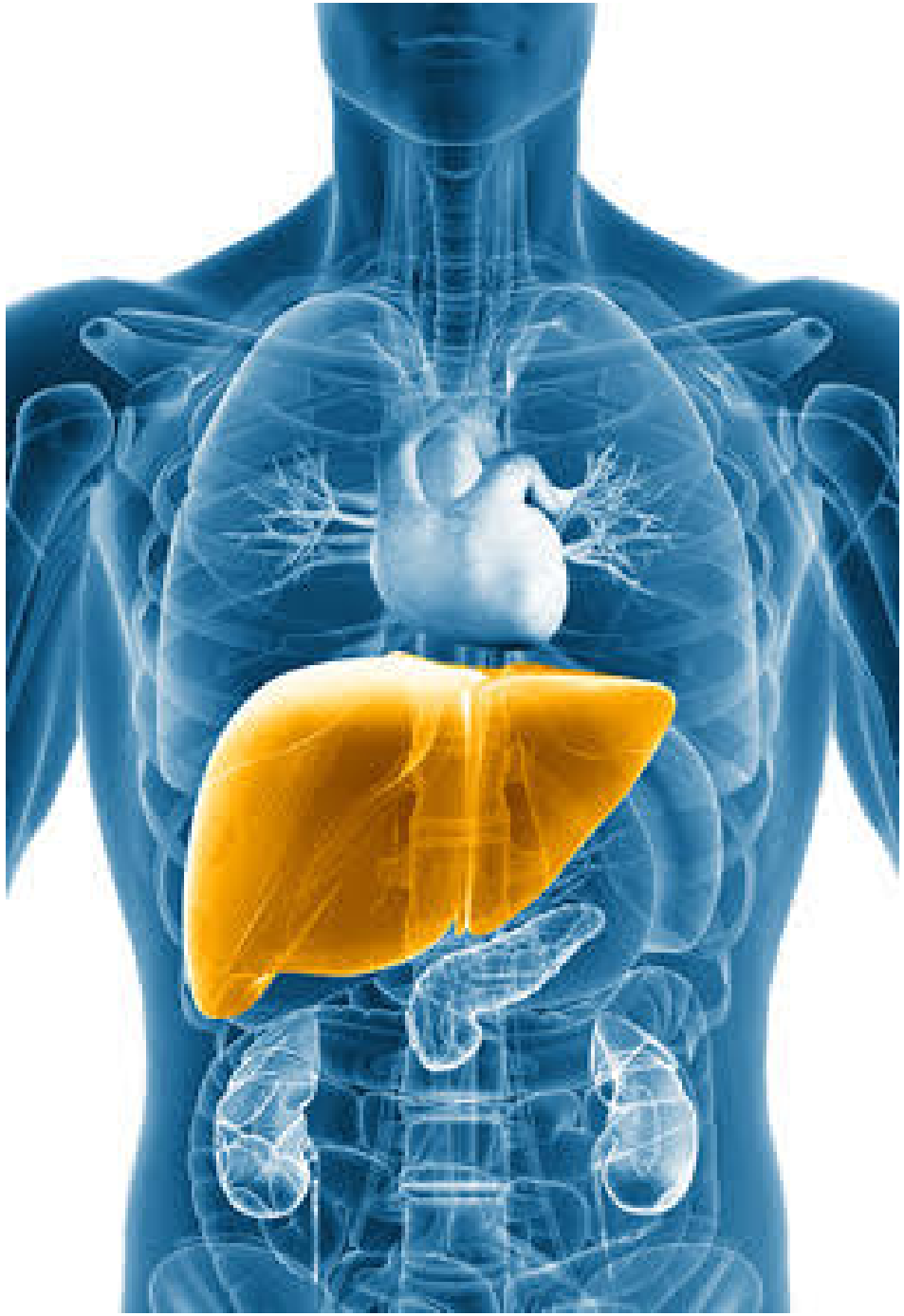

Imaging Site Training

"To evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of multiple doses of HM15136 in obese or overweight subjects with co-morbidities (a Phase 1 study)"

Study ID: HM-GCG-102
Sponsor: Hanmi Pharmaceutical

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Imaging site training agenda

- Who we are and our role in this study
- Overview of study objectives and design
- Site training plan
- MRI study kit
- Imaging workflow and sequences
- Subject positioning and FOV placement
- Good quality imaging and avoiding artifacts
- Data transfer to Antaros
- GCP training
- Next steps for site qualification

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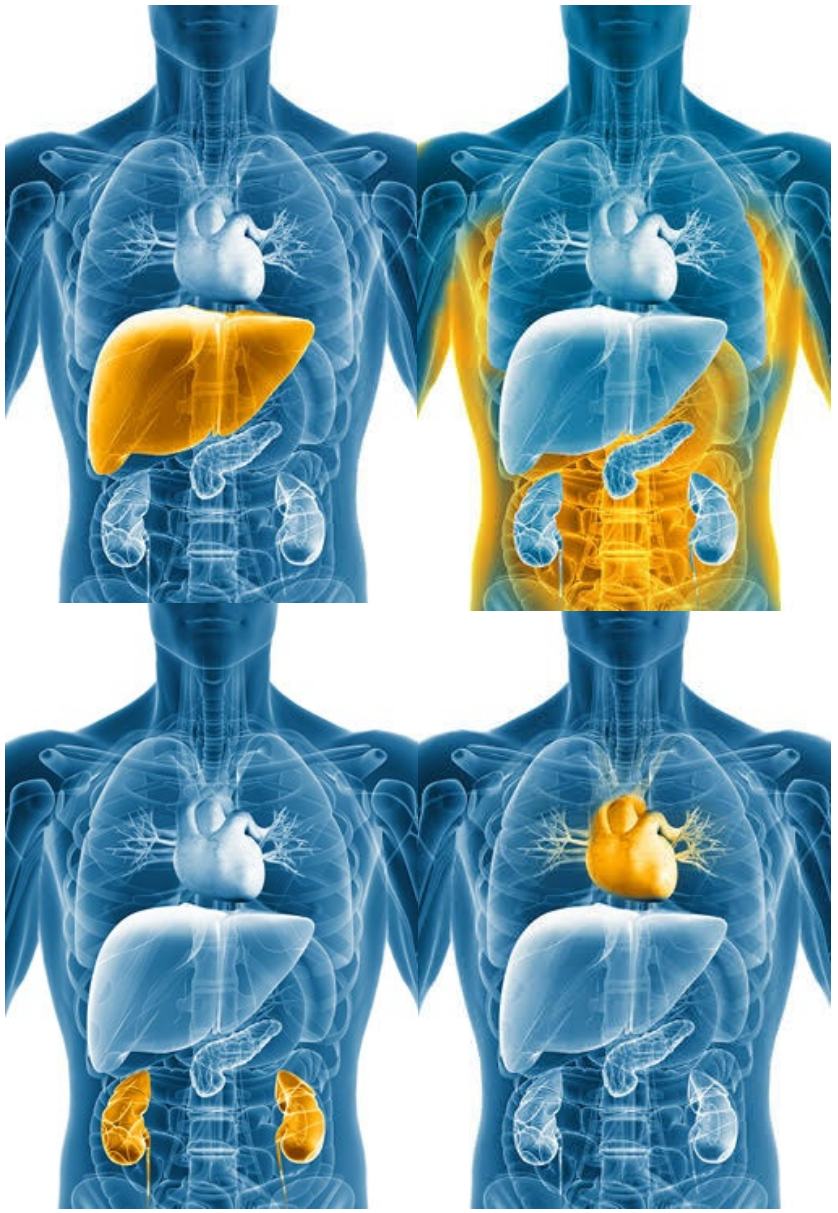
Antaros Medical
Who we are and what we do

Who we are:
- Imaging CRO founded in Aug 2014
- Based in Sweden
  - Imaging Corelab in Uppsala
  - Central office in Mölndal
- 60+ employees

What we do:
- Work with pharma companies, biotechs and academic institutions
- Work on **imaging in clinical trials** and development of new imaging techniques

What we'll do on this study:
- Responsible for the imaging on the HM-GCG-102 study
  - Design of imaging in study
  - Site set-up and training
  - Image analysis



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Study overview

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Overview of study objectives
Imaging objectives in the HM-GCG-102 study

- This is a Hanmi phase 1 study to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of multiple doses of HM15136 in obese or overweight subjects with co-morbidities

PRIMARY OBJECTIVE	-
SECONDARY OBJECTIVE	-
EXPLORATIVE OBJECTIVE	Change from baseline (Day -1) to Day 85 in MRI-PDFF and Abdominal visceral fat (VAT) $PDFF^{Day85}$ only if $PDFF^{Day-1}$ ≥10%

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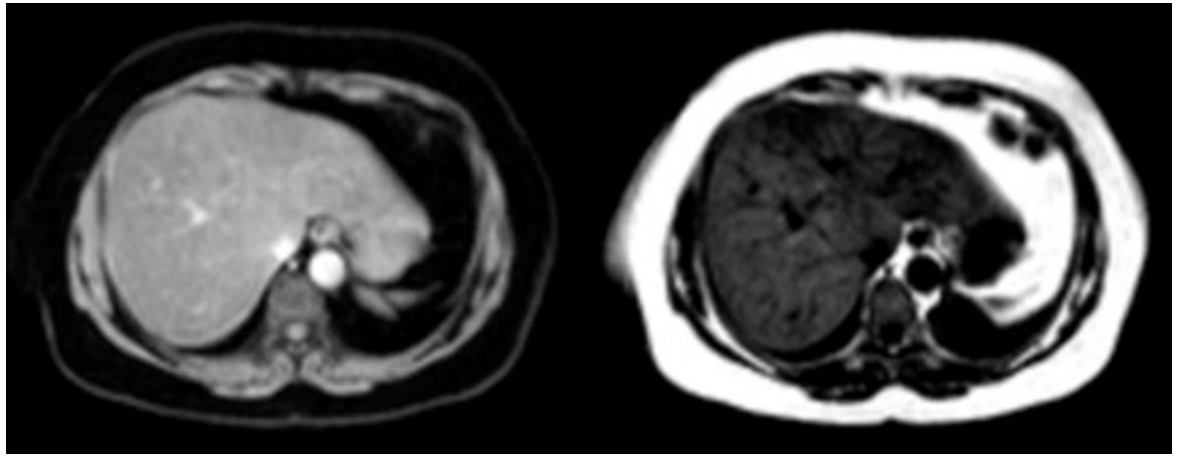
Overview of study objectives
Imaging endpoints

- We will be looking at the following liver MRI endpoints:
  - Liver fat by MRI proton density fat fraction (PDFF)
  - Abdominal visceral fat (VAT)



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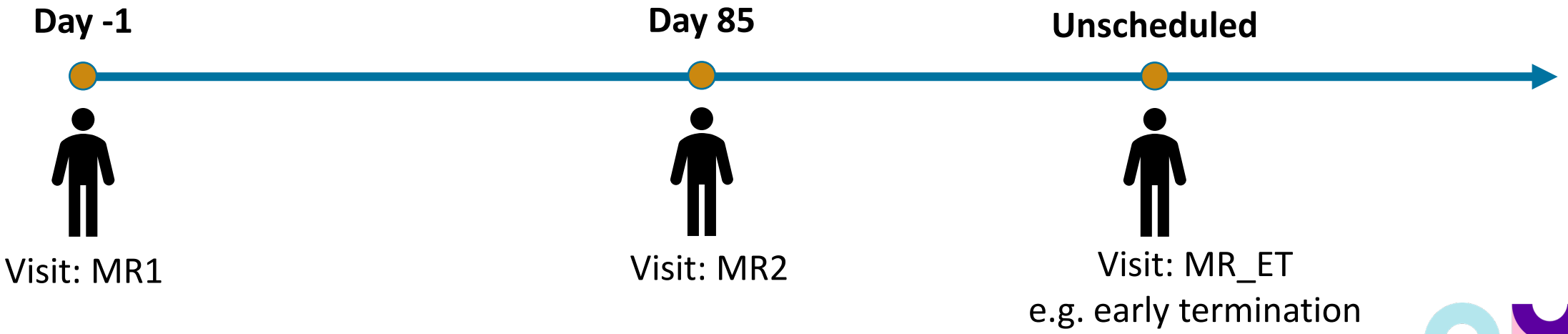
Overview of study design
Study design and planned imaging visits

- Approximately 72 subjects at one single imaging site
  - Site location: Sharp & Children's, USA
- The study will start August/September 2019
- Each subject will have 2 scans
  - Imaging visits MR1 and MR2 at Day -1 (baseline) and Day 85
  - Note 1; Possibly an unscheduled scan, e.g. in case of early termination (MR_ET)
  - Note 2; PDFF at MR2 only if fat fraction 10% or more at MR1 (VAT not affected)



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Site training and set-up

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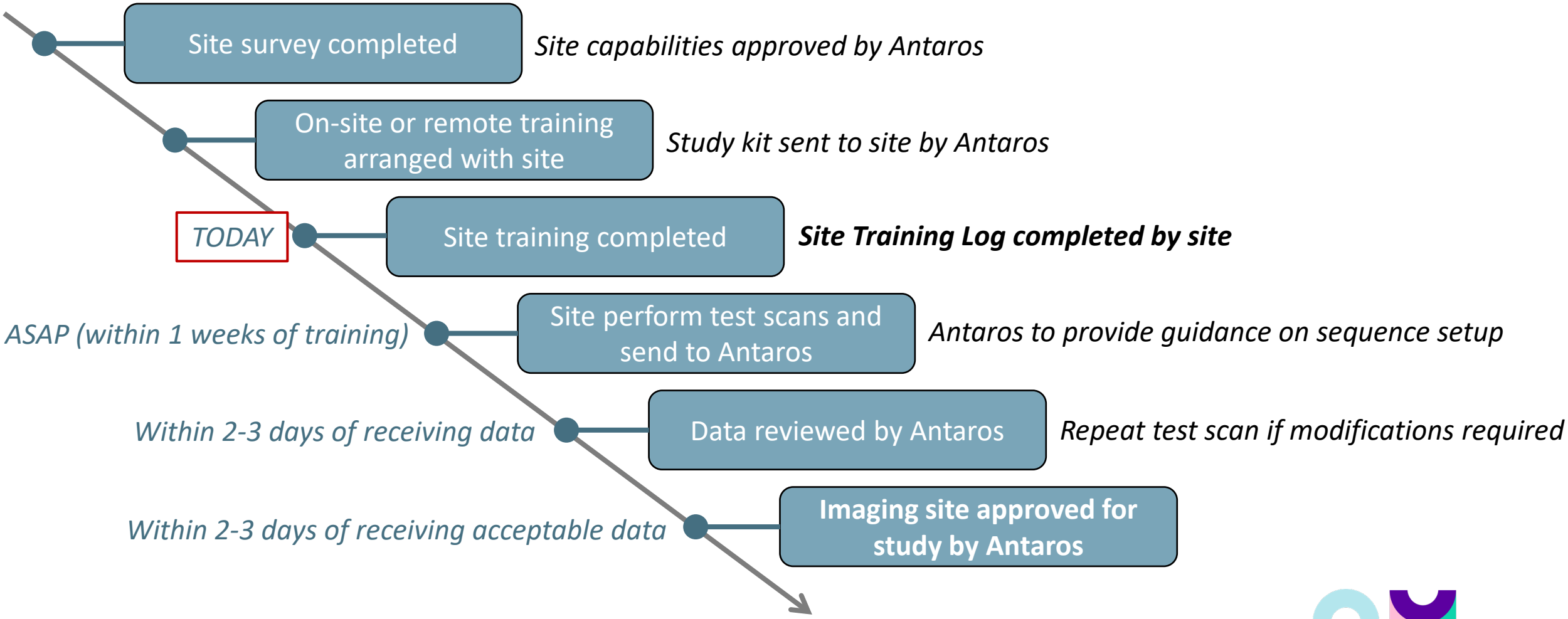
Site training and qualification plan

Steps to getting your site ready for patient scanning



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Study materials
Imaging site binder

1	Imaging Manual
2	Appendices to Imaging Manual: A – Login Details
3	Scan Log - Completed
4	Scan Log - Unused
5	Site initiation Visit / Remote Training
6	Imaging Site Training Log
7	Imaging Site Training Material (incl. GCP)

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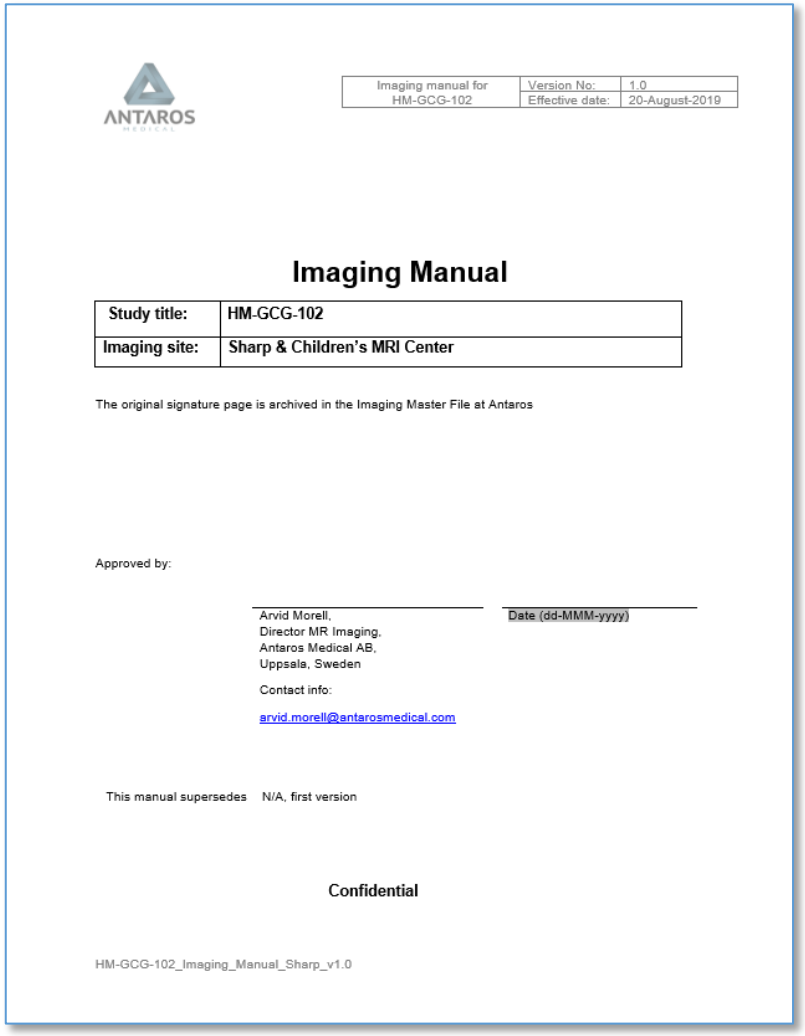
Study materials
Imaging Manual



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Imaging manual for HM-GCG-102	Version No:	1.0
	Effective date:	20-August-2019

Imaging Manual

Study title:	**HM-GCG-102**
Imaging site:	**Sharp & Children's MRI Center**

The original signature page is archived in the Imaging Master File at Antaros

Approved by:

Arvid Morell,
Director MR Imaging,
Antaros Medical AB,
Uppsala, Sweden

Date (dd-MMM-yyyy)

Contact info:

arvid.morell@antarosmedical.com

This manual supersedes N/A, first version

Confidential

HM-GCG-102_Imaging_Manual_Sharp_v1.0

Appendix A: Login details for data transfer

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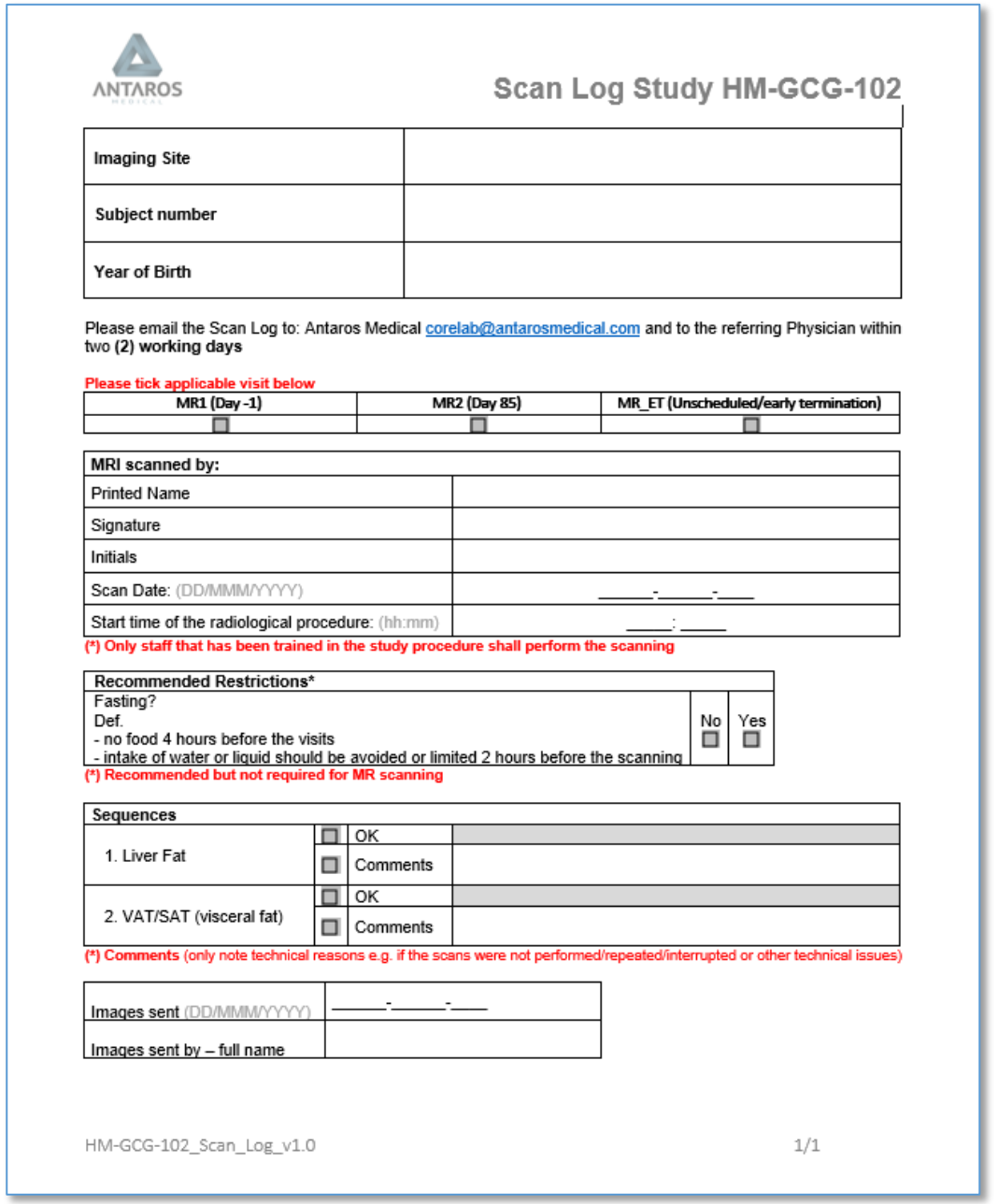
Study materials
Scan Log

Note – at follow-up visits, refer to notes on previous Scan Logs for each subject to ensure consistent imaging across visits



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Scan Log Study HM-GCG-102

Imaging Site	
Subject number	
Year of Birth	

Please email the Scan Log to: Antaros Medical corelab@antarosmedical.com and to the referring Physician within two **(2) working days**

Please tick applicable visit below

MR1 (Day -1)	MR2 (Day 85)	MR_ET (Unscheduled/early termination)
☐	☐	☐

MRI scanned by:	
Printed Name	
Signature	
Initials	
Scan Date: (DD/MMM/YYYY)	_____-_____-____
Start time of the radiological procedure: (hh:mm)	____:____

(*) Only staff that has been trained in the study procedure shall perform the scanning

Recommended Restrictions*		
Fasting? Def. - no food 4 hours before the visits - intake of water or liquid should be avoided or limited 2 hours before the scanning	No ☐	Yes ☐

(*) Recommended but not required for MR scanning

Sequences		
1. Liver Fat	☐ OK	
	☐ Comments	
2. VAT/SAT (visceral fat)	☐ OK	
	☐ Comments	

(*) Comments (only note technical reasons e.g. if the scans were not performed/repeated/interrupted or other technical issues)

Images sent (DD/MMM/YYYY)	_____-_____-____
Images sent by – full name	

HM-GCG-102_Scan_Log_v1.0 1/1

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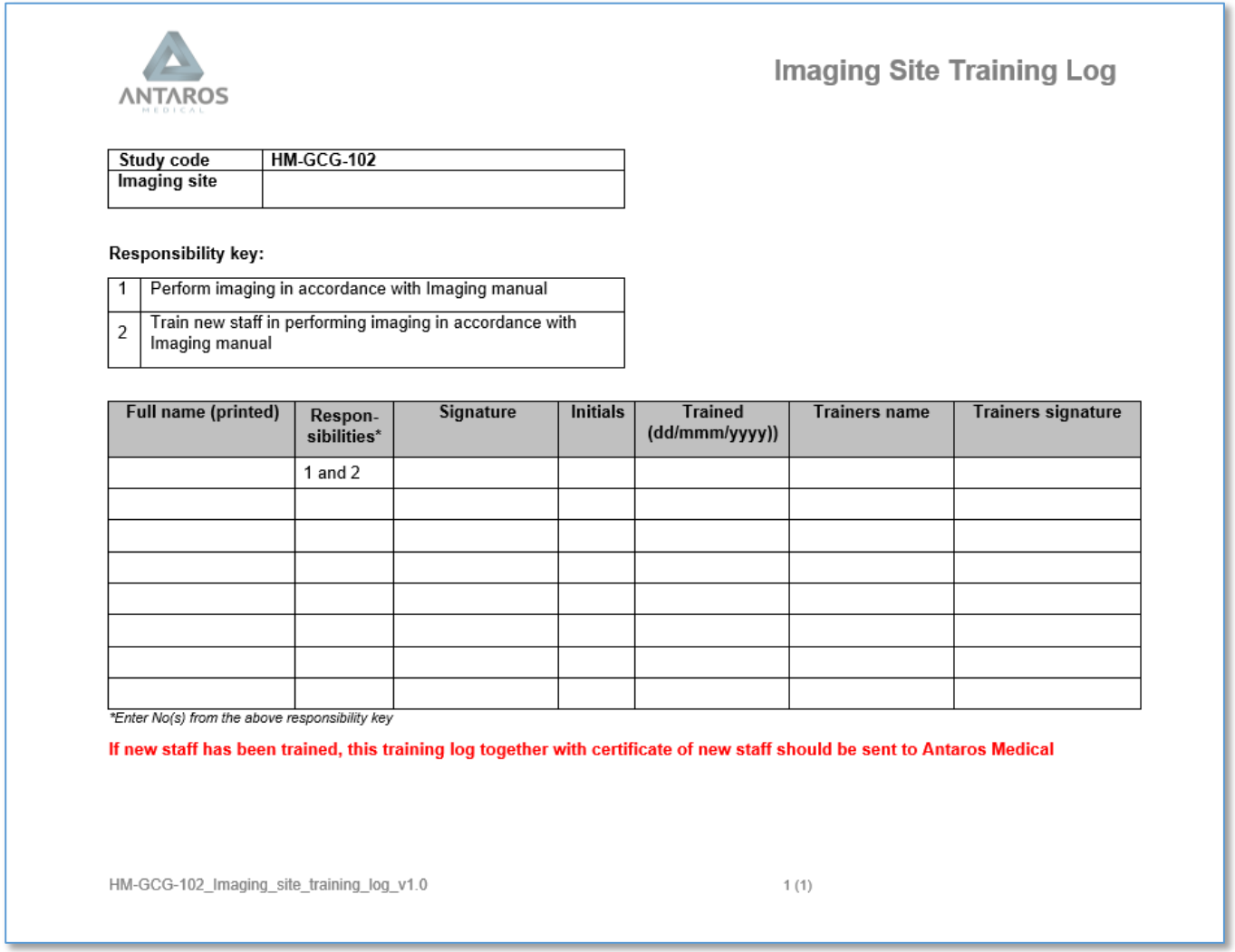
Study materials
Site Training Log



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Imaging Site Training Log

Study code	**HM-GCG-102**
Imaging site	

Responsibility key:

1	Perform imaging in accordance with Imaging manual
2	Train new staff in performing imaging in accordance with Imaging manual

Full name (printed)	Respon-sibilities*	Signature	Initials	Trained (dd/mmm/yyyy))	Trainers name	Trainers signature
	1 and 2					

**Enter No(s) from the above responsibility key*

If new staff has been trained, this training log together with certificate of new staff should be sent to Antaros Medical

HM-GCG-102_Imaging_site_training_log_v1.0 1 (1)

Note – study trained personnel can train others! In this case, please complete and forward a Site Training Log to Antaros

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The imaging workflow

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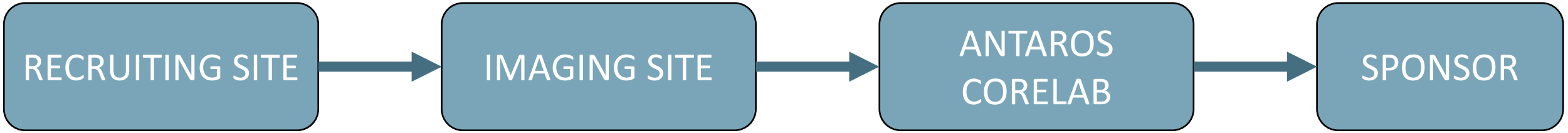
Imaging workflow
General workflow for imaging



- Refers patients to the imaging site
- Obtains informed consent

- Performs subject imaging according to Imaging Manual
- Transfers image data to Antaros

- Performs image QC checks
- Analyses image data
- Transfers results to the Sponsor at end of trial

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Imaging workflow
Overview of subject imaging visit

Informed consent performed at recruiting site

BEFORE THE SCAN

- Patient arrives at the imaging facility
- Perform routine MRI safety questionnaire
- Complete Scan Log during the visit
- *Confirm that patient has not eaten within 4 hours or consumed liquid within 2 hours*

PERFORMING THE SCAN

- Load the pre-prepared study measurement program/scan card
- Position subject supine in scanner, head first, knees on cushion
- Perform scans:
  - Liver survey scans during BH
  - Liver fat (PDFF) scan during BH
  - VAT/SAT volume scan during BH
- Complete study Scan Log

Use scanner and coil selected for this study

All breath holds at end-expiration

AFTER THE SCAN

- Export data
- Code the data
- Data transfer…

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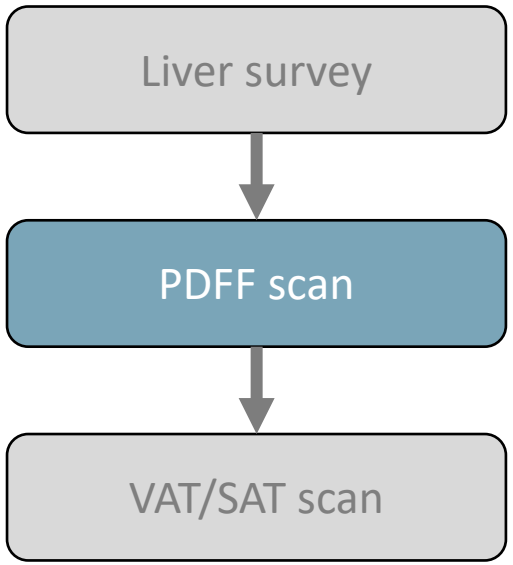
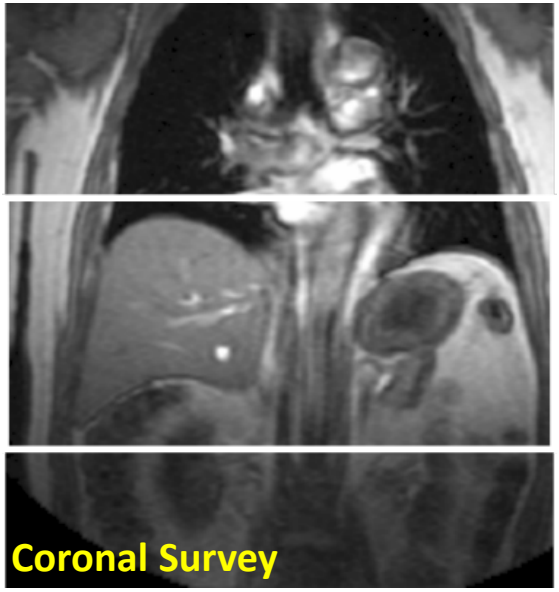
Imaging workflow
Running the imaging sequences – Liver fat (PDFF)



All scans acquired at end-expiration breath-hold

Do not change the FOV or angle of the scans except as specified in the Imaging Manual



NOTE – PDFF maps should be reconstructed and transferred alongside image data

- **Axial** 3D PDFF scan
  - IDEAL-IQ (GE) / mDIXON-Quant (Philips) / LiverLab (Siemens)
  - Or custom Antaros sequence for your site (only if indicated at training for your site)
- **Approximately 15 slices with 10 mm** thickness (alternatively 30 slices with 5 mm thickness)
- Position the axial scan to cover **as much liver as possible (**as shown)
  - *If the entire liver does not fit inside the slab,* ***cut equal amounts of liver in both foot and head directions***
- Run the scan in a **single breath-hold**
- Following scan, check image to ensure successful breath-hold
  - If not, repeat the scan and make a note in the Scan Log

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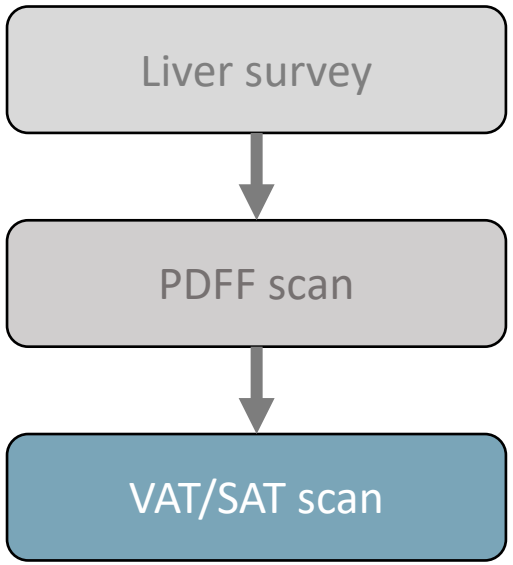
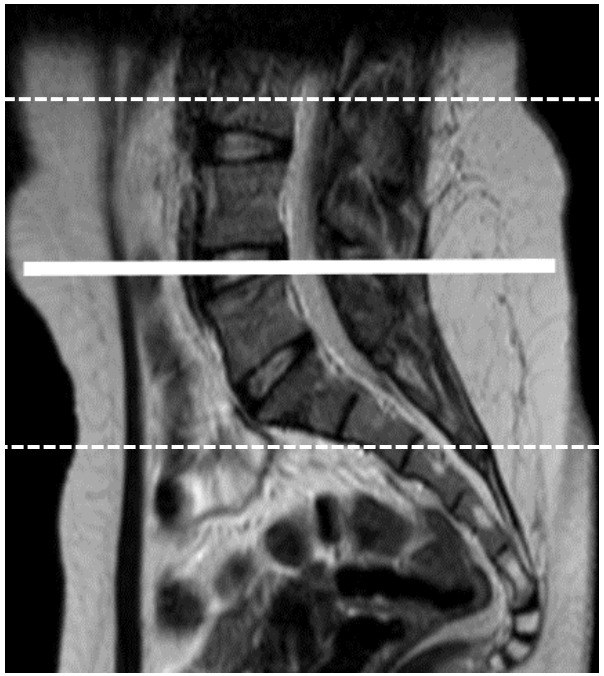
Imaging workflow
Running the imaging sequences – Adipose tissue volume (L)



All scans acquired at end-expiration breath-hold



Do not change the FOV or angle of the scans except as specified in the imaging manual

- Run a sagittal survey of the lumbar spine if not already included in the previous surveys
- Position the axial water/fat scan **3D LAVA-FLEX(GE), mDIXON(Philips), eDIXON (Siemens)** centered on the L4-L5 interface as shown in the figure.
- 20 slices with 10 mm, alternatively 40 slices with 5 mm thickness
  - ***Use 450 mm FOV (or larger if available), make sure to avoid fold-over artifacts.***
  - In there's foldover anyway, make a note in the Scan Log
  - The same number of slices and slice thickness **MUST** be used at follow-up scans
- Perform the scan in a single breath-hold
- Following scan, check image to ensure successful breath-hold
  - If not, repeat the scan and make a note in the Scan Log

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Good quality imaging and avoiding artifacts
Common issues and how to deal with them

- Avoid errors in imaging FOV placement by following the instructions in the imaging manual
- Respiration artifacts:
  - If obvious respiration artifacts occur, redo the scan and make a note in the Scan Log
  - If a patient has problems with breath-holding, try asking them to do very shallow breathing instead to minimize artifacts
- Ensure settings are consistent between visits for the same subject
  - Refer to previous Scan Logs for notes on subject-specific changes to the imaging protocol

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Data transfer

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Data transfer
Anonymization/coding of the image data

- Verify that the scan has been sent to PACS
- In the patient browser, modify the following details:
    - Substitute the **Subject Name** with the study 6-digit **Subject ID**, e.g. 101001
        - For test scans, use “Test Person 1”
    - Substitute the subject’s **Patient ID** with the **Visit Code**
    - MR1, MR2 or MR_ET (early termination)
        - For test scans, use “Test scan”
    - Remove the **Accession Number**
    - Remove the **Referring Physician**
    - Replace the **month and day in the subject’s date of birth** with 01-Jan
      (e.g. a subject with date of birth 29/10/1956 becomes 01/01/1956)
- Note – this information (e.g. name, date of birth, etc.) MUST be removed from images and image headers prior to transfer to Antaros

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Data transfer
Transfer of data to Antaros

- Following coding of the data, export the images in DICOM format from the scanner
- Transfer the images to a computer and pack the data in a zip file
- Upload the data to Sharepoint
  - See Appendix A of the Imaging Manual for instructions
  - In case of image transfer issues, transfer data by courier on a CD
- The **Scan Log** should be transferred alongside each scan
- Images should be transferred to Antaros as soon as possible but no later than **48 hours after the scan**
- An e-mail notification will be sent to Antaros Medical and to the Principal Investigator by the system to alert them that new data is available
- For general enquires and help for this study, please e-mail Antaros at corelab@antarosmedical.com

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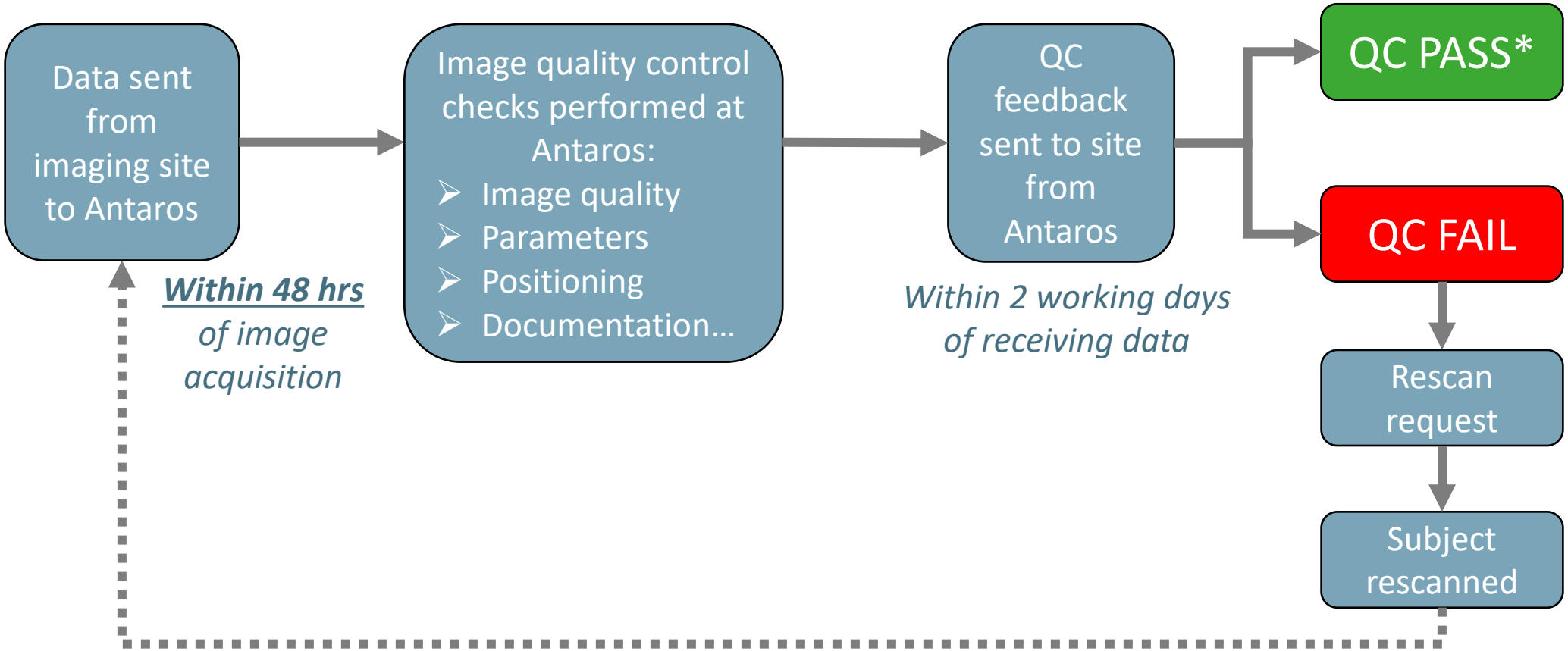
Image quality control
Antaros QC feedback process

*MRI site will only be contacted if there are issues with the data



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Good clinical practice (GCP)

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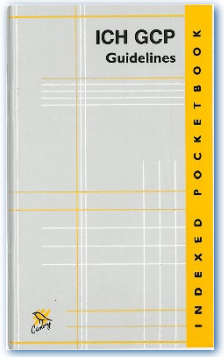
GCP – Introduction



- GCP is an international ethical and scientific quality standard for:
  - designing,
  - conducting,
  - recording and
  - reporting trials that involve the participation of human subjects

- Compliance with this standard provides public assurance that the:
  - rights, safety and well-being of trial subjects are protected,
  - consistent with the principles that have their origin in the Declaration of Helsinki,
  - and that the clinical trial data are credible

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GCP – Adequate resources

- There must be qualified personnel and adequate facilities to safely conduct the study
- Personnel must have sufficient information/training on the protocol, and their responsibilities in the study

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GCP – Compliance with protocol

- The investigator / institution should conduct the study according to protocol
- The investigator shall not deviate from the protocol without agreement by the sponsor and prior approval by the ethics committee (and the authority) in the form of a protocol amendment
- The investigator shall document and explain any deviations from approved protocol

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GCP – Informed consent

- Subjects have all given their consent to participate in the study by signing and dating an informed consent form

- Subjects have the right to withdraw immediately from the scanner (and from the study)

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GCP – Safety reporting

- ***S**erious **A**dverse **E**vent*

- Any untoward medical occurrence that:
  - results in death
  - is life-threatening
  - requires inpatient hospitalization or prolongation of existing hospitalization
  - results in persistent or significant disability/incapacity
  - is a congenital anomaly/birth defect

- All SAE must be reported immediately to the principal investigator at the recruiting site

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GCP – Documentation

- The investigator must ensure that data reported to the Sponsor are accurate, complete and legible
- Image data and scan logs should be retained by the MRI staff in accordance with GCP and local regulations
- The transfer of data to Antaros is described in the Imaging Manual

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GCP – To summarize

- Only staff trained on protocol procedures can perform study activities
- Protocol must be adhered to and no deviations are allowed
- Severe Adverse Events must be reported immediately

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Next steps

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Next steps
Roles and responsibilities during the study

Antaros

- Design and develop imaging protocol
- Site training and qualification
- Providing imaging guidelines and imaging support during study
- Patient and image tracking
- Image receipt
- Quality Control (QC) of images
- Communication (queries) to imaging sites
- Image analysis and reporting

Imaging site

- Follow the imaging guidelines provided by Antaros
- Code data and mask patient confidential information
- Transfer all images to Antaros within 48 hrs of scan
- Respond to queries from Antaros
- Inform Antaros about personnel changes and training requirements
- Inform Antaros of changes to MRI scanner hardware and/or software
- Work according to GCP standards

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Next steps
Roles and responsibilities for getting your site qualified

- **Antaros**: Provide you with the imaging protocol and imaging manual to allow you to set up the protocol for this study
- **You**: Implement the imaging protocol on your scanner
  - Please reach out to us if you have any problems or need guidance to do this ☺
- **You**: Perform test scans for each of the scans as soon as possible (within the next few days)
- **You**: Transfer test data to Antaros for review
- **You**: Also transfer the examcard and/or a PDF of the protocol which will help with data evaluation

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Next steps
Roles and responsibilities for getting your site qualified

- **You**: Send a completed Site Training Log to Antaros (file the original in your site study binder) plus radiographer certificates/CVs
- **Antaros**: Will review the test images and provide feedback
- **You**: Implement modifications to protocol (if any) based on feedback
- **You**: Train any other local staff, as required
  - Please send us a Site Training Log for any additional internal trainings
- **Antaros**: Issue site qualification certificate and notify Sponsor you are ready!

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We look forward to working with you!

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