RECAST-3 – Working Practice Document

Title: Site Monitoring, No. 009

Introduction

The Stroke Trials Unit, Nottingham is the Coordinating Centre and thus responsible for monitoring RECAST-3 trial sites in the UK.

The Trial Manager, or where required, a nominated designee of the Sponsor, (referred to as the monitor throughout the WPD) shall carry out monitoring of trial data at least once during the period of the study for each site that recruits a patient. There may be situations whereby issues are highlighted that warrant further visits (see section 10). It is the responsibility of the monitor to check and report on the trial conduct, the trial documentation, and ensure that procedures have been followed in accordance with the protocol, GCP and with the applicable regulatory requirements.

Each site that recruits a patient to RECAST-3 will have a site monitoring visit (SMV) at least once during recruitment. SMVs may be conducted remotely, the details of which are explained in this WPD, or occasionally onsite. The expectation is that sites will complete the monitoring documents, which will be signed off by the PI and returned to the coordinating centre for review.

Evidence of monitoring will be made available for inspection by the regulatory authority as required.

1. Aims

The purpose of the SMV is to assess each recruiting site by examining the source data in order to:

- Verify that the site has all necessary approvals in place in order to conduct the trial and that no participants were recruited before these were in place.
- Ensure that valid consent has been obtained in line with the protocol and a copy of the correct version of the form is present in the patient file and medical records.
- Ensure compliance with the trial protocol and MHRA guidance.
- Check version control of all master documents held in the Investigator Site File (ISF).
- Confirm key eligibility criteria for a selection of recruited patients.
- Confirm that clinical data matches source documentation and electronic data.
- Confirm administration of the trial device.
- Check that the devices are stored appropriately and accounted for.
- Ensure that the site is meeting its responsibility for the maintenance of the ISF.
- Confirm all records have been entered correctly on the trial database.
- Check the responsibility (delegation) log, training records, CVs and GCPs of all investigators and ensure that these are kept up to date.
- Determine whether serious adverse events have been appropriately reported and verified within the applicable regulatory requirements.

2. Prior to arranging the SMV

The monitor will check whether any of the following are outstanding prior to the SMV:

- Data - the monitor will check that data entry is complete and up-to-date, and any data queries have been resolved
- Randomisation paperwork – the monitor will review the uploaded documentation for each participant and ensure that all the necessary documentation has been uploaded to the secure vault (e.g. consent form, contact details).
- Scans – the monitor will ensure that all required scan images have been uploaded.

If any of the above is missing, the monitor will include this in the email to site when arranging the SMV for it to be resolved before the return of the monitoring documentation.

3. Arranging the SMV

An SMV will be triggered once the site has recruited its first four patients; with data complete up to and including the discharge/death CRF. There is no fixed frequency for additional monitoring, this will depend on factors such as recruitment and data entry and will be reviewed on a site-by-site basis.

Sites will be notified of the remote SMV via an email sent to the main research contact and principle investigator. This correspondence will inform the site what they need to do to undertake the remote SMV.

For all visits, a random subset of trial participants will be selected from the trial database, and those participants will be monitored during the SMV.

4. Monitoring of Investigator Site File (ISF)

The ISF should contain the necessary essential documentation for the conduct of the trial. These documents serve to demonstrate that the investigator and the sponsor are compliant with the standards of ICH-GCP and other regulatory requirements. When the SMV is arranged, sites will be provided with an ISF checklist (see appendix 1 for an example checklist – the most up to date version will be sent to sites in advance of the SMV) which contains all the necessary documentation that should be filed in the ISF.

Any trial documentation not stored in the ISF must be referenced using a file note explaining its location and stored in the relevant area of the ISF. This should be documented when sites complete the ISF checklist.

5. Monitoring of Patient Notes

When the SMV is arranged, sites will be provided with a patient file checklist (see appendix 2 for an example checklist – the most up to date version will be sent to sites in advance of the SMV) for each patient that is selected to be monitored). The purpose of this is to validate the information provided in the eCRFs with the source data from the medical notes. Examples of documents to be checked are outlined below:

Participant Trial File

- Participant/relative information sheet (PIS/RIS)
- CRFs
- Scan reports
- All documents stored in the participant trial file must be correctly anonymised; with full trial ID (e.g. C001 / 0001 / X-Z)

Medical Records

- Written entry of participant/relative's consent and version of consent used
- Written entry of patient being recruited into the RECAST-3 trial
- Presence of sticker requiring retention of medical notes until 7 years post-trial completion
- Presence of the relevant information sheets, signed consent form(s) and trial-specific GP letter

Treatment compliance

- Treatment compliance will be checked by confirming that the randomised treatment was delivered, as documented in the medical notes.

6. After the SMV

Once the site has completed the ISF and patient file checklists, they should be signed and dated by the site representative who undertook the monitoring and the principle investigator. The documents should then be returned to the coordinating centre (RECAST-3@nottingham.ac.uk) where they will be reviewed by the monitor. The monitor will issue a monitoring letter and action list to the site's principle investigator and site representative.

Once the actions have been marked as resolved by the site team, the completed action list should be returned to the coordinating centre. The site monitoring visit log should also be completed by the site and monitor. The monitor should confirm the SMV is complete by sending an email to the site attaching the fully signed and completed documentation, which should be filed in the ISF.

7. Ongoing Trial Monitoring

As part of the ongoing monitoring throughout the duration of the trial, the following paperwork should be uploaded to the secure vault when a patient is recruited to the trial, to be reviewed by the coordinating centre:

- Consent forms
- Participants contact details (for follow-up)
- Scan reports and data

For more information on the secure vault upload process and the scan data upload process, please see WPD 005 Secure Vault Uploads – Site Process and WPD 004 Uploading Images to the RECAST-3 Database.

Sites should also send anonymised participant screening and enrolment logs (RF1 TA011) to the coordinating centre on a monthly basis. See WPD 001 Screening and Enrolment Log for more information.

Ongoing monitoring also includes the reporting of serious adverse events – the details of what qualifies as different types of adverse events can be found in the trial protocol.

Central monitoring of the trial database is also carried out by the coordinating centre, with checks of the data for unusual patterns, irregularities and anomalies.

8. Triggered Monitoring Visits

The coordinating centre will conduct a monitoring visit at least once during the period of the study, although there may be situations whereby issues are highlighted that warrant further visits. A triggered monitoring visit may be performed on request by the Trial Management Committee (TMC), or where concerns have been raised during a central monitoring review or following a routine monitoring visit that has identified specific concerns requiring further investigation.

On-site monitoring visit triggers include (but are not limited to):

- A high frequency of protocol queries from site staff
- A high level of findings through central monitoring oversight
- A high level of findings during a previous monitoring visit
- A high number of protocol deviations
- Poor conversion rate from screening to randomisation (low recruiting/no recruitment)
- Low or high SAE reporting rate compared with other sites
- Poor data quality (long data entry delays, high query rate and high percentage of missing data)
- Poor adherence to the trial interventions
- High staff turnover

NB: High denotes a higher frequency than would be expected.

9. Conclusion

The SMV is an essential part to any trial. It is important that all sites follow the protocol and that the trial data collected is of the highest quality in accordance with ICH-GCP guidelines.

Appendix 1

RECAST-3 Site Monitoring Visit– Investigator Site File Checklist (EXAMPLE)

Site No: Site Name:
Date of Completion: Principle Investigator:

	Yes (please initial)	No	N/A	Comments
Is there an Investigator Site File? Is this paper or electronic? (please answer in comments)				
1. Does it contain the following: a) Contact details of trial office staff & emergency phone numbers b) Delegation Log i. Filenote confirming use of electronic delegation log for the research team ii. Paper version for ward staff c) Training logs i. Research team ii. Ward staff d) Signed and dated CVs and GCPs (in date) and updated as per sites policies and procedures				NB:- Emergency contact numbers are available once logged in to the database – please ensure these are documented in your site file in case you are unable to access the database.
2. Study protocol and associated documents – current versions Please ensure that all superseded documents are scored through with date and marked as superseded. These should be stored behind the current approved versions. a) Signed Protocol Current: Superseded versions: b) Information sheets and consent forms on local headed paper: Current approved versions: Participant Information Sheet Consent Form PIS Re-Consent Consultee Information Sheet Consultee Declaration Form Telephone consent record				

Superseded versions: Participant Information Sheet Consent Form PIS Re-Consent Consultee Information Sheet Consultee Declaration Form Telephone consent record c) GP letter on local headed paper Current: Superseded versions:				
3. Approval and Agreements a) Initial REC approval letter i. England: 27/05/2020 ii. Scotland: 11/06/2020 b) Initial HRA Approval letter 04/12/2023 c) Amendment approvals: d) Initial local R&D approval letter (or original confirmation of capability and capacity from R&D). e) Signed non-commercial research agreement (signed by Sponsor, Trust and PI) f) Organisational Information Document g) Regulatory green light email from Sponsor h) Letter of Insurance, dated: i. 1st Aug 2023 – 31st July 2024 (remove if not applicable for the site) ii. 1st Aug 2024 – 31st July 2025 b) UKCRN Adoption Confirmation dated: 20th March 2020				
4. Case report forms (CRFs) completed, if not stored in patient files: Randomisation Day 1 Follow-up Day 2 Follow-up Treatment logs End of Treatment Discharge or death in hospital Serious adverse event Protocol violation Site-to-site transfer				

Data correction request				
5. AT4 electronic tourniquet device documents **Device serial number:** a) Completed device supplies log and/or delivery note b) Confirmation of local MPE approval c) Anetic Aid test report d) Anetic Aid AT4 device service reports e) Product Training Guidance - AT4 Electronic Tourniquet – Issue 01, 11/10/2023 f) Please confirm that the AT4 Device has a RECAST-3 label attached g) Where is the device stored when not in use (please answer in comments)				
6. Monitoring and auditing a) Sponsor site monitoring documents: i. Monitoring visit log ii. ISF checklists iii. Patient file checklists iv. Monitoring letter v. Completed action lists (if applicable) b) Internal monitoring/audit reports c) Local Annual Reports				
7. Serious Adverse Events a) SAE/SADE/USADE/outcome events report forms signed and dated by PI (where applicable) (Check all SAEs on website have been printed and signed by PI, report as all seen or otherwise report those missing which need adding). b) Safety reporting notifications (where applicable) **c)** Protocol violation report forms signed and dated by PI (where applicable)				
8. Informed consent forms a) Signed informed consent forms (master copies) b) Signed GP letters (master copies) c) Participant screening and enrolment log (RF1 TA011) d) Patient notes labels				
9. Miscellaneous a) Relevant, important correspondence				

b) WPDs:				
001 Screening and Enrolment Log				
002 Entry of Missing Data				
003 Decontamination of Equipment				
004 Uploading images				
005 Secure vault uploads				
006 Event reporting				
007 Manual Randomisation				
008 Protocol Deviations and Violations				
009 Site Monitoring				
010 Site closedown				

Any further comments:

Completed by: Signed:
Date:

Principle Investigator: Signed:
Date:

To be completed by CC monitor on receipt:
Name: Signed:
Date:

Appendix 2

RECAST-3 Site Monitoring Visit – Patient File Checklist (EXAMPLE)

Site No: **Site Name:**
Date of Completion: **Principle Investigator:**

Participant ID:

	Present in medical Records? (please initial)		Discrepancies/ Comments:
	Yes:	**No:**	
Consent			
Patient/Relative/Physician consent (circle)			**Consent form complete?**
Re-consent form			**N/A (circle)**
Verbal/written consent (circle)			**If verbal, followed up with written consent?**
Randomisation result			
Confirmation of eligibility			
Consented by staff on delegation log			**Name:**
Sticker for retention of medical records (or appropriate 'flag' for electronic records)?			
Date of consent/randomisation match?			**Enter date:**
Version Control			
	Version:		**Copy in medical notes?**
	Number	**Date:**	
GP letter			
Copy of information sheet used			
Copy of signed consent form			

Does the RANDOMISATION eCRF data correspond with the hospital notes?				
Randomisation	**eCRF:**	**Yes:**	**No:**	**Comments**
Date of birth				
Date/Time of onset of stroke				
Stroke type				
Blood pressure (BP)				
Heart rate				
Thrombolysis or thrombectomy?				N/A (circle)
Pre-stroke mRS				
Glasgow coma scale (GCS)				
NIHSS				

Does the DAY 1 FOLLOW-UP eCRF data correspond with the hospital notes?				
Day 1	**eCRF:**	**Yes**	**No**	**Comments**
Thrombolysis drug used				N/A (circle)
Date/time of thrombolysis				N/A (circle)
Date/time of groin puncture				N/A (circle)
Date/time of vessel reperfusion				N/A (circle)
Local/general anaesthetic used				N/A (circle)
Dominant hand				
Weight				
Risk factors				
Antihypertensive medications				
Antiplatelet medications				
Anticoagulant medications				
Hypoglycaemic agents				
Opioid analgesics				
Baseline scan & report Date & time: Result of scan:				
AI software used?				
ECG				
Creatinine (µmol/L)				
eGFR (mL/min)				
Glucose (mmol/L)				
NIHSS				
Clinical frailty scale				

Does the DAY 2 FOLLOW-UP data correspond with the hospital notes?				
Day 2 follow-up	**eCRF:**	**Yes**	**No**	**Comments**
Adverse events				If unreported serious adverse events, complete table below (including SADEs/USADEs/Outcome events)
Glasgow coma scale (GCS)				
NIHSS				

Does the END OF TREATMENT FOLLOW-UP data correspond with the hospital notes?				
End of treatment follow-up	**eCRF:**	**Yes**	**No**	**Comments**
Total number of doses (partial/full) received matches number of doses recorded on treatment logs and in the medical notes?				
Regained capacity to consent?				
Adverse events				If unreported serious adverse events (including

				SADEs/USADEs/Outcome events), complete table below
Antihypertensive medications				
Opioid analgesics				
Treated with intermittent pneumatic compression stockings since admission?				
Day 2 (clinical) scan (if applicable) Date & time: Result of scan:				
Creatinine (µmol/L)				
eGFR (mL/min)				
Glasgow coma scale (GCS)				
NIHSS				

Do the medical notes confirm that all RIC/Sham treatments were delivered as per randomisation?		
No:	**Yes:**	**Comments:**

Does the DISCHARGE OR DEATH IN HOSPITAL eCRF correspond with the hospital notes?				
Discharge or Death in Hospital	**eCRF:**	**Yes**	**No**	**Comments**
Date/time of discharge or death				
Discharge disposition				
Co-enrolled trials				
Final diagnosis				
If ischaemic stroke, likely aetiology				N/A (circle)
Adverse events				If unreported serious adverse events (including SADEs/USADEs/Outcome events), complete table below
Creatinine (µmol/L)				
eGFR (mL/min)				
mRS				
Diabetes?				
Cholesterol (mmol/L)				
Blood pressure at discharge				
Extracranial neck vessel stenosis				
FOIS				
Antihypertensive medications				
Antiplatelet medications				
Anticoagulant medications				
Lipid-lowering medications				

Does the following SAE/SADE/USADE OUTCOME data correspond with the source hospital data?				
SAE No:		**Yes:**	**No:**	**Comments:**
	Date/Time:			
SAE No:		**Yes:**	**No:**	**Comments:**
	Date/Time:			

Are all SAE/SADE/USADE/OUTCOME reports filed in ISF and signed by PI? **YES /NO /N/A**

Have there been any unreported SAEs/SADEs/USADEs/OUTCOMES? **YES/NO**
If yes, please report details of SAEs to the site team, PI and coordinating centre:

Details of SAE/SADE/USADE:	**Date/Time:**	**Causality:**

Ensure details of SAEs/SADEs/USADEs are added to the database by completing the SAE eCRF

Does the following protocol violation data agree with the source hospital data?					
Date/time submitted	**Type of protocol violation**	**Explanation/comments**	**Yes:**	**No:**	**Comments**

Are all protocol violation reports filed in ISF and signed by PI? **YES/NO/N/A**

Have there been any unreported protocol violations? **YES/NO**
If yes, please report protocol violations to the site team, PI and coordinating centre:

Date/time	**Type of protocol violation**	**Explanation/comments**

Ensure details of protocol violations are added to the database by completing the protocol violation eCRF

Additional queries/ comments:

Completed by: Signed:
Date:

Principle Investigator: Signed:
Date:

To be completed by monitor on receipt:
Name: Signed:
Date: