PhEAST – Working Practice Document

Title: Site Monitoring, No. 005

1. Introduction

The Nottingham Coordinating Centre is responsible for monitoring PhEAST 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 site at least once during the period of the study, unless issues are highlighted warranting a further visit (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 PhEAST will have a site monitoring visit (SMV) at least once during recruitment. Due to the ongoing COVID-19 pandemic, the monitor will not be visiting sites for the foreseeable future. SMVs will therefore 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.

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 the EU Clinical Trials Directive.
- 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).

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 patient; with data complete up to and including the discharge/death CRF. SMVs may be triggered throughout the trial (see section 10).

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.

The first recruited participant will be monitored at the initial SMV, as well as any other participants that have been recruited since the notification of the SMV. For any further visits, a random subset of trial participants will be created from the trial database, and these 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)

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) 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)
- Any hand written CRFs
- 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 PhEAST trial
- Presence of sticker requiring retention of medical notes until 7 years post date of issue of the final study report
- Presence of the relevant information sheets, signed consent form(s) and trial-specific GP letter

7. Device Accountability

Treatment logs will be checked against the data downloaded from the device which should show a total of 6 treatments for each participant.

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 (pheast@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)

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.

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 unless issues are highlighted warranting a further visit. 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

PhEAST Site Monitoring Visit– Investigator Site File Checklist (EXAMPLE)

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PhEAST Site Monitoring Visit– Investigator Site File Checklist

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

	Yes	No	N/A (please initial)	Comments
Is there an Investigator Site File?				
Does it contain the following: a. Cover sheet b. Trial office contact sheet V1.0 20220214 c. Investigator site file index				
Section A Pre-Trial Opening				
A.1 Trial Development Documentation a. File note (this section is not applicable for the TSF and will be stored in the TMF at the coordinating centre).				
A.2 Study protocol and associated documents – current versions a. Signed Protocol Current: v2.0 20211202 Signed PI protocol signature page v2.0 20211202 Superseded: b. Information Sheets and Consent Forms on **local headed paper**: Current: **England** I. Participant information sheet v2.0 20211202 II. Participant consent form v2.0 20211202 III. Participant Short pictorial PIS v.0 v2.0 20211202 IV. Consultee information sheet v2.0 v2.0 20211202 V. Consultee delaraton form v2.0 v2.0 20211202 VI. Consultee tel declaration form v2.0 v2.0 20211202 VII. Participant re-consent form v2.0 v2.0 20211202 VIII. GP letter v2.0 20211202				

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Scotland

I.	Participant information sheet v3.0 20220204
II.	Participant consent form v2.0 20220204
III.	Participant Short pictorial PIS v.0 v2.0 20220204
IV.	Legal representative information sheet v3.0 v2.0 20220204
V.	Legal representative consent form v3.0 v2.0 20220204
VI.	Legal representative telephone consent v3.0 20220204
VII.	Participant re-consent form v3.0 20220204
VIII.	GP letter v2.0 20220104

c. Patient Details Sheet

A.3 Approval and Agreements

a. Initial REC approval letter
England: dated 06/12/2021
Scotland: dated 09/02/2022

b. Initial HRA Approval letter 07/01/2022

c. Site-specific approvals
(i) Sponsor Regulatory Greenlight
(ii) R&D approval
(iii) Signed non-commercial research agreement
(iv) Organisation Information Document (OID)

d. Additional HRA documents
(i) SoECAT (authorised: 11/03/2020)

e. IRAS form
304658 dated 04/10/2021

f. Sponsorship statement 04.10.2021

g. Letters of Insurance, dated:
(i) 1st Aug 2021 – 31st July 2022

A.4 Staff Participation

a. Delegation Log (RF2 TA008)

b. Signed and dated CVs and GCP (in date) updated as per site's policies and procedures for all staff on the delegation log

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c. Attendance at Investigator Training (RF1 TA008) signed by all staff on the delegation log d. Phagenesis Training Log (RF1TA008) e. SOP TA008 Trial Initiation e. Training slides: (i) **20220318 V1.0**				
A.5 Medical Testing and Pharmacy (where applicable) a. Confirmation of MPE approval b. Separate device training and manuals etc. c. Supplies log V1.0 20220308				
A.6 Randomisation and Blinding a. Coordinating centre file note				
A.7 Database Build a. Coordinating centre file note – not applicable for the TSF (stored in the TMF at the coordinating centre)				
Section B: Ongoing Trial				
B.1 Study Protocol Amendments and Approvals a. RF1 TA013 Amendment Log				
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				
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. Blank SAE form (RF1 TA014)				

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b. 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). c. Safety reporting notifications (where applicable) d. Protocol violation report forms (where applicable)				
B.7 Biological Materials a. Coordinating centre file note				
B.8 Audit and Reporting a. Site Visit Log (1.0 20220217) b. Monitoring reports for previous visits (if applicable) c. Completed monitoring visit action lists (if applicable)				
B.9 Vendor Management a. Relevant Phagenesis documentation				
B.10 Miscellaneous a. Relevant, important correspondence b. File note template (V1.0 20220218) c. Completed file notes d. WPDs (i) 001 Screening and Enrolment Log (ii) 002 Consent (iii) 003 Manual Randomisation (iv) 004 Decontamination of Equipment (v) 005 Site Monitoring E. Newsletters –				

Any further comments:

Completed by: **Signed:**

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Date:

Principle Investigator: **Signed:**
Date:

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

Appendix 2

PhEAST Site Monitoring Visit – Patient File Checklist (EXAMPLE)

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PhEAST Site Monitoring Visit – Patient File Checklist

Centre No: Site Name:

Patient ID: Date of completion:

Investigators present:

Contents:	Paper/ Electronic Medical Records Available? (please initial)				Discrepancies/ Comments:
	Yes:	No:			
Patient consent					
Consultee declaration					
Randomisation result and eligibility					
Consented by authorised investigator:			Name of investigator:		
Sticker for retention of medical records					
Date of consent/ randomisation match?			Enter date:		
Correct version of information sheet used			Enter V no & date:		
Correct version of consent / declaration version used			Enter V no & date:		
GP letter					
Copy of information sheets used					
Copy of signed consent form					

1. Does the eligibility and baseline eCRF data agree with hospital notes? Especially, eligibility criteria.

Eligibility	Yes:	No:	Comments
Age >=18 years?			
Recent stroke between 4 and 31 days previously?			
Clinical dysphagia			
Non-stroke dysphagia			
Pre-stroke dysphagia?			
Pre-stroke dependency			
Ongoing or anticipated ventilation/intubation/tracheostomy?			
Use or planned use of electrical or magnetic stimulation			

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Malignant middle cerebral artery syndrome			
Pacemaker?			
Need for >2 litres of oxygen/minute?			
Two or more NGT tubes pulled out unless nasal bridle in place?			
Investigator feels patient will not tolerate PES catheter?			
Expected to be discharged or transferred to a site not running the trial during the 6 days of PES treatment period?			
Participating in another randomised controlled treatment trial for post-stroke dysphagia?			
Baseline:			
DOB			
Age			
Sex			
Ethnicity			
Pre-morbid mRS			
Previous Stroke			
Date of stroke			
Stroke type			
Stroke lesion location			
Stroke syndrome			
NIHSS score			
Index stroke, visible on admission imaging?			
Lesion of frontal operculum, visisible of admission imaging?			
Date of admission to hospital			
Thrombolysis			
Intra-arterial therapy			
Hemicraniectomy			
Evacuation / shunt			
Vascular surgery			
Admission to (neuro-) critical /intensive care unit?			
Date of admission to ICU?			
Received ventilation in ICU?			
Days ventilated?			
Required a tracheotomy / tracheostomy?			
mRS score now			
NIHSS now			
Dysphonia?			
Dysarthria?			
Abnormal gag reflex?			
Abnormal spontaneous cough?			

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Abnormal cough after water swallow?			
Voice change after water swallow?			
Weight			
Height			
BMI			
Barthel Index			
DSRS fluids			
DSRS diet			
DSRS supervision			
DSRS total			
FOIS			
Feeding status score			
I avoid some foods because of my swallowing problem			
I have changed the way I swallow to make it easier to eat			
I'm embarrassed to eat in public			
PAS score			
Other trials			
Aspiration score			
PRESS score			
Onset to randomisation (days)			

2. Does the DAY 1-6 treatment eCRF data agree with the hospital notes?

Treatment eCRF	Yes	No	Comments
Day 1			
Day 2			
Day 3			
Day 4			
Day 5			
Day 6			

3. Does DAY 14 follow up eCRF data agree with the hospital notes?

Follow up eCRF	Yes	No	Comments
Day 7			
Day 14			

4. Does the DISCHARGE OR DEATH IN HOSPITAL eCRF agree with the hospital notes?

Discharge or Death in Hospital	Yes	No	Comments
Discharge or death			

5. Are all CRF forms signed and dated?

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CRF forms signed and dated?	Yes	No
Forms not signed & dated:		

6. Does the following SAE/ OUTCOME data agree with the source hospital data?

SAE No:		Yes:	No:	Comments:
	Date/Time:			
	Event details:			

Are all SAE reports filed in ISF and signed by PI? YES/NO

Have there been any unreported SAE's? YES/NO
If yes, please report SAE to site team, PI and coordinating centre:

Details of SAE:	Date/Time:	Causality:

Ensure details of SAE are added to the database

7. Adverse events

AE No:		Yes:	No:	Comments:
	Date/Time:			
	Event details:			

8. 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

Have there been any unreported protocol violations? YES/NO

If yes, please report protocol violations to site team, PI and coordinating centre:

Date/time	Type of protocol violation	Explanation/comments

Ensure details of protocol violations are added to the database

9. Have you discussed the database corrections with the investigator and/or PI?
YES/ NO

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Additional queries/ comments:

PI Signature:
Date:

Trial Monitor Signature : Date: