



MRI Measurement of Liver Iron Concentration

Instruction Manual



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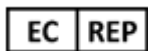
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FerriScan Patient Scanning Checklist

**IF YOU ARE HAVING PROBLEMS WITH ANY OF THESE IMAGING PARAMETERS, PLEASE
CONTACT RESONANCE HEALTH FOR ASSISTANCE.**

**RESONANCE HEALTH CANNOT ACCEPT IMAGE DATA FOR FERRISCAN ANALYSIS THAT DOES
NOT COMPLY WITH THESE PARAMETERS.**

A 1 litre plastic bag of infusion saline solution is included with the patient.	<input type="checkbox"/>
Field of View <ul style="list-style-type: none"> Is EXACTLY the same for all TEs. Includes the ENTIRE cross section of the patient, the majority of the saline bag, and approximately 2.5cm (1 inch) of surrounding background space on every side if possible. Rectangular Field of View (RFOV) may be used to save scan time. 	<input type="checkbox"/> <input type="checkbox"/>
Single Spin Echo sequence should be used. DO NOT use Turbo Spin Echo or Fast Spin Echo or Gradient Echo sequence. A T1-weighted single spin echo sequence from brain or abdominal sequence group may be used as a template, or a MEMP-STE sequence for GE scanner/s.	<input type="checkbox"/>
Do not use any filters, RF coil sensitivity normalization, motion compensation, fat suppression or spatial saturation (e.g. SAT-GE, CLEAR-Philips, Prescan-Normalise / FS / iPAT-Siemens). Some breathing artifact is expected in the image data.	<input type="checkbox"/>
No. of Slices is 11	<input type="checkbox"/>
Repetition Time (TR) is 1000ms.	<input type="checkbox"/>
Slice Thickness is between 5.0 – 6.0mm and is exactly the same for all TEs.	<input type="checkbox"/>
Real Slice Gap is between 5.0 – 6.0mm (centre to centre distance 10 -12 mm) and is exactly the same for all TEs.	<input type="checkbox"/>
Acquisition matrix and image size (or reconstruction matrix) is 256 (columns) by N (rows) where $N \leq 256$. The exact same settings must be maintained for all TEs. (The number of rows will depend on the degree of rectangular field of view used, 75% would be 192 rows for example).	<input type="checkbox"/>
Flip Angle is set at 90 degrees.	<input type="checkbox"/>
Images with TEs of 6.0, 9.0, 12.0, 15.0, 18.0 ms for 1.5T or 5.0-6.0, 7.0, 9.0, 11.0, 13.0 ms for 3T have been acquired (11 slices for each TE for patients and FerriScan Phantoms).	<input type="checkbox"/>
Prior to the patient leaving the scanner, the images should be reviewed to check for the following: <ul style="list-style-type: none"> the coil elements have functioned correctly on all series excessive artifact is not present the level of patient movement is minimal Consider rescanning any series that are not acceptable.	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>
The FAST electronic Patient Job Request Form is consistent with the patient information entered into the image header.	<input type="checkbox"/>

Introduction to FerriScan

This manual provides instructions for:

- implementing the FerriScan imaging protocol on your MRI scanner,
- how to scan a patient for FerriScan analysis,
- how to transfer image data to Resonance Health for analysis, and
- how to access results.

It is essential that these instructions are read carefully and followed accurately.

FerriScan is provided as an image analysis service by Resonance Health, an ISO 13485 certified company. Image data is transferred electronically and securely to Resonance Health for central analysis and a FerriScan Report of the patient's liver iron concentration is returned, within a target turnaround time of two business days. A technical description of FerriScan is described in Appendix 6.

FerriScan requires a unique imaging protocol to be established on the MRI scanner. You may require assistance from your MRI supplier to establish the FerriScan protocol on your scanner.

FAST is a secure web-based system for transferring image data to Resonance Health and for FAST users to access patient results and reports. When using the Secure Web Transfer system in FAST, data transferred to and from the FAST system is encrypted. The system utilises the HTTPS protocol with 128 bits SSL encryption (certified by RapidSSL).

Access to FAST can be requested by the nominated FAST Access Authorizer, and once processed by Resonance Health Staff, FAST users can access FAST via www.resonancehealth.com.

It can be accessed by selecting the FAST Login link at www.resonancehealth.com. Unique Login IDs and passwords are required to access FAST which will be provided by Resonance Health. Detailed instructions for using FAST are provided under a separate document, FAST User Guide.

Step 1: Determine suitability of MRI scanner for performing FerriScan

FerriScan requires a 1.5 or 3 tesla MRI Scanner. No specific hardware or software is required. Resonance Health will provide an MRI Centre Scanner Details Form to collect information about your scanner and determine its suitability for FerriScan. Siemens, Philips and GE scanners are currently being used for FerriScan in centres around the world.

NOTE: For **GE scanners** the model must be a HDx (V4 or V5) with “scantools 14 (or above)” platform. Scantools 14 (and above) has a special sequence called the “memp-ste” sequence which is required to enable the MRI scanner to achieve an echo time (TE) of 6.0ms for 1.5T, and (TE) of 5.0 – 6.0ms for 3T, which is necessary for the FerriScan protocol to be implemented.

Step 2: FerriScan imaging setup

Resonance Health will courier a FerriScan Phantom which includes the “Instructions for Use – FerriScan Phantom” to the MRI site detailing the FerriScan imaging requirements. The Phantom is used to verify the correct image acquisition for FerriScan. The instructions for MRI scanner set up for FerriScan are detailed under [FerriScan Imaging Protocol](#) section within this manual.

Step 3: Phantom Scan

The MRI site scans the Phantom with the FerriScan imaging protocol. Resonance Health will review the Phantom images to confirm if the FerriScan imaging requirements have been set up correctly. **The MRI site must pass their phantom scan before patient imaging can commence.** The instructions for FerriScan Phantom scan are detailed under [Scanning the FerriScan Phantom](#) and [FerriScan Scanner Verification](#) sections within this manual. Please note that Resonance Health is unable to accept any patient data prior to the verification of your scanner for FerriScan use.

Step 4: Patient scanning for FerriScan liver iron concentration measurements

The instructions for scanning patient for FerriScan are described under [FerriScan Subject Patient Scanning Procedure](#) section within this manual.

Step 5: Electronic transmission of MRI image data to Resonance Health via FAST

All image data is securely transferred to Resonance Health via a web-based portal called FAST. For each set of image data transferred to Resonance Health, an electronic Job Request Form must be submitted via FAST. Detailed instructions for using FAST are provided under a separate document, FAST User Guide.

Step 6: Resonance Health provides the FerriScan liver iron concentration Report

Patient's FerriScan results and report are issued and released on FAST. Detailed instructions for using FAST are provided in a separate document, FAST User Guide.

FerriScan Imaging Protocol

The imaging protocol settings required for FerriScan are outlined in the section below.

NOTE: 3T scanners equipped with dual transmission system can be used for FerriScan protocol (**NOT with single transmission system**).

1. Find a default single spin-echo sequence that will be suitable for imaging a liver in an axial plane.
2. Copy or save the default sequence in the desired area for FerriScan scans.

Tip: For some scanners (e.g. Siemens Magnetom Vision) it may be necessary to also save a standard abdomen scout sequence.

3. Modify the sequence to match the mandatory fixed and FOV settings required for FerriScan as per Tables 1 and 2:

Table 1: Mandatory fixed settings for FerriScan image acquisition

Parameter	Setting
Sequence Type	Single Spin Echo (NOT TSE or FSE or GRE), MEMP-STE for GE Scanner
TE	6.0*, 9.0, 12.0, 15.0, 18.0 ms for 1.5T 5.0-6.0, 7.0, 9.0, 11.0, 13.0 ms for 3T
TR	1000 ms
Slice Orientation	Axial
No. Slices	11
Slice Thickness	5 – 6 mm
Real Slice Gap (Centre to centre distance 10 -12 mm)	5 – 6 mm (100% of slice thickness)
Acquisition matrix and image size (reconstruction matrix)	256 x N (Note: $N \leq 256$ and any Interpolation option must be OFF)
Half-Fourier	Yes
Flip Angle	90 degrees
Scan Mode	Multi-slice
Excitation Order/Multi-slice Mode	Interleaved (except on GE scanners)
Gradient Mode & RF Pulse Type	FAST (Maximum)
Phase Encoding Direction	Anterior – Posterior (Set to COL, not ROW)
No. Acquisitions	1
No. Measurements	1
Pixel Bandwidth (Water Fat Shift – WFS)	Set the lowest bandwidth (WFS) value that will allow you to achieve TE=6.0ms (1.5T) or 5.0-6.0 ms (3T) and set the other TE series to the same bandwidth (WFS). Recommended bandwidth (WFS): 220 – 490 Hz/pixel (WFS – 0.55 - 0.6) depending on scanner type and magnetic field strength.
Percent Sampling	100% (may be lower on GE scanners)
Scanner Gain Lock	Yes, contact RH for help if needed

Filters / Normalisation / Fat Suppression / Saturation	None No RF coil sensitivity normalisation, motion compensation, fat suppression or spatial saturation
Scan Time	100 s (1 min 40 s) or shorter per TE series

*6.6 ms may be acceptable for Siemens Espree, subject to further assessment

NOTE: The mandatory fixed settings MUST be adhered to for the image data to be accepted for FerriScan Analysis. All imaging parameters (except for TE) are to remain constant for both FerriScan Phantoms and patients. For GE scanners a special sequence type (PSD) called “memp-ste” is required to achieve the minimum TE of 6.0ms (1.5T) or 5.0-6.0ms (3T). This is available from scantools 14 or above. To access the sequence, enter “memp-ste” in the PSD field at the bottom of the Image Sequence selector pane of the Protocol Builder.

Table 2: FOV & Voxel settings for FerriScan Phantom image acquisition

Parameter	Settings
FOV	Must include the ENTIRE cross section of the FerriScan Phantom, the majority of the saline bag, and some background space. Recommended initial setting of 400 mm, but subject to change with patient size.
Rectangular FOV / RFOV% / Phase FOV	75 % or 6/8 Ensure the above requirements are still met.
Reconstruction Matrix	256×256
Voxel Size	Adjust it as per the following if needed: Voxel Size = FOV/256 and MUST maintain it consistent for all 5 TE series for a Philips scanner. No need to change for other types of scanners in general.

NOTE: The FOV must not be altered between the TE series.

For Philips scanners the voxel size must be manually adjusted so that:

$$\text{Voxel size} = \text{FOV} / 256$$

For example; for a FOV of 400mm the voxel size should be set to $400/256 = 1.56\text{mm}$. Ensure to set the reconstruction voxel size to the same value and the reconstruction matrix to 256.

4. Save the sequence so that it can easily be retrieved for future FerriScan use.

Tip: Create a TE6 (1.5T) or TE5-6 (3T) sequence as per requirements then use it as a template to create other 4 TE sequences to keep the consistency of parameter settings.

Scanning the FerriScan Phantom

Preparing the FerriScan Phantom

1. Open the outer box of the FerriScan Phantom and remove the inner box. DO NOT open the inner box. The unopened inner box is to be scanned intact.
2. Leave the FerriScan Phantom inner box in the scanner room for 3 to 4 hours prior to scanning to stabilise the temperature.
3. Make a note of the FerriScan Phantom LOT number (this is supplied on the inner and outer box), as this will need to be entered when registering the study.
4. Place the FerriScan Phantom on the scanner bed in the correct orientation in accordance with the labelling on the inner box. Ensure the "TOP" is facing the ceiling and the "FRONT" is facing the "front" of the scanner.
5. Place a 1 litre bag of saline solution next to the FerriScan Phantom (see Figures 1 and 2).

Tip: Some MRI scanners automatically sense the load on the coil and override the SAR calculated from the weight entry. If this occurs, the image data may not be suitable for FerriScan scanner verification. To avoid this, it is recommended that the coil is loaded with two additional saline bags. One at the front and one at the back of the FerriScan Phantom (in addition to the bag always included to the side).

6. Place approximately 5 cm (or 2 inches) of padding above the FerriScan Phantom, to ensure the phantom and saline bag are away from direct contact with the abdomen/torso coil.
7. Place the abdomen/torso coil on the top of the padded FerriScan Phantom and use additional padding and/or straps as necessary to ensure the anterior array element is secure and approximately 15 – 20 cm (6 to 8 inches) from the posterior elements.

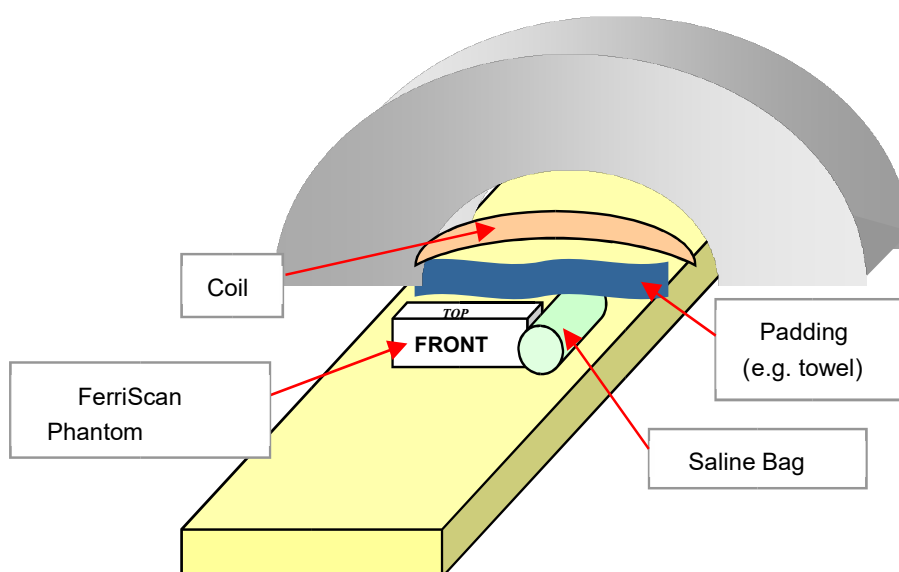


Figure 1: FerriScan Phantom, saline bag, and coil position in scanner



Figure 2: FerriScan Phantom and saline bag arrangement on scanner bed.

Scanning the FerriScan Phantom

1. Image acquisition is to be performed using the previously established FerriScan protocol.
2. Register the study in accordance with your standard procedure, using the entire FerriScan Phantom LOT number (as taken from the box) in the Patient ID field, and the words "FerriScan Phantom" in the Patient Name field.
3. Enter the Patient's Weight for the FerriScan Phantom as 80 kg (to ensure sufficient signal is acquired).
4. Run the scout sequence.
5. Open the previously established TE = 6.0 ms (1.5T) or 5.0-6.0 ms (3T) sequence.
6. Using the coronal scout image, position the 11 slices to cover the FerriScan Phantom so that there are at least 3 complete cross-sectional images of the vials within the phantom.
7. Adjust the FOV to cover the entire FerriScan Phantom and saline bag [a 400 mm FOV is recommended with a rectangular FOV (RFOV% or phase FOV) of 75% or 6/8].

Note: Once established, the FOV is to remain constant for all TE series. This is most important and one of the most common FerriScan imaging errors.

8. Run the TE = 6.0 ms (1.5T) or 5.0-6.0 ms (3T) image acquisition (see Figure 3 for an example of a typical image).

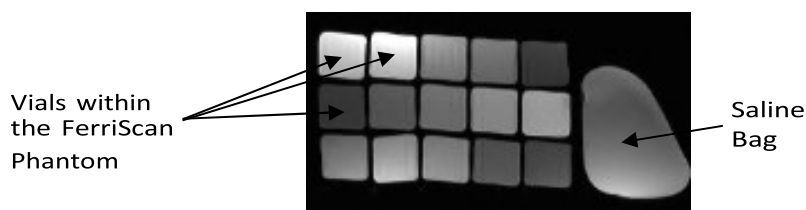


Figure 3: Typical single spin-echo axial image with 15 vials and saline bag visible within the FOV.

9. Run the remaining single-spin-echo measurements for TEs of 9.0, 12.0, 15.0 and 18.0 ms (1.5T) or TEs of 7.0, 9.0, 11.0 and 13.0 (3T).

10. When all images have been acquired, save the DICOM in Classic / Single-Frame / Interoperability and NOT Enhanced DICOM format. Make sure that the DICOM images are saved in one of the following DICOM Extensions = { ".dcm", ".ima" }

Image Data Preparation for Secure Web Transfer to Resonance Health

1. Compress or 'zip' the folder/s containing the FerriScan Phantom image data using a compression tool of your choice (for example 'WinZip™' and 'Stuff-It™'). To assist with data transfer, it is recommended to create a single compressed folder, or five separate compressed folders (one for each TE series).
2. The data is now ready for transfer, proceed to Phantom Job Request Form.
3. More details for securely transferring your image data to Resonance Health via FAST are provided in a separate document, the FAST User Guide.

A Phantom process flow is also summarised under [FerriScan Phantom Scanning Flow Chart](#) section within this manual.

FerriScan Scanner Verification

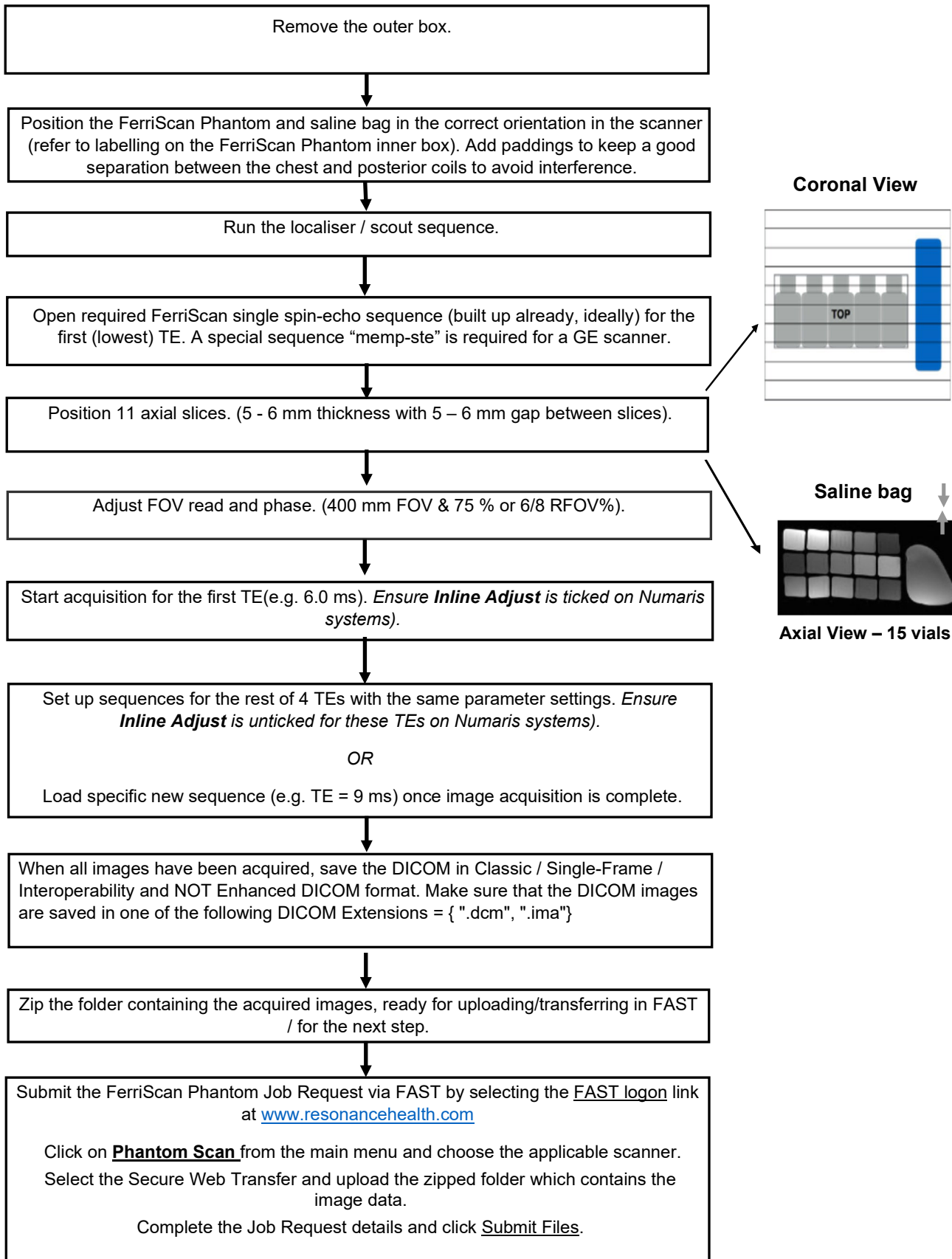
Resonance Health is unable to accept any patient data prior to the verification of your scanner for FerriScan use. Scanners require verification in the following circumstances:

1. Setting up your scanner for FerriScan for the first time.
2. If you purchase a new scanner.
3. If your MRI scanner has recently gone through significant software or hardware changes, such as operating system upgrades and/or gradient system changes.
4. Newly purchased MRI scanners.
5. If you are using FerriScan services within a Clinical trial, you are required to verify your scanner every 12 months or as per trial requirements.

Following the successful analysis of the FerriScan Phantom data, you will be provided with an official letter of scanner verification (see example in [APPENDIX 1: Scanner Verification Letter](#)). Only once this letter has been received, you may you begin to scan patients for FerriScan.

The letter will be transferred electronically via FAST and will be available for you to download in PDF format. When the letter is available, you will be notified by email to check FAST.

FerriScan Phantom Scanning Flow Chart



Subject Scanning Flow Chart

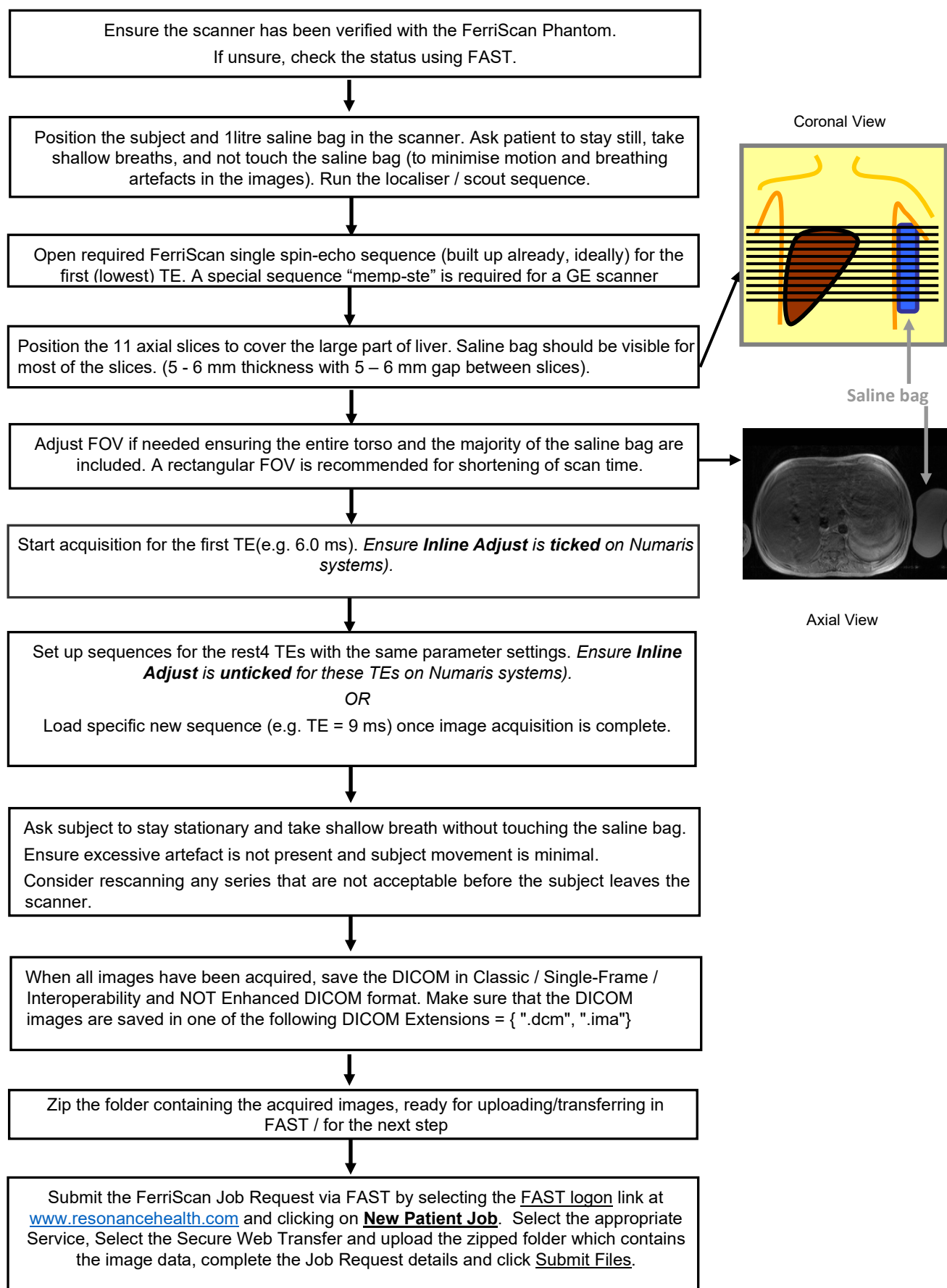


Image Data Preparation for Secure Web Transfer to Resonance Health

Note: If the image data requires de-identification of the patient information, please do so and provide only the trial-specific anonymised identifier for the patient, before compressing the image data folders.

Please DO NOT de-identify the Acquisition Date (Tag 0008,0022), the scanner make (Tag 0008, 0070), the scanner model (Tag 0008, 1090) and the device serial number (Tag 0018, 1000).

Compress or 'zip' the folders containing the patient data using a compression tool of your choice (for example WinZip™ and Stuff-It™.) To aid data transfer, create preferably one single compressed folder or alternatively five separate compressed folders (one for each TE series). It is expected the zipped file folder size is at least > 2 MB, otherwise, the required image files may not be moved/copied properly.

The data is now ready for transfer, proceed to the New Patient Job Request Form.

More details for securely transferring your image data to Resonance Health via FAST are provided under a separate document, FAST User Guide.

FerriScan Report Access via FAST

Resonance Health produces a FerriScan Report that will be made available to you on FAST for download in PDF format. FAST users will be notified via email when this becomes available.

A sample FerriScan report is provided in [APPENDIX 2: Sample Liver Iron Concentration Report](#).

APPENDIX 1: Scanner Verification Letter



01 July 2022

MRI Centre

Scanner Verification Letter

Dear Doctor

We are delighted to advise that your Verification data, (Job Number 10005000) scanned on 25 Jun 2022 on your Siemens Avanto, 123456 scanner has been successfully completed and accepted for analysis services. You may now commence patient or clinical trial scanning on this scanner.

Please note that it is a requirement that scanning parameters used to verify scanner acceptance remain the same for all patient or clinical trial scanning. Please refer to your MRI Centre Manual for further instructions.

In addition, verification of the MRI scanner is required in the following circumstances:

1. If you purchase a new scanner,
2. If you are using Clinical Trial services, reverification is required on an annual basis or as stated in specific trial requirements,
3. Following any major software or hardware upgrades to an existing scanner. For further information regarding what constitutes a major upgrade please email support@resonancehealth.com.

MRI Centres will be notified by email when their scanner is due for reverification. A new Phantom will be sent as required.

Should you or anyone else at your organisation have any questions about our service, please do not hesitate to contact us.

I would like to take this opportunity to sincerely thank you for your participation and we look forward to working with you in the future.

Kind Regards

Service Centre Manager
Resonance Health
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APPENDIX 2: Sample Liver Iron Concentration Report

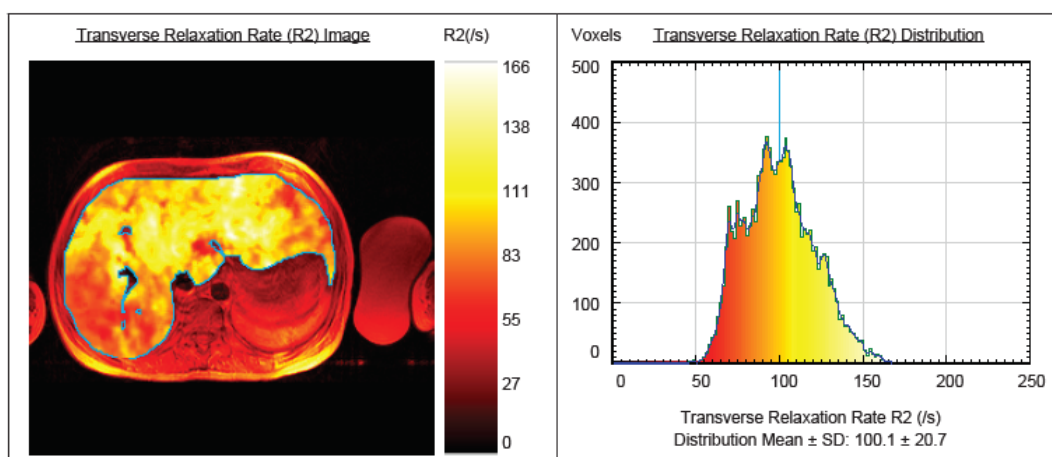


Liver Iron Concentration Report

Report No: 10000001_S12 Scan Date: 19 May 2019
 Birth Date: 10 Aug 2003 Analysis Date: 20 May 2019
 Patient Name: PATIENT, Patient
 Patient ID: ABC-12345678
 Referrer: Dr Doctor
 MRI Centre: MRI Centre Name

Average Liver Iron Concentration **6.8 mg/g dry tissue** (NR: 0.17-1.8)
121 mmol/kg dry tissue (NR: 3-33)

Normal range (NR) is taken from Bassett et. al., Hepatology 1986; 6: 24-29



Note: The area of the liver image used for the FerriScan analysis excludes large vascular structures and other image artefacts.

Table showing Liver Iron Concentration thresholds in Transfusional Iron Overload only

Extract from Olivieri et al, Blood 1997; 89, 739-61

LIC Range	Clinical Relevance
0.17-1.8 mg Fe/g dw	Normal range in non-disease patients in healthy population
3.2-7.0 mg Fe/g dw	Suggested optimal range of LIC for chelation therapy in transfusional iron loading
7.0-15.0 mg Fe/g dw	Increased risk of complications
>15.0 mg Fe/g dw	Greatly increased risk of cardiac disease and early death in patients with transfusional iron overload

A follow-up FerriScan may be required every 6 - 12 months.

Authorised by: Service Centre Manager

Resonance Health Analysis Services Pty Ltd

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APPENDIX 3: Glossary

CD	Compact Disc
cm	Centimetre
DICOM	Digital Imaging and Communications in Medicine
DOB	Date of Birth
DVD	Digital Video Disc
FAST	FerriScan Analysis Service Tracking system
FAQ	Frequently Asked Questions
FOV	Field of View
ID	Identification
kg	kilogram
mm	millimetre
MRI	Magnetic Resonance Imaging
ms	Millisecond
SNR	Signal Noise Ratio
No.	Number
PACS	Picture Archiving and Communication System
PDF	Portable Document Format
Pty Ltd	Proprietary Limited
R_2	Proton Transverse Relaxation Rate
RHAS	Resonance Health Analysis Services Pty Ltd
RF	Radio Frequency
RFOV	Rectangular Field of View
ROI	Region of Interest
SAR	Specific Absorbed Rate
T	Tesla
T_2	Proton Transverse Relaxation Time Constant
TE	Echo Time
TR	Repetition Time
USA	United States of America

APPENDIX 4: Frequently Asked Questions

What is FerriScan?

FerriScan is a non-invasive MRI-based technique for the accurate measurement of liver iron concentrations (LIC). It is recognised as the new 'gold standard' for measuring body iron stores. It is clinically proven to have high sensitivity and specificity for the measurement of LIC over the entire range encountered in clinical practice.

Table 1: Liver Iron Concentration Thresholds and Associated Risks (1.5T)

LIC threshold (mg Fe/g dry weight)	Clinical relevance	FerriScan Sensitivity (95% CI)	FerriScan Specificity (95% CI)
1.8	Upper 95% of normal	0.94 (0.86-0.97)	1.00 (0.88-1.00)
3.2	Suggested lower limit of optimal range for LICs for chelation therapy in transfusional iron loading	0.94 (0.85-0.98)	1.00 (0.91-1.00)
7.0	Suggested upper limit of optimal range for LICs for transfusional iron loading and threshold for increased risk of iron-induced complications	0.89 (0.79-0.95)	0.96 (0.86-0.99)
15.0	Threshold for greatly increased risk for cardiac disease and early death in patients with transfusional iron overload	0.85 (0.70-0.94)	0.92 (0.83-0.96)

The risks associated with each LIC threshold are taken from Olivieri and Brittenham, *Blood* 1997: 89, 739-61.

The sensitivity and specificity of FerriScan measurements for discrimination of needle biopsy iron assay values above the clinically important LIC thresholds are taken from St Pierre *et al. Blood* 2005: 105, 855-61.

Table 2: Liver Iron Concentration Thresholds and Associated Risks (3.0T)

LIC threshold (mg Fe/g dry weight)	Clinical relevance	FerriScan Sensitivity (95% CI)	FerriScan Specificity (95% CI)
1.8	Upper 95% of normal	1.00 (0.92-1.00)	1.00 (0.54-1.00)
3.2	Suggested lower limit of optimal range for LICs for chelation therapy in transfusional iron loading	0.98 (0.85-0.98)	0.91 (0.59-1.00)
7.0	Suggested upper limit of optimal range for LICs for transfusional iron loading and threshold for increased risk of iron-induced complications	0.90 (0.73-0.99)	1.00 (0.85-1.00)
15.0	Threshold for greatly increased risk for cardiac disease and early death in patients with transfusional iron overload	1.00 (0.77-1.00)	0.97 (0.86-0.99)

The risks associated with each LIC threshold are taken from Olivieri and Brittenham, *Blood* 1997: 89, 739-61.

The sensitivity and specificity of FerriScan analysis based on 3.0T protocol with FerriScan 1.5T LIC result as a reference standard for the clinically important LIC thresholds are taken from an internal report (to be published).

FerriScan comprises of a MRI protocol combined with an offline quality assured data analysis service, which uses a patented technology for processing the MR images to generate the LIC result. Data is acquired on 1.5 T or 3.0T (equipped with dual transmission system) MRI scanners. Each scanner is tested with a set of standards (FerriScan Phantom) before patient measurements are made.

Patients are required to spend approximately 10 minutes in the MRI scanner. No invasive procedures are required, and no contrast agent is administered. The raw image data are then transmitted electronically to Resonance Health through a secure internet link. A LIC report is made available through the secure link usually within two business days of submitting the raw data.

Resonance Health is certified to the international quality standard ISO 13485 to ensure the company consistently meet customer and regulatory requirements applicable specifically to medical devices.

FerriScan has gained regulatory clearance from the FDA (USA), is ARTG included (Australia) and bears the CE marking (Europe). In 2017 Resonance Health processed the 50000th FerriScan analysis and the service is now available in 33 countries.

How does FerriScan work?

FerriScan is based on the principle of measuring and imaging proton transverse relaxation rates (R_2) in liver tissue. Liver R_2 has been shown to be highly sensitive and specific to liver iron concentration.^{1,2} Measurements are achieved through the acquisition of a series of single spin echo images with a range of spin echo times. Patients are scanned with a bag of normal saline, which acts as an external reference for detection of signal gain changes. After transmission of the raw data to Resonance Health, a series of image pre-processing steps is executed in order to take into account image background noise, gain drift between images, breathing motion artefacts, and RF signal intensity variation.

The series of images is then analysed to generate an R_2 value for each voxel of a liver slice and hence an R_2 image of the liver. The mean R_2 value within the liver is then used to yield a mean liver iron concentration using a calibration curve that has been determined through the measurement of liver R_2 and needle biopsy liver iron concentration in initially 105 human subjects¹ and verified more recently with 233 human subjects.³ The expansion of FerriScan protocol from 1.5T to suitable 3T MRI scanners has been developed using the 1.5T FerriScan as a reference standard reporting the 1.5T FerriScan equivalent liver iron concentration (LIC).

³

¹St. Pierre, T.G., Clark, P.R., Chua-anusorn, W., Fleming, A.J., Jeffrey, G.P., Olynyk, J.K., Pootrakul, P., Robins, E., and Lindeman, R. (2005) Non-invasive measurement and imaging of liver iron concentrations using proton magnetic resonance. *Blood*. 105, 2. 855-861.

²Clark, P.R., Chua-anusorn, W., and St. Pierre, T.G. (2003) Proton transverse relaxation rate (R_2) images of liver tissue: mapping local tissue iron concentrations with MRI. *Mag. Reson. Med.* 49, 572-575.

³St. Pierre, T.G., Beshlawy, A.E., Elalfy, M., Jefri, A.A., Zir, K.A., Daar, S., Habr, D., Kriemler-Krahn, U., and Taher, A. (2010) Multicentre validation of spin density projection assisted R_2 -MRI for the non-invasive measurement of liver iron concentration. Abstract presented at ASH, Orlando, USA 4-7 December 2010.

³Internal study report, 2022, to be published.

Do we need any new software or hardware?

FerriScan can be set up on most 1.5 T and 3.0 T (equipped with dual transmission system) MRI scanners (Philips, Siemens or GE). GE scanners with “Scantool 14” (or above) platform are suitable. Centres using older GE system may need to contact their GE representative to obtain a special pulse sequence called “memp_ste”. There is no requirement for you to purchase any additional hardware or software.

What is a FerriScan Phantom?

The FerriScan Phantom is a sealed pack of 15 vials containing 15 different concentrations (0 mM to 3.2 mM) of manganese chloride ($MnCl_2$) solution in 0.1% hydrochloric acid (HCl). The concentrations are selected to provide a range of R_2 values commensurate with those encountered in measurements of the liver. The FerriScan Phantom is supplied as an outer box containing the “Instructions for Use: FerriScan Phantom” and a sealed inner box containing vials of $MnCl_2$ solutions. The inner box should never be opened. The inner box should be scanned as part of the MRI scanner validation procedure. A FerriScan Phantom must be scanned on every MRI scanner to be used for FerriScan, prior to scanning any patients, to verify the correct scanner configuration.

APPENDIX 5: FerriScan Scanner Specific Setup Instructions

Template

- Locate correct sequence as a template
- T1 or T2 weighted brain/abdominal Spin Echo (SE) Sequence for Siemens and Philips scanners
- MEMP-STE Sequence for GE scanners

Sequence

- Modify the template sequence as per the FerriScan protocol for the 1st TE series
- Use the saved 1st TE sequence as a template to create other 4 TE series

Phantom Scan

- Scan a phantom using the FerriScan sequences
- Upload the FerriScan DICOM images for scanner verification

Appendix 6: Liver Iron Measurement Using MRI FerriScan Protocol Summary

1. Key Scanning Parameters

The following pulse sequence parameters are used on a 1.5T or 3.0T static field scanner:

- Single Spin Echo (SE) or “**memp-ste**” for GE. Do **NOT** use Turbo Spin Echo (TSE) or Fast Spin Echo (FTE) or Gradient Echo (GRE) sequence
- TR: 1000ms
- TE: 6, 9, 12, 15, and 18 ms (1.5T) or 5-6, 7, 9, 11, and 13 ms (3.0T)
- FOV: 400×300 mm or bigger subject to patient size
- Acquisition Matrix Size: 256 x 192
- Slice Number: 11
- Slice Thickness: 5.0 to 6.0 mm
- Slice Gap: 5.0 to 6.0 mm (real gap, after taking out the slice thickness)
- Half-Scan (Partial Fourier in Phase or Fractional NEX)
- Base Resolution: 256
- Axial imaging plane
- Phase Encoding Direction: A-P (Set to COL, **not** ROW)
- Scan Time: targeting at < 2 min per TE
- Free breathing for patient scan, however ask the patient to take shallow rather than deep breaths
- CONSISTENCY is very important

2. External Reference – Saline Bag

At least one bag of infusion normal saline solution **MUST** be included in every scan and at least partially visible within the FOV.

Appendix 7: GE Scanner Setup

NOTE: 3T scanners equipped with dual transmission system can be used for FerriScan protocol (**NOT with single transmission system**).

1. Pulse Sequence

To achieve the required parameters for FerriScan, your GE machine must use a special sequence type (PSD) called "memp-ste". This PSD is an undocumented feature included in current commercial release (scantools 14, 15). It does not appear automatically in the familiar Imaging Sequence selector pane of the Protocol Builder. To access memp-ste you must type memp-ste in the PSD type in box at the bottom of that window.

Do **NOT** use Turbo Spin Echo (TSE) or Fast Spin Echo (FTE) or Gradient Echo (GRE) sequence.

2. Critical Scanning Issues

- Do not select an interleaved sequence as this will create 2 concatenated sequences and double the acquisition time.
- Use a localizer sequence to create axial, sagittal and coronal localizers, and multi-plane prescription of the axial spin echo sequences. This will assist you in positioning and adjusting the field of view (FOV) appropriately.
- The FOV can be altered depending on the size of the patient, but always make it big enough to include all of the abdomen and at least part of the saline bag.
- You can use a rectangular field of view, but you must have square pixels. Therefore, the aspect ratio of the field of view and the matrix must be equal.
- All geometric and position parameters must remain constant across all the series within an examination.

3. General Scanning Concepts

The parameters listed on the following page have proven successful for many sites using the GE supplied 'memp-ste' pulse sequence. These parameters are using full echoes with 75 % Fourier averaging. The bandwidth and NEX can be lowered, if necessary, provided a single spin echo with TE 6ms for 1.5T and TE 5.0-6.0ms for 3T, can be achieved using full echoes. Likewise, a slice thickness of up to 6.0 mm is also acceptable. Please note however that all parameters (except TE) must remain the same over all 5 image series.

4. Explicit Sequence Parameter settings

Note: These settings are viewed in the "old" model. In the modern interface the same parameters are accessible in slightly different page combinations.

APS	Turned ON for the 1 st TE (6 ms for 1.5T or 5-6 ms for 3T), but must be turned OFF for all other echo times*
RF1	90
RF2	180
TR	1000ms
Number of Echoes	1
TE	6.0, 9.0, 12.0, 15.0, 18.0 ms (1.5T) or 5.0-6.0, 7.0, 9.0, 11.0, 13.0 ms (3.0T) in separate sequences

Short TE Flag	1
Bandwidth	± 31 - 62 kHz** (or smaller if possible)
Vbw	ON
FOV	40 x 30cm (3/4 phase FOV)
Matrix Size	256 x 192 (Square pixels)
Slice Thickness	6 mm
Slice Gap	5-6 mm
NEX	0.5 - 0.75***
EDR	On
Phase Encoding	A - P (Set to COL, not ROW)

* This is to lock the receiver gain settings across the series. Excite HDx systems will have a different way of achieving this through the use of the new Smart Prescan function. Receiver control is critical.

** Bandwidth may depend on gradient power but adjust it to allow an echo time of 6.0ms (1.5T) or 5.0-6.0 (3T) to be acquired and keep it the same for all TE values. Use the lower band when possible, to improve SNR.

*** The smallest selectable NEX value will depend on your software and gradient levels; set it after selecting the bandwidth and TE of 6.0ms (1.5T) or 5.0 – 6.0 (3T). You must use the same NEX value for all TE values.

Appendix 8: PHILIPS Scanner Setup

NOTE: 3T scanners equipped with dual transmission system can be used for FerriScan protocol (**NOT with single transmission system**).

1. Pulse Sequence

Single Spin Echo (SSE or SE) sequence can be created using a T1 or T2 weighted brain/abdominal sequence as a template with modified scanning parameters required. Name the sequence as FerriScan.

Do **NOT** use Turbo Spin Echo (TSE) or Fast Spin Echo (FTE) or Gradient Echo (GRE) sequence

2. Explicit Sequence Parameter settings

Note: These settings are viewed in the “old” model. In the modern interface the same parameters are accessible in slightly different page combinations.

Initial	
Coil selection	SENSE-body
Element section	1234
FOV RL (mm)	400 (This is to be made larger for patients)
AP (mm)	300 (This equates to a RFOV of 75%. For patients a lower percentage may be used to reduce scan time, but all of the skin surfaces and most of the saline bag must be visible)
Voxel size RL (mm)	1.56 (for a FOV of 400mm, subject to change when a different FOV is used as per formula†)
AP (mm)	1.56 (for a FOV of 400mm, subject to change when a different FOV is used as per formula†)
Stacks	1
Slice thickness (mm)	5.0 – 6.0
Foldover direction	AP (Set to COL, not ROW)
TE (ms)	6.0, 9.0, 12.0, 15.0, 18.0 ms (1.5T) or 5.0-6.0, 7.0, 9.0, 11.0, 13.0 ms (3.0T) in separate sequences
TR (ms)	1000
NSA	1
Preparation phases	Auto
Images	Magnitude

Geometry	
Coil selection	SENSE-body
Element section	1234
Connection	D
Dual Coil	No
CLEAR	No
FOV RL (mm)	400
RFOV (%)	75
Voxel size RL (mm)	1.56 (for a FOV of 400mm, subject to change when a different FOV is used as per formula†)
AP (mm)	1.56 (for a FOV of 400mm, subject to change when a different FOV is used as per formula†)

Foldover suppression	No
Matrix scan	256
Matrix reconstruction	256
SCAN PERCENTAGE	100
SENSE	No
k-t BLAST	No
Stacks	1
Type	Parallel
Slices	11
Slice thickness	5
Slice gap	5
Slice orientation	Trans
Foldover direction	AP (Set to COL, not ROW)
Fat shift direction	L
Minimum number	1
Slice scan order	Interleaved
Large table movent	No
Plan Align	No
Rest Slab	0

Contrast	
Scan mode	MS
Technique	SE
Modified SE	No
Acquisition Mode	Cartesian
Fast Imaging mode	None
Echoes	1
Partial echo	No
TE ms	6.0, 9.0, 12.0, 15.0, 18.0 ms (1.5T) or 5.0-6.0, 7.0, 9.0, 11.0, 13.0 ms (3.0T) in separate sequences
Flip Angle	90
TR	User defined
ms	1000
Half scan	Yes
Water Fat Shift	user defined
Pixels	0.55 - 0.6 (1.5T or 3.0T)
Shim	AUTO
(Fat suppression) SPIR	No
SPAIR	No
Water suppression	No
BB pulse	No
Proset	No
MTC	No
Diffusion mode	No
SAR mode	Moderate
B1 mode	Default
PNSmode	Low
Gradient mode	Maximum
SofTone mode	No

Motion	
Cardiac synchronisation	No
Respiratory compensation	No
Flow compensation	No
NSA	1

Dyn/Angio	
Manual Start	No
Dynamic Study	No

Post/Proc	
Preparation phases	Auto
Manual offset freq.	No
MIP/MPR	No
Images	M
Autoview images	M
Reference tissue	Liver
Preset Window	Soft
Reconstruction mode	Immediate
Save Raw data	No
Hard copy protocol	No
Geometry correction	No

Info Window	
SAR w/kg /level	<0.1/0
PNS %/level	17%/normal
Scan duration per TE	1:40 (may vary slightly depending on RFOV)
Act TR	1000
Act TE ..	6,9,12,15,18 (1.5T) or 5-6,7,9,11,13 (3T)
ACQ voxel MPS mm	1.56/1.56/5.0 (for a FOV of 400mm, subject to change when a different FOV is used as per formula‡)
REC voxels MPS	1.56/1.56/5.0 (for a FOV of 400mm, subject to change when a different FOV is used as per formula‡)
Scan percentage	100
Packages	1
Min slice gap	0.5 mm
Max slices	95
WFS	0.55–0.6 pixels 364-395 Hz/pixel *
Min TR-SE	130/0/50
Relative Signal	100%

Note: *Water Fat Shift (bandwidth) must remain constant across all series, as unacceptable changes in signal intensity, image geometry and chemical shift can occur when this parameter is allowed to vary. On Nova gradients it has been noted that with the Water Fat Shift defined as 0.598 (0.6), the Info page will show WFS as 0.551 pixels for TE06, and 0.598 for all other echo times when the WFS should be adjusted to 0.55 for all TEs. ‡ Voxel Size = FOV/256 (for example, if the FOV is 400 mm then the Voxel Size should be set at 400/256 = 1.5625.

Appendix 9: SIEMENS Scanner Setup – Magnetom Vision

NOTE: 3T scanners equipped with dual transmission system can be used for FerriScan protocol (NOT with single transmission system).

1. Pulse Sequence

Single Spin Echo (SSE or SE) sequence can be created using a T1 or T2 weighted brain/abdominal sequence as a template with modified scanning parameters required. Name the sequence as FerriScan. Please create a protocol group called “FerriScan” and store the Spin echo sequence and a scout sequence.

Do **NOT** use Turbo Spin Echo (TSE) or Fast Spin Echo (FTE) or Gradient Echo (GRE) sequence

2. Storing a Scout Sequence

The standard Siemens liver scout protocol will allow a fast positioning guide.

From the Siemens side, under the “Abdomen_routine group”, select the scout protocol, and click “change” to enter protocol change. Click “save” and save the protocol calling it “Scout”, in the FerriScan group.

3. Explicit Sequence Parameter settings

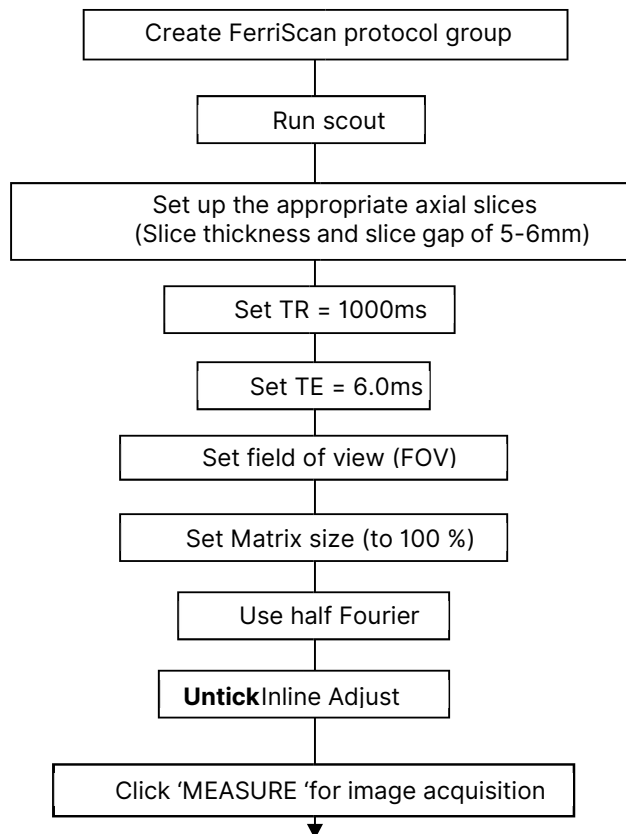
Note: These settings are viewed in the “old” mode of Magnetom Vision. In the modern interface the same parameters are accessible in slightly different page combinations.

TR	1000 ms
TE	6.0*, 9.0, 12.0, 15.0, 18.0 ms (1.5T) or 5-6, 7, 9, 11, 13 ms for 3.0T in separate sequences
Flip Angle	90 degrees
No. Slices	11
Thickness	5 – 6 mm
Orientation	Transverse
Excit. Order	Interleaved
Dist Fact	1.00
Matrix:	100 % 256*192
Ph-OS	0%
HF (Half Fourier)	On
Read-OS	On
FOV	400 mm
Rect. FOV	6/8
No. Acq.	1
No. Meas.	1
Interpolate	Off
Phase Images	Off
Contrast Agent	Off
Trigger/Gate	Off
Filter	Off
Coil	CP Body Array
Active Array Elements	1,2,3,4
Bodyscout	No
Swap Phase Enc.	Off
Swap Select Sign	Off
Inline Adj.	On for TE = 6 ms (1.5T) or 5-6 ms (3T), off for all other series
Shim Adj.	No

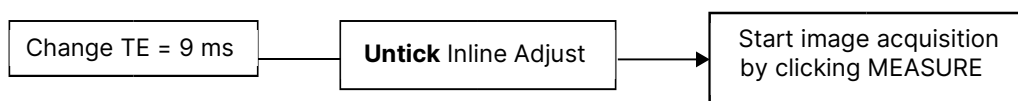
Free Slice	-
Free Sats	0
Fat Saturation	No
MT-Sat	No

*6.6 ms may be acceptable for Siemens Espree, subject to further assessment

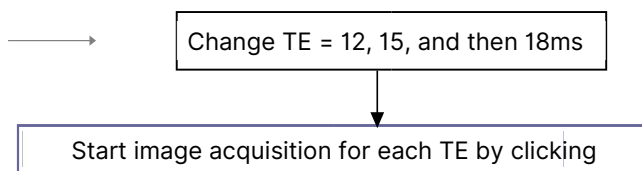
The 'Inline Adjust' function allows your machine to establish suitable gain settings on the TE=6ms (1.5T, value can be different for 3T) series and turning it off after this series will ensure that these gain settings are maintained in the remaining series.



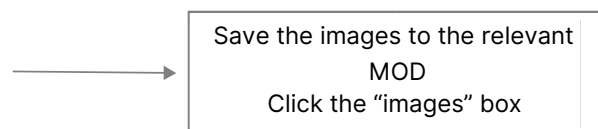
When image acquisition (1.5T sequence as examples, different 3T TE values) is complete,



When image acquisition is complete



When all images have been acquired



Appendix 10: SIEMENS Scanner Setup – Sonata

NOTE: 3T scanners equipped with dual transmission system can be used for FerriScan protocol (**NOT with single transmission system**).

1. Pulse Sequence

Single Spin Echo (SSE or SE) sequence can be created using a T1 or T2 weighted brain/abdominal sequence as a template with modified scanning parameters required. Name the sequence as FerriScan.

Do **NOT** use Turbo Spin Echo (TSE) or Fast Spin Echo (FTE) or Gradient Echo (GRE) sequence.

2. Setting up the FerriScan Sequence under the SYNGO Platform

Ensure the files are in the order of TE = 6, 9, 12, 15, and 18 ms (1.5T) or 5-6, 7, 9, 11 and 13 ms (3.0T) for scanning.

In total, 11 single spin echo images are acquired at echo times of 6, 9, 12, 15, and 18 ms (1.5T) or 5-6, 7, 9, 11 and 13 ms (3.0T), at a repetition time of 1000. Please keep to this ordering of the echo times. This is best accomplished by defining separate sequence files for each echo time and arranging them in the order given. To lessen the scan time, the images are acquired with the phase at halfFourier. Each scan takes approximately 1.5 minutes.

Once the 5 spin echo sequences are created, edit the following properties on the FerriScan_09, 12, 15, and 18 (1.5T) or 07, 09, 11 and 13 (3.0T) sequences:

Under the “Execution” subtask card, select the “Start measurement without further preparation” checkbox for all sequences. You may choose to add a voice output file, reminding the patient to lie still, relax and breathe gently. (Voice output files are site specific. See section F11 - 15 of your SyngoMR 2004A Operators Manual.

For the FerriScan_09 (1.5T) or FerriScan_07 (3.0T) to FerriScan_18 (1.5T) FerriScan_13 (3.0T) series go to the “Copy References” subtask card, select the “Copy Reference is active” checkbox. Browse the list of source protocol steps and choose FerriScan_06 (1.5T) FerriScan_05 (3.0T) as the source protocol. Choose “Measurement Parameters” as the Copy parameter group. After you have finished building the FerriScan protocol, save and export it as an EDX file for safe keeping. Update this EDX file if changes are necessary.

3. Explicit Sequence Parameter settings

Note: These settings are taken from the Parameters section of sequence control, as viewed in the “old” mode of Sonata. In the modern interface the same parameters are accessible in slightly different page combinations.

SEQUENCE Panel Settings	
Asymmetric Echo	OFF
Contrast	1
Bandwidth	275 Hz/Px, or higher (in order to achieve a TE of 6 ms for 1.5T or 5-6 ms for 3T)
Averaging Mode	Short term
Multi-slice Mode	Interleaved
Allowed Delay	0 seconds
RF Pulse Type	Fast
Gradient Mode	Fast

ROUTINE Panel Settings	
TR	1000 ms
TE	6, 9, 12, 15, 18 ms for 1.5T or 5-6, 7, 9, 11, 13 ms for 3.0T (in separate sequences).
Slices	11
Slice Thickness	5.0 – 6.0 mm
Slice Thickness	5.0 – 6.0 mm
Distance Factor	100%
Phase Encoding Direction	A – P (Set to COL, not ROW)
Phase Oversampling	0 %
FOV Read	400 mm (could be larger for big patients)
FOV Phase	75 %
Averages	1
Concatenations	1
Filter	None
Coil Elements	BO1, BO2, SP3, SP4

RESOLUTION Panel Settings	
Base Resolution	256
Phase Partial Fourier	5/8

Note: NO filtering is to be performed. The scan time for each spin-echo measurement should be approximately 1.5 min for TR 1000.

CONTRAST Panel Settings	
Averages	1
Flip Angle	90 (deg.)
Fat Suppr	None
Water Suppr	None
Magn Preparation	None
MTC	Unticked

GEOMETRY and SYSTEM Panel Settings	
Multi-slice Mode	Interleaved
Series	Interleaved

SYSTEM Panel Settings	
Gain	High

Revision Record

Version	Date	Description of Change
1.0	30 Jun 2022	Original issue, document transferred from M-9 FerriScan MRI Centre Manual.
2.0	11 Jul 2022	Correction to Verification Letter and new Sample report images

