RECAST-3 – Working Practice Document

Title: Site Monitoring, No. 009

1. Introduction

The Nottingham Coordinating Centre is responsible for monitoring RECAST-3 trial sites in the UK.

The Trial Coordinator, 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.

The monitor will not be visiting sites for the majority of site monitoring visits (SMV), monitoring will be conducted remotely (the details of which are explained in this WPD). 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. A face-to-face visit may be triggered if there are ongoing concerns about a site despite remedies being suggested to resolve issues.

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

2. 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.

3. 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, device accountability logs and prescription charts).
- 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.

4. 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.

5. 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.

6. 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)
- Dose accountability log
- Scan reports
- All documents stored in the participant trial file must be correctly anonymised; with full trial ID (e.g. C01 / 001 / 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

7. Device Accountability

Dose accountability logs will be checked against the data downloaded from the device which should show a total of 4 doses across 2 days for each trial patient.

8. 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.

9. 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
- Participant contact details (for follow-up)
- Dose accountability logs
- Prescription charts
- 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 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.

10. 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.

11. 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?				
Does it contain the following: a. Trial office contact sheet b. Investigator site file index c. Trial identifier front sheet				
Section A Pre-Trial Opening				
A.1 Study protocol and associated documents – current versions a. Signed Protocol Current: Signed PI protocol signature page b. Information Sheets and Consent Forms on **local headed paper**: Current: **England** (i) Participant Information Sheet (ii) Consent Form (iii) PIS Re-Consent (iv) Consultee Information Sheet (v) Consultee Declaration Form (vi) GP Letter **Scotland** (i) Participant Information Sheet (ii) Consent Form (iii) PIS Re-Consent (iv) Welfare Attorney Information Sheet (v) Welfare Attorney Consent Form (vi) GP Letter c. Telephone Consent Record d. Case report forms (CRFs)				

Current (i) Randomisation (ii) Baseline (iii)Day 2 Follow-up (iv) Discharge or death in hospital (v) Serious adverse event form (vi) Protocol violation form (vii) Data correction request form e. File note template				
A.2 Approval and Agreements a. Initial REC approval letter England: dated 27/05/2020 Scotland: dated 11/06/2020 b. Initial HRA Approval letter c. Initial MHRA approval letter d. Site-specific approvals (i) Sponsor Regulatory Greenlight (ii) R&D approval (iii) Signed non-commercial research agreement (iv) Organisation Information Document (OID) e. Additional HRA documents (i) SoECAT (authorised: 16/09/2021) f. Sponsorship statement g. Funding letter h. Letters of Insurance, dated: (iii) 1st Aug 2021 – 31st July 2022				
A.3 Staff Participation a. Delegation Log b. Signed and dated CVs and GCP (in date) updated as per site's policies and procedures for all staff on the delegation log c. Attendance at Investigator Training (RF1 TA008) signed by all staff on the delegation log d. Ward Staff Training Log e. Training slides				
A.4 Medical Testing and Pharmacy (where applicable) a. Completed supplies log b. Confirmation of MPE approval c. Device manual				

d. Dose accountability log				
A.5 Randomisation and Blinding				
Section B: Ongoing Trial				
B.1 Study Protocol Amendments and Approvals				
B.2 Staff Participation (ongoing trial) Updates where applicable				
B.3 Informed Consent a. Signed informed consent forms (master copies) b. Signed GP letters (master copies) c. Completed patient details form (All these are un-anonymised documentation which must be filed either in ISF or if not, a file note entered to say where it can be found. MUST NOT be filed with un-anonymised data). d. Participant screening and enrolment log (RF1 TA011) e. Patient notes labels f. Patient details template g. Recruitment cover sheet (blank)				
B.4 Medical Testing and Pharmacy Updates where applicable				
B.5 CRFs and Source Documents File note documenting where source documents and patient files are kept				
B.6 Serious Adverse Events a. SAE 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. SUSAR notifications (where applicable) c. Protocol violation report forms signed and dated by PI (where applicable)				
B.7 Biological Materials				
B.8 Audit and Reporting a. Site Visit Log b. Monitoring reports for previous visits (if applicable) c. Completed monitoring visit action lists (if applicable)				
B.9 Miscellaneous a. Relevant, important correspondence b. Completed file notes c. WPDs				

Any further comments:

Completed by: Signed:
Date:

Principle Investigator: Signed:
Date:

To be completed by 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:**

Patient number:

	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			
Sticker for retention of medical records?			
Date of consent/randomisation match?			**Enter date:**
Version Control			
	Version:		
	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)

Dominant hand				
Risk factors				
Antihypertensive medications				
Antiplatelet medications				
Anticoagulant medications				
Hypoglycaemic agents				
Opioid analgesics				
Baseline scan & report uploaded?				
Creatinine (µmol/L)				
eGFR (mL/min)				
Glucose (mmol/L)				
NIHSS				

Does the DAY 2 FOLLOW-UP data correspond with the hospital notes?				
Day 2 follow-up	**eCRF:**	**Yes**	**No**	**Comments**
Dose accountability log uploaded and in notes?				
Adverse events				If unreported adverse events, complete table below
Glasgow coma scale (GCS)				
NIHSS				

Does the DAY 4 FOLLOW-UP data correspond with the hospital notes?				
Day 4 follow-up	**eCRF:**	**Yes**	**No**	**Comments**
Day 2 scan & report uploaded?				
Adverse events				If unreported adverse events, complete table below
Antihypertensive medications				
Opioid analgesics				
Creatinine (µmol/L)				
eGFR (mL/min)				
Glasgow coma scale (GCS)				
NIHSS				

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				
Final diagnosis				
If ischaemic stroke, likely aetiology				N/A (circle)
Adverse events				If unreported adverse events, complete table below
COVID-19 test				
mRS				
Diabetes?				

Blood pressure at discharge				
Extracranial neck vessel stenosis				
FOIS				
Antihypertensive medications				
Antiplatelet medications				
Anticoagulant medications				
Lipid-lowering medications				

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

1. **Are all SAE reports filed in ISF and signed by PI?** **YES /NO /N/A**

2. **Have there been any unreported SAEs?** **YES/NO**

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

Ensure details of SAE 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**

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

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

Additional queries/ comments:

Completed by: Signed:
Date:

Principle Investigator: Signed:
Date:

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