PLORAS Protocol

Full title: Predicting Language Outcome and Recovery After Stroke

Short title: PLORAS

Sponsor: University College London (UCL)

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Written with regard for the Health Research Authority (HRA) guidance

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Research references

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Contents

1 Summary

The aim of the study is to provide a clinical protocol that will predict speech and language outcome and recovery after stroke. The system we are developing takes a structural brain image of a new stroke survivor with a language disorder (aphasia) - with or without a motor speech disorder (dysarthria, dyspraxia) - and produces probabilistic estimates of long-term outcome, based on how the speech and language abilities of other stroke survivors with 'matching' lesions changed over time [1].

The project rests on a database that records three types of information from many hundreds of stroke survivors including: i) speech, language and communication abilities (from participant-reported outcome measures and objective assessment), ii) brain imaging data (from structural Magnetic Resonance Imaging or Computerised Tomography), with associated information (e.g. time post-stroke), and iii) sensory and demographic information (vision, hearing, age, education, ethnicity, etc.). Critical lesion sites for speech and language symptoms are identified by linking i) and ii) above. A combination of all data types (i, ii and iii) then enters the PLORAS system, which predicts the degree, type and time course of recovery in new stroke survivors, and how this might be affected by speech and language therapy.

The concept of recovery is complex, and includes 'impairment recovery' and 'functional recovery' (here defined as recovery of ability to carry out day-to-day tasks). We adopt a similar approach to the Living with Aphasia: Framework for Outcome Measurement [2], an adapted version of the International Classification of Functioning, Disability and Health framework – whereby (i) impairment recovery relates to domains (e.g. body functions and structures; (ii) functional recovery relates to activities and participation; with (iii) these two types of recovery seen as overlapping, and (vi) contributing to the overall concept of recovery.

PLORAS primarily focusses on measuring impairment recovery because: (i) impairment is typically the patients' greatest concern, especially in the acute stage, and (ii) it is easier to generate impairment recovery predictions, from group level study, than recovery of participation in activities which are more individual, dynamic, and situation-based. The information we acquire on functional recovery (see below under Functional recovery measure (5.2.4g) will be used as supplementary information to our impairment-based recovery predictions.

To ensure that prognoses are intuitive for participants, our goal is to provide impairment recovery predictions using terminology that participants use to describe their own language and communication abilities. For example, difficulties may be described in understanding speech, finding words, pronouncing words or generating sentences. This is assessed, for all participants, with questionnaires and formal language assessments.

In order to be successful, we need to study large numbers of stroke survivors who have, or had, post-stroke aphasia (with or without dysarthria/dyspraxia). The information from this study will enable us to make predictions about likely recovery patterns in future stroke survivors with

speech and language difficulties. This will help guide both clinical and experimental therapeutic interventions.

2 Rationale

Currently, it is not possible for clinicians to provide helpful, personalised and accurate predictions of how speech and language might recover after brain damage because the factors explaining why stroke survivors recover at different rates are not understood [3,4,5]. Our approach is to understand, control and utilize sources of inter-participant variability. In order to do this, we need to collect data from hundreds of stroke survivors who vary from one another in terms of the lesion location and a wide range of demographic factors (e.g. age, education, ethnicity, etc.). The same speech and language assessments are used with all participants. This allows us to compare different groups of participants while controlling for all experimental factors. Our current database [6], with brain scans and language assessments taken months or years after stroke, from more than 2000 participants, indicates that the most effective predictor of speech and language recovery is lesion site (assessed from the brain scans).

Previous studies have demonstrated that damage to many left hemisphere brain areas can disrupt speech and language [7-11] but they have not demonstrated that the effects of damage to the same region are consistent across large populations of patients. Indeed, the effect of damage to one region may depend on the degree of concurrent damage to other brain regions or non-lesion factors such as therapeutic interventions. In the last decade, technical advances in the analysis of neuroimaging data have improved the precision with which we can identify lesion location [12-13] while computational advances allow us to combine and compare data from large populations of participants [14]. We therefore have new approaches to tackle old problems.

Our study investigates the extent to which variability in the speed and degree of speech and language recovery arises from (i) the availability of intact neural structures that can learn to support lost functions, and (ii) non-lesion factors (e.g. therapy type/dose or demographics) that affect the ability to use these intact structures. This requires an investigation into how the effect of lesion and non-lesion variables interact with one another. For example, when lesion site is controlled, we expect to find that recovery is slower or less complete when early speech and language impairments co-occur with other impairments (e.g. perceptual or memory difficulties); and, conversely, faster and more complete when receiving more intensive early therapy. In both examples, stroke survivors may have the neural resources available to support recovery but vary in whether or not they learn to engage these resources effectively.

3 Objectives

This study has three active components: 1) expanding the database, 2) using the database to identify predictors of speech and language recovery, and 3) developing software that can automatically generate prognoses for new stroke survivors.

3.1 Expanding the database

Our database was set up in 2005 to allow easy access to all participant variables [6]. Using this database, we are starting to make accurate predictions about speech and language recovery for some lesion sites. In order to increase the range of predictions we can make, we need to expand participant recruitment and conduct longitudinal studies on participants with post-stroke speech and language disorders, starting any time point after their stroke (days to decades) and continuing every 3-6 months in the first year, with further follow-ups until full recovery or study end. Accounting for time post-stroke is important because we have already found that, in the majority of participants, speech and language abilities improve with years post stroke [15], even in the absence of experimental or therapeutic interventions.

It is currently difficult to know how many participants will be needed before we have the desired range of lesion sites at each time point post stroke (see discussion of power analysis below). Nevertheless, we continue to monitor the participant database at regular intervals so that we know which types of lesion sites are still required.

3.2 Identifying predictors of speech and language recovery

Building on conceptual and computational developments over recent years [1,14-16], we have developed a new approach for identifying lesion sites that relate to cognitive impairments in powerfully predictive ways [17]. We start by identifying sets of brain areas where damage has a consistent effect on speech and language function (e.g. fast or slow recovery). The degree of consistency in previously tested participants indicates the likelihood that the same damage will affect recovery in future stroke survivors. We will iteratively update our knowledge of how lesion sites affect recovery, factoring in how other non-lesion variables (e.g. the amount and type of therapy) influence recovery and how the effect of one variable (e.g. therapy) depends on another (e.g. lesion site). Each new prediction will then be tested in new participant samples whose data were not used to create the prediction.

3.3 Software to generate prognoses for new participants

We plan to develop an automated, easy to use, web-based system for predicting speech and language outcomes in new stroke survivors. In brief, for each new stroke survivor, the software (i) identifies lesion sites from brain scans [12-13], (ii) categorises the stroke survivors according to lesion site, symptoms and demographics, (iii) finds participants in our database with similar lesions and demographics (participant-matching), and (iv) infers a likely recovery profile for speech and language abilities in the new stroke survivor (stroke survivor-prognoses) based on what is known about the recovery of the matching participants. The accuracy of each prediction will be continually assessed, and the software and prediction rules will be updated accordingly.

4 Description of the population to be studied

We are studying stroke survivors who have had one or more strokes that have resulted in a language disorder (aphasia) - with or without a motor speech disorder (dysarthria, dyspraxia).

They can be enrolled at any time since stroke and will continue to participate, while funding is available, until (i) their communication abilities are back to normal, or (ii) they withdraw from the study. Participants are primarily recruited from Clinical Research Network (CRN) sites (see Participant recruitment below).

4.1 Inclusion/exclusion criteria

In order to be included in the study, participants must meet all of the following criteria**:**

- **A medical diagnosis of one or more strokes** (at any time in past) in cerebral or cerebellar regions.
  - The cause of the stroke can be ischemic or haemorrhagic.
  - It must be visible **(>1cm^3)** on a brain scan (according to lesion-measuring software or Consultant/Radiologist report).
  - We exclude patients with strokes that only damage the brainstem, or were the consequence of a subdural haematoma or subarachnoid haemorrhage, because these sites are already known not to be related to speech or language impairments.
- **Evidence of mild, moderate or severe spoken communication difficulties post-stroke.**
  - Patients must either i) have aphasia at the time of recruitment, or ii) have had problematic aphasia symptoms that lasted for at least 7 days after their stroke.
  - In addition, patients may also have a motor speech disorder (dysarthria, dyspraxia).
  - Evidence can be from a variety of sources, such as the multidisciplinary team, interactions with the patient or patient/carer reports.
- **Able to complete our questionnaires/assessments with or without assistance.**
  - Formal language assessments, which are standardised on an English-speaking population, will only be conducted on patients who were fluent speakers of English prior to their strokes. This is to ensure that errors are not the result of learning English as an additional language.
  - Patients who do not speak English can be included using patient-reported outcome measures, if i) they have aphasia in their spoken language, and ii) they have someone who can translate our assessments, which are written in English. Understanding recovery in multiple languages will contribute to our ongoing evaluations of how prediction accuracy is influenced by the language spoken, the number of languages spoken and proficiency of each spoken language [13,18].
- **No hearing and vision problems (unrelated to stroke) that cannot be corrected** (unable to be certain that symptoms/errors on assessment result from stroke rather than poor vision/hearing only).
- **Capacity to consent** or have a family member/close friend (consultee) who can sign a declaration form indicating the participant's wishes.
- **Willingness to participate.**
- **Not under the age of 18** (our ethics approval is for adults only).

- **No significant medical or psychiatric co-morbidity** that might influence attention to, interpretation of, or co-operation with, any of the assessments.
- **No other neurological condition in addition to stroke** e.g. Dementia, Multiple Sclerosis, Parkinson's Disease, Motor Neurone Disease. This is to ensure that symptoms/errors noted during assessments result from the stroke rather than other conditions. Controlled epilepsy and meningiomas can be included, unless neurosurgery for these or other conditions resulted in aphasia.

4.2 Sampling bias

For stroke survivors who meet all the inclusion criteria and are invited to participate but decline, we ask for permission to record the reason for non-participation (without capturing any personally identifiable information). Likewise, for participants who have enrolled but then dropout before study completion, the reason will be recorded. With these participants' consent, we will also request to record age, health factors (physical or mental), ethnicity and native language. The same information is requested from participants enrolled in the study who dropout before their recovery is complete. All these details will be used to assess sampling bias, factors that affect drop out, and the impact of these variables on the accuracy of predictions for future stroke survivors.

4.3 Power analyses

Data from every participant we include will add value to everyone's confidence in future prognoses (see below). The proposed sample size is therefore dictated by the cost of staff to monitor participant recovery and analyse the factors influencing recovery. Wellcome have awarded us funds to monitor recovery in 1000 additional participants (September 2022-2027). We will continue to apply for funding to ensure the accuracy and confidence in future prognoses. A sample size of 1000, will allow us to:

- Systematically dissociate the multiple variables that influence the degree and speed of recovery over time, for example, the exact location of the stroke, the amount and type of therapy received, and the pre-stroke language experience of the participant. Our prognoses for future stroke survivors depend on understanding the effects of these variables.
- Generate confidence in our predictions for future stroke survivors by increasing the number of previous participants who contribute to the prediction. For example, we can be more confident if a prediction is based on the consistency of recovery profiles from a hundred previous participants, with the same lesion features, than if the prediction is only based on data from 10 previous participants.
- Identify and learn about participants who have unusual symptoms, lesions, demographics and/or recovery profiles. This will allow us to generate and test hypotheses about when and why our prognoses are inaccurate. In practice, no test sample will ever be large enough to completely obviate the need to record exceptions (as is recognised, for example, in the way new drugs are trialled). This is why we will continue to apply for funds to increase our

participant sample - and share our data with other researchers whose goal is to improve the lives of patients with post-stroke aphasia.

5 Methods

5.1 Participant recruitment

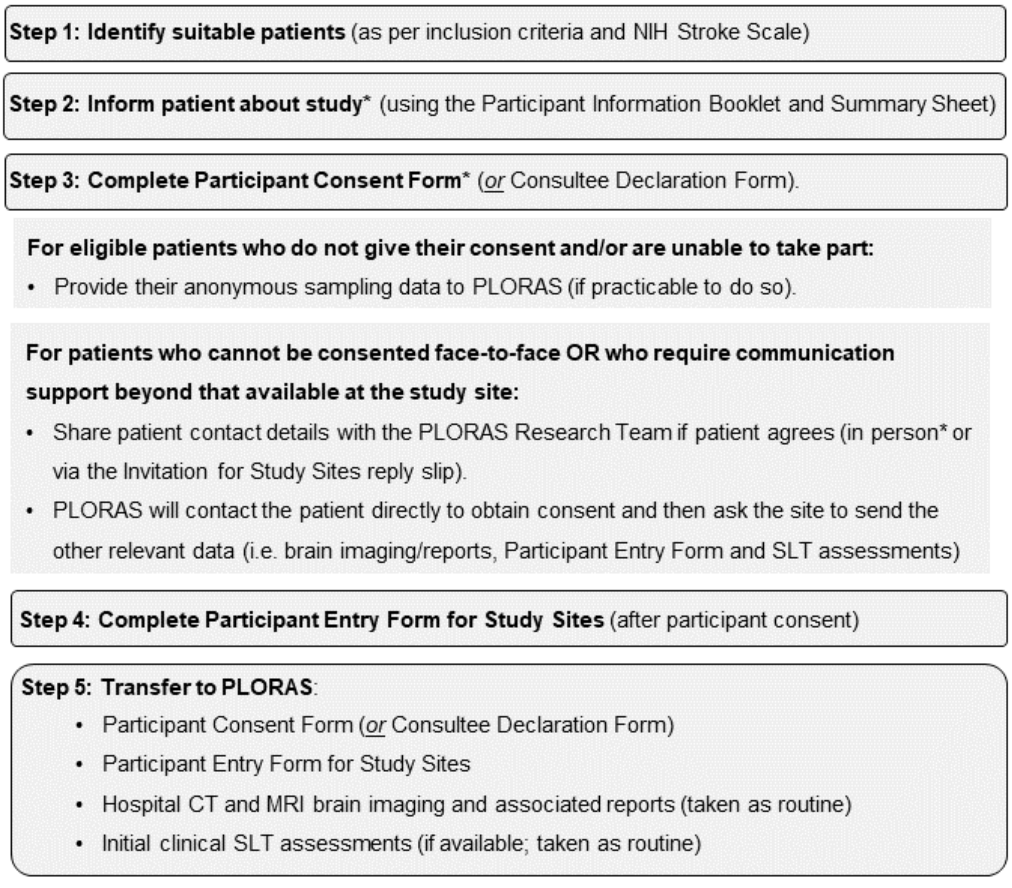
Participants enter the study via two main routes:

5.1.1 Study Sites

The primary route into PLORAS is recruitment at PLORAS Study Sites by research and health professionals. Study Sites are set up via initial contact with the PLORAS Team, and subsequent completion of an Expression of Interest form. Participants can be recruited (i) directly from a variety of settings (e.g. hospital wards and clinics) as per local Clinical Research Network (CRN) permissions, (ii) indirectly, e.g. using hospital and research databases, or (iii) from the community (e.g. stroke groups and events).

Study Sites are involved in screening, information provision, recruitment, consent and the provision of hospital brain scans, relevant medical information (e.g. neurological history and symptoms) and clinical speech and language therapy records (following participant consent). Documents for recruitment and other helpful information for Study Sites are provided as part of Study Site set up. See Figure 1 for an overview of the recruitment process for Study Sites.

Figure 1: Study Site Recruitment Overview



5.1.2 Self-referral/other

Participants can also self-refer to PLORAS after being informed about the study from other sources, e.g. health professionals (not affiliated to a Clinical Research Network study site), collaborators (e.g. speech and language therapists and other research studies), existing research participants, via the community (e.g. at stroke clubs, presentations and exhibitions) and via the media (e.g. print and online advertisements, TV/radio coverage, websites, Facebook, Twitter, leaflets and posters). Participants can contact us via telephone/email, or via the PLORAS website (www.ucl.ac.uk/ploras).

5.2 Participant procedures

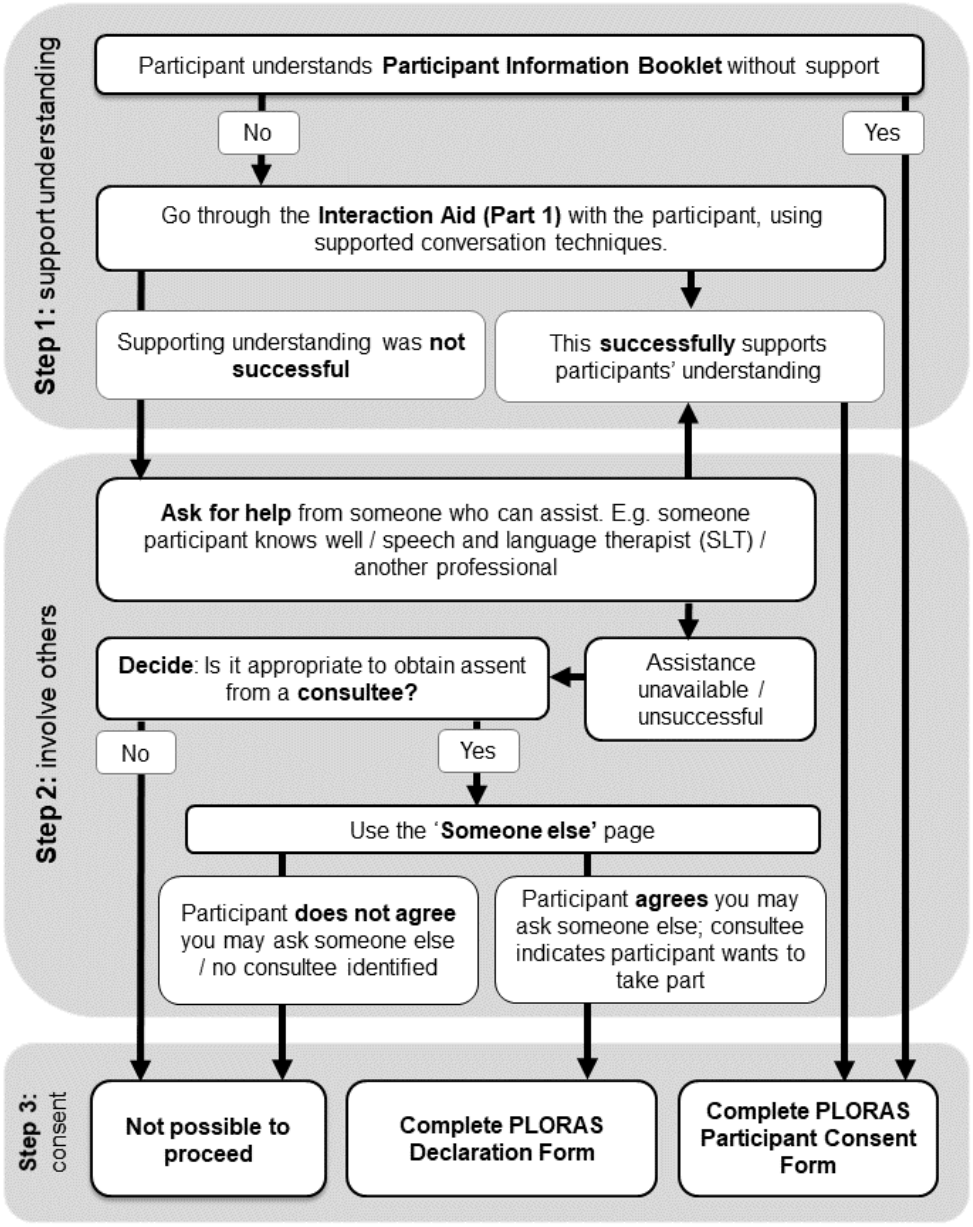
5.2.1 Information provision

Our information booklet conveys the goal of the study and what it involves. It is specifically designed to be accessible to participants with aphasia. Participants who struggle to read and understand the full information booklet will also be provided with a supplementary one-page summary ('Participant Information Summary Sheet') to aid their understanding of the key initial participation information. All participants will be encouraged to take their time to consider whether they wish to take part in the study. If, after entering the study, participants are invited to take part in other research activities, they will be presented with activity specific information sheets and consent forms. For example, participants with extensive damage to left frontal and temporal brain regions will be invited to contribute to our related study: ELORAS ('Explaining Language Outcome And Recovery After Stroke') - *IRAS number: 265430, Research Ethics Committee reference: 19/LO/1755*). An additional information sheet which outlines the role of a consultee is also available. This can be provided to individuals (e.g. a family member or close friend) assisting the participant's inclusion in the study.

a. Initial consent

Study Sites: participant consent will initially be taken by Clinical Research Network staff, after the participant has been informed about the study, see Figure 2. To support the informed consent conversation with participants experiencing more severe communication difficulties, an Interaction Aid will be made available to CRN staff. This resource contains guidance, images and phrases which can be used by the CRN staff member during the consent process. A training video and e-learning resources will also be available to train CRN staff to use the Interaction Aid.

Figure 2: Consent Flowchart



This initial consent process includes provision of the participant's contact details and identifiers (name, date of birth and NHS number) and permission to share the following participant information with the PLORAS Team:

- Hospital brain scan images;
- Relevant medical records (i.e. stroke details, brain imaging reports and speech and language therapy records);
- Questionnaire (Entry Form);
- Contact details.

Principle Investigators at study sites will be responsible for ensuring that staff consenting participants are suitably trained to take informed consent, including assessing capacity/adhering to the Mental Capacity Act (2005), establishing any advanced decisions or statements from the participant and consulting a consultee around study consent, where appropriate.

Self-referral/other: for self-referred participants**,** initial consent procedures are conducted by the PLORAS Team or healthcare professionals who are acting as researchers. All those taking consent will have completed Good Clinical Practice Training and the Health Research Authority (HRA) 'Research involving participants lacking mental capacity' module (or similar). They should also be familiar with the Mental Capacity Act's key principles and two stage test of capacity (2005).

b. Further consent

If CRN staff are unable to complete the consent statements outlined in Part 2 of the Consent form during the initial consent process (i.e. due to the participant's communication difficulties), a Speech and Language Therapist member of the PLORAS Team, with the appropriate skills, will contact the participant to assess whether the participant is able to provide fully informed consent. If the participant is not able to complete the Consent form, their data will not be included in the study. For those who consent to participate, the PLORAS Team will always ask for further consent regarding further assessments, contact by other Stroke research groups or receipt of the PLORAS newsletter.

c. Method of consent

Consent will be obtained at study sites and by the PLORAS Team using paper or electronic methods. The participant (or their consultee where appropriate) will be asked to provide their signature via wet-ink (paper forms) or a simple electronic signature (electronic forms). Depending on the assessment/form, the simple electronic signature might be a stylus or finger drawn signature, a typed name, or a tick box in a declaration form.

In cases where the participant has capacity but cannot make i) a **legible** written mark or ii) **any** written mark, then an independent witness (someone who is not involved in the study) should provide their details in the relevant signature section of the consent form.

A copy of the consent forms (or declaration forms if using a consultee) will be provided to the participant/consultee. A copy will also be retained by the PLORAS Team (saved electronically and stored on the PLORAS database) and by the study site that referred them (as applicable to the study site).

d. Adults lacking capacity

Adults lacking capacity to consent may be enrolled with the involvement of a personal consultee who is a person that cares for the participant (not professionally or for payment), is interested in their welfare, and is willing to help. They will probably be a family member, but could be another person (e.g. close friend). If no personal consultee is available or willing, participants will be asked who can be consulted about their participation in the research. The consultee advises on what the participant's wishes and feelings would be if they were able to consent for themselves, and on whether they should take part. The consultee does not give consent, only advice, and will be asked to sign a consultee declaration form. If, after

enrolment, the consultee has concerns or thinks the participant should be withdrawn they should contact the PLORAS Team.

5.2.2 Data collection by Study Sites

For participants who consent to the study, Study Sites provide the PLORAS Team with: i) a completed Consent Form/Declaration Form, ii) a completed Participant Entry Form, iii) hospital brain scans and reports, and iv) where available, clinical speech and language therapy records. Suitable methods for transferring data to the PLORAS team are outlined on our Clinical Research Network FAQ webpage: www.ucl.ac.uk/ploras/crn-faqs. Once transferred, all these data are stored on the PLORAS database. For participants who were eligible but not recruited, Study Sites will provide anonymous sampling bias data where practicable.

a. Participant Entry Form

The Participant Entry Form includes the following data:

- Participant site code and identification number;
- Additional contact details (e.g. of a family member or friend who can be contacted on behalf of the participant);
- Relevant neurological details (including: date and type of stroke, and whether the participant has had other neurological diagnoses);
- National Institute of Health Stroke Scale Scores (Best Language, Dysarthria, Visual, Extinction and Inattention, Motor Leg, Motor Arm);
- Details of post-stroke brain imaging (e.g. date, type and where carried out);
- Speech and Language Therapy department details;
- Co-enrolment details;
- Details of other languages spoken;
- Initial and current speech and language symptoms (self-report);
- Other factors (e.g. difficulties with hearing/vision or fatigue/lack of concentration) that might influence cognitive function or communication;
- Whether the participant has access to technology (e.g. a computer, laptop, tablet or smart phone with internet access) which will allow them to be contacted at home for assessment by the PLORAS research team (e.g. by email, web-based interfaces (on-line assessments), video conferencing or telephone).

b. Hospital scans and reports

Study Sites provide copies of clinical scan data (i.e. brain scans acquired for routine clinical assessment) with reports, for all participants who are consented to the PLORAS study at their site. Clinical scan data are transferred securely from hospital sites to the PLORAS Team, as per the methods outlined on our FAQ webpage: https://www.ucl.ac.uk/ploras/crn-faqs. Our preference is for scan data to be sent to us electronically (via the PLORAS External Site or the Sectra Image Exchange Portal), however when electronic scan transfer is not possible, scans can be sent on hard discs.

We are recommending sites pseudonymise the scan data before sending to us. This can be done by removing any personally identifiable details and labelling the scan data with a unique participant code (Study Sites can use a combination of their site code and the participant ID number, e.g. UCLH0001). Skull-stripping is not required, nor is removal of the scan date, protocol or sequence information (as we use this information).

We do not routinely pay for scans; however, costs for copying and transferring images can be covered by our research grant when required. Specifically, we can contribute **up to** £30 for scans that cannot be sent electronically (covering disc and postage), and **up to** £20 for scans that are sent electronically but incur a PACs/radiology team charge for preparing the imaging.

Sites should let us know (prior to sending scan data and invoicing) if and which of the above costs, may be incurred.

c. Speech and language therapy records

It would be valuable to the study to receive copies of clinical speech and language therapy records. Participants have the opportunity to consent to this in the Consent Form. The records may include assessment scores, reports, and therapy summaries. The data will be used for additional information on participants' impairments and therapy received. With patient consent, the PLORAS Team will contact speech and language therapists directly, and ask them to complete our **Therapy Questionnaire (see 5.2.3)**.

d. Sampling questionnaire

Where practicable, research nurses are asked to keep an anonymous record of participants who meet our inclusion criteria but (i) were not invited to participate, (ii) were invited but declined to participate or (iii) were invited but unable to participate. Further details requested include the reasons participants are excluded, along with their demographics (e.g. age, range, ethnicity, native language). No personal or identifiable details will be recorded. The data will be used to assess sampling bias. It may also be used to help us identify and reduce barriers to recruitment.

5.2.3 Data collection by speech and language therapists

Speech and language therapy departments, at study sites, will be provided with the software and technology to administer our formal language assessments (see Section 5.2.4f below) to patients under their care. This will provide further information about the initial presentation of symptoms for some participants. It is unlikely that all participants will receive these assessments because (i) the participants may be too unwell while in hospital or (ii) hospital staff/therapists may not have sufficient time.

All participants will be asked, by the PLORAS Team, for details of any speech and language therapy that they receive, including the name and location of their therapist. With patient consent, the PLORAS Team will contact speech and language therapists directly, and ask them to complete our **Therapy Questionnaire**. This asks about several aspects of therapy, including (but not limited to): (1) the amount, frequency and timing of therapy, (2) any factors

which may affect the provision of therapy (e.g. participant health, service demands), and (3) what participant factors enhance or impede that participant's response to therapy (e.g. fatigue, mental and/or physical ill-health, motivation level).

5.2.4 Data collection by PLORAS Team

Members of the PLORAS Team (and healthcare professionals who are acting as researchers in the study) collect data using questionnaires and standardised speech and language assessments. These may be administered to participants and/or their carers via online video conferencing, over the phone, face-to-face, or via email. For online questionnaires and assessments, an approved team member will send instructions via email. Participants will be presented with a consent declaration to read and agree to (by ticking a box) prior to accessing the questions or assessment. This is to ensure that they remain informed about the purposes of the data collection.

a. **Participant Entry Form** (for participants recruited by self-referral/other methods)
This collects the same data as the Participant Entry Form completed by Study Sites, with the addition of the participant's name and date of birth (to allow the team to identify the participant).

b. **Communication Recovery Measure**
Our new patient-reported outcome measure (PROM) uniquely captures each participant's perspective on their speech and language impairment. They report (i) whether they currently have any difficulties with speech production (motor and/or language), comprehension, reading and writing, (ii) details of their impairments and (iii) whether they use any other communication methods. The full questionnaire is administered/repeated, with respect to communication ability at 1 week, 3 months, 6 months, 9 months and one year post-stroke and thereafter until full recovery or study end. The data are used to gain insight into the participant's own experience of speech and language symptoms. If a data point cannot be collected in real-time (how do you feel today), it will be collected retrospectively (how did you feel at 1 week, 1 month, 3 months, 6 months, 9 months and one year). To consider the influence of memory on retrospective reports, the time post-stroke that the questionnaire is administered will be recorded. For participants who are unable to complete the questionnaire, the participant's carer can answer the same questions, e.g. to rate their opinion of the participant's abilities in those language modalities, at the same time points post-stroke, and of the impact on their participation in everyday life.

c. **'About You' Questionnaire**
This collects information on: vision, hearing, handedness and footedness (pre- and post-stroke), years of education (after the age of 16 years), occupation, dyslexia diagnosis, ethnicity, sex and gender.

d. **Language Practice Questionnaire**
This asks participants about i) their speech and language therapy, including the frequency and type of practice they do at home, the name and location of their speech and language

therapist, and whether therapy helped them to achieve their goals and expectations, and ii) everyday language use, for example the type and frequency of speech and language use in their daily lives (e.g. whether they speak on the telephone, read books, listen to the radio, engagement in activities such as work or groups). It also asks whether they have accessed any other treatment approaches (drug therapies or brain stimulation). With patient consent speech and language therapists will be contacted directly (see Section 5.2.3 above).

e. Multilingual Questionnaire

This questionnaire asks for details of other languages the participant speaks. Part 1 asks about the participant's use of these languages after their stroke, how the stroke affected each language, and how each language is recovering – for different modalities (speaking, understanding, reading, writing). It will be repeated every 6-12 months until the participant has fully recovered. Part 2 asks for details of acquisition for each language, including the age learnt, and context of language use, and pre-stroke proficiency. It also asks for details of the languages their parents spoke.These details allow us to record how accurate our predictions are in different languages and people who speak multiple languages.

f. Formal language impairment assessment with the Comprehensive Aphasia Test

For participants whose self-report aphasic symptoms (i) persist for more than three months after stroke, we will arrange a full language assessment using the Comprehensive Aphasia Test (CAT). The CAT is a standardised language assessment comprising a cognitive screen and language battery, including tests of comprehension and production of both single words and sentences presented in both auditory and written format [20]. The subtests are administered in a standard fashion with stimuli presented via a computer screen or book and responses recorded either manually or via electronic audio and video recordings, or both. The CAT will be administered face-to-face or online by a research assistant/speech and language therapist trained in supporting communication for people with aphasia. Online video-linked communication will be supported via a secure video conferencing platform. Audio and/or video data will be collected where the participant has consented to this. If this method is not feasible (e.g. participant does not have access to computer, Wi-Fi etc.), we will try our best to accommodate a face-to-face assessment in the participant's own home or at our research centre.

g. Functional recovery measure

We are using **another patient-reported outcome measure (PROM),** the Aphasia Impact Questionnaire-Concise (AIQ-concise) to understand the impact of participants' aphasia on their everyday functioning [19]. The AIQ-concise is a 21-item validated subjective outcome measure which asks about the stroke survivor's communication, participation and well-being/emotional state. Administration time is approximately 20-30 minutes. This will be completed for all participants who still report aphasia/have impaired formal language assessment scores at 6-12 months (six months is minimum time-point recommended for administration). The AIQ-concise yields a numerical score, which we will use to track change

in functional recovery over time. We will use this information to analyse how change in impairment impacts on long-term functional recovery.

h. Participant Exit Form (thank you letter)

This form is given to participants when we cease data collection (e.g. participant has recovered, no longer wishes to take part, or study end). The form thanks them for their participation, asks for feedback, and repeats questions (asked at the beginning of participation) about whether they agree to be contacted by the PLORAS Team about other stroke research activities and the PLORAS newsletter.

i. Further studies

Depending on a participant's symptoms and enthusiasm to participate further, they may be invited to take part in supplementary activities such as: tests of apraxia; language assessments in other languages spoken, functional magnetic resonance imaging (fMRI) to understand which parts of their brain have learnt to support their recovered speech and language abilities, and/or discussion forums to help us improve our research methods (see next section). Separate consent will be obtained for any subsequent involvement.

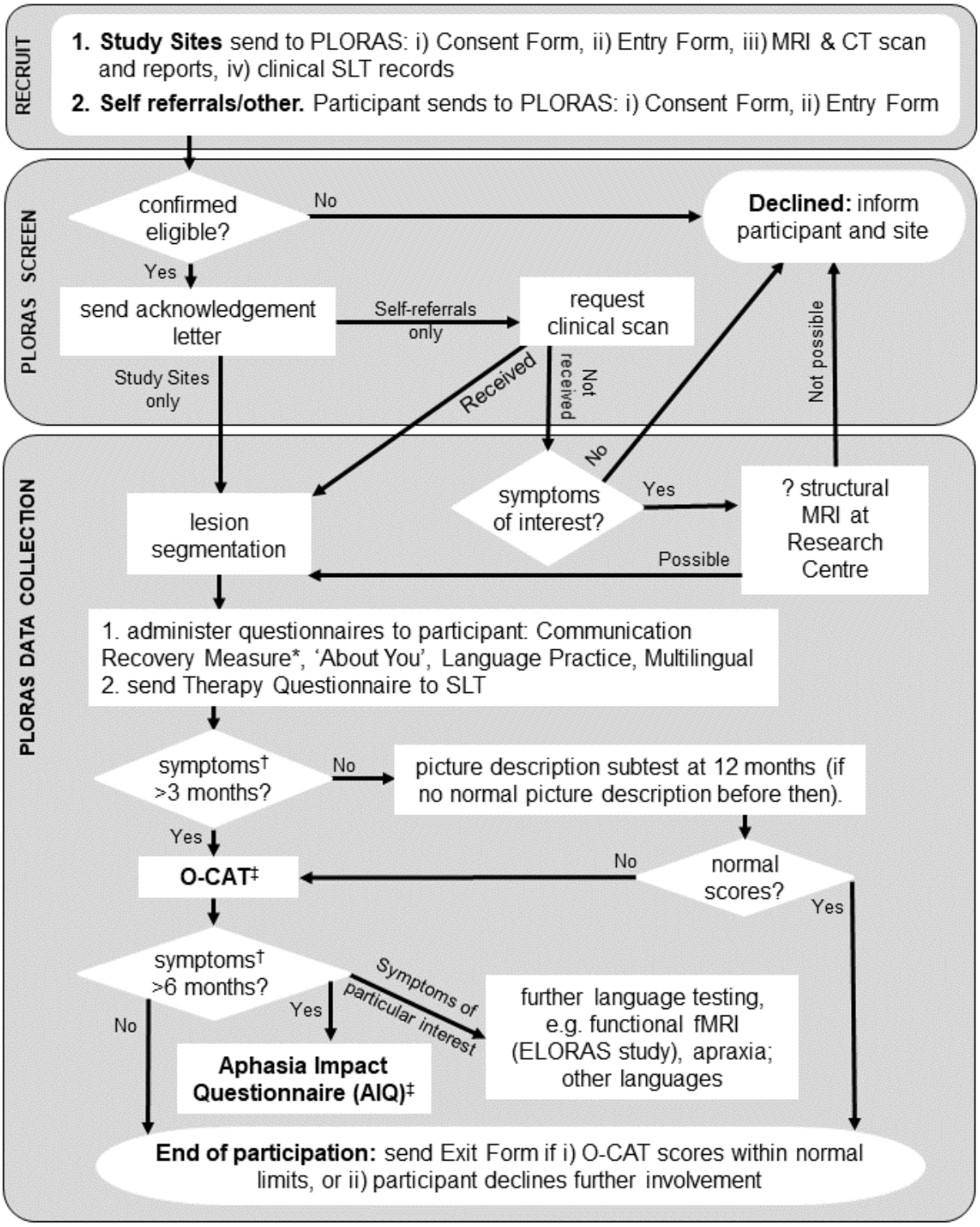
5.3 Participant involvement in research procedures

We seek participant input into our research processes and procedures, including the delivery of recovery prognoses, the contents and administration of our assessments, our training videos and the implementation of the study results into clinical practice. For example, participants may be asked to take part in focus groups investigating their perspective on issues directly relevant to the research such as the delivery of recovery prognoses.

Participant involvement may be via short questionnaires/surveys, small focused discussion groups taking place in person or online, or being filmed for training/taking part in live training. These will be carried out on an ad hoc basis. All involvement will be facilitated by members of the PLORAS Team trained in supporting communication for people with aphasia. Data from the groups will be recorded through video recording and/or researcher field notes and will be analysed using Thematic Analysis.

Participants invited to be involved in research procedures (face-to-face or online) will be contacted by the PLORAS Team by telephone or email. For discussion groups, interested participants will be sent an information sheet and asked to complete a consent form (either face-to-face on the day, or electronically during an initial video-call with a researcher). Any initial video-calls will be arranged individually with each participant prior to the group). A copy of the consent form will be provided to the participant and also retained by the PLORAS Team (saved electronically and stored on the PLORAS database). Instructions for online meetings and using video-conferencing software are provided in the relevant information sheet which includes a link to a short, accessible video tutorial.

Figure 3: Overall process flowchart



* Administer Communication Recovery Measure at 1 week, 1, 3, 6 & 9 months and 1 year (can be retrospective) and thereafter until full recovery or study end.
† Refers to speech and language symptoms.
‡ Repeat every 3-6 months in the first year, with further follow-ups until full recovery or study end.

Table 1A: Data collected and transferred to our database from study sites

Participant consent responses including their contact preferences.
Personal data including: name, DOB, contact details (and, if necessary, additional contact details e.g. of a friend or family member).
Clinical data including: brain imaging (with associated reports), NHS number, stroke date and type, stroke symptoms, selected National Institute of Health Stroke Scale Scores, time since onset of symptoms, aphasic syndrome subtype, relevant information about other neurological conditions and past medical history, other factors that might affect neurological function and communication, clinical speech and language assessment reports, etc.
Other data: other languages spoken, details for Speech and Language Therapy department, co-enrolment to other studies, details about participant's access to technology.
Anonymised sampling bias data: reasons for excluding eligible participants and their demographics (including age, ethnicity and native language).

Table 1B: Additional data collected by PLORAS Team

Participant consent responses including their contact preferences.
Questionnaire data, including: About You questionnaire, Multilingual questionnaire, Therapy Questionnaire, Language Practice Questionnaire, Participant-reported outcome measures (PROMs).
Formal language assessment scores/transcripts completed for research (e.g. CAT).
Communication between PLORAS Team and participant/carer/Study Site, etc.
Audio and video recordings of participants, either individually or during group discussions.
Transcriptions of group discussions.

6 Quality control and quality assurance

6.1 Ethics

This study has been reviewed by the London Queen Square Research Ethics Committee and received a favourable ethical opinion.

6.2 Data handling and record keeping

This study will comply with:

- UCL Data Protection Policy
- Common Law Duty of Confidentiality
- Data Protection Act 2018
- UK General Data Protection Regulation (UK GDPR)
- Computer Misuse Act 1990

- NHS Code of Practice on Confidentiality
- Good Clinical Practice
- The International Conference on Harmonisation of Tripartite Guidelines (CPMP/ICH/135/95), including all aspects of data collection and management.

6.3 Data transfer (handling, processing and storage)

- Data collected from participants will be uploaded directly and securely to the PLORAS database and automatically encrypted where appropriate. CDs with clinical scan data will be shredded after the scans have been uploaded to the database.
- Paper data (which may include a copy of consent forms) are stored in a locked cabinet at UCL. Paper files will be archived at the UCL Records Office when they no longer need to be referred to. All data in the database and cabinets can only be accessed by authorised personnel. The degree of access depends on what the data are being used for.
- Only authorised members of the PLORAS Patient Team can access personal data (name, address, date of birth etc.) to check participant eligibility and contact participants regarding their involvement in the study (e.g. to administer the questionnaires and assessments outlined in section 5.2.4) or to arrange follow-up activities as outlined in sections 5.2.5 and 5.3 above.
- Other members of the PLORAS Team (e.g. analysis-only team) can access non-identifiable data for data-analysis and publication (rather than participant recruitment and testing).
- Researchers outside the PLORAS Team do not have any access to the database. Those conducting ethically approved studies can be sent data from the PLORAS Team. This will not include any personal information unless the participant has already participated in the other team's study.

  Participants providing data online (which is uploaded directly to the PLORAS database) will not be able to retrieve the data back once submitted or see other data collected. If an online form has not been completed after consent, the participant will be sent reminders to complete it (including email, post and telephone call). Incomplete forms, with insufficient information for study inclusion will be deleted, after a set time. For more information about how we handle, process and store participant data. Please see the **PLORAS Privacy Notice** (version 2.0),

  Study sites should complete the **Organisation Information Document** provided in the PLORAS Local Information Pack *before* any data is transferred to the PLORAS Team at UCL. This replaces the former **Data Sharing Agreement** that was in place between PLORAS and Study Sites prior to February 2023. Suitable methods for transferring data to the PLORAS Team are outlined on our FAQ webpage: https://www.ucl.ac.uk/ploras/crn-faqs

  Professor Cathy Price (CI) is the custodian of the data which will be stored for 20 years after study end, providing an extremely rich data set for future investigations. After this time, all personal data will be destroyed in accordance with all applicable legal and regulatory requirements, including the UK General Data Protection Regulation (UK GDPR) and Data Protection Act 2018, and any amendments thereto. UCL will act as the data controller of such

data for the study. Eventually, the plan is to transfer anonymised datasets to an open source database for widespread use and new applications.

This project is covered by the UCL Data Protection Registration, reference number Z6364106/2013/08/42, section 19, research: health research.

6.4 Archiving

UCL and each participating study site recognise that there is an obligation to archive study-related documents at the end of the study (as defined within this protocol).

The Chief Investigator confirms that she will archive the study master file at UCL for 20 years from the study end.

The Principal Investigator at each participating study site agrees to archive their respective site's study documents for 5 years from the study end – unless local guidelines state otherwise, in which case they may be followed provided that all study data has been successfully transferred to UCL.

7 Financing and insurance

7.1 Details

This is a non-commercial study funded by Wellcome, the Medical Research Council and the Stroke Association.

7.2 Cover for negligent and non-negligent harm

Negligent harm cover is provided by the NHS Indemnity Scheme Arrangements and non-negligent insurance is provided by UCL.

University College London holds insurance against claims from participants for harm caused by their participation in this clinical study. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, if the study is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical study. University College London does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or otherwise.

7.3 Publication policy

The results of the study will be reported in the following ways: peer reviewed scientific journals; online (including www.ucl.ac.uk/ploras) internal report; conference presentation; written feedback to research participants; presentation to participants or relevant community groups.

In line with Wellcome's position statement in support of open and unrestricted access to published research, copies of all authors' research papers, supported in whole or in part by Wellcome funding, will be made freely accessible on the Internet at the time of publication. This will be facilitated through the Wellcome/the National Center for Biotechnology (NCBI) at

the US National Institutes of Health (NIH) manuscript submission system: PubMed Central (PMC). http://www.pubmedcentral.gov

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9 Appendices

9.1 Appendix 1: Required documentation

List here all the local documentation you require prior to initiating a Study Site (e.g. CVs of the research team, participant Information Sheet (PIS) on headed paper etc.).

Documentation	Required	Optional	Comments
Delegation log	X		
CVs and Good Clinical Practice (GCP) certificates for the research team		X	CVs and Good Clinical Practice training should be approved locally by the Trust's R&D department as required - the PLORAS Team do not need copies.
Fully executed Organisation Information Document	X		
NHS Permissions Letter/Confirmation of capacity and capability	X		
Localised study documents		X	Sites can localise relevant study documents - the PLORAS Team do not need copies of these.

9.2 Appendix 2: Guide to PLORAS documents

(Used by: PRT = PLORAS Research Team, SS = Study Sites)

A4 Recruitment Poster	1b	4 (04.04.2023)	PRT, SS
Invitation for Study Sites	1d	8 (21.08.2023)	SS
Participant Information Booklet	2	6 (13.10.2022)	PRT, SS
Participant Information Summary Sheet	2P	2 (21.08.2023)	PRT, SS
Privacy Notice	2a	2 (13.10.2022)	PRT, SS
Consultee Information Sheet	2-C	6 (13.10.2022)	PRT, SS
Discussion Groups Information Sheet	2D/2D-P	1 (14.05.2020)	PRT
Online Discussion Groups Information Sheet	2OD	2 (02.06.2023)	PRT
Online Discussion Groups Information Sheet	2OD-P	2 (02.06.2023)	PRT
Participant Consent Form	3	8 (21.08.2023)	PRT, SS
Consultee Declaration Form	3-C	8 (21.08.2023)	PRT, SS
Participant Entry Form for Study Sites	4	7 (02.06.2023)	SS
Participant Entry Form	4-P	6 (13.10.2022)	PRT
Discussion Groups Consent Form	4D	1 (14.05.2020)	PRT
Online Discussion Groups Consent Form	4OD	2 (02.06.2023)	PRT
Online Discussion Groups Consent Form	4OD-P	2 (02.06.2023)	PRT
Interaction Aid	--	1 (August 2023)	SS
Sampling questionnaire	--	1 (TBC)	SS
Therapy questionnaire	--	1 (TBC)	PRT
About You Questionnaire	--	1.1 (21.08.2023)	PRT
Communication Recovery Measure	--	1 (TBC)	PRT
Language Practice Questionnaire	--	1 (TBC)	PRT

Multilingual Questionnaire	--	2 (TBC)	PRT
Participant Exit Form	--	1 (TBC)	PRT

9.3 Appendix 3: Amendment history

List details of all protocol amendments here whenever a new version of the protocol is produced. Protocol amendments must be submitted to the Sponsor for approval prior to submission to the REC.

Please note: The protocol was not updated as part of amendments 2, 3, 5 and 8. As such, these have been omitted below.

Amendment No.: Original submission | **Protocol version no.:** V2 (NB. V1 was subject to amendments and only V2 was implemented) | **Date issued:** November 2013 **Author(s) of changes:** Cathy Price **Details of changes made:** N/A
Amendment No.: SA4 | **Protocol version no.:** V3 | **Date issued:** 03.11.2014 **Author(s) of changes:** Cathy Price; Rachel Bruce **Added:** URL link for study sites to access recruitment documents and information; Requests for participant medical information (for MRI safety checks) may be directed to the research team who recruited them; Recommendations for the pseudonymisation and transferral of scan images; Exclusion criteria 'Symptoms lasting < 7 days', 'Brainstem stroke (only), subdural haematoma, subarrachnoid haemorrhage, Transient Ischaemic Attack and lacunar stroke'. **Updated:** References to 'Stroke Research Network' changed to 'Clinical Research Network'; Participants recruited under 'The Neural Basis of Language' (00/N032) will be asked to consent to PLORAS; Clearer distinctions made between study sites providing hospital scans as routine ('external sites+') and those not. Criteria specified for scans provided; For participation occurring over separate days additional consent will not be taken; A Data Sharing Agreement must be signed by study sites prior to them transferring data; Scan data received on CD will be uploaded to a secure server and shredded; Sources of funding to include the 'Stroke Association'; Formatting changes and removal or correction of inaccurate information.
Amendment No.: SA6 | **Protocol version no.:** V4 | **Date issued:** 16.02.2016 **Author(s) of changes:** Cathy Price; Rachel Bruce **Added:** Participants taking part using their routine hospital scan will be sent the Aphasia Recovery and Therapy Questionnaire and a covering letter (1g).
Amendment No.: SA7 | **Protocol version no.:** V5 | **Date issued:** 12.12.2017 **Author(s) of changes:** Cathy Price; Rachel Bruce **Added:** New grant code; Participants may be recruited from study sites in Wales; More information about the questionnaires used by the PLORAS Team; Recruitment sources: 'collaborators from clinics at UCLH', 'directly from health professionals'; New section outlining

recruitment at PIC sites. **Updated:** New centre name (and corrected postcode) and 'Wellcome Trust' changed to 'Wellcome'; Minor changes to text punctuation and phrasing for consistency; Further distinctions between different study site types and details for screening and consent processes; Participants recruited under 'The Neural Basis of Language' (00/N032) returning for repeat assessments/scans, will be invited under PLORAS; 'Inclusion' and 'Exclusion' sections combined and clarified; Removed version number from reference to Data Sharing Agreement.; Sources of funding to include the 'Medical Research Council'; Formatting changes and removal or correction of inaccurate information.

Amendment No.: SA9 | **Protocol version no.:** V6 | **Date issued:** 14.05.2020
Author(s) of changes: Cathy Price; Shamima Khan
Added: For clinical scans provided a stroke diagnosis must exist and the stroke must be visible; Details for recruiting participants remotely; Description of online consent methods used by PLORAS when collecting data from participants; New section 'Qualitative data collection' describing other activities PLORAS may carry out with participants. **Updated:** Removed references to The Neural Basis of Language (00/N032) study; Removed URL link for study sites to access recruitment documents and information; Description of participant research activities; We may collect data online where possible (i.e. following COVID-19 pandemic) and administer questionnaires at any stage of participation; Clinical scans will be requested for all consenting participants as routine. Reasons clarified and methods for such data transfers specified; Removed separate process for participants taking part using clinical scan (now irrelevant); Participants may be invited back for additional activities (focus groups, online discussion groups or functional magnetic resonance imaging – ELORAS study: 19/LO/1755); References to 'Data Protection Act 2018' and the 'General Data Protection Regulation (GDPR)'; List of data collected and transferred to the PLORAS database; Minor changes to text punctuation and phrasing for consistency.

Amendment No.: SA10 | **Protocol version no.:** V7 | **Date issued:** 13.10.2022
Author(s) of changes: Cathy Price; Rachel Bruce; Shamima Khan
Added: Title page (study references for IRAS and CPMS); Summary (greater detail and reasons for measuring impairment recovery, information recorded on database now includes "participant-reported outcome measures", "Computerised Tomography", "sensory information" and additional examples of demographic information); Rationale (detail to elaborate upon existing information); Objectives ("the accuracy of each prediction will be continually assessed, and the software and prediction rules will be updated accordingly" to 3.2 and step for 'categorising stroke survivors' to 3.3); Description of population to be studied ("Evidence of mild, moderate or severe spoken communication difficulties post-stroke" added to 4.1, new subsection 4.2); Methods (figure 1 and 2, table 1A and 1B); Methods (figure 1 and 2, extra details for section 5.2, new subsection 5.2.3, new forms and measures described in sections 5.2.2 (c-d), 5.2.3 and 5.2.4 (b-d, g-h)); Ethics (added "…unless local guidelines state otherwise, in which case they may be followed provided that all study data has been successfully

transferred to UCL." to 6.4); References; Appendices (new sections including 9.1, 9.2 and 9.3). **Updated:** Title page (UCL banner, grant code, key contacts table); removed abbreviations list page; Summary (changed "the PLORAS system predicts recovery from aphasia in new participants" to "…predicts the degree, type and time course of recovery in new stroke survivors, and how this might be affected by speech and language therapy", changed "participants who have had a stroke, some of whom have continuing problems with their language and some who don't" to "stroke survivors who have, or had, post-stroke aphasia (with or without dysarthria/dyspraxia)"); Rationale (text simplified, number of participants on database increased, "In the last 5 years…" changed to " In the last decade…", removed outdated text and replaced with new paragraph "Our study investigates…" outlining focus on the interaction between effects of lesion and non-lesion variables); Objectives (updated information for 3.1, 3.2 and 3.3, changed "…lesion sites that result in speech and language difficulties…" to "…lesion sites that relate to cognitive impairments…" in 3.2, changed "identify lesion site" to "identify lesion site from brain scans" in 3.3); Description of population to be studied (section presented earlier, inclusion and exclusion criteria refined, previous figure 1 (screening flowchart) removed, updated text to reflect new funding and justifications for proposed sample size in 4.3); Methods (section refined and simplified, removed redundant subsections for site types and variations in recruitment processes, removed reference to participants undergoing research MRI and safety screening, removed section outlining criteria and methods for MRI scan acquisition, updated description of procedures in 5.2.1, 5.2.2, 5.2.4 and 5.3; removed expenses information); Ethics (specified 'UK GDPR', updated information in 6.3, removed "Radiographers conducting the MRI scans will have access to personal data for safety reasons"); References; Other (Minor changes throughout i.e. punctuation/phrasing; formatting; removal of surplus or redundant information, correction of inaccurate information; section numbers added).

Amendment No.: NSA040 | **Protocol version no.:** V8 | **Date issued:** 04.04.2023
Author(s) of changes: Cathy Price; Shamima Khan

Added: Methods (added link to PLORAS website in 5.1.2; added reference to Participant Information Summary Sheet in 5.2.1; added reference to CRN FAQ webpage for information relating to data transfer methods in 5.2.2); Appendix 2 (added Participant Information Summary Sheet and A4 Recruitment Poster to table, updated version and date for Consent Form and Consultee Declaration Form). **Updated:** Figure 1 (minor rewording for reference to study information sheet/booklet); Quality control and assurance (outlined that the former Data Sharing Agreement has been replaced by the Organisation Information Document); Appendix 1 (replaced reference to 'Data Sharing Agreement' with 'Organisation Information Document').

Amendment No.: NSA041 | **Protocol version no.:** V8.1 | **Date issued:** 02.06.2023
Author(s) of changes: Shamima Khan
Updated: documents listed in Appendix 2.

Amendment No.: SA11 | **Protocol version no.:** V9 | **Date issued:** 21.08.2023
Author(s) of changes: Shamima Khan

Updated: Description of population to be studied (minor rewording of the inclusion criteria for clarification in 4.1). Methods (minor rewording for clarification relating to consent methods and reference to Interaction Aid added in 5.2.1a, 5.2.1b, 5.2.1c and Figure 1. Also, minor rewording of multilingual questionnaire description in 5.2.4e); Appendix 2 (document versions updated). **Added:** Methods (additional text about clinical scan data transfer and costs added to 5.2.2b); Figure 2 ('Consent flowchart' and renumbered previous Figure 2 to Figure 3). Quality control and assurance (added our FAQ webpage URL to 6.3 which outlines suitable data transfer methods).