Big CACTUS

A study to assess the clinical and cost effectiveness of aphasia computer treatment versus usual stimulation or attention control long term post stroke (CACTUS)

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This document describes a clinical trial, and provides information about procedures for entering participants. The protocol is not intended for use as a guide to the treatment of other patients. Amendments may be necessary; these will be circulated to known participants in the trial.

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Abbreviations

AE	Adverse event
Carer QoI	Carer Quality of Life measure
CAT	Comprehensive Aphasia Test
CI	Chief Investigator
CLRN	Comprehensive Local Research Network
CONSORT	Consolidated standards of reporting trials
COAST	Communication Outcomes After Stroke
CRF	Case report form
CTRU	Clinical Trials Research Unit
DMEC	Data Monitoring and Ethics Committee
EQ5D	European Quality of Life measure (5 Dimensions)
GCP	Good Clinical Practice
HRQoL	Health related quality of life
ICER	Incremental cost effectiveness ratio
ICF	International Classification of Functioning, Disability and Health
IMP	Investigational Medicinal Product
HTA	Health Technology Assessment
NICE	National Institute for Health and Clinical Excellence
NIHR	National Institute for Health Research
NHS	National Health Service
PI	Principle Investigator
QALY	Quality adjusted life year
R&D	Research and Development
RCT	Randomised control trial
REC	Research ethics committee
SAE	Serious adverse event
SOP	Standard operating procedure
SHSC	Sheffield Health and Social Care (NHS Foundation Trust)
SLT	Speech and language therapist/therapy
TOMS	Therapy Outcome Measures
TMG	Trial management Group
TSC	Trial Steering Committee
VAS	Visual analogue scale

Definition of terms

Aphasia	A neurological language deficit affecting the ability to understand, talk, read and write
Stroke	An acute neurological event (infarct or haemorrhage) of sudden onset

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Protocol amendments since Version 1.0

Protocol version 1.0, 30 October 2013 amended to version 2.0, 20 June 2014. Summary of main changes:

I. Trial Summary, page 7 & page 20: One part of the primary outcome has been moved to the secondary outcome as agreed by both the Trial Management Group and Trial Steering Committee. One of the primary outcomes had two measures associated with it. To reduce complexity of analysis the primary outcome (conversation) will be measured by the Therapy Outcome Measures alone. The number of target words used in conversation will now be a secondary outcome.

II. Duration (page 13) & Data recorded during the intervention period (page 20): Clarification that follow-ups should be carried out within one month of each time-point. This will reduce participant burden by ensuring that there is at least 2 months between outcome measure assessments at 6, 9 and 12 months.

III. Participant Identification, page 14: A section has been added from the IRAS form to provide more information.

IV. Planned inclusion and exclusion criteria, page 14: Clarification of wording - Exclusion criteria point 2 has been removed and re-worded as point 7 of the Inclusion Criteria. Points 5 and 6 of the Inclusion criteria have been clarified and scoring added.

V. Change to number of target words from 96 to 100 (pages 17 & 18, and Appendix 2 & 4): The upgraded software no longer use sets of 12 words, so we are now using 100 words, instead of 96 (8 sets of 12).

VI. Data recorded during intervention period, page 22 & Appendix 3: An additional 3 month phone call will be made by the PI to check on the participant's health and the usual care they are receiving.

VII. Safety Assessments, pages 23 & 24: Additional information has been added about Adverse Events and Serious Adverse Events, including examples of events, and the reporting process.

VIII. Flow charts in Appendix 2 3 & 4, pages 34-37, have been amended as above.

Protocol amendments since Version 2.0

Protocol version 2.0, 20 June 2014 amended to version 3.0, 12 February 2015. Summary of main changes:

I. Pages 5 and 6: All confirmed NHS sites and Principal Investigator details have been added

II. Duration, page 14: Further clarification has been given of when follow-ups should be made. The sentence "Follow-ups should be carried out within one month of each time-point" has been amended to “Follow-ups should be carried out in the month following each time-point’ (e.g. 6-7 months, 9-10 months, 12-13 months)." This is to ensure that the follow-ups are carried out within six to seven months, for example, not before 6 months. The phrase 'within one month of each time-point' could be interpreted to mean a few weeks before the time-point.

III. Regular self-managed practice, page 18: An additional 'Per protocol' definition for intervention use has been added for clarity - "across at least a four month period will be considered per protocol". The recommended amount of practice is 3 x 20 mins per week for 6 months (eg. approximate total of 24 hours). The practice must be spread over at least 4 of the 6 months, but it doesn't matter how much practice occurred in each of the months to be considered part of the per protocol analysis.

IV. Table 1 'Summary of outcome measures', page 22: The Carerqol measure had been omitted in error from the table; additional information has been added to the EQ5D section, listing the three different versions of the EQ5D to be used in the trial.

V. Statistics, Section 9, page 25: The paragraph 'Assumptions for the sample size calculation' has been amended as the figures were documented the wrong way round for 'assessment of conversation' and 'patient rated improvement'.

VI. Data Handling & record keeping, section 11, pages 29 and 30 - this has been amended to match the information provided on the original ethics form in IRAS, to clarify how patient identifiable information is transferred and stored securely on the web-based database.

VII. Appendix 1 and 2, pages 34 and 35: added "age 18" as this had been omitted in error from the flow chart.

VIII. Appendix 2, Flow diagram, page 35: added "with at least 50% accuracy (score of 5/10)" to the Eligibility criteria 'Ability to perform a simple matching task in StepByStep', to provide more detail of the scoring and to be consistent with the 'Planned inclusion and exclusion criteria' on page 14 of the protocol.

IX. Appendix 2 Flow diagram, page 35: amended the 'Informed consent' section to say 'forced alternative cards' instead of ‘yes/no cards’ as the wrong description of the cards to be used was written in error.

Protocol amendments since Version 3.0

Protocol version 3.0, 12 February 2015 amended to version 4.0, 17 July 2015. Summary of main changes:

I. Trial treatment, section 7, pages 19-20: the description of the intervention arm was written prior to the trial starting, based on the pilot study, some minor adjustments to the intervention protocol were decided prior to the study starting and these are reflected in the changes made to this section. These include 1) using version 5 (rather than 4.5) of the StepByStep software, 2) using different documents to maintain and record fidelity of StepByStep setup, 3) using a feedback form for communication between SLT and volunteer/ therapy assistant and 4) not training volunteers or assistants to use word pair barrier games.

II. Trial treatment, section 7, pages 21-22: a section has been added to detail how the intervention fidelity will be evaluated, this explains how existing measures will be used and additional measures will be collected. The additional measures include a quiz for lead therapists to explore drift in knowledge about the intervention over time, a measure of working alliance to be completed by the volunteers/therapy assistants and three additional questions to be added to the participant diary.

Protocol amendments since Version 4.0

Protocol version 4.0, 17 July 2015 amended to version 5.0, 31 May 2017. Summary of main changes:

I. Page 4-6: Change in Principal Investigator details

II. Page 6: Change in Service User member on Trial Steering Committee (previous member resigned due to ill-health)

III. Page 12 and page 25: Clarification of measuring the picture naming task as not all participants were assessed on 100 words, a percentage rather than a number is required for analysis. Wording amended from "The change in the number of words" to "The change in word finding ability of words personally relevant to the participant will be measured by a picture naming task (100 words with a maximum of 2 points each). The word finding score will be expressed as a percentage of the total score and change in the percentage 6 months from baseline will be calculated."

IV. Page 12: Clarification of the statistical analysis to reduce ambiguity about it's interpretation amended from "Primary and key secondary outcomes will be analysed using a Hochberg testing procedure." to "Primary and key secondary outcomes will be analysed using a multiple linear regression model adjusted for baseline measures and stratification factors. Hochberg testing procedure will be used to control for multiplicity due to multiple treatment comparisons and three endpoints (co primary and key secondary)."

V. Page 15: Clarification of objectives measured separately between participants and carers. Point 3 amended from "To investigate whether patients receiving self managed computerised speech and language therapy and their carers perceive greater changes in social participation in daily activities and quality of life (participation)." to exclude the

VI. wording "and their carers".

VII. Page 15: wording added to the subsequent paragraph "and the impact on the carer quality of life".

VIII. Page 16: Clarification on the Consort diagram of the two distinct measures within the CarerCOAST by adding "CarerCOAST (last 5 items for carer)" (See changes to pages 26 and 27 below.)

IX. Page 18: Point 5. Wording changed from "Ability to retrieve 10-90% of words" to "Ability to score 5-43 / 48 on the CAT Naming Objects sub-test [25] (Mild 31-43, Moderate 18-30, Severe 5-17)" as scores not percentages were used on the randomisation system.

X. Pages 19 and 20: Further clarification of scores not percentages used for the CAT Naming Objects test: page 19 "If the word finding score is less than 5 (10%), or greater than 43 (90%)."; page 20 "(Mild 31-43, Moderate 18-30, Severe 5-17)."

XI. Page 25: Details have been added about the process followed for rating the videos in relation to one of the primary outcome measures measures,the change in functional communication using the activity scale of the Therapy Outcome Measures: "We will carry out a benchmarking session using the TOMS with potential raters to get consensus as to how the TOMS will be used in this project, followed by inter and intra rater reliability tests using 10 practice videos. Raters selected for final rating of all participant videos will have intra rater reliability of at least 70% practice videos rated within 0.5 between time 1 and time 2, and inter- rater reliability of at least 70% videos rated within 0.5 of the median scores at both time points. Refer to separate document 'Process for selection of TOMS raters and scoring procedure October 2016' for additional detail."

XII. Pages 26 and 27, including table on page 27: Clarification of the CarerCOAST. The CarerCOAST assesses carer perception of patient's communication effectiveness, and impact of the patient's communication on the carer's quality of life. The measure has 20 items. The first 15 items assess carer perception of patient's communication while the last 5 items measure the patient's communication difficulties on the carer's quality of life. This distinction needs to be clarified in the protocol as they will be analysed separately. Wording amended to include "the last five items of the CarerCOAST."

XIII. Pages 26 and 27: Clarification that carer will complete the EQ5D carer questionnaire by including the word 'carer'.

XIV. Page 31: Clarification of the statistical analysis to reduce ambiguity about it's interpretation: "Primary and key secondary endpoints for the comparisons of Control to Intervention and Active Control to Intervention will be analysed using a Hochberg testing procedure which allows for an investigation of all three endpoints whilst maintaining the overall Type I error at 5% [35]" amended to "Primary and key secondary endpoints will be analysed using a multiple linear regression model adjusted for baseline measures and stratification factors. Treatment comparisons (Intervention vs Usual Care and Intervention vs Attention Control) will be based on Hochberg testing procedure to allow for an investigation of all three endpoints (co primary and key secondary) whilst maintaining the overall Type I error at 5% [35]."

XV. Pages 32 and 33: Clarification of the statistical analysis to avoid ambiguity of interpretation. Re-worded from: "The mean difference in percentage improvement of words named correctly between the treatment and control groups, adjusted for baseline naming ability, will be analysed using an analysis of covariance (ANCOVA). Terms for treatment and baseline will be fitted into the model. Assumptions underlying the analyses will be assessed by inspection of residual plots. Homogeneity of variance will be assessed by plotting the studentised residuals against the predicted values from the model, whilst Normality will be assessed by use of Normal probability plots. If the assumptions for the analysis of variance are violated then appropriate transformations may be applied or alternative analyses may be performed. Similar analyses will be undertaken for the endpoints of COAST and the activity scale of the TOMS. The endpoints at 9 and 12 months

will be similarly analysed for exploratory purposes. Likewise an investigation of trends over time will be made. "

Re-worded to: "For the change in word finding (expressed as a percentage) at 6 months from baseline, the measure of intervention effect will be the mean difference in change in word finding ability between the Intervention and Usual Care groups, and the Intervention and Attention Control groups. A multiple linear regression model adjusted for baseline word finding ability and stratification factors (centre and severity of word finding) as fixed effects (39).

The outcome will be modelled as a function of:

- word finding ability at baseline,
- treatment group (Usual Care, Attention Control, Intervention),
- centre as a fixed effect and,
- the severity of word finding as a fixed effect (mild, moderate, and severe).

Results will be reported and presented as adjusted mean difference in word finding ability between the Intervention and Usual Care groups, and the Intervention and Attention Control groups, and Attention Control and Usual Care (for exploratory), with its associated 95% CI and associated P-value.

Improvement in functional communication at 6 months assessed using activity domain of the TOMS, which is a coprimary endpoint will be analysed in the same manner as for the change in word finding ability but adjusted for baseline functional communication (rather than the change in word finding ability at baseline) in addition to stratification factors.

Likewise, the endpoints at 9 and 12 months and other continuous outcomes will be analysed using a similar approach for exploratory purposes."

XVI. Page 33: Details of the key subgroup analyses have been added:

"Analysis will be carried out on key subgroups:

1.Severity of word finding difficulty

Mild 31-43

Moderate 18-30

Severe 5-17

2. Length of time post-stroke

The research team will undertake a blinded review to determine the groups by plotting the primary outcomes against length of time post-stroke.

3. Baseline comprehension ability based on the CAT sentence comprehension scores

Within normal limits 27-32 (based on CAT cut off score for normal/aphasic)

Mild comprehension impairment 18-26

Moderate comprehension impairment 9-17

Severe comprehension impairment 0-8

(0-8 = inconsistently understanding at 2 Information Carrying Word (ICW) level; 9-17 = consistently understanding at 2-3 ICW level/simple sentence structures but not complex sentence structures; 18-26 = some understanding of complex sentence structures but not consistent.)"

Trial Summary

Big CACTUS is a pragmatic randomised controlled trial (RCT) to compare outcomes for people with persistent aphasia using computerised speech and language therapy (SLT) at home with those having usual care (standard speech and language therapy provision or general daily communication activity), or attention control (daily completion of puzzle book activities). The study uses a CE marked medical device as used for its intended purpose. The sample size is 285 patients (95 per arm). The estimated recruitment rate is one participant per month at each site. An internal pilot phase with a review of progression criteria half way through the recruitment phase is planned.

Setting

Computer therapy exercises will be provided in participants' own homes. Recruitment, assessment and tailoring computer exercises will be coordinated by 20 Speech and language therapy (SLT) departments across the UK, with a 15 month recruitment period at each site.

Target population

People presenting with word finding difficulties as part of their aphasia (language disorder affecting understanding, talking, reading and writing) at least 4 months post stroke with no upper limit.

Health technologies being assessed

Participants will be supported to self manage continued daily word finding exercises for using the StepByStep© computer software for 6 months. Computer exercises will be tailored to individual needs by a SLT, followed by volunteer or SLT assistant visits for support.

Measurement of costs and outcomes

All outcome measures will be made at baseline, 6, 9 and 12 months by blinded speech and language therapist assessors at each site.

Primary outcomes:

1. The change in word finding ability of words personally relevant to the participant will be measured by a picture naming task (100 words with a maximum of 2 points each). The word finding score will be expressed as a percentage of the total score and change in the percentage 6 months from baseline will be calculated.
2. Improvement in functional communication will be measured by blinded ratings of video recorded conversations between a SLT and participants, using the activity scale of the Therapy Outcome Measures.

Key secondary outcome:

Improvement in patient perception of communication will be measured using the COAST - a patient reported measure of communication participation and related quality of life.
Use of learnt vocabulary in the context of conversation will be measured using a checklist of target words during rating of the videoed conversations at 6 months.

Cost effectiveness measurement

A cost-utility analysis will be undertaken from the NHS and personal social service perspective. Intervention and SLT time costs will be estimated for individuals. The EQ5D (accessible and by proxy versions) will be administered at all time points and combined with standard valuation sources to measure quality adjusted life years (QALYs) gained in each group. EQ5D and CarerQoL scores will also be elicited from carers. An economic model developed alongside the pilot study will be updated. Differences between costs and QALYs in the 3 groups will be described and the incremental cost effectiveness ratio(ICER)will be calculated.

Analysis

Primary and key secondary outcomes will be analysed using a multiple linear regression model adjusted for baseline measures and stratification factors. Hochberg testing procedure will be used to control for multiplicity due to multiple treatment comparisons and three endpoints (co primary and key secondary).

1. Introduction

Stroke is the largest cause of disability in the UK with communication impairment affecting one third of survivors. Speech and language therapy (SLT) is often received weekly initially but rarely continues after the first few months. Medical instability, fatigue and confusion may reduce full engagement with language therapy in the early weeks post stroke, reducing the opportunity for people to achieve their potential for recovery. The prevalence of speech and language disorders 6 months after stroke is therefore still considerable (50 per 100,000). There is evidence that people can continue to improve their language skills for several years, continuing to lessen the effects of aphasia. As the consequences of aphasia remain a problem long term, investigation of interventions to reduce this health burden in the chronic stages post stroke is crucial. The National Service Framework for Long term conditions (2007) and the National Stroke Strategy (2007) recommend people receive rehabilitation for as long as they benefit from it. Treatment of aphasia that persists beyond the first few months post stroke is often not available through NHS services as ongoing therapy is costly through face to face SLT and places greater demands on already limited resources.

Meta-analysis in a Cochrane review (2012) of speech and language therapy (SLT) for aphasia following stroke suggests some effectiveness, particularly if delivered intensively [1]. Adequately powered RCTs in this field are rare except for recent studies of SLT intervention in the first few weeks post stroke. Laska et al [2] randomised 123 patients with aphasia to receive 45 minutes of SLT a day for 21 days starting within 2 days of stroke onset, or no SLT intervention. Severity of the aphasia was not reduced. A recently completed HTA funded study, ACTNoW [3] randomised 170 people in hospital post stroke to SLT intervention for up to 4 months or attention control (conversation with paid visitors). No significant differences between groups were shown. As aphasia persists for many stroke survivors, therapy in the longer term also warrants investigation using adequately powered RCTs. Although rapid spontaneous recovery may occur in the first few months, there is preliminary evidence to suggest targeted and intensive SLT treatments can promote further improvement in the longer term [4,5,6,7].

Targeted therapies with good preliminary evidence to date include: 1) Constraint Induced Aphasia Therapy (CIAT) - use of language in games to make, reject or clarify requests for targeted items for 30 hours over 2 weeks [4,8,9]. A preliminary systematic review of 10 studies conducted over the decade concluded that the evidence for this technique is favourable [10]. Model oriented aphasia therapy (MOAT), which tailors treatment according to patients' individual symptoms, was found to be comparable to CIAT when delivered at similar intensity [11]. Raymer et al 2008 found personal relevance or 'salience' of the language material being practiced to be important when targeting therapy [5]. Robey (1998) found that treatments delivered at more than 2 hours a week resulted in greater change than treatments delivered at less than an hour and a half a week whilst Backheit et al (2007) found no evidence of difference for 5 versus 2 hours of SLT for 12 weeks [12,13]. The Cochrane review of aphasia therapy warns that the more intense the therapy the higher the withdrawal/non compliance [1]. While the optimum intensity remains unclear, it is generally acknowledged that regular therapy practice is a factor in treatment success. The resources required to achieve intensive therapy in the long term is prohibitive in the current financial climate and lower cost options for the support of repetitive, intensive practice are needed. There is evidence that non speech and language therapy professionals can be employed successfully to support therapy activity [3,14]. Computer technology can also provide the potential for supporting intensive treatment in the long term.

Computer therapy developed for the treatment of aphasia has been reported to be useful in the provision of targeted language practice and provides opportunities for independent home practice as part of a self management approach to maximise practice intensity [15,16], improving outcomes for reading, spelling and expressive language [17,18,19]. The Department of Health report, 'Our Health, Our Care, Our Say' (2006) recommends self management for long term conditions supported through technological innovation [20]. However, to date, studies of self managed computer therapy for aphasia have been limited to descriptive case series with only 2 reported RCTs, both for reading treatment [16,21,22]. Although these studies were not fully powered, they indicate potential effectiveness of computer therapy. Such computer based services for long term management of aphasia therapy could provide a low cost therapy option. However, the actual cost effectiveness has not been investigated.

Our StepByStep computerised approach to long term aphasia therapy (detailed in the intervention section) combines current evidence underpinning language therapy with practical considerations of treatment delivery. Skills of a qualified speech and language therapist are used to select individually targeted therapy exercises, computer software is provided for regular self managed practice of therapy exercises, and volunteers support language practice and computer use [23].We carried out a pilot study evaluating this approach with 34 people with persistent aphasia. They were randomly assigned to using this available computer software designed for treating aphasia, or usual long term care (most frequently this was social support). On average people with aphasia practiced their speech exercises on the computer independently for 25 hours over 5 months. The therapy significantly improved ability to use spoken words when compared to usual care (P=0.014). The results indicated that self managed computer therapy supported by volunteers (total of 4 hours on average) could help people with aphasia to continue to practise, improving their vocabulary and confidence talking. Patients and carers found it an acceptable alternative to face to face therapy. Self managed computer therapy could improve the quality of life of people with persistent aphasia, at relatively low cost to the NHS and society [24].

The proposed study builds on the work of the pilot to investigate the clinical and cost effectiveness of using this computer therapy approach to deliver targeted, intensive long term aphasia therapy for word finding in a definitive phase III RCT.

Intervention under study: Independent speech and language therapy practice for word retrieval through use of computerised therapy exercises. The computer intervention will be tailored to the individual's needs by a qualified speech and language therapist. Participants will be encouraged to practice daily for at least 20 minutes for a 6 month period. Trained volunteers or speech and language therapy assistants will provide support to motivate practice. This intervention is designed for people with the language disorder, aphasia, acquired a minimum of 4 months prior to randomisation as a consequence of stroke.

Products: The intervention under study makes use of a computer software package called StepByStep© marketed by Steps Consulting Ltd.

Risks and Benefits. This study is not an investigation of a medicinal product (IMP) and entails no invasive procedures. Benefits indicated by the pilot study include greater ability to use language and have conversation and improved confidence. The only risk identified was fatigue.
This trial will be conducted in compliance with the protocol, GCP and regulatory requirements.

2. Aims and objectives

The aim of the study is to provide definitive evidence of the clinical and cost effectiveness of targeted, intensive speech and language impairment based therapy intervention for word finding delivered through self managed computer exercise for persisting post stroke aphasia. This builds on a successful 3 year RfPB funded pilot RCT conducted by this team which informed possible effects, measures, feasibility, recruitment rates, compliance, cost effectiveness analysis and a power calculation. Results demonstrating feasibility are published in Stroke 2012:43; 1904-191 [24].

The World Health Organisation (2001) recommends use of the International Classification of Functioning, Disability and Health (ICF) to describe and evaluate the impact of health problems on a person's life [25]. The first three objectives therefore seek to identify the effect of self managed computer treatment for persisting aphasia on the ICF dimensions of impairment, activity, and participation compared to usual care alone or attention control:

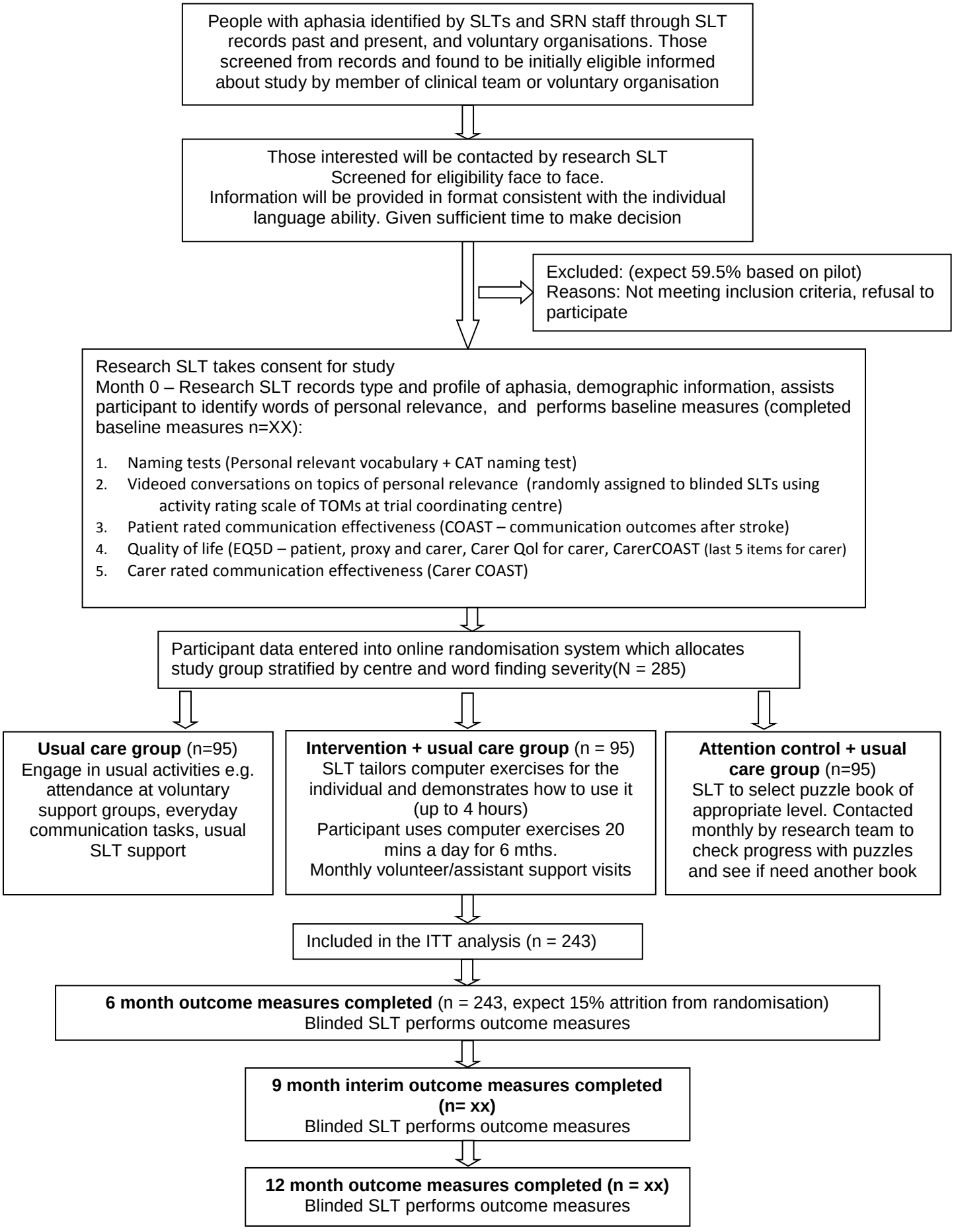
1. To establish whether self managed computerised speech and language therapy for word finding increases the ability of people with aphasia to use vocabulary of personal importance (impairment).
2. To establish whether self managed computerised speech and language therapy for word finding improves functional communication ability in conversation (activity)
3. To investigate whether patients receiving self managed computerised speech and language therapy perceive greater changes in social participation in daily activities and quality of life (participation).
4. To establish whether self managed computerised speech and language therapy is cost effective for persistent aphasia post stroke.
5. To identify whether any effects of the intervention are evident 12 months after therapy has begun.

Secondary objectives include investigating the generalisation of treatment to retrieval of untreated words (impairment); the carer perception of communication effectiveness (participation) and the impact on the carer quality of life; and identification of any possible adverse events. The primary outcome time point will be 6 months after randomisation (end of treatment) with further follow up at 9 and 12 months.

3. Trial Design

The study will use a pragmatic, parallel group randomised controlled adjunct trial design – all participants will receive usual care -comparing outcomes for people with persistent aphasia 4 months or more post stroke who are randomly allocated to either:
1) Usual care
2) Self managed computerised speech and language therapy in addition to usual care
3) Attention control in addition to usual care.

Figure 1: Flow of participants through the trial (Consort diagram)



Blinding

This is a single blind study. The patient participants are not blind to their treatment allocation. The SLTs performing baseline assessments will do this prior to randomisation. A second SLT at each site, blinded to group allocation will perform 6, 9 and 12 month follow up assessments as in the pilot study. The SLT setting up the treatment will ask participants not to discuss treatment with the person coming to carry out follow up measures. It is possible that un-blinding will happen during conversation and the SLTs will be asked to record instances of this. A primary outcome is functional communication in conversation. Video recordings of conversations at baseline, 6, 9 and 12 months will be presented in random order to SLTs in the project coordinating centre to rate, blind to treatment allocation and follow up time.

Allocation schedules will be kept centrally and at site. Measures will be taken by sites to maintain blinding of the research SLT who will conduct outcome measures.

Duration

Each participant will be in the trial for 12 months. Participants will be identified and recruited over an 18 month period in total, and 15 months at each site. Each participant will receive their intervention for 6 months with follow ups at 6 months, 9 months and 12 months. Follow-ups should be carried out in the month following each time-point (e.g. 6-7 months, 9-10 months, 12-13 months).

There are no formal statistical criteria for stopping the trial early. Decisions to stop the trial early on grounds of safety or futility (with regard to recruitment) will be made by the Trial Steering Committee. Progress of the study will be assessed against progression criteria after approximately 22 months.

Data Source

Names, addresses and telephone numbers will be previously recorded on NHS databases, along with identification of having had a stroke with resulting aphasia. This only applies to those recruited from NHS caseloads.

5. Selection and withdrawal of participants

Refer to Appendix 1 for flow diagram of identification and first sift for potential participants.

Participant Identification

Participants will be recruited from approximately 20 speech and language therapy departments across the UK, both from current and past patient records and contacts with longer term voluntary support groups. Speech and language therapy departments agreeing to participate in the project will be asked to identify potential participants. The study will also be advertised using **posters** (to include images selected by the PPI group) in libraries and GP surgeries in each locality so that potential participants unknown to SLT departments and voluntary groups can self present to the local research team. Potential participants (those identified as having had a stroke, and a diagnosis of aphasia, 4 months or more post stroke, aged 18 years or above) will be contacted by the research speech and language therapist in each local project centre. This person will be a member of the local clinical team. The participant will be sent project summary information letting them know about the study which is followed up by a telephone call 1-2 weeks later to establish whether they are interested in knowing more about the study or not. If they are interested, the research speech and language therapist will make an appointment to visit them at home at a time convenient to the potential participant.

Speech therapy databases will be reviewed to identify potential participants. These databases will usually include personal information such as full name, date of birth, contact details, GP, reason for admission to hospital/speech therapy service etc. This information will therefore only be seen by speech and language therapists who are part of the clinical team treating or having treated these patients and will not be accessed by any members of the wider research team. A screening log will be completed by the therapist who is identifying potentially eligible patients from the database. Data recorded and sent back to the Clinical Trials Research Unit will include unidentifiable information including initials, gender and age. We also wish to collect the post code sector (not full post code) to see if socioeconomic area is a factor in participation. The reason for not arranging an appointment will be captured on the screening log if freely given.

Planned inclusion and exclusion criteria

Participants will be included if:

1. Aged 18 or over
2. Diagnosis of stroke(s)
3. Onset of stroke at least 4 months prior to randomisation
4. Diagnosis of aphasia, subsequent to stroke, as confirmed by a trained speech and language therapist.
5. Ability to score 5-43 / 48 on the CAT Naming Objects sub-test [25] [Mild 31-43, Moderate 18-30, Severe 5-17]
6. Ability to perform a simple matching task in StepByStep© with at least 50% accuracy (score of at least 5/10; to confirm sufficient vision and cognitive ability).
7. Ability to repeat at least 50% of words in simple word repetition task in StepByStep© program (score of at least 5/10).

Participants will be excluded from the study if:

1. They have another pre-morbid speech and language disorder caused by a neurological deficit other than stroke. (A formal diagnosis can be reported by the participant or relatives and confirmed by the recruiting speech and language therapist).
2. They require treatment for a language other than English (as the software is in English)
3. They are currently using the StepByStep© computer program or other computer speech therapy aimed at word retrieval/naming.

Many people post stroke will have physical impairment which makes a standard computer difficult to use. If allocated to the computer intervention, appropriate ways of accessing the computer speech therapy will be provided such as the use of tracker balls, therefore physical disability is not an exclusion criterion. There is no maximum amount of time post stroke for inclusion in this study as treatment efficacy was shown in the pilot study for participants of 10 years and more post stroke.

Refer to Appendix 2 for flow diagram of recruitment and assessments.

Screening for eligibility

At the first visit to the potential participant, before providing detailed information about the study, the research speech and language therapist will confirm whether or not the person is eligible. They will request verbal consent to carry out the naming test of the Comprehensive Aphasia Test [26]. This test is used in routine practice and will establish the severity of the

word finding deficit. If the word finding score is less than 5 (10%), or greater than 43 (90%), an explanation will be given that this type of computer therapy is not suitable for them. They will be thanked for their time but no more information about the study will be provided. If they are still interested in computer based therapies, they can be directed to the aphasia software finder http://www.aphasiasoftwarefinder.org (last accessed on 24 Oct 2013) developed to help patients with aphasia identify software that is most suitable for them. If the potential participant has eligible word finding scores, the research speech and language therapist will ask them to have a go at a simple matching task on the computer to confirm ability to see the screen and perform simple tasks.

Recruitment

The level of support required to enable a person with aphasia to provide informed consent is dependent upon the severity and profile of the aphasia. In order to provide information in a format consistent with each individual's language ability, a Consent Support Tool (CST) will be used. In the absence of any other published tool to identify the most appropriate style of information to provide on an individual basis, this consent support tool was developed and refined with the assistance of people with aphasia and their carers' in the Patient and Public Involvement (PPI) advisory group during the pilot study and has been validated in a further piece of work [27]. The research speech and language therapist at each site will request verbal consent from the potential participant to carry out part A of the CST (10 minutes). The result will indicate which style of information they are most likely to understand. Three different styles of information sheet are available to enable as many participants as possible to be involved in their own decision whether to consent to their participation in this study. Patient information sheet 1 is in large print with key words emboldened (for those who can understand written paragraphs). Patient information sheet 2 is for those who can read simple sentences but not full paragraphs. It follows standard aphasia friendly principles with one idea presented per page in short simple sentences of large font. Key words are emboldened and each idea is represented by a pictorial image. Patient information sheet 3 is for those who can understand with significant support. Each idea is presented on a power point slide with simple text, key words emboldened and picture support. Each sentence should be presented in turn by the speech and language therapist, read aloud to the potential participant and supported with gesture, showing objects and drawing. The next sentence is then presented. The consent support tool will also identify individuals for whom carer assent is required (those with severe aphasia who find it difficult to understand information, even with the support of adapted/pictorial information formats). These potential participants will be shown a short video clip of the computer programme being used and of someone working on a puzzle book. Participants will be given sufficient time to consider their participation before informed consent is taken by a research SLT. Participants providing their own informed consent will be provided with an aphasia friendly consent form and asked to initial all boxes before signing. If potential participants with severe aphasia indicate an interest, a relative (in Scotland the person's legal representative or nearest relative) will be asked to read the full information sheet 1 and a covering letter detailing their responsibility, and will be asked to sign a carer declaration on behalf of their relative with aphasia (in Scotland they will be asked to sign a consent form). At the request of the PPI group, all patients will be given a copy of either the standard information sheet or the aphasia friendly information booklet to keep and a picture summary on one side of A4 paper. For those participants with a carer, the carer should be asked if they are willing to complete some outcome measures related to their own quality of life and perception of their relative's communication ability. They should be provided with the carer information sheet detailing their potential involvement and asked to sign a consent form.

Withdrawal

Participants may withdraw from active participation in the study on request. Individuals removed from active participation in the intervention will not be replaced and will be followed up for all outcome information unless they also request no more follow up. Reason for withdrawal from the intervention, if known, will be recorded on a CRF.

6. Randomisation and enrolment

After signing the consent form, and following baseline assessments, the participant will be randomised to one of the three trial intervention arms. Randomisation will be performed by an online randomisation system developed and maintained through the Sheffield CTRU. The randomisation sequence will be generated in advance by the trial statistician. Randomisation will be stratified by centre (as heterogeneity between centres is expected), and according to severity of word retrieval based on percentage scores on the naming test of the Comprehensive Aphasia Test (Mild 31-43, Moderate 18-30, Severe 5-17). The research speech and language therapist who took the consent will either enter the participant demographic details, word finding severity, recruitment centre and confirmation of consent directly onto the randomisation system (if internet access easily available), or will contact the central trial team at the University of Sheffield by telephone and provide these details for a member of the core team to enter into the randomisation system. The research speech and language therapist will then inform the participant which group they have been allocated to and draw their attention to the description of this group in the information sheet.

7. Trial treatment

1. Usual care control arm

Usual care for this pragmatic study may consist of participation in a range of activities to a greater or lesser extent. Usual care varies across the country in terms of type, frequency and length of provision, and is dependent upon available resources in each locality. Findings from the pilot study confirmed that usual care four months or more following a stroke may include the following:

1. Face to face speech and language therapy support focussing on assistance with compensatory strategies, provision of communication aids or psychological support with adjustment to the aphasia.
2. Attendance at support groups such as Stroke Association 'Communication support groups', Chest Heart and Stroke Scotland's Voluntary Support Service groups, peer support groups, groups organised by other charities/voluntary organisations.
3. Informal communication support provided through conversation with family and friends.
4. Some people may still receive speech and language therapy interventions targeting the language impairment itself (reading, writing, speaking, and understanding) in some areas of the country but this was not evident in the 84 people assessed for eligibility in the pilot.

Those who are randomised to the usual care group will not receive any project specific intervention. Usual care will be recorded on the baseline CRF.

2. Self managed computerised therapy intervention

A structured intervention is proposed in addition to usual care as tested in the pilot study. The intervention targets word retrieval as it is one of the challenges most frequently experienced by people with aphasia, restricting their communication. The intervention was designed by speech and language therapists specialising in aphasia intervention and use of computer software for treatment. The three key components of the intervention were designed to incorporate key factors that research suggests positively influence aphasia therapy outcomes combined with practical considerations:

1. Qualified SLT assessment of participant's language profile to tailor computer exercises using the StepByStep© software (version 5) so that they target the specific language deficit identified. Creation of exercises using target words of personal relevance to the participant.
2. Daily independent word finding practice with the tailored computer exercises by the participant for 6 months.
3. Volunteer/SLT assistant support to enhance adherence to the computer exercises and to encourage transfer of new words into functional daily situations.

1. Qualified speech and language therapist assessment, tailoring of exercises and monitoring:

The research SLT (one at each site) will tailor computer exercises to the individual using 100 words of personal relevance chosen by the participant. There is a large bank of photographs within the computer programme and if something extra is required (e.g. picture of a family pet, grandchild, or favourite football team) it can easily be photographed digitally and added by the SLT. The computer software [28] enables the SLT to select exercises using these words that follow steps in the therapy process that the therapist would take if delivering it face to face. The SLTs delivering this intervention will receive training on how to set up appropriate exercise steps during the site initiation visit. The SLTs base the selection of exercises on language skills demonstrated in the initial language assessments. To maintain fidelity of the intervention, they will be shown the therapy manual accompanying the StepByStep computer therapy approach, and to evaluate fidelity they will record which exercise steps are selected based on the skills identified. The SLT will provide initial demonstration of the software exercises and spend up to 2 hours (spread over 2-3 sessions) checking that the individual is able to use the software and monitoring the appropriateness of the tailored exercises. The SLT will also review the need for additional pieces of hardware such as tracker balls in order to make it physically possible for participants to use the computer.

2. Regular self managed practice

The participant will then be asked to work through the exercises on the computer aiming to practice each day for 20-30 minutes. Participants will be given a 6 month period to work though the therapy material on the computer and practice using the new vocabulary in their daily lives. Practise with the computer for a minimum of 20 minutes 3 times a week at home on average across at least a four month period will be considered per protocol. The amount of practice will be captured automatically by the computer programme. This is less than the 2 hours a week of therapy suggested to be minimally effective practice intensity in the literature, but accounts for periods of illness and holiday expected to occur in a 6 month period. As this is a pragmatic trial, those participants who have the software installed on their own

computers will not be prevented from continuing to practice if they wish, following the 6 month supported intervention time. If computers were loaned, they will be taken back after 6 months to give to a new participant (as permanent loan of equipment would be unusual in practice).

3. *Volunteer support to assist with treatment adherence and carry over into daily activity*

To enhance treatment compliance, the SLT will provide training to local volunteers who already have a working relationship with the SLT department (based in NHS trusts, local voluntary organisations, or student SLTs) or SLT assistants based in the department. They will use the 3 hour training programme and instruction book developed and evaluated during the pilot study. The volunteer will be asked to visit the participant for a minimum of 4 hours (the recommendation will be once a month for an hour, or every two weeks for half an hour (to suit the patient), carrying out the following tasks:

1. provide technical assistance
2. observe and encourage use of computer exercises
3. check results and discuss difficulties
4. assist participant to move on to harder tasks in the therapy process pre-programmed by the SLT
5. encourage the use of new words in everyday situations through conversation and discussions with family about how to encourage use
6. set up new vocabulary sets if all 100 words have been completed

The participants will be able to contact the volunteer/SLT assistant by telephone for technical advice on computer use between planned visits if necessary. Volunteers/SLT assistants will be invited to meet together with their peers and the research SLT for an hour every two months for support and discussion of issues arising and new practice material required by their participant. After each planned visit to the participant the volunteer/ therapy assistant will complete a feedback form giving the SLT feedback on what they did in the session, what went well/not well and any issues/questions. The volunteer may contact the SLT by e-mail or telephone between support sessions to report any concerns/difficulties.

The majority of the practice time involved in the intervention is self managed by the participant through regular use of the aphasia computer software. As described above, the intervention will be tailored, initiated and monitored by a speech and language therapist (approximately 4 hours therapy time in total), and supported by volunteers/ SLT assistants (minimum 4 hours face to face contact time). These times are based on averages found in the pilot study. The SLTs, SLTA's and volunteers will be asked to keep diaries of resource use showing direct and indirect (telephone, computer set up) time spent and therapist grade. If a participating SLT department has existing access to the StepByStep telehealth module, therapists or therapy assistants could use this as a source of monitoring which will be recorded as indirect time spent. Therapists will limit this method of monitoring to once every two weeks. Resource use will include the cost of the software. This will be installed by the SLT on participants' home computers. If any participant does not have access to a computer, the software will be loaned on a project lap top. In the pilot study, 50% of participants needed to borrow a lap top, therefore each of the 20 recruitment centres will be asked to make 2-3 lap tops available (5 are expected to be randomised to the intervention at each site). Some departments have existing lap tops. If departments need to purchase lap tops for the purpose of treatment in the study, the cost would need to be met through excess treatment costs. A small number of lap tops will be made available for loan from University of Sheffield for centres where particular difficulties are encountered.

3. Attention control arm

The third group in this study intends to control for the potential impact of elements of the intervention which of themselves do not provide or require specific speech and language intervention.

Participants randomised to this arm will be provided with generalised non language based activities to carry out and general attention in addition to usual care. On allocation to this group, the SLT conducting baseline assessments will provide books of standard puzzles that can be purchased from most supermarkets or high street shops. Each book will contain enough activities for one to be carried out each day for at least a month. Examples of puzzles include getting through a maze, spotting the difference between pictures, matching objects that are the same, games of noughts and crosses, word searches etc. The SLT will provide age appropriate puzzle books that match the participant's linguistic and cognitive ability as indicated by the baseline assessments. Puzzle books will be colour coded into levels of easy, medium and hard by the clinicians on the research team centrally and a leaflet will be provided to give SLTs guidance on skills required for each level.

A member of the research team will contact the participants or their carer by telephone or e-mail (whichever is preferred by the participant) once a month to mimic the attention provided by volunteers in the intervention arm. They will ask if they are enjoying the activities, how many they have managed to do, whether they would like a new puzzle book sent to them for the coming month and whether they would like the same level of difficulty or an easier or harder one. The participants will also have access to these contact details to enable them to ask for easier or harder books at any time if necessary, again, mimicking the access to the volunteers/SLT assistants and type of attention available in the intervention arm.

The StepByStep© software is central to the intervention described in section 3. The software is produced by Steps Consulting Ltd. As the software constitutes an excess treatment cost, it will be purchased from Steps Consulting Ltd by the NHS trusts acting as study sites. Each participant in the intervention arm will be provided with the software and the SLT will install it on their own computer or one loaned by the NHS trust or project team. Installation is by CD Rom or data stick.

4. Evaluation of intervention fidelity

Evaluation of intervention fidelity requires assessment of intervention adherence as well as other factors that moderate adherence such as quality of delivery and participant responsiveness [29]. As a complex intervention it is vital that we understand how the StepByStep approach is being delivered in the Big CACTUS trial.

<u>Existing data collection to inform fidelity assessment</u>

As this is a self-managed intervention, adherence of the participants in using the intervention as intended will be monitored through volunteer or assistant visits with reminders to practise daily and assistance with using the full range of exercises set. The speech and language therapist will also monitor practice through feedback provided by the volunteer or assistant and record the time period in which the software was available for the participant. In addition, the software will automatically capture the amount of practice on a key file which will be returned to the study coordinating team centrally to be reviewed for total practice time and patterns of practice (see page 18).

Information about adherence of the SLT and volunteer/ therapy assistant delivering the intervention will be collected through diaries of direct and indirect time spent with the

participant (see page 24) including session number, duration and content. The speech and language therapists delivering this intervention will receive training on how to set up appropriate exercise steps. To enable monitoring of the intervention fidelity, they will be asked to complete a checklist which guides their selection of exercises based on the participant language profile identified during assessment. These will be reviewed centrally by the study quality monitor. The key files from the participants' software will enable comparison of a random selection of exercises provided with the corresponding checklist completed.

Additional data to be collected to inform fidelity assessment

In a separate study with key stakeholders about the StepByStep approach it has been suggested that some additional measures should be added to explore how the intervention was delivered and received.

The knowledge and skill of the SLT in conducting the trial and delivering the intervention has already been assessed by a quiz completed 5 months after they randomised their first participant to check learning from the training. However, in order to explore changes in the therapist's knowledge about the intervention over time we will also ask them to complete the intervention section of the quiz at 10 and 15 months. An information sheet will be provided informing the SLTs how we intend to use the information from the 10 and 15 month time points, and retrospectively from the 5 month time point. Participants will be asked to sign and return a consent form if they are willing to participate.

The volunteers/therapy assistants' relationship with the participant is a key component of the intervention as they will be the main source of support during the intervention. Collecting data directly from the participants with aphasia would be the most reliable way of measuring this relationship, but due to the complexity of existing alliance scales they would not be suitable to use with this population. As such the volunteers/therapy assistants will be asked to complete the Working Alliance Inventory – Short Revised – Therapist (WAI-SRT) version after their three month visit (e.g. if visiting once a month after 3rd visit, but if visiting once every two weeks after 6th visit) to the participant [30]. An information sheet will be provided prior to their completion of the WAI-SRT to ensure that they understand how their data is being used and they will be asked to sign and return a consent form if they are willing to participate. The alliance scale can be sent back to the research team directly by the volunteer/therapy assistant or it can be returned via the SLT.

Three additional questions will be added to the patient diary, which is there to record any difficulties or negative impacts of the intervention (see table 1, page 24), on the third occasion it is sent out (e.g. 3 months into the intervention period). Reading the questions will require a certain level of written understanding, as such they will only be sent to participants who have a carer involved in the study or demonstrated written understanding of 3 key words or more on the Consent Support Tool. The questions are about difficulties that might impact on the patient's adherence to the intervention, including: 'how motivated are you to practise your StepByStep computer therapy excises?', 'how easy is it to use the StepByStep computer therapy?' and 'are the words on the StepByStep computer therapy words you want to say?'. Participants will be asked to circle how they feel on a visual analogue scale from 1-10. There is a box to be selected by the carer/relative if they are completing it on behalf of the participant. The Big CACTUS patient and public involvement (PPI) group contributed to the development of the additional questions deciding which pictures and wording would best help them to understand the questions.

Analysis of intervention fidelity

Descriptive statistics will be used to present the results of the fidelity evaluation detailing the level of participant, SLT and volunteer/therapy assistant adherence and other potential moderators of adherence, such as therapist skill, volunteer/assistant alliance and motivation. Analysis will be conducted to explore the baseline characteristics (e.g. age) associated with participant adherence to the intervention to inform guidelines for clinicians about who can manage intensive therapy practice using the StepByStep approach. In addition, to contribute to the continued development of the StepByStep approach a component analysis will be conducted to identify the essential components of the intervention, by exploring which components of the intervention (practice time, motivation, alliance between volunteer/therapy assistant, etc.) are associated with a positive primary endpoint.

8. Assessments and procedures

Outcome measures

Primary

1. The change in word finding ability of words personally relevant to the participant will be measured by a picture naming task (100 words with a maximum of 2 points each). The word finding score will be expressed as a percentage of the total score and change in the percentage 6 months from baseline will be calculated.

2. Change in functional communication will be measured by blinded ratings of video recorded conversations between a SLT and participants, using the activity scale of the Therapy Outcome Measures [31]. Conversations will be structured around topics of personal relevance to the participants by the SLT performing baseline measures to ensure sensitivity of the measure. The same topic guide will be followed by blinded SLTs performing outcome measures. Independent SLTs blinded to treatment allocation and measurement time point will rate the videoed conversations at the project coordinating centre. We will carry out a benchmarking session using the TOMS with potential raters to get consensus as to how the TOMS will be used in this project, followed by inter and intra rater reliability tests using 10 practice videos. Raters selected for final rating of all participant videos will have intra rater reliability of at least 70% practice videos rated within 0.5 between time 1 and time 2, and inter- rater reliability of at least 70% videos rated within 0.5 of the median scores at both time points. Refer to separate document 'Process for selection of TOMS raters and scoring procedure October 2016' for additional detail.

Key secondary

Improvement in patient perception of communication will be measured using the COAST at 6 months - a patient reported measure of communication related activity, participation and quality of life validated for evaluating SLT interventions in the HTA ACTNoW project [32].

Other secondary

Evidence of treatment effect will be measured by repeating all outcome measures at 9 and 12 months from baseline in addition to the primary end point of 6 months. The 9 month time point is included as an interim measure as withdrawal from the study was found to increase over time in the pilot study.

Use of learnt vocabulary in the context of conversation will be measured using a checklist of target words during rating of the videoed conversations.

Generalization of treatment to retrieval of untreated words will be measured using the naming test from the Comprehensive Aphasia Test.
Carer perception of communication effectiveness will be measured using the Carer COAST [33]. Adverse events/effects of treatment will be reported through diaries.

Cost effectiveness

A cost-utility analysis will be undertaken from the NHS and personal social service (PSS) perspective. The cost effectiveness outcome will be the incremental cost effectiveness ratio, where effectiveness is measured in quality adjusted life years (QALYs). The incremental analysis will include all three of the trial arms. Resource costs will be estimated for patients including intervention software and hardware, and SLT input time, combined with standard costing sources. Volunteer time will also be recorded and costed for inclusion in a supplementary societal analysis.

The EQ5D will be administered at all time points and combined with standard valuation sources to measure QALYs gained in each treatment arm. An accessible version of the EQ5D designed and tested for people with aphasia in the pilot study will be completed by participants and the carers will complete the standard version by proxy. Carers will also complete the EQ5D carer, the last five items of the CarerCOAST, and CarerQol for themselves as indicators of their quality of life.

Table 1. Summary of outcome measures

Outcome	Measure	Participant time	Method of collection
Change in word finding ability	Naming of 100 personally relevant words	30 mins	Taken at baseline by research SLT recruiting participant prior to randomisation. 6, 9 and 12 months by blinded SLT.
Change in functional communication	10 minute videoed conversations structured around topics of personal interest. Activity scale of TOMS used to measure conversational ability	10 mins	Conversations at baseline by research SLT, Blinded SLT follows same topic guide at 6, 9 and 12 months. Videos randomised and rated centrally by blinded assessors.
Change in patient perception of communication & quality of life	COAST self reported questionnaire.	10 mins	Administered by research SLT at baseline, blinded SLT at 6, 9, and 12 months.
QALY's for cost effectiveness	EQ5D for patient and carer (accessible, carer and by proxy)	10 mins	As above

Generalisation to untreated words	Naming test from Comprehensive Aphasia Test	15 mins	As above
Carer perception of change in communication	Carer COAST **(first 15 items)**	8 mins	As above
Carer quality of life	CarerCOAST **(last 5 items)**	2 mins	As above
Carer quality of life	CarerQol	10 mins	As above
Negative effects of treatment	Patient **diary** to record any difficulties, negative impacts of intervention		Patients/carers – central team to send monthly letter reminding to send back in prepaid envelope.

Data recorded during intervention period

Initial assessment will be performed by the local research SLT once informed consent has been given. This will include collection of demographic data: aphasia type, age, gender, time post onset of stroke, and type and location of stroke (if known). Numbers of personally relevant words named correctly in response to picture presentation will be recorded. Pictures from the naming test of the Comprehensive Aphasia Test, not used in therapy, will be presented and the number named correctly will be recorded. Scores will be used to identify baseline naming severity for the stratified randomisation. Conversation topics will be identified from personally relevant vocabulary. A conversation of approximately 10 minutes will be video recorded. The topics and questions asked by the SLT in the baseline conversation will form a topic guide to be used in follow up conversations. Participants and carers will be asked to complete the COAST and carer COAST respectively as a measure of their perception of communication and quality of life. The participants will be asked to complete the accessible version of the EQ5D and the carers will complete the standard EQ5D by proxy, as well as the EQ5D carer, the last five items of the CarerCOAST and the CarerQol for themselves as indicators of quality of life.

Randomisation to treatment group will follow baseline assessments. During the intervention period, SLTs and SLTA's involved with the participants in all groups will be asked to complete a diary of direct and indirect time spent with the participant. Participants will be asked to complete monthly diaries reporting any adverse effects of the intervention.

All outcome measures will be repeated at 6 months (treatment end), and approximately 9 and 12 months from baseline to identify long term intervention effects. As the dropout rate increased after treatment end in the pilot, the primary outcome will be at 6 months. Follow-ups should be carried out within one month of each time-point.

A 3 month phone call (or visit if more appropriate) will be made by the PI to the participant to record usual care and adverse events or serious adverse events from the participant's perspective, in the last three months.

Procedures for withdrawal from the trial treatment or from the study

The participant/carer will inform the local research speech and language therapist if they want to discontinue the intervention. Regardless of the fact that participants are withdrawn from the trial treatment, every attempt will be made to follow up the participants unless they

specifically request withdrawal from the trial. Data collected up to this point will be included and analysed.

Discontinuation of treatment
If the participant becomes ineligible (for example due to a further stroke), they will be asked if they wish to continue participating in the study. If the participant no longer has the capacity to make that decision themselves, their carer/relative (in Scotland Legal Representative/nearest relative) will be asked to help make that decision after re-reading the information sheet. They will be asked to provide a signed carer declaration (in Scotland a signed carer consent form) following the same process set out for recruitment of participants lacking capacity. The participant will continue to be followed up unless they request otherwise. If the participant does not wish to continue or a carer cannot provide a signed declaration (in Scotland signed consent) in the event of loss of capacity, the anonymised data collected to that point will be retained for analysis but no more data will be collected.

Procedures for attempted follow-up of participants "lost to follow-up"
Participants will be considered lost to follow up if the local research speech and language therapist or the therapist conducting outcome measures fails to make contact to arrange an appointment after a minimum of 4 attempts (over a 4 week period). This applies to all baseline and outcome time points following written consent.

Site & Trial Closure Procedures
The end of the trial is defined as completion of all follow-up data collected and monitoring for the last visit of the last participant. At the point at which all CRF's have been collected and entered (or centres have failed to respond despite reminders) and all data have been entered and cleaned, closure of the database will be approved.

Safety assessments
Adverse events associated with the intervention are not anticipated given the low risk intervention (in line with similar studies managed by CTRU). However, if adverse events do occur these will be recorded by the therapist on the CRF and database. Adverse events do not need to be reported by fax to the CTRU.

Adverse events may include: increased fatigue, fits or seizures, worsening vision or visual difficulties, increasing frequency or severity of headaches, accidents (e.g. falls) or injuries.

If a hospital admission, or any other event considered serious occurs, these will be reported as Serious Adverse Events (SAEs). We will not report further stroke related events as SAE's as these are expected within this population.

The following criteria will be used when assessing SAEs:

Intensity (severity):
1. Mild - does not interfere with routine activities
2. Moderate - interferes with routine activities
3. Severe - impossible to perform routine activities

Relationship to the trial activity (Computerised speech therapy or puzzle books):
1. Unrelated - There is no evidence of any causal relationship.

2. Unlikely - There is little evidence to suggest there is a causal relationship. There is another reasonable explanation for the event (e.g. the participant's clinical condition).
3. Possible - There is some evidence to suggest a causal relationship. However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition).
4. Probable - There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
5. Definite - There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.
6. Not assessable - There is insufficient or contradictory information which cannot be supplemented or verified.

Reporting procedures

SAEs will be reported in accordance with the CTRU Standard Operating Procedure PM004 Adverse Events & Serious Adverse Events.

The Principal Investigator (PI), or delegated investigator, is responsible for reporting all SAEs to CTRU in Sheffield by fax within 24 hours of discovering the SAE. All SAE forms will be stored in the Site File.

The CTRU will inform the Sponsor and CI, who are responsible for assessing the seriousness and reporting to relevant regulatory bodies, where appropriate. Serious Adverse events should be reported by the CTRU to the Head of Department/School, using the Sponsor's adverse event report form, as soon as possible and normally within 5 working days. A copy of the report should be kept in the Trial Master File for reference and a copy sent to the Head of Operations Section, Research and Innovation Services.

If an SAE is categorised by the PI/CI as related and unexpected the REC must be informed within 15 days of CTRU being alerted. This is the responsibility of the Trial Manager at the CTRU, or delegated person in their absence. This should be reported to the REC using the Safety report form for non-CTIMPs (Clinical Trial of Investigational Medicinal Products).

Reporting SAEs to relevant bodies will be conducted by the CTRU and will be documented in the Trial Master File. AEs and SAEs will be reported regularly in data reports to the oversight committees.

Participants using the computer intervention will also be recording any perceived negative effects in a diary which will be returned to the CTRU on a monthly basis and recorded on the CRF. This will be reviewed periodically by the Chief Investigator who will contact the local PI if considered clinically important (e.g. fatigue from computer use).

9. Statistics

Sample size:

The study aims to recruit 285 participants across 20-24 speech and language therapy departments (study sites/centres). The target for each site is 15 participants in total with 5 randomised to each of the three study arms.

The sample size of 285 patients in total (95 per arm) is the maximum sample size estimate across the two primary endpoints (word finding ability and functional conversation) and key secondary endpoint (patient perception of communication ability) for 90% power and a two sided significance level of 5%.

Assumptions for the sample size calculation:

For improvement in word retrieval the estimated effect size is 10%, with a standard deviation (SD) of 17.38%, from an analysis of covariance (based on results of the pilot study). For assessment of conversation the estimated effect size is 0.45 of a SD (with a correlation between baseline and outcome of 0.5 previously observed in the ACT NoW study). For patient-rated improvement using the COAST questionnaire the estimated effect size is 7.2, with a standard deviation (SD) of 13.5 (with an assumed correlation between baseline and outcome of 0.5). The observed dropout rate was 5 out of 33 (15%; 95% CI: 5 to 32%) in the pilot study, which translated to a completion rate of 28/33 (85%; 95% CI: 68 to 95%) [34].

Internal pilot

The initial phase of the study will be conducted as an internal pilot trial and will include clear criteria to inform decisions about progression. Data from the internal pilot will be included in the final analysis. The criteria will include features recommended by the NIHR HTA who have funded this research (e.g. recruitment as a percentage of full study recruitment targets and retention in follow up).

The internal pilot trial will be limited to six sites (>25% of the total), representative of the sites which will be in the substantive study. However, during this phase we will recruit and commence set up processes for all the intended sites. To limit the site set up to the internal pilot trial centres only would result in a delay of many months for the full study if it were to continue, with significant associated additional cost.
In accordance with the guidance on progression rules for HTA internal pilot trials the lag phase expected before recruitment reaches the target rate will be excluded. For the substantive study the lag phase includes the period for obtaining approvals, site recruitment and staff training. The progression criteria will be reviewed 8 months from site set-up of the 6th site in the internal pilot trial. We are estimating that this will be approximately 22 months from contract start.
Based on recruitment rates from the previously published pilot study we will aim to recruit participants at an average rate of 1 participant per site per month. At the end of the internal pilot trial phase the 6 pilot trial sites will have been recruiting for a minimum of 8 months. The progression will be based on achieving the following criteria:

Numbers recruited: The target for these 6 sites will be 36 participants. The progression target for numbers recruited from these 6 sites will be 30. This will be equivalent to the number recruited in total in our previous pilot study and will enable comparison with previous recruitment rates to confirm whether our projections for the substantive study are accurate. There will also be information available from other sites which have completed set up and started to recruit by 22 months, therefore we expect at least 40 participants to have been recruited by the end of the internal pilot phase in total.

Recruitment as % of full study recruitment targets: At the end of the internal pilot trial, progression will depend on having recruited 30 participants i.e. 10% of the total population recruited from 25% of the sites (NB this is only midway through the recruitment phase for these sites). If we only achieve this number, we would be on line to recruit only 80% of the sample size within the study period. We would then bring on the additional 4 contingency sites which are included in the costs to raise the recruitment to the sample size. If we did not meet this number it would indicate that the larger study was unlikely to be feasible.

Retention to first outcome measure time-point at 6 months (primary outcome): The sample size calculation is based on an attrition rate of 15% at 90% power. The progression criterion for retention will be set to ensure a minimum power of 80%. This will be achievable with a retention rate of 65% which will still ensure that the results are generalisable. In the pilot study, the retention rate was 85% with a 95% confidence interval of 68% to 95%. Thus, 65% is outside of the confidence interval from the pilot study.

Identification and retention of volunteers: Sites can provide support to patients in the intervention arm of the trial from paid speech and language therapy assistants or volunteers. Use of volunteers will be reviewed at the end of the internal pilot phase. It is expected that all participants in the intervention arm will be offered support from a volunteer who continues to provide the support for 6 months. Progression criteria for continued use of volunteer support will be set at 80% of participants having been offered a volunteer and 70% of participants continuing to be supported by the same volunteer for their 6 month treatment period. If these progression criteria are not achieved, continuation of the study will be with paid assistant support only.

In summary, 8 months after set up of the 6th site, our progression criteria indicating feasibility of the full trial will now be:

1. Recruitment of no fewer than 30 participants (10% of the target for the full trial)
2. A minimum retention rate of 65%

Patients with at least one post randomisation observation will be included in the analysis. Missing data will be described using summary statistics. All data collected will be summarised as appropriate. Data will be checked and cleaned prior blind to the actual treatment allocation. Data checking will be conducted throughout the study and prior to any analysis of the data.

Analysis

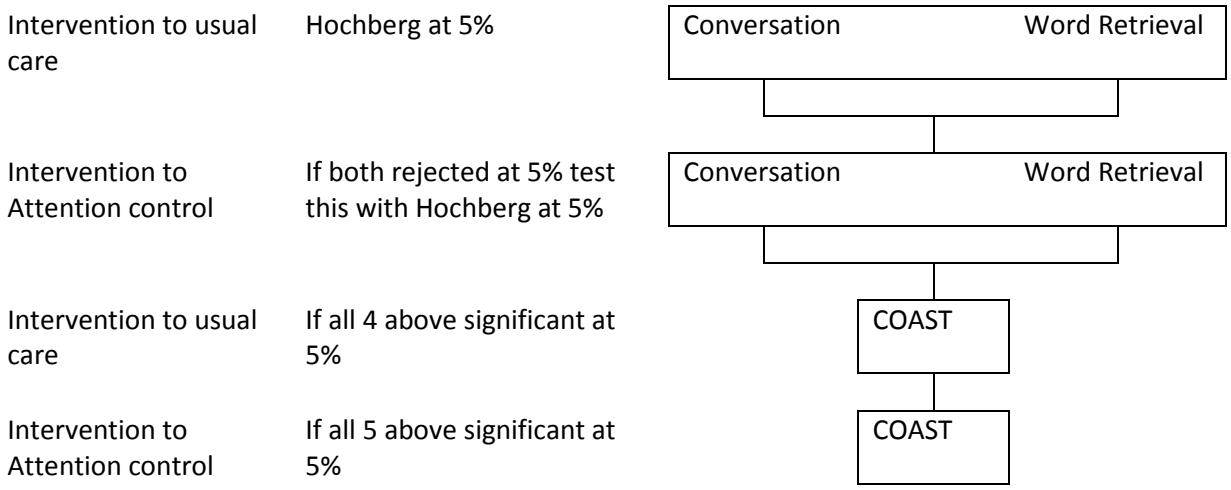
Primary and key secondary endpoints will be analysed using a multiple linear regression model adjusted for baseline measures and stratification factors. Treatment comparisons (Intervention vs Usual Care and Intervention vs Attention Control) will be based on Hochberg testing procedure to allow for an investigation of all three endpoints (co primary and key secondary) whilst maintaining the overall Type I error at 5% [35].

Significance will be declared for the comparison of Usual Care to intervention if and only if both primary outcomes, word retrieval and conversation, are significant at the 5% level or if either comparison is significant at 2.5%.

If and only if significance is declared for both primary outcomes, a similar comparison of Attention Control to Intervention will be made. Significance will be declared for the comparison of Attention control to Intervention if and only if both word retrieval and conversation are significant at the 5% level or if either comparison is significant at 2.5%.

If and only if significance is declared for the comparison of Attention Control to Intervention for both comparisons will the key secondary outcome measure (Patient perception of communication and related quality of life, measured using COAST rating scale) be used in a further comparison of Usual care to intervention. If and only if this comparison is significant at the 5% level will intervention be compared to attention control based on COAST.

Diagram 1. Schematic diagram of statistical testing procedure



Primary analysis will take an intention to treat approach (ITT) for all key measures and further exploratory analysis of participants who complied with the intervention will be undertaken using the same statistical tests according to the per protocol principle (PP). The primary time point is 6 months. Only patients with post randomisation observations will be included in the primary analysis at 6 months. As a sensitivity analysis responses will be imputed as appropriate with details provided in the statistical analysis plan.

For the change in word finding (expressed as a percentage) at 6 months from baseline, the measure of intervention effect will be the mean difference in change in word finding ability between the Intervention and Usual Care groups, and the Intervention and Attention Control groups. A multiple linear regression model adjusted for baseline word finding ability and stratification factors (centre and severity of word finding) as fixed effects (39).

The outcome will be modelled as a function of:

- word finding ability at baseline,
- treatment group (Usual Care, Attention Control, Intervention),
- centre as a fixed effect and,

- the severity of word finding as a fixed effect (mild, moderate, and severe).

Results will be reported and presented as adjusted mean difference in word finding ability between the Intervention and Usual Care groups, and the Intervention and Attention Control groups, and Attention Control and Usual Care (for exploratory), with its associated 95% CI and associated P-value.

Improvement in functional communication at 6 months assessed using activity domain of the TOMS, which is a co-primary endpoint will be analysed in the same manner as for the change in word finding ability but adjusted for baseline functional communication (rather than the change in word finding ability at baseline) in addition to stratification factors. Likewise, the endpoints at 9 and 12 months and other continuous outcomes will be analysed using a similar approach for exploratory purposes.

Key subgroup analysis

Analysis will be carried out on key subgroups:

1. Severity of word finding difficulty
   - Mild 31-43
   - Moderate 18-30
   - Severe 5-17

2. Length of time post-stroke

   The research team will undertake a blinded review to determine the groups by plotting the primary outcomes against length of time post-stroke.

3. Baseline comprehension ability based on the CAT sentence comprehension scores
   - Within normal limits 27-32 (based on CAT cut off score for normal/aphasic)
   - Mild comprehension impairment 18-26
   - Moderate comprehension impairment 9-17
   - Severe comprehension impairment 0-8

(0-8 = inconsistently understanding at 2 Information Carrying Word (ICW) level; 9-17 = consistently understanding at 2-3 ICW level/simple sentence structures but not complex sentence structures; 18-26 = some understanding of complex sentence structures but not consistent.)

<u>Economic analysis</u>
A cost-utility analysis will be undertaken from the NHS and personal social service (PSS) perspective. Due to the use of volunteers to help participants with their use of the computer program we will undertake a supplementary analysis taking a societal perspective. Costs will be estimated for individual patients including intervention costs and SLT support and co-ordination time combined with standard costing sources [36]. In the pilot study we collected other resource use data (on, for example, GP and hospital visits and prescribed medications) via patient and carer diaries but these did not show important differences between

treatment groups and we will not collect such data in the full trial. The EQ5D questionnaire will be administered at every data collection time point and will be combined with standard valuation sources to measure the quality adjusted life years (QALYs) gained in each treatment arm [37]. An accessible version of the EQ5D designed for people with aphasia was trialled in the pilot study. This has not been validated but represents a way in which EQ5D scores can be elicited directly from patients. We will administer this version of the EQ5D alongside the standard version which will be completed by carers (where the participant has a carer) by proxy. EQ5D and CarerQoL scores will also be elicited from carers, and a life satisfaction question will be included.
We developed a Markov model to estimate the cost-effectiveness of the computer intervention alongside our previous pilot study. Model parameters were informed by clinical data from the trial. We estimated that the intervention was likely to be cost effective, with an incremental cost effectiveness ratio (ICER) of £3,058 per QALY gained, however results were uncertain and the value of obtaining further (perfect) information was very high (EVPI was approximately £37 million). This model will be updated with data from the full trial. The third "attention control" group will be added to the model. Differences between costs and QALYs in the three groups will be described and an incremental analysis will be performed with ICERs calculated. Probabilistic sensitivity analysis will be undertaken to allow the production of cost-effectiveness acceptability curves [36] and value of information analyses [38].

10. Trial supervision

The University of Sheffield will act as sponsor for the trial. Two committees will be established to govern the conduct of this study: the Trial Steering Committee (TSC), and the Trial Management Group (TMG). These committees will function in accordance with Sheffield CTRU standard operating procedures.

The TSC will consist of an independent chair with clinical and research expertise in the topic area, and two other topic experts as the sponsor sees fit and as agreed by the grant awarding body. The TSC will meet at least every 6 months with more frequent meetings as necessary to supervise the overall conduct of the trial in accordance with SOP GOV002, and to monitor safety.

A part time CTRU Trial Manager and part time Speech and language therapist trial coordinator will contact the Chief Investigator and meet with the Assistant Director of the CTRU at weekly intervals while co-ordinating the trial. The TMG will meet at least at three-month intervals and will consist of: the Chief Investigator, the project collaborators, the trial managers and the study statistician. The TMG are accountable to the trial steering committee for the implementation of the trial and entails monitoring of the trial recruitment, data management, randomisation, patient safety, delivery of intervention, adherence to protocol, timescale, and budget management in accordance with SOP GOV001.

A separate PPI advisory group will meet approximately every 3 months. This group will consist of people with aphasia and their carers, and be facilitated by the speech and language therapist trial coordinator and the research assistant. Their role will be to assist with the design of patient information sheets, make recommendations regarding patient recruitment, assist with the lay interpretation and presentation of results and represent the study in the public domain. Due to the nature of the communication difficulties experienced by this group, attendance at the TSC and TMG where the conversation is fast paced and

academic is likely to be uncomfortable and unproductive. Meeting separately means discussions of topics relevant to the study can be carried out slowly with support of a trained speech and language therapist. The speech and language therapist coordinator will attend the TMG and TSC to feedback from this group.

In-house monitoring will be carried out by the research team at the central office in line with the Data Management and Monitoring Plan CTRU Standard Operating Procedure DM009.

11. Data handling and record keeping

Data management will be provided by the University of Sheffield Clinical Trials Research Unit (CTRU) who adhere to their own Standard Operating Procedures (SOPs) relating to all aspects of data management including data protection and archiving. Data entry onto a remote web-based data capture system will be completed by the research team at the central office or by research SLTs at participating sites. Data quality is the responsibility of the Sheffield CTRU Trial Manager and the CTRU Data Management Team. The detailed data management and data quality issues will be set out in a data management and monitoring plan (DMMP) in accordance with CTRU SOP DM009.

Participant confidentiality will be respected at all times. Completion of the case report form/s will be the responsibility of the PI at each participating site.
Participant names and contact details (including personal address, email and telephone numbers) will be entered on the study database by the PI. This resides on Sheffield University's Clinical Trials Research Unit in-house data management system. The system uses industry standard techniques to provide security, including password authentication and encryption using SSL/TLS.

Access to the system is controlled by usernames and encrypted passwords, and a comprehensive privilege management feature can be used to ensure that users have access to only the minimum amount of data required to complete their tasks. This can be used to restrict access to personal identifiable data.

Only members of the central research team who are responsible for contacting participants (for example, to send out puzzle books and newsletters) will have access to these details. Patient identifiable data on CRFs will be transferred between the research site and the co-ordinating centre (University of Sheffield) in order to perform data entry and to undertake additional research and monitoring activities set out in the Statistical Analysis Plan (SAP) and DMMP. Original CRFs will be retained in the investigator site file.

Data will be collected and retained in accordance with the Data Protection Act 1998. Anonymised trial data will be entered into a validated database system designed to a specification agreed between Sheffield CTRU and the Chief Investigator. The system will be accessible remotely via a web browser, with the data stored securely on a central server. Access will be controlled by the use of assigned logins and encrypted passwords. The system will have a full electronic audit trail and will be regularly backed up. Quality control procedures will be applied to validate the trial data. Error reports will be generated where data clarification is required. Output for analysis will be generated in a format and at intervals to be agreed between Sheffield CTRU and the Chief Investigator. Trial documents (paper and electronic) will be retained in a secure location during and after the trial has finished in accordance with CTRU SOP PM015 Study Files and Filing.

Archiving

All source documents will be retained for a period of 5 years following the end of the trial. Each investigator is responsible for ensuring records are retained and securely archived at site during the retention period and information supplied to the Chief Investigator. Where trial related information is documented in the medical records those records will be retained for at least 5 years after the last patient last visit. Access will be restricted to the sponsor and regulatory authorities.

Data from the study will be stored by the Central Office in accordance with the CTRU Archiving Standard Operating Procedure (SOP PM012) for 5 years following completion. Archived documents will be logged on a register which will also record items retrieved, by named individuals, from the archive. Electronic data will be stored in an 'archive' area of the secure CTRU server for a minimum of five years to ensure that access is future-proofed against changes in technology. Electronic data may also be stored (e.g. on a compact disc) with the paper files.

12. Data access and quality assurance

The sponsor will permit monitoring and audits by the relevant authorities, including the Research Ethics Committee. The investigator will also allow monitoring and audits by these bodies and the sponsor, and they will provide direct access to source data and documents in line with SOP QU001 and SOP DM009.

The study will use the CTRU's in-house data management system for the capture and storage of participant data. The system stores all data in a PostgreSQL database on virtual servers hosted by Corporate Information and Computing Services (CiCS) at the University of Sheffield. Industry standard techniques are used to provide security, including password authentication and encryption using SSL/TLS. Access to the system is controlled by usernames and encrypted passwords, and a comprehensive privilege management feature is used to ensure that users have an appropriate level of access to data required to complete their tasks. This can be used to restrict access to personal identifiable data.

Participant confidentiality will be respected at all times. Patient/participant names and contact details will be collected and entered on the database. Access to these personal details will be restricted to users with appropriate privileges. All other data will be anonymised and will only be identifiable by participant ID number, and no patient identifiable data will be transferred from the database to the statistician. The CRF will collect demographic details.

The data management system provides validation and verification features which will be used to monitor study data quality, in line with CTRU SOPs and the DMMP. Error reports will be generated where data clarification is required.

13. Publication

Dissemination will be undertaken through peer reviewed scientific journals and clinical and academic conferences. We will also ensure regular dissemination to the advisory group and provide regular project bulletins to interested parties via the study website.

The study team are obliged, by the terms of its contract, to notify the HTA programme of any intention to publish the results of HTA-funded work at least 28 days in advance of publication in a journal. This also applies to public oral and poster presentations. The Trial Steering Committee will be also be notified of publications which report the final output of the study.

14. Finance

The trial has been financed by the NIHR HTA and details have been drawn up in a separate agreement.

15. Ethics approval

The trial will be submitted to a NHS Research Ethics Committee (REC) through the Integrated Research Application System (IRAS). The approval letter from the ethics committee and copy

of approved patient information leaflet, consent forms and CRF/ questionnaires will be sent to the CTRU before initiation of the study for each site and participant recruitment.

The trial will be submitted for NHS research governance approval for each recruitment site.

16. Regulatory approval

This trial will be submitted for NHS R&D approval by participating sites.

17. Indemnity / Compensation / Insurance

The University of Sheffield has in place insurance against liabilities for which it may be legally liable and this cover includes any such liabilities arising out of this research project.

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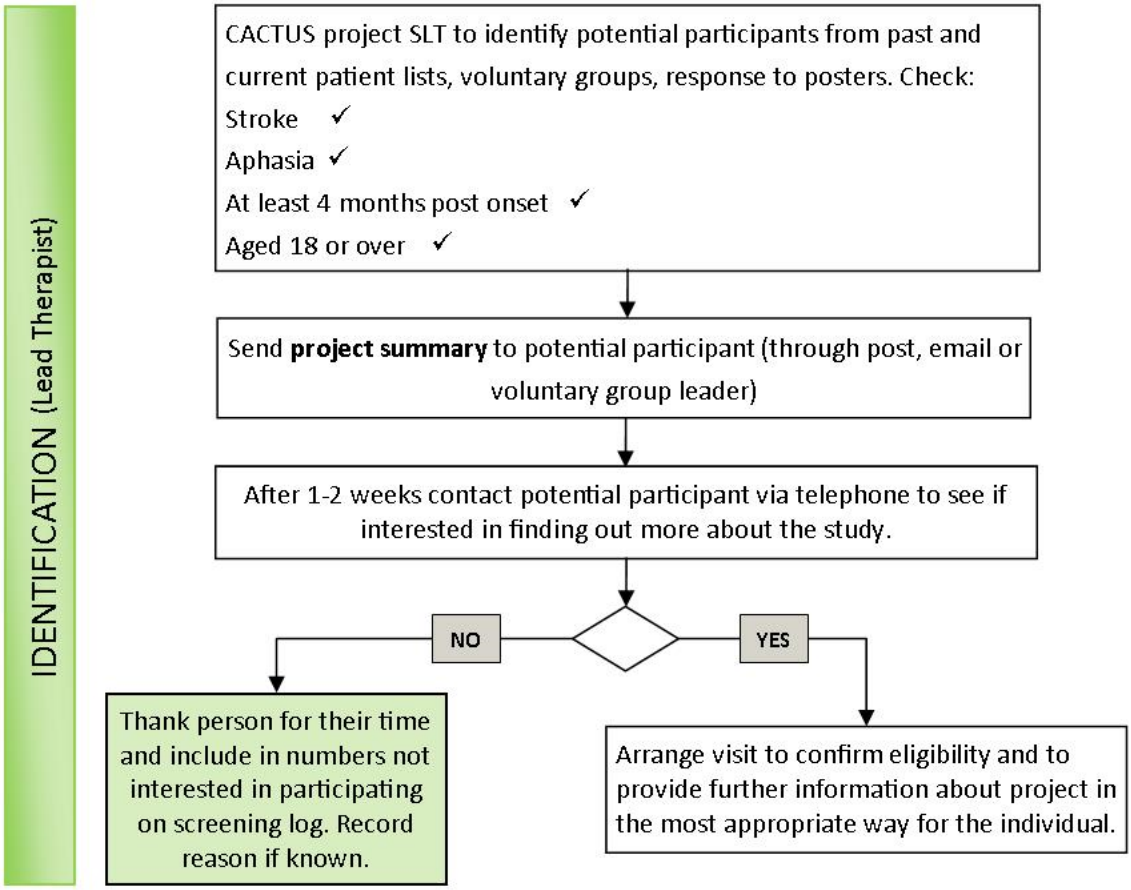
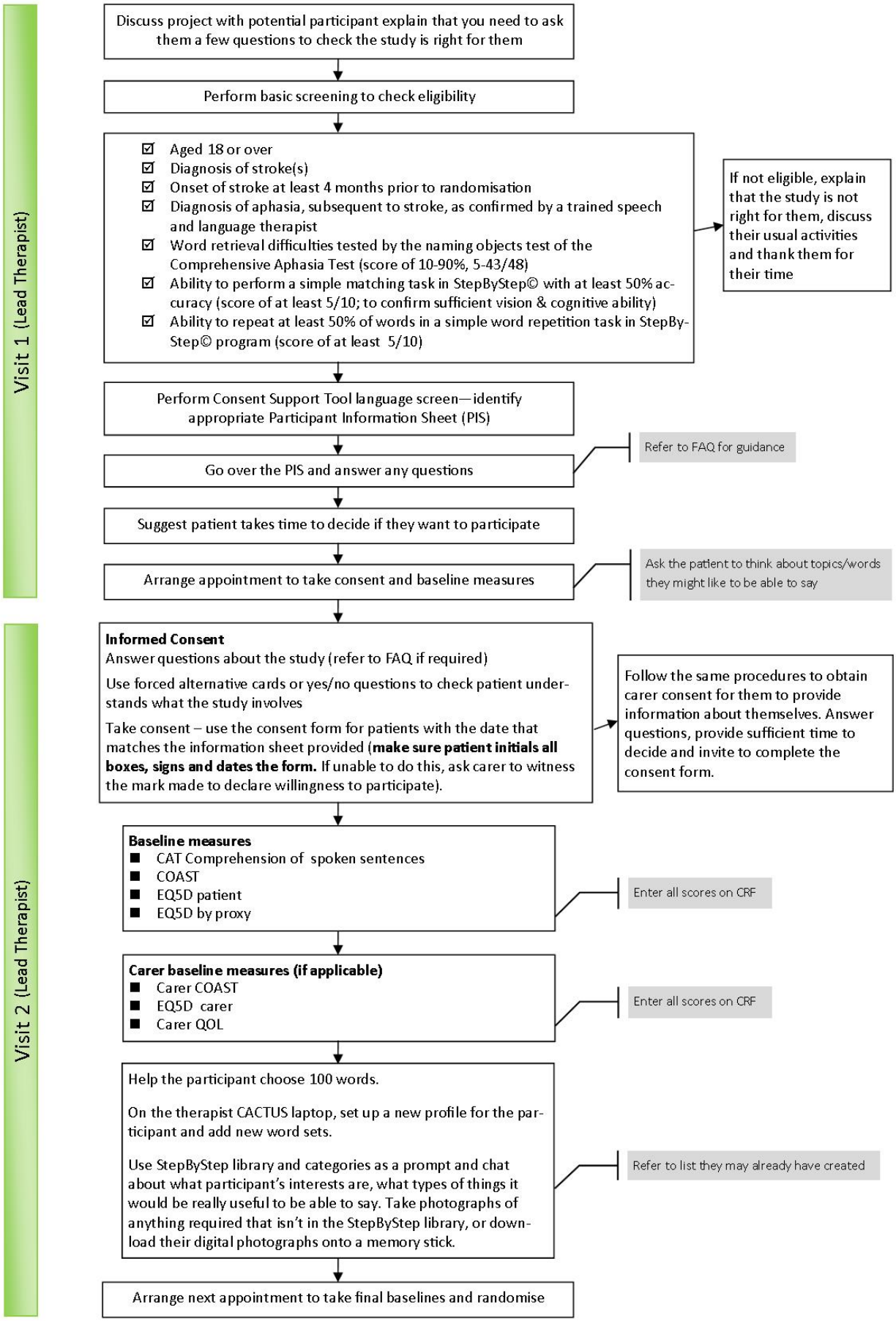
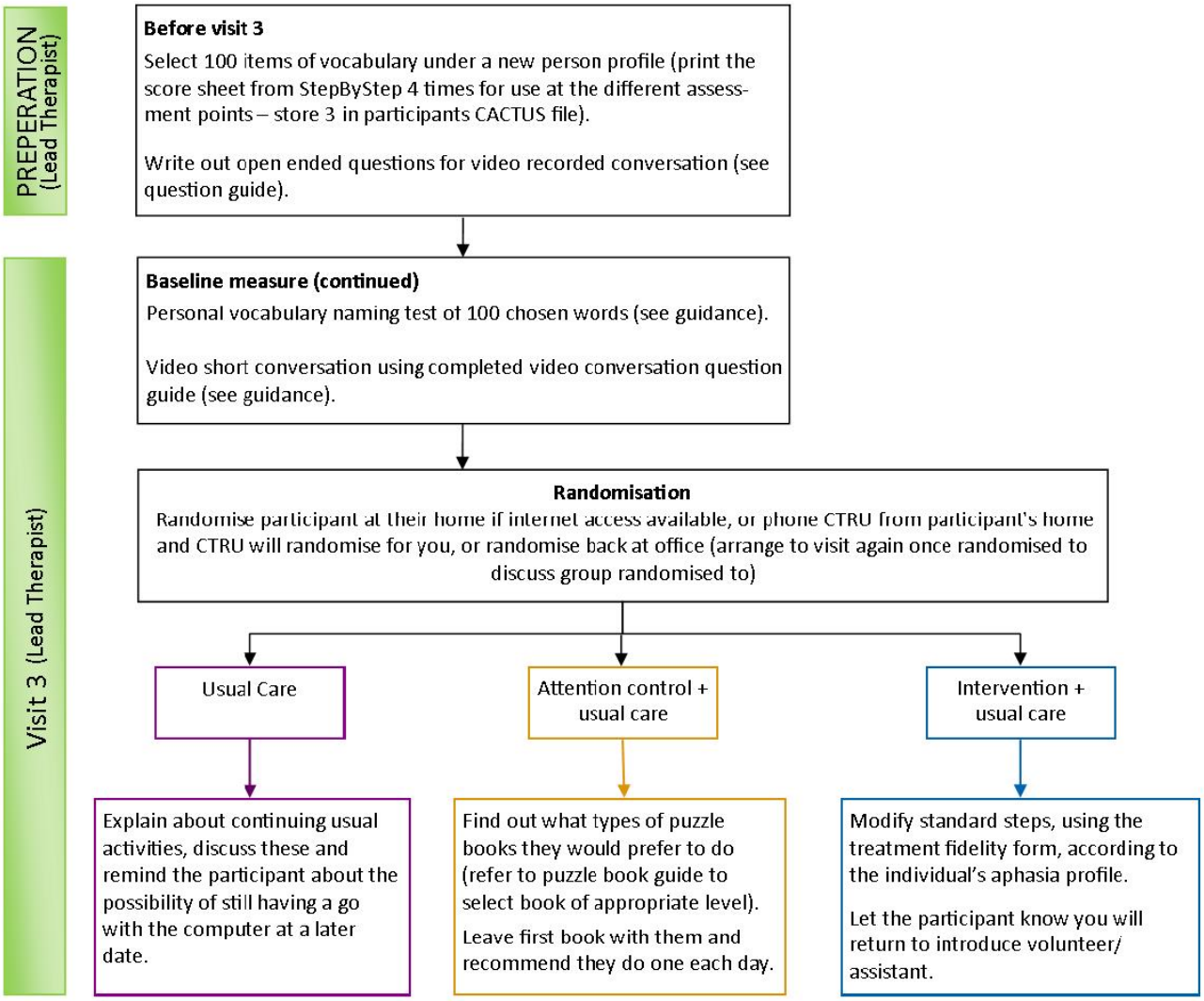
Appendix 1: Identification flow diagram

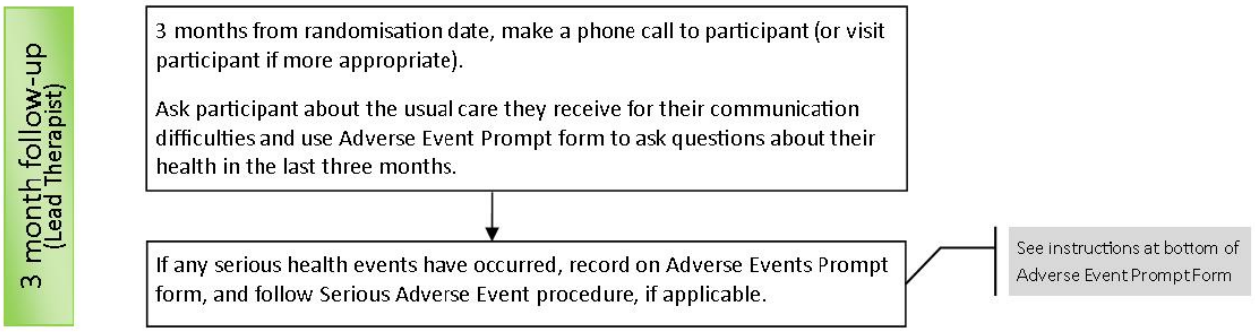


Appendix 2: Baseline assessment and randomisation

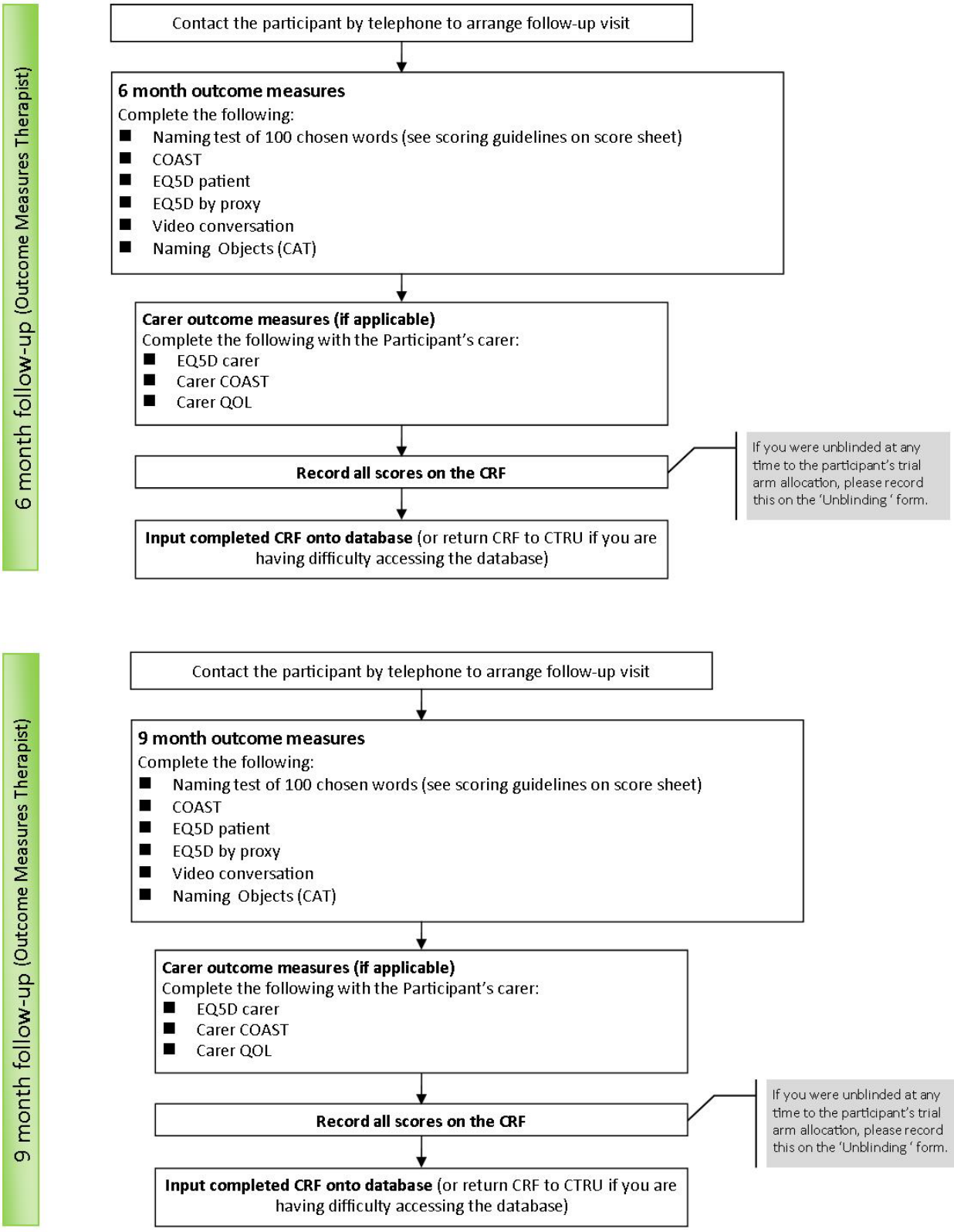
Guidance for taking consent and baseline information for CACTUS participants

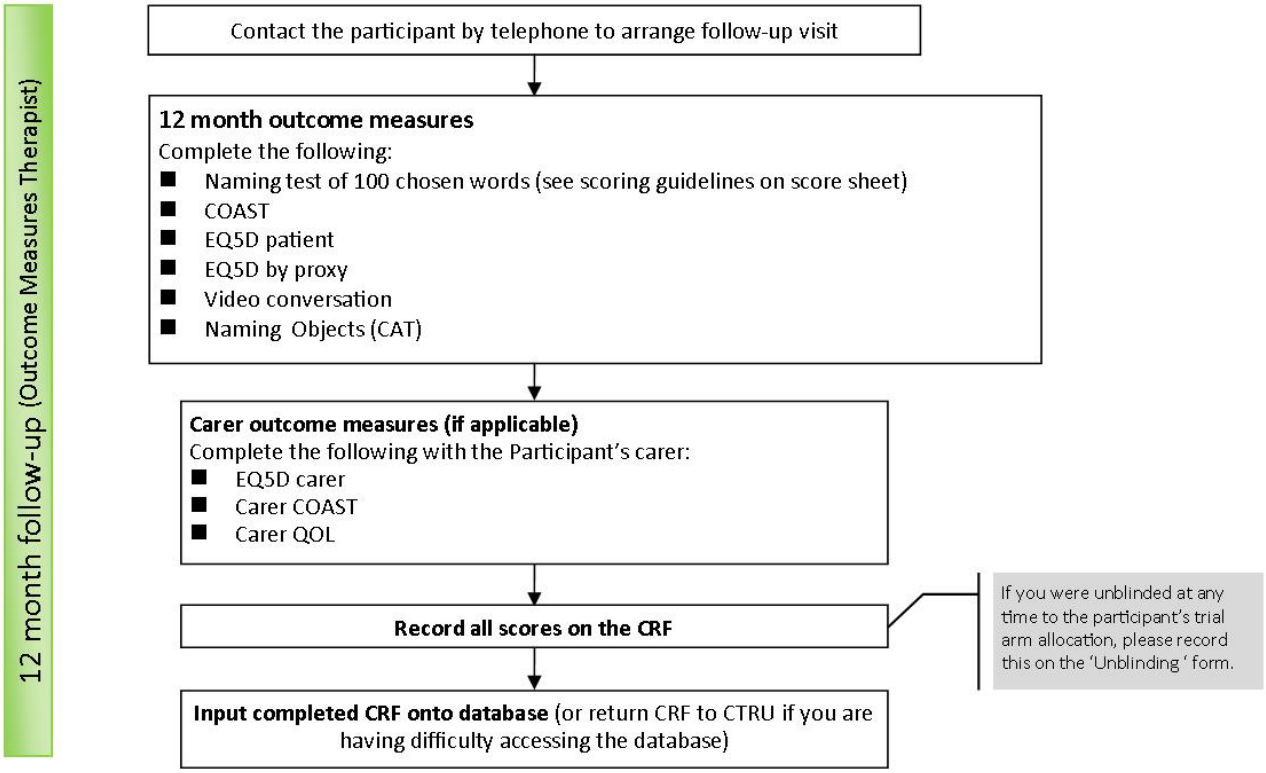



PREPERATION (Lead Therapist)
Before visit 3
Select 100 items of vocabulary under a new person profile (print the score sheet from StepByStep 4 times for use at the different assessment points – store 3 in participants CACTUS file).
Write out open ended questions for video recorded conversation (see question guide).
Visit 3 (Lead Therapist)
Baseline measure (continued)
Personal vocabulary naming test of 100 chosen words (see guidance).
Video short conversation using completed video conversation question guide (see guidance).
Randomisation
Randomise participant at their home if internet access available, or phone CTRU from participant's home and CTRU will randomise for you, or randomise back at office (arrange to visit again once randomised to discuss group randomised to)
Usual Care
Attention control + usual care
Intervention + usual care
Explain about continuing usual activities, discuss these and remind the participant about the possibility of still having a go with the computer at a later date.
Find out what types of puzzle books they would prefer to do (refer to puzzle book guide to select book of appropriate level).
Leave first book with them and recommend they do one each day.
Modify standard steps, using the treatment fidelity form, according to the individual's aphasia profile.
Let the participant know you will return to introduce volunteer/ assistant.


3 month follow-up (Lead Therapist)
3 months from randomisation date, make a phone call to participant (or visit participant if more appropriate).
Ask participant about the usual care they receive for their communication difficulties and use Adverse Event Prompt form to ask questions about their health in the last three months.
If any serious health events have occurred, record on Adverse Events Prompt form, and follow Serious Adverse Event procedure, if applicable.
See instructions at bottom of Adverse Event Prompt Form

Appendix 4: Six, nine and twelve month follow-up assessments




12 month follow-up (Outcome Measures Therapist)
Contact the participant by telephone to arrange follow-up visit
12 month outcome measures
Complete the following:
Naming test of 100 chosen words (see scoring guidelines on score sheet)
COAST
EQ5D patient
EQ5D by proxy
Video conversation
Naming Objects (CAT)
Carer outcome measures (if applicable)
Complete the following with the Participant's carer:
EQ5D carer
Carer COAST
Carer QOL
Record all scores on the CRF
If you were unblinded at any time to the participant's trial arm allocation, please record this on the 'Unblinding ' form.
Input completed CRF onto database (or return CRF to CTRU if you are having difficulty accessing the database)

Appendix 5: Instructions for carrying out naming primary outcome measures

Add each topic into the naming exercise in StepByStep in turn. Present each picture as it comes up. Provide a phonemic cue if unable to name the picture after 10 seconds. Note if able to produce the word with cue score 0. If you suspect the picture hasn't been recognised provide a semantic cue but score 0.

Scoring instructions:
Verbal, phonemic and neologistic errors are not permissible. Where it is clear that the correct word has been retrieved but is distorted in its production due to a dysfluency, mild dyspraxic error or dysarthric distortion, score as fully correct (score of 2). Any response that includes the target response should be marked as correct.
Score 2 points for a correct prompt answer (within 5 seconds)
Score 1 point if correct word produced after a delay of more than 5 seconds (mark as D) and/or for a self correction (mark as Sc)