PhEAST *–* Working Practice Document

**Title:** **Site Monitoring, No. 005**

### Introduction

The Nottingham Coordinating Centre is responsible for monitoring PhEAST trial sites in the UK.

The Trial Manager, and EU National Coordinator delegates - referred to as the ‘monitor’ throughout this document - shall carry out monitoring of trial data at sites at least once during the period of the study, unless issues are highlighted warranting a further visit (see section 10). The Trial Manager is responsible for monitoring data at all UK sites, whereas the EU National Coordinator delegates are responsible for monitoring data in each of the participating EU countries. It is the responsibility of these monitors to check and report on the trial conduct, the trial documentation, and ensure that procedures have been followed in accordance with the protocol and 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.

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 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 ICH-GCP certificates 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.

### 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 database’s 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.

### Arranging the SMV

A SMV will be triggered once the site has recruited its first two patients; with data complete up to and including the discharge/death form. 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 Principal Investigator. This correspondence will inform the site what they need to do to undertake the remote SMV.

The recruited participants, and any additional patients recruited since the notification of the SMV, will be monitored at the initial 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.

### 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.

### 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 (electronic case report forms) with the source data from the medical notes. Examples of documents to be checked are outlined below:

Participant Trial File

#### Participant/relative/legal representative information sheets (PIS/RIS)

#### Any completed CRFs

#### Anonymised data should be kept separate from un-anonymised data

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 the relevant information sheets, signed consent form(s) and trial-specific GP letter

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

### Device Accountability

The device accountability log will be checked by the monitor at face-to-face visits, or made sent via email if form is unavailable during the visit.

### After the SMV

Once the monitor has completed the ISF and patient file checklists, they should be signed and dated by the site representative who undertook the monitoring and the Principal Investigator. The documents should then be returned to the coordinating centre ([pheast@nottingham.ac.uk](mailto: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 Principal 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.

1. **Ongoing Trial Monitoring**

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

* Consent forms (including informant consent)
* Participant contact details (for follow-up)
* GP letters

Sites should also send participant screening figures to the coordinating centre on a monthly basis, and record details of any enrolled patients on the Screening and Enrolment log (RF1 TA011).

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.

### 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.

### 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

**Site No:**  **Site Name:**

**Principle Investigator:**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Yes | No | N/A | Comments |
| (please initial) | | |
| Is there an Investigator Site File? |  |  |  |  |
| Does it contain the following: |  |  |  |  |
| a. Cover sheet  b. Trial office contact sheet V3.0 20240404  c. Investigator site file index |  |  |  |  |
| Section A Pre-Trial Opening | | | | |
| A.1 Trial Development Documentation   1. 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: v10.0 20240508  Superseded, *if applicable*:  v2.0 20211202  v3.0 20220225  v4.0 20220624  V5.0 20220809  v6.0 20221219  v7.0 20230328  v8.0 20231015  v9.0 20231121   1. Information Sheets and Consent Forms on local headed paper:   Current:  England   |  | | --- | | 1. Participant information sheet v4.0 20220809 | | 1. Participant consent form v3.0 20220513 | | 1. Aphasia Friendly PIS and ICF v2.0 20220809 | | 1. Consultee information sheet v6.0 20230328 | | 1. Consultee declaration form v4.0 20230328 | | 1. Consultee tel declaration form v3.0 20220513 | | 1. Participant re-consent form v3.0 20220513 | | 1. GP letter v3.0 20220513 | | 1. Informant information sheet v1.0 2022 20220624 | | 1. Informant consent form v3.0 20221219 | | 1. Informant tel consent form v3.0 20221219 |   Superseded *if applicable*:  England   |  | | --- | | 1. Participant information sheet v2.0 20211202 2. Participant information sheet v3.0 20220513 | | 1. Participant consent form v2.0 20211202 | | 1. Participant Short pictorial PIS v.0 v2.0 20211202 2. Participant aphasia friendly PIS and ICF 20220624 | | 1. Consultee information sheet v2.0 v2.0 20211202 2. Consultee information sheet V3.013/05/2022 3. Consultee information sheet V4.009/08/2022 4. Consultee information sheet v5.0 20221219 | | 1. Consultee declaration form v2.0 v2.0 20211202 2. Consultee declaration form v3.0 20220513 | | 1. Consultee tel declaration form v2.0 v2.0 20211202 | | 1. Participant re-consent form v2.0 v2.0 20211202 | | 1. GP letter v2.0 20211202 2. Informant consent form v1.0 20220627 3. Informant tel consent form v1.0 20220627 |   Current:  Scotland   |  | | --- | | 1. Participant information sheet v6.0 20230307 | | 1. Participant consent form v4.0 20230307 | | 1. Aphasia Friendly PIS and ICF v2.0 20221027 | | 1. Legal representative information sheet v6.0 20230307 | | 1. Legal representative consent form v5.0 20230307 | | 1. Legal representative telephone consent v5.0 20230307 | | 1. Participant re-consent form v5.0 20230307 | | 1. GP letter v3.0 20221027 | | 1. Informant consent form v2.0 20230307 | | 1. Informant information sheet v1.0 20220624 | | 1. Informant tel consent form v1.0 20220624 |   Superseded:  Scotland   |  | | --- | | 1. Participant information sheet v3.0 20220204 2. Participant information sheet v4.0 20220513 3. Participant information sheet v5.0 20221027 | | 1. Participant consent form v2.0 20220204 2. Participant consent form v3.0 20220513 | | 1. Participant Short pictorial PIS v.0 v2.0 20220204 2. Aphasia Friendly PIS and ICF v1.0 20220629 | | 1. Legal representative information sheet v3.0 20220204 2. Legal representative information sheet v4.0 20220513 3. Legal representative information sheet v5.0 20221027 | | 1. Legal representative consent form v2.0 20220104 2. Legal representative consent form v3.0 20220204 3. Legal representative telephone consent v4.0 20220513 | | 1. Legal representative telephone consent v3.0 20220204 2. Legal representative telephone consent v4.0 20220513 | | 1. Participant re-consent form v3.0 20220204 2. Participant re-consent form v4.0 20220513 | | 1. GP letter v2.0 20220104 2. Informant consent form v1.0 20220624 | |  |  |  |  |
| 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) *(if applicable)*  d. Additional HRA documents  (i) SoECAT (authorised 13/06/2023)  (ii) SoECAT (authorised: 11/03/2020) (superseded)  e. Original 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  (iii) 1st Aug 2023 to 31st Jul 2024  (iv) 1st Aug 2024 to 31st Jul 2025 |  |  |  |  |
| A.4 Staff Participation  a. File Note A4 Site File – Delegation Logs  b. Signed and dated CVs and ICH-GCP (in date) updated as per site’s policies and procedures for all staff on the delegation log   1. Attendance at Investigator Training (RF1 TA008) signed by all staff on the delegation log 2. Phagenesis Training Log (RF1TA008) 3. Training slides: 4. ***V9.0 20240606*** 5. V8.0 20231122 (superseded) 6. V7.0 20230503 (superseded) 7. V6.0 20230127 (superseded) 8. V5.0 20221214 (superseded) 9. V4.0 20221027 (superseded) 10. V3.0 20220811 (superseded) 11. V2.0 20220328 (superseded) 12. V2.1 20220412 (superseded) 13. V2.2 20220504 (superseded) 14. V2.3 20220527 (superseded)   **OR FILE NOTE TO STATE WHERE LATEST VERSION IS KEPT (I.E WEBSITE)** |  |  |  |  |
| A.5 Medical Testing and Pharmacy *(not applicable)* |  |  |  |  |
| A.6 Randomisation and Blinding  a. Coordinating centre file note v1.0 20231301 |  |  |  |  |
| 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. Documents pertaining to approved amendments, as well as RF1 TA013 Amendment Log.  b. Aphasia-friendly resources (SA/10/24):  i. Communication Aid For Use During PES Treatment v1.0 20240416.  ii. PES Treatment Guide for Participants v1.0 20240530.  iii. Treatment Tick-List for Participant v1.0 20240416.  iv. Aphasia Friendly Participant Information on PES Treatment v1.0 *(no date).* |  |  |  |  |
| B.2 Staff Participation (ongoing trial)  Updated training logs |  |  |  |  |
| B.3 Informed Consent  a. Signed informed consent forms *(or file note to state these are stored within patient files)*  b. Signed GP letters *(or file note to state these are stored within patient files)*  d. Participant screening and enrolment log (RF1 TA011) |  |  |  |  |
| **B.4 Medical Testing and Pharmacy**  a. Evidence that base station has been approved for use internally *(e.g. medical physics / clinical engineering approval)*.  b. Supplies log V1.0 20220308 |  |  |  |  |
| **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 – may be electronic on REDCap) (Check all SAEs on website have been signed by PI – electronically or physically.  b. Safety reporting notifications (where applicable)  c. Protocol violation report forms (where applicable) |  |  |  |  |
| B.7 Biological Materials  a. Coordinating centre file note v1.0 20230201 |  |  |  |  |
| B.8 Audit and Reporting   1. Site Visit Log (1.0 20220217) 2. Monitoring reports for previous visits (if applicable) 3. Completed monitoring visit action lists (if applicable) |  |  |  |  |
| B.9 Miscellaneous   1. Relevant, important correspondence. 2. File note template (V1.0 20220218). 3. Completed file notes. 4. WPDs *(or file note to say these are viewed on PhEAST documents website):* 5. 001 Screening and Enrolment Log 6. 002 Consent 7. 003 Manual Randomisation 8. 004 Decontamination of Equipment 9. 005 Site Monitoring 10. 008 Blinding 11. 009 Document Preparation 12. 010 Secure Vault Uploads 13. 011 Cognition Sub-study 14. 012 Randomisation   e. Newsletters |  |  |  |  |

**Any further comments:**

**Completed by: Signed:**

**Date:**

**Principle Investigator: Signed:**

**Date:**

*To be completed by trial monitor on receipt:*

**Name: Signed:**

**Date:**

**Appendix 2: 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: | |  |
| 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 |  |  |  |  |  |
| Informant consent? |  |  |  |  |  |
| Informant consented by authorised investigator (if applicable?) |  |  |  |  |  |

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

|  |  |  |  |
| --- | --- | --- | --- |
| **Eligibility** | Yes: | No: | Comments |
| **Inclusion** | | | |
| Age >=18 years? |  |  |  |
| Recent stroke between 2 and 31 days previously? |  |  |  |
| Clinical dysphagia (FOIS = 1, 2 or 3) |  |  |  |
| NIHSS item 1a score of 0, 1 or 2 (requires repeated stimulation to arouse) |  |  |  |
| Baseline DSRS supervision score of 3 or 4. |  |  |  |
| **Exclusion** | | | |
| Non-stroke dysphagia |  |  |  |
| Pre-stroke dysphagia |  |  |  |
| Pre-stroke mRS 4 or 5 |  |  |  |
| Ongoing or anticipated ventilation/intubation/tracheostomy |  |  |  |
| Use or planned use of electrical or magnetic stimulation, or other dysphagia devices |  |  |  |
| Malignant middle cerebral artery syndrome |  |  |  |
| Pacemaker, cochlear implant or  implantable cardioverter-defibrillator in situ |  |  |  |
| Need for >35% of oxygen |  |  |  |
| 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 in first 14 days |  |  |  |
| Participating in another randomised controlled treatment trial for post-stroke dysphagia |  |  |  |
| Palliative Care |  |  |  |
| Pregnancy |  |  |  |
| Already enrolled in another CTIMP |  |  |  |
| Presence of a pharyngeal pouch |  |  |  |
| Dysphagia likely to be short-term only |  |  |  |
| Patient risk-feeding at time of screening |  |  |  |

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?

a)

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

b)

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

c)

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

d)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| 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 reported in REDCap? YES/NO/NA

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: