimize the number of files to transfer.

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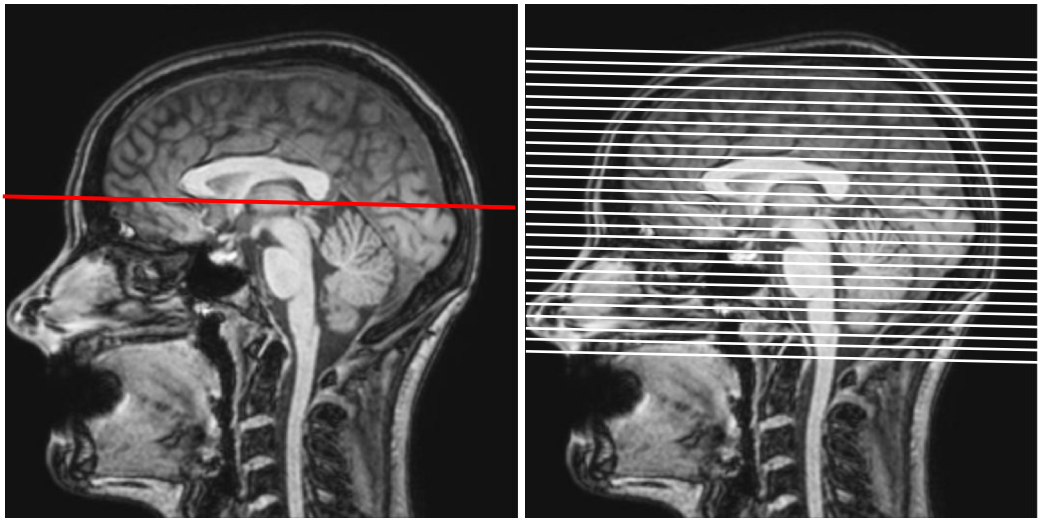
6.3.5 2D sequences – FLAIR, PD/T2 and T1 Gd

a. MRI parameters: Please refer to the QRG *'Technical Parameters for MRI of the Brain'* for direction on how to acquire these sequences. Bioclinica should be notified if your imaging facility will not be able to follow the parameters listed but many of the values are only approximate and may vary for your specific scanner. Some general guidelines are listed below (also including 3DT1 basic settings):

b. Orientation: Angulate Axial 2D sequences parallel to the subcallosal* line. *[Figure 4 left]*

Figure 4 - Orientation of Axial 2D sequences (red line, left) and stack placement (right)



*** The subcallosal line joins the undersurface of the front (rostrum) and back (splenium) of the corpus callosum. Use 3-plane localizer for prescription.**

c. Positioning: Position on mid-sagittal slice. Be sure to obtain coverage of the entire brain by including one slice of air above the skull. The acquisition stack should be placed at the most superior point of the brain, and fully cover the cerebellum as well as all the brain in the lateral and the anterior-posterior planes *[Figure 4 right]*. If extra axial slices are required to achieve this coverage, please acquire those slices. You may optimize the TR time (maintaining 2 groups of concatenations) to minimize scan time as long as the minimum TR is achieved.

d. Spatial Saturation Band: Inferior slab saturation should be applied for PD/T2 sequence only. Use approximately 50-mm flow saturation band inferior to the MRI slices and positioned just below the inferior slice and parallel to slice stack to reduce inflow effects (see *Figure 4 right*).

e. Fat Saturation: to be turned on for PD/T2, if available (Vendor specific terms include Fat Sat and SPIR).

f. Parallel imaging: allowed (acceleration factor up to 2)

IMPORTANT ► In order to improve consistency between Axial sequences

1. Set angulation and positioning for the FLAIR sequence, by referring to the most relevant sagittal view from the localizer
2. Carry over those settings for the PD/T2 and T1 Gd sequences

Acquisition parameters must be identical across visits. Any deviation will be queried and may result in data loss.

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6.3.6 Gadolinium injection

Please consider the below guidelines for consistent injection across subjects and visits:

- Use your local injection procedures.
- Make sure that local kidney function tests are performed at screening and the local policy governing the use of Gd-based contrast agent on GFR-compromised subjects is strictly followed prior to considering Gadolinium injection. Cyclic contrast agents are preferred (such as ProHance, Gadovist or Dotarem) to minimize the risk of Nephrogenic Systemic Fibrosis (NSF).
- Other than the above comment, there are no restrictions in which contrast agent to use. Ideally, please use the same product for all scans.
- Inject 0.1 mmol/kg over 30 seconds.
- There should be at least 5 minutes between injection and scanning the post-contrast Axial 2D T1-weighted MRI sequence. As noted in 6.3, you can acquire the PD/T2 sequence right after injection, which should last long enough to avoid any waiting time before scanning the post-contrast T1.
- Should the bed have to be pulled out during the contrast injection, please perform another localizer to ensure consistent positioning prior to resuming scanning.

6.3.7 Cervical spine MRI – T1, STIR and T2*

Sagittal sequences (T1 and STIR):

- Complete coverage of the **cervical spine** is required. Completely cover the cervical spine in R-L direction. The recommended number of slices will achieve required coverage in most cases. In exceptional cases, add as many slices as needed to ensure complete coverage.
- The FOV should be prescribed so that its superior edge is 15-20 mm above C1 vertebral body (approximately at the level of mid-pons).
- Set angulation and positioning for the T1 sequence and carry over those settings for the STIR.
- It is recommended to use a spatial saturation band placed on anterior neck to reduce swallowing artifacts over cervical spine, as shown.

Axial sequence (T2*):

- Multi-echo gradient echo is required (GE: MERGE, Philips: mFFE, Siemens: MEDIC), in order to improve contrast.
- Complete coverage of the cervical spine is preferred.
- If full coverage is difficult to achieve and number of slices cannot be increased without greatly impacting scan time, position the top slice at the middle of C2/C3 disc and cover as much as possible caudally (e.g. downwards).

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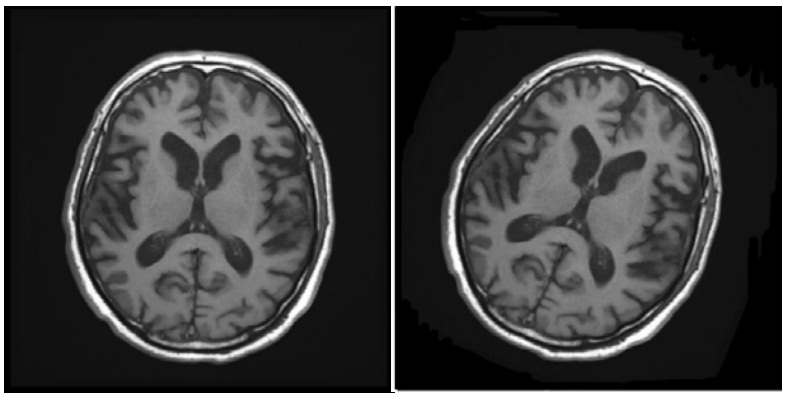
7.0 Common problems seen with subject MRI scans

Image quality is key to the accuracy of MS lesion detection and volume measurement. Anything that alters this (movement, inhomogeneity, chemical shift) potentially compromises such measures. **It is highly recommended that the raw images are viewed after each series to determine whether quality is sufficient for submission. If problems are detected, the scan should be repeated while the subject is at the MRI imaging facility.** The following sections illustrate examples of common problems that can be encountered while acquiring MRI images and possible solution.

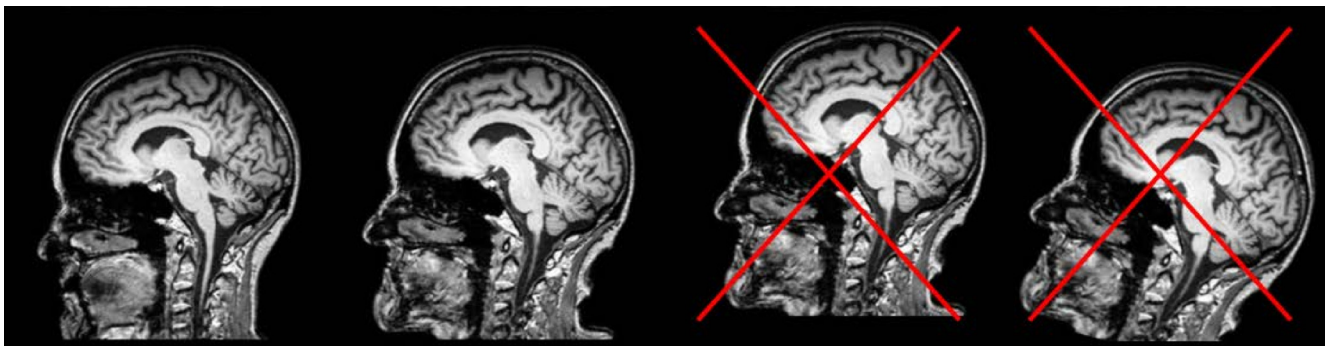
7.1 Incorrect Orientation / Image Plane Misalignment

2D sequences:



Re-positioning must be identical across visits of the same subject and as precise as possible. Also, the Z-centre / middle slice must always be positioned the same way so we get consistent coverage of the brain and no slice shift. Special care should be taken to make sure that the positioning of the stack of slices is similar to the Screening examination, in order to minimize the impact of partial volume effect when comparing examinations longitudinally.

3DT1 sequence:



Screening	Follow-up Positioning is OK	Follow-up Incorrect centering	Follow-up Incorrect angulation

Possible Remedies:

- Always refer to Screening scan when positioning the acquisition box and prescribing the stack of slices on follow-up scans.
- If subject moved significantly, reposition subject and reacquire ALL scans

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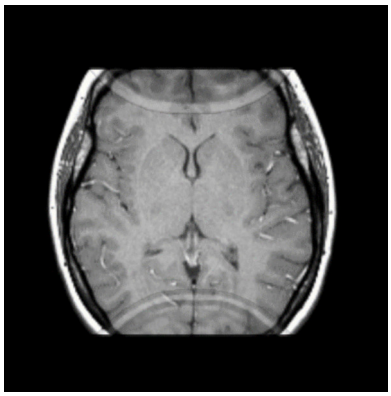
7.2 Swap of Read and Phase Encoding Directions



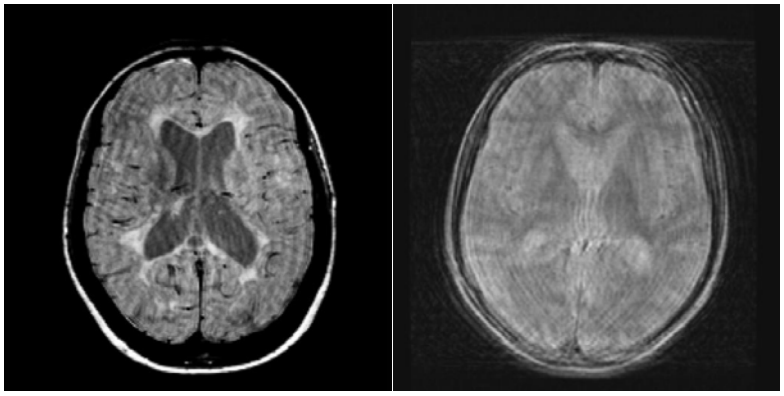
In this example, the read and phase encodings were swapped. The read direction was in the left-right direction instead of the anterior-posterior direction, which resulted in the aliasing (folding) of the brain and skull into image field of view. Note that GE scanners list frequency (read) direction, while Siemens and Philips scanners list phase encoding direction.

Possible Remedy:

- Check the read direction (or phase encoding direction) is correctly specified.

7.3 "Ghosting" Artifacts

In these examples the images exhibit ghosting. Ghosting can be created by motion (subject's movement, table bed vibrations, CSF or vessel flow, etc.) scanner instability, or physics phenomenon (e.g., eddy currents).



Possible Remedies:

- Ensure that the subject is comfortable.
- If motion artifacts are the result of subject head motion, reacquire the sequence after tightly securing the subject's head with additional restraints (as defined in 5.2 "Subject Positioning") and emphasize the importance of remaining still. If a break is needed and time allows, permit the subject to exit the scanner and then reacquire all images once the subject feels ready to re-enter the magnet.
- If motion artifacts are not due to mechanical problems (i.e., table bed vibrations) or subject movement, the problem is most likely related to maladjustments of the scanner system.

Maladjustments and instabilities should be suspected if all measures to eliminate motion artifacts have been exhausted. A large number of service or adjustment problems can be encountered with the MRI scanner. Among them are:

- Receiver gain too high
- Errors in phase encoding gradients

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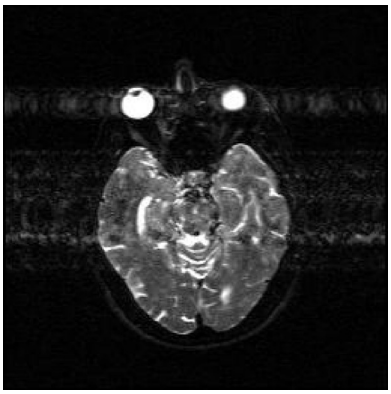
- Unbalance of receivers
- RF transmitter instability
- Eddy current

Remember to rerun the Pre-scan routine if you encounter artifacts that you think might be machine related. If all else fails, contact your service engineer.

7.4 Flow Compensation



In the T2-weighted image shown to the right, the flow compensation was not applied during acquisition resulting in artifacts from cerebrospinal fluid (CSF) motion running through the anatomy of the brain. The artifacts running through the eyes come from the eyes motion and cannot be avoided, but they do not have any influence on brain anatomy depiction.

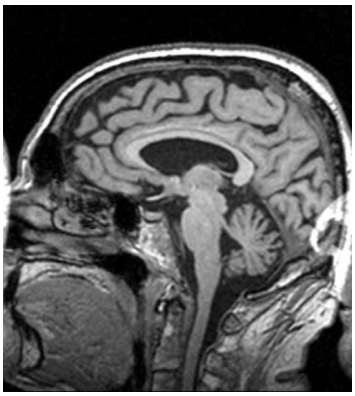
Possible Remedies:

- Use flow compensation

7.5 Aliasing (Folding) in 3D T1

These images show aliasing (nose wrap). Fold-over generally occurs when the subject's head size is larger than the acquisition box. **Note that nose wrap is NOT an issue when the overlapping area does not impact brain tissue (as on the left image below)**.

Acceptable



Not acceptable

Possible Remedies:

- For GE scanners, if the acquisition box does not fully cover the subject's head, increase FOV. Note that this modified FOV will have to be used for all visits of that specific subject.
- For Siemens and Philips scanners, you may use up to 20% (more typically 5-10%) of phase oversampling/fold-over suppression to eliminate fold-over in the AP direction.

In no instances should the specified number of slices be reduced regardless of how small the head is.

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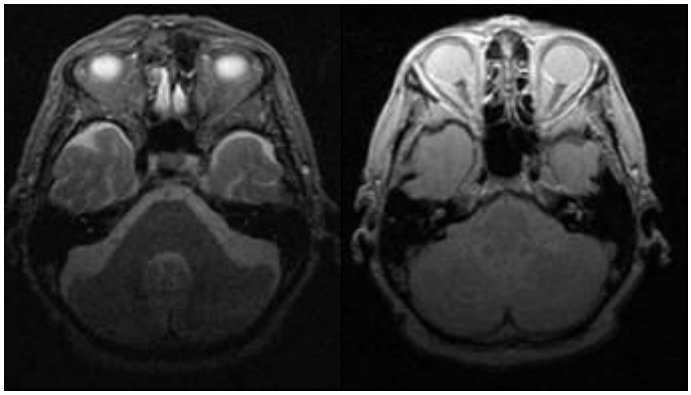
7.6 Signal Loss

7.6.1 Inferior Slices

In this example, there was a signal drop at the lower part of the brain. This is usually due to improper positioning of the subject's head, an incorrectly tuned RF coil or an improper or bad connection.

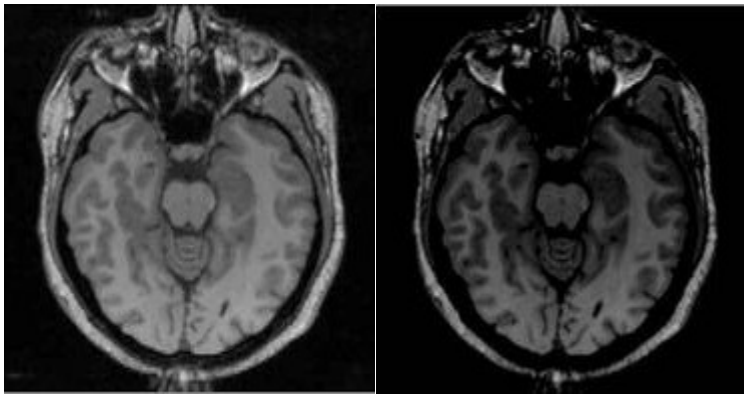


Possible Remedies:

- Ensure that the subject is positioned correctly in the head coil. Rerun the localizer, 3-plane scout and verify that the prescription of the mid-plane sagittal slice is centered at the thalamus. Reposition subject's head if necessary and rescan.
- Check that the RF coil is properly connected. (This may require that you enter the magnet room and check a cable).

7.6.2 Inhomogeneity or Shading Artifact

The images below are from the same slice with two different window/level settings. It is apparent that the signal is stronger on the posterior portion of the head.



Possible Remedies:

- Ensure volumetric radio frequency (RF) head coil is used. Surface coils are not permitted.
- If a phased array coil was used, the proper vendor specific homogeneity filter must be used (PURE for GE, CLEAR for Philips and Pre-scan Normalization for Siemens). Check with Bioclinica before using phased array coils without these filters. Note that if you do not use this filter for Screening images, continue to NOT use the filter, even if it becomes available.

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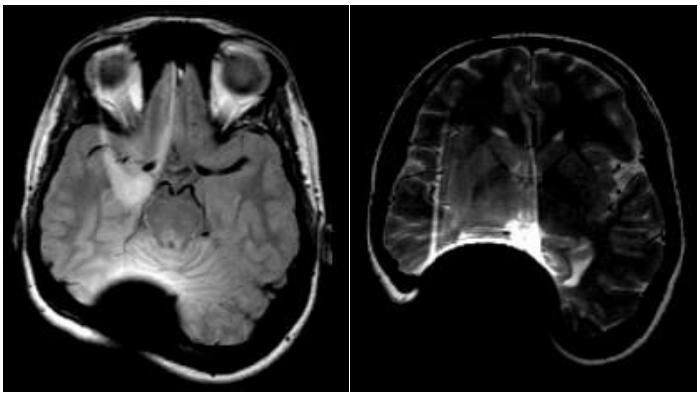
- Ensure that the subject is positioned correctly in the head coil. Rerun the localizer, 3-plane scout and verify that the prescription of the mid-plane sagittal slice is centered at the thalamus. Reposition subject's head if necessary and rescan.
- Rerun automatic or manual pre-scan.
- Investigate with your field engineer whether the coil or receiver gain needs service.

7.7 Metal Artifact

Magnetic field distortions: In this example there is blacking out due to the presence of metal near the participant's head.



Possible Remedy:

- Make sure the participant is not wearing any metal. Check for hair clips, metallic makeup (i.e., permanent eyeliner), necklace, safety pins, removable dentures and bridges, and facial jewelry. Remove metal and rescan. Certain mascara and tattoos will also cause artifacts.
- If the metal cannot be removed and the artifacts hinder anatomical depiction of the brain, the subject may have to be excluded.

NOTE: After repositioning subject, rerun the Pre-scan routine before re-scanning.

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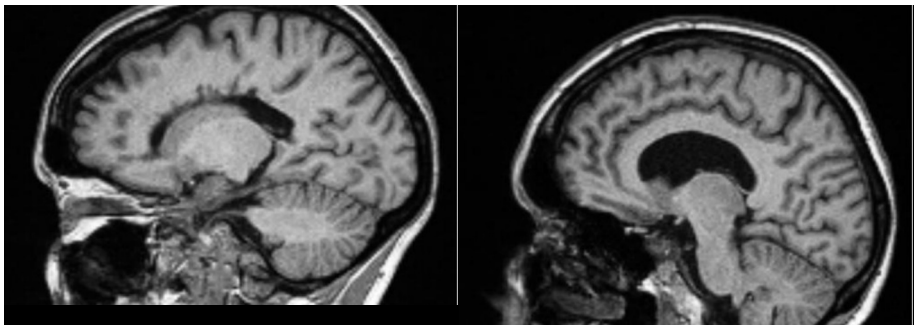
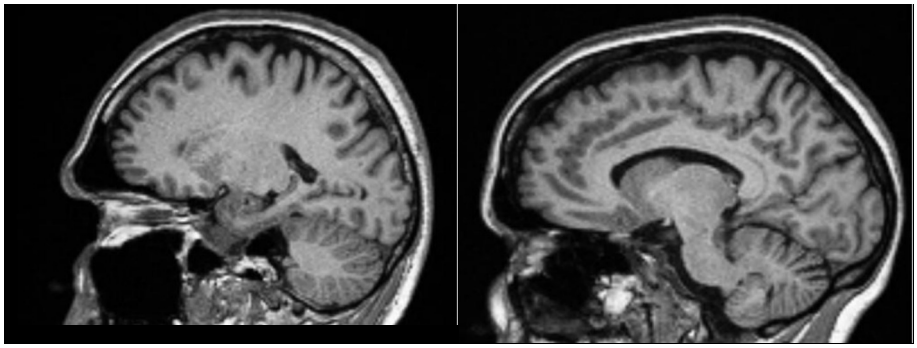
7.8 Inadequate Head Coverage



(a) Image is cut too close superiorly (b) Image is inadequate inferiorly



(c) Adequate head coverage (d) Adequate head coverage

In the above figure, images (a) and (b) illustrate examples of inadequate head coverage. Images (c) and (d) exemplify adequate head coverage. Please make certain that the field of view is large enough to include the whole head in the image. Ideally there should be air visible posteriorly, laterally, and superiorly beyond the full extent of the scalp. In the anterior portion of the brain, please ensure that the full extent of the brain and CSF are visible. Centering the subject in both the center of the RF coil and FOV is critical.

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8.0 Data Submission Procedures

At the end of the exam, MRI images should be submitted to Bioclinica within 24 hours of acquisition (1 business day) according to the procedures described in this section. MRI images are to be submitted to Bioclinica via our secure electronic portal, https://smart.bioclinica.com (formerly known as SynarcConnect). It is required to submit using this portal.

8.1 Submitting MRI Data via Bioclinica's Electronic Portal

Imaging facility personnel, the Study Coordinator or a different designated study team member will upload the MR images via the internet at Bioclinica's secure electronic portal – SMART Submit. Bioclinica will provide a personal login name and password for each person who like to upload data for the study.

For information on how to transmit images, see the **SMART Submit Quick Reference Guide.**

In the event the imaging facility experiences difficulties in uploading the images to the SMART Submit, contact the Bioclinica web support service at smart.submit@bioclinica.com for assistance. The Helpdesk is available 24 hours a day, 7 days a week.

8.2 Submitting Data via Courier

UPS is the designated courier for this study. Air waybills (AWBs) will be provided for backup purposes only if the electronic portal is not working or there are other circumstances where web submission is not available after troubleshooting with the Bioclinica Helpdesk.

If Bioclinica confirms that you must use a courier, complete the sender sections of the pre-printed airway bill and keep a copy for tracking purposes. Place the MRI Transmittal Form and labeled media for each participant into a shipping envelope (NOT in the AWB sleeve).

Contact your local UPS to schedule your package pick-up taking into account the latest call and pick-up time.

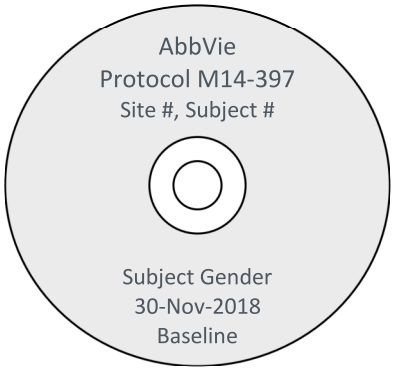
8.3 Submitting MRI Data Archived on Digital Media

When preparing to send the archived MRI exam data on digital media, complete and include the Transmittal Form. The MR imaging facility should retain the pink copy and send the remaining pages (white and yellow) to Bioclinica (as defined in Appendix I "Instructions for Completing the Transmittal Form for Subject MRI") along with the digital media containing the exam data.

To submit MR images on digital media, export the data to a CD in **uncompressed DICOM** format. Use one CD per participant visit.

CD: Use a black permanent marker to label the CD with:

- Sponsor name (AbbVie)
- Study protocol number (M14-397)
- Site Number (3 digits)
- Subject Number (6 digits= 1 + 3-digit site # + 2-digit screening #)



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- Subject Gender
- Exam date in alphanumeric format (i.e., 30-Nov-2018)
- Visit (Screening, Week 24, 52, Early Termination, Unscheduled, Test).
- NOTE: Subject Date of Birth will not be collected for this study.

8.4 Supplies Provided by Bioclinica

Bioclinica will be providing the following electronic supplies to the supply contact noted on the PTQ:

  - Quick Reference Guide for the Acquisition of Subject MRI Scans
  - Scanner-specific Quick Reference Guide for the Acquisition of MRI Scans
  - SMART Submit Quick Reference Guide

- For Back-Up purposes only, printed Transmittal Forms and Airway Bills will be available upon request for sites who need to submit via courier.

The supplies listed above will be provided by email after receipt of a Pre-Trial Questionnaire that meets Bioclinica's preliminary imaging facility requirements for the trial. These supplies will also be posted on Bioclinica's web portal called the SMART portal for sites to be able to download.

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APPENDIX I: Instructions for Completing the MRI Transmittal Form

To properly complete the transmittal form for subject MRI scans, please follow the guidelines below and also refer to the SMART Submit Manual and QRG attached.

Site, Subject and Visit Information

- Complete the subject demographic information including the Subject identification (i.e., site number, and subject number).

  Important Note: Subject Date of Birth will not be collected on the transmittal form

- Check the appropriate box to indicate the visit.

FIELD	
STUDY SITE ID:	Enter **3-digit Site ID**
PARTICIPANT NUMBER	Enter **6-digit Subject Number**. (6 digits= 1 + 3-digit site # + 2-digit screening #) Note: for the Test Scan, enter '1 + 00000'
DATE OF BIRTH:	**Subject Date of Birth will not be collected for this study.**
VISIT INFORMATION:	For Subject Visits select the Visit name (e.g., Screening, Week 24, Week 52, Early Discontinuation, or Unscheduled) Note: For the Test Scan, select **Test Scan**) Indicate if this is a repeat exam requested by Bioclinica in the Comments and indicate resubmission.

Exam Information

- Complete date of MRI exam using the alphanumeric date format: DD-MMM-YYYY (e.g., 11-Dec-2018 for December 11, 2018).
- Document any relevant comments (these may include, but are not limited to, positioning or scheduling issues, or if this is a repeat scan requested by Bioclinica).

Data Shipment to Bioclinica

- Check form for completion and accuracy.
- If submitting scans via the SMART Submit portal, print a copy of the electronic Transmittal Form from the SMART Portal for your records.
- If unable to use the SMART Submit portal, enclose white and yellow copy of transmittal form with digital media and send via courier to Bioclinica. Keep the pink copy in the imaging facility's study records.

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APPENDIX II: Transmittal Form for MRI Scans

BIOCLINICA®

AbbVie Protocol M14-397
Transmittal Form for MRI Scan

Site Information — **To be completed at study site**

Study Site ID: ☐☐☐

Subject ID Number: ☐☐☐☐☐☐☐

1 + 3 digit site + 2 digit screening number
For Test enter '100000'

Subject DOB information will not be collected

Visit:
- ☐ Screening
- ☐ Test
- ☐ Week 24
- ☐ Week 52
- ☐ Early Discontinuation
- ☐ Unscheduled

Exam Information — **To be completed at study site**

MRI Sequences Submitted (See Quick Reference Guide for exact MRI exam sequence parameters. Note: Gadolinium not required for test scan):

- 2D Axial FLAIR
- 3D T1-weighted
- 3D Axial MT
- 2D Axial PD/T2
- 2D Axial T1 Gadolinium
- 2D Axial DTI
- 2D Sagittal T1 (Spine)
- 2D Sagittal STIR (Spine)
- 2D Axial T2* (Spine)

Exam Date: ☐☐ / ☐☐☐ / 20☐☐ (D D / M M M / Y Y Y Y)

Comments: _____

Technologist Initials: ☐☐☐ (F M L)

Do not write below this line. For Bioclinica use only.

Data Receipt — **To be completed at Bioclinica**

Comments: _____

Received:

Initials: ☐☐☐ (F M L)

Date Received: ☐☐ / ☐☐☐ / 20☐☐ (D D / M M M / Y Y Y Y)

RESERVED FOR BIOCLINICA BARCODE

Bioclinica Tracking Number: 10005789 10 20181017

*** Distribution: File PINK copy at Study Site. Send Original (WHITE) and YELLOW pages to Bioclinica. ***

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