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. Site monitoring can be conducted either face to face or remotely, dependent on factors outlined later on in this document.

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

The patient file checklist will be completed by the trial manager, and countersigned by the PI once all (if any) actions have been completed

7. Device Accountability

The device accountability log will be checked by the trial manager at face to face visits.

8. After the SMV

Once the trial manager and / or the site representative 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
- Low recruitment

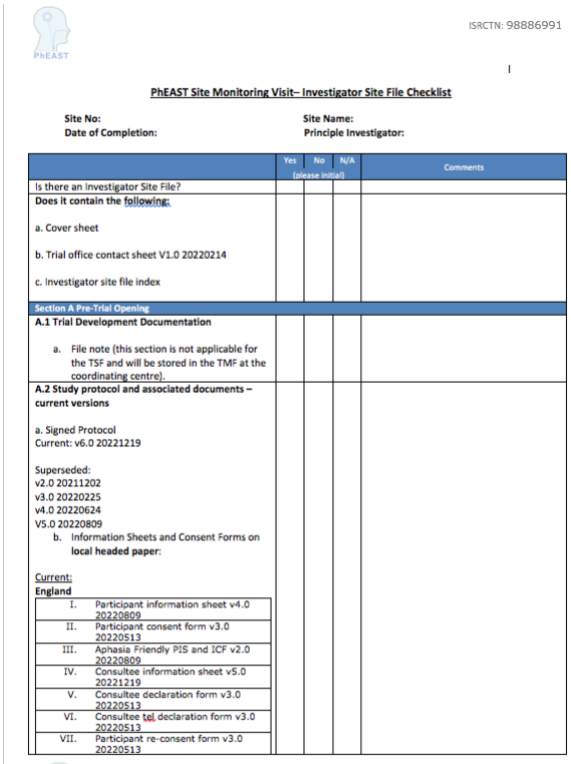
NB: High denotes a higher frequency than would be expected.

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)

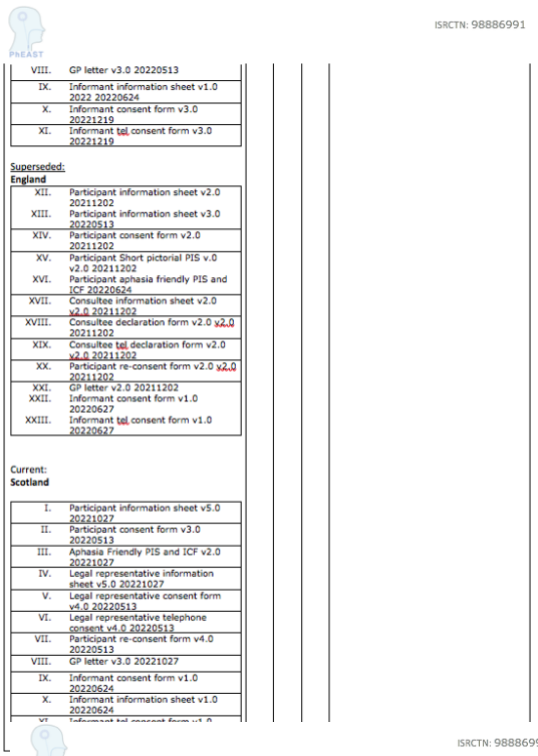


ISRCTN: 98886991

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: v6.0 20221219				
Superseded: v2.0 20211202 v3.0 20220225 v4.0 20220624 V5.0 20220809				
b. Information Sheets and Consent Forms on **local headed paper:**				
Current: **England**				
I. Participant information sheet v4.0 20220809				
II. Participant consent form v3.0 20220513				
III. Aphasia Friendly PIS and ICF v2.0 20220809				
IV. Consultee information sheet v5.0 20221219				
V. Consultee declaration form v3.0 20220513				
VI. Consultee tel declaration form v3.0 20220513				
VII. Participant re-consent form v3.0 20220513				



ISRCTN: 98886991

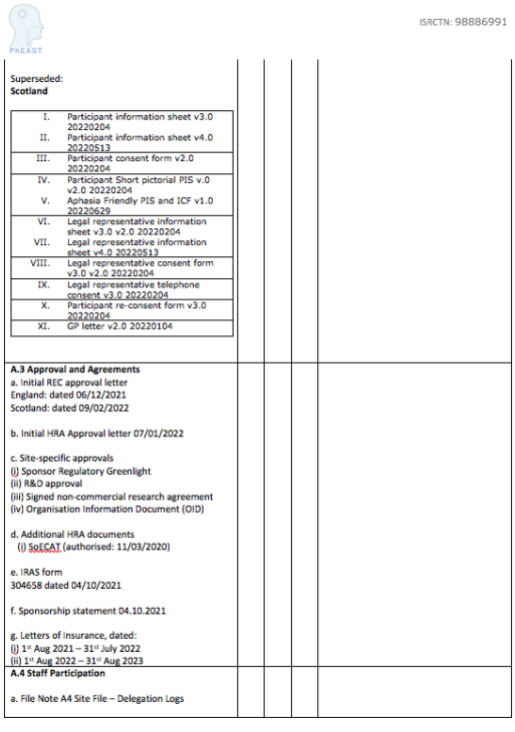
VIII.	GP letter v3.0 20220513			
IX.	Informant information sheet v1.0 2022 20220624			
X.	Informant consent form v3.0 20221219			
XI.	Informant tel consent form v3.0 20221219			

Superseded:
England

XII.	Participant information sheet v2.0 20211202			
XIII.	Participant information sheet v3.0 20220513			
XIV.	Participant consent form v2.0 20211202			
XV.	Participant Short pictorial PIS v.0 v2.0 20211202			
XVI.	Participant aphasia friendly PIS and ICF 20220624			
XVII.	Consultee information sheet v2.0 v2.0 20211202			
XVIII.	Consultee declaration form v2.0 v2.0 20211202			
XIX.	Consultee tel declaration form v2.0 v2.0 20211202			
XX.	Participant re-consent form v2.0 v2.0 20211202			
XXI.	GP letter v2.0 20211202			
XXII.	Informant consent form v1.0 20220627			
XXIII.	Informant tel consent form v1.0 20220627			

Current:
Scotland

I.	Participant information sheet v5.0 20221027			
II.	Participant consent form v3.0 20220513			
III.	Aphasia Friendly PIS and ICF v2.0 20221027			
IV.	Legal representative information sheet v5.0 20221027			
V.	Legal representative consent form v4.0 20220513			
VI.	Legal representative telephone consent v4.0 20220513			
VII.	Participant re-consent form v4.0 20220513			
VIII.	GP letter v3.0 20221027			
IX.	Informant consent form v1.0 20220624			
X.	Informant information sheet v1.0 20220624			



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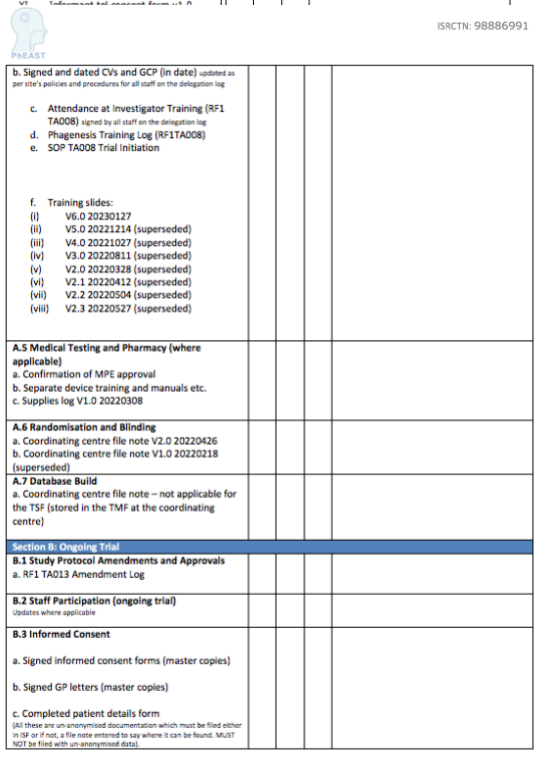
Superseded:
Scotland

I.	Participant information sheet v3.0 20220204			
II.	Participant information sheet v4.0 20220513			
III.	Participant consent form v2.0 20220204			
IV.	Participant Short pictorial PIS v.0 v2.0 20220204			
V.	Aphasia Friendly PIS and ICF v1.0 20220629			
VI.	Legal representative information sheet v3.0 v2.0 20220204			
VII.	Legal representative information sheet v4.0 20220513			
VIII.	Legal representative consent form v3.0 v2.0 20220204			
IX.	Legal representative telephone consent v3.0 20220204			
X.	Participant re-consent form v3.0 20220204			
XI.	GP letter v2.0 20220104			

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 (ii) 1st Aug 2022 – 31st Aug 2023				
A.4 Staff Participation a. File Note A4 Site File – Delegation Logs				



ISRCTN: 98886991

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. Phagenesis Training Log (RF1TA008)				
e. SOP TA008 Trial Initiation				
f. Training slides: (i) V6.0 20230127 (ii) V5.0 20221214 (superseded) (iii) V4.0 20221027 (superseded) (iv) V3.0 20220811 (superseded) (v) V2.0 20220328 (superseded) (vi) V2.1 20220412 (superseded) (vii) V2.2 20220504 (superseded) (viii) V2.3 20220527 (superseded)				
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 V2.0 20220426 b. Coordinating centre file note V1.0 20220218 (superseded)				
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).				

Appendix 2 PhEAST Site Monitoring Visit – Patient File Checklist (EXAMPLE)

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. 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. Safety reporting notifications (where applicable) c. 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 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 (vi) 008 blinding (vii) 009 Document Preparation (viii) 010 Secure Vault Uploads (ix) 011 Cognition Sub-study E. Newsletters –				

Any further comments:

Completed by: **Signed:**
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)

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) Yes:	No:			Discrepancies/ Comments:
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?			

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?			
Palliative Care			
Pregnancy			

2. Does the baseline data agree with the hospital notes?

Baseline	Yes	No	Comments
Day 000			
Day 000 Clinical			
Day 000 EQ-5D-5L			
Day 000 IQCODE			
Day 000 Cognition			

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 14 Primary Outcome			
Day 14 EQ-5D-5L			
Day 14 IQCODE			
Day 14 Cognition			

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?

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:			
	Date/Time:			
	Event details:			

Are all SAE reports filed in ISF and signed by PI? YES/NO/Not applicable

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. 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/Not applicable

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

Additional queries/ comments:

PI Signature:

Date:

Trial Monitor Signature :

Date:

Researcher Signature:

Date: