Clinical Investigational Plan

DINR

Full title of Investigation:	Digital Interventions in Neuro-Rehabilitation: Digital Interventions in Neuro-Rehabilitation (DINR): A digital neuro intervention (DNI) for word retrieval (anomia). The development and testing of a web-based therapy application for people with naming difficulties who have had a Stroke (iTALKbetter).
Short title:	Digital Interventions in Neuro-Rehabilitation (DINR): iTALKbetter
Version and date of Clinical Investigation Plan (CIP):	Version 4.0, 25.02.2019
Sponsor:	University College London (UCL)
Sponsor CIP number:	18/0071
Funder (s):	NIHR

Revision History:

Version numbers	**Date**	Summary of revisions in the case of amendments	Protocol Updated by [insert name & Signature]
1	**18.03.2018**		
2	**31.07.2018**		Henry Coley-Fisher Dr. Catherine Doogan
3	**07.02.2019**	Separated each app	Dr Catherine Doogan Emily Upton
4	**25.02.2019**	Statistical recommendations from MHRA added.	Henry Coley-Fisher Prof Alex Leff

Signatures

The Chief Investigator (CI) and the JRO have discussed this Clinical Investigation Plan (CIP). The investigator agrees to perform the investigations and to abide by this CIP.

The investigator agrees to conduct the Investigation in compliance with the approved CIP, EU Good Clinical Practice (GCP) and UK Regulations for Devices (SI 2002/618; as amended) for regulated studies, the UK Data Protection Act (1998), the Trust Information Governance Policy (or other local equivalent), the Research Governance Framework (2005 2nd Edition; as amended), the Sponsor's SOPs, and other regulatory requirements as amended.

Chief investigator

Prof Alex Leff

		25.02.19
	Signature	Date

Sponsor Representative

UCL	Signature	Date

Contents

LIST OF ABBREVIATIONS

ADE	Adverse Device Effect
AE	Adverse Event
CA	Competent Authority
CI	Chief Investigator
CIA	Clinical Investigation Agreement
CIP	Clinical Investigation Plan
CRF	Case Report Form
CRO	Contract Research Organisation
DINR	Digital interventions in Neuro-rehabilitation
DNI	Digital Neuro-intervention
DCF	Data Clarification Form
DD	Device Deficiency
EC	European Commission
EU	European Union
EUDAMED	European Medical Devices Regulatory Database
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HRA	Health Research Authority
IB	Investigator Brochure
ICF	Informed Consent Form
IMD	Investigational Medical Device
ISF	Investigator Site File
JRO	Joint Research Office
MA	Marketing Authorisation
MHRA	Medicines and Healthcare products Regulatory Agency
NCA	National Competent Authority
NHS	National Health Service
NHS R&D	National Health Service Research & Development
NICE	National Institute of Clinical Excellence
NIHR	National Institute of Health Research
NIST	National Institute of Standards and Technology
PI	Principal Investigator
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SALT	Speech and Language Therapy
SOP	Standard Operating Procedure
TMG	Trial Management Group
UADE	Unanticipated Adverse Device Effect
UK	United Kingdom
USADE	Unanticipated Serious Adverse Device Effect

WTCN	Wellcome Trust Centre for Neuroimaging

Sponsor

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A.1 Overall Synopsis of Clinical Investigation

Title:	Digital Interventions in Neuro-Rehabilitation (DINR): A digital neuro intervention (DNI) for word retrieval (anomia). The development and testing of a web-based therapy application for people with naming difficulties who have had a Stroke (iTALKbetter).
Short title:	Digital Interventions in Neuro-Rehabilitation (DINR): iTALKbetter
Device:	A digital intervention in Neuro-rehab (DNI). A word-retrieval app for people who have had a Stroke.
Objectives:	Digital Interventions in Neuro-Rehabilitation (DINR): A digital neuro intervention (DNI) for word retrieval. The testing of a web-based therapy application for people with naming difficulties through a small scale randomized controlled trial. **iTALKBetter** will provide an app-based therapy for people with word retrieval difficulties who have had a stroke (naming app for a wide variety of common words and phrases). The primary objective is to ascertain if iTALKbetter does improve performance on the trained items (compared to untrained). Secondary outcomes will include improvements in social activity and participation and participant and/or carer reported outcome measures (PROMS). We also plan to capture brain-based data (structural MRI) in order to test a series of secondary hypotheses relating to both how and why the therapy may work in some participants but not in others.
Type of Investigation:	A single site, randomised, control trial.
Investigation design and methods:	This is a summary of the protocol for the study funded by the National Institute of Health Research (NIHR). The main aim of this Phase 2 study is to test the clinical efficacy of the DNI through a randomised small-scale clinical trial. The participants will take the app home on a mobile device and 'play' the therapy. After the trial the participant will return the device and we will delete any content on the device and reload the DNI.

	iTALKbetter is a small-scale, randomised, clinical trial for people with word retrieval difficulties who have had a stroke. Participants will be randomised (using minimisation) to one of two versions of the therapy: 1) deterministic iTALKbetter, 2) reactive iTALKbetter. Participants will complete 5 assessment sessions (T1-T5) at UCL – they will complete neuropsychological assessments, receive brain imaging scans, and complete a program of therapy using the DNI.
Investigation duration per participant:	**30 weeks**
Estimated total Investigation duration:	**3 years**
Planned Investigation sites:	Single-site is **UCL**.
Total number of participants planned:	**30**
Main inclusion/exclusion criteria:	***a) Inclusion criteria*** Any type of stroke but at least 6 months after onset. Evidence of aphasia on the Comprehensive Aphasia Test (Swinburn, 2004). English as their dominant language Able to tolerate MRI brain scan Able to give informed consent Able to use the DNI (app) ***b) Exclusion criteria*** No diagnosis of developmental language disorders

No diagnosis of severe dementia or primary progressive aphasia
No major co-existing neurological or psychiatric diagnosis

No contraindications to brain scanner (e.g. the presence of ferromagnetic implants or other metallic or electronic objects in the body, weight over 24 stone, claustrophobia or pregnancy).

Statistical methodology and analysis:

Behavioural data:

Behavioural baseline data will be analysed using minimisation (Altman, BMJ 2005) to ensure that the two groups are not unbalanced on key demographic variables, including baseline performance during the randomisation procedure.

Data from all timepoints will be analysed using a repeated-measures ANOVA to determine whether there is an interaction between time (therapy block vs baseline) and item (trained vs untrained). The effect of the between-group factor (therapy type) is a secondary outcome measure which will also be analysed using a repeated measure ANOVA but with this extra factor added in: more formally, a three-way interaction between time (therapy block vs baseline), item (trained vs untrained) and therapy type (iTB: deterministic vs reactive).

Neuroimaging data:

Collected at three of the time points. Structural magnetic resonance imaging (MRI) data will be used to identify the lesion location. Brain structure at three time points (T2, T3 and T4) will be analysed using Voxel-Based Morphometry (Ashburner and Friston, 2000) within the Statistical Parametric Mapping software (SPM12) to identify whether the therapy induces any structural brain changes over time. We will employ multi-parameter mapping MRI methodology for the structural brain scans (Callaghan et al, 2014).

A.2 Background and Rationale

Background

Mortality from stroke in the UK has reduced from 21% in 1999 to 12% in 2008. However, stroke prevalence has been increasing, the consequence of socioeconomic and scientific advances that have improved survival; which means that more people are surviving with long-standing disability. Language impairment (aphasia) is the second most common major impairment after stroke, with a prevalence of 250,000 in the UK. Aphasia may respond to therapy many months and years after the stroke occurs, but provision of specialist therapy (speech and language therapy - SALT) is far below that needed to provide optimal rehabilitation (Code and Heron, 2003).

We will address this by targeting a common symptom of post-stroke aphasia: impaired word retrieval problems. This is particularly important in patients receiving rehabilitation for associated disabilities as poor speech production can impair participation/compliance with treatment programmes. Our study is designed to improve word retrieval in patients with post-stroke aphasia, who are in the chronic phase (>6 months post-stroke).

The main aim is to test the clinical efficacy of a novel, web-based, DNI. iTALKbetter will provide an effective training tool that patients can use to practice independently. This will free-up SALT time to provide additional assessment, supervision and functional intervention in a highly cost effective manner.

iTALKbetter will provide an app-based therapy for people with word retrieval difficulties who have had a stroke (naming app for a wide variety of common words and phrases).

This Digital Neuro Intervention (DNI) will provide the opportunity for the necessary increased rehabilitation to help people recover lost naming function. This will alleviate NHS Speech and Language Therapist (SALT) time and put users in control of when and where they carry out practice-based language therapy.

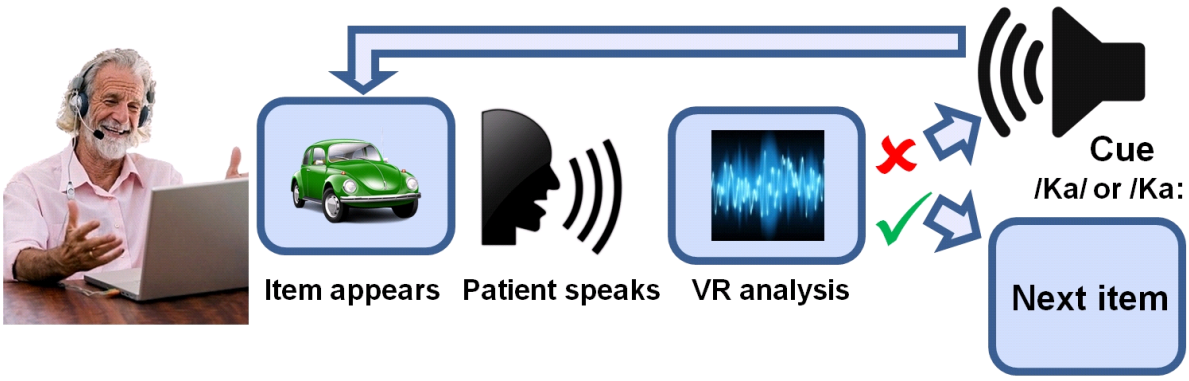
A.3 Identification and description of the Investigational Device

Purpose

iTALKbetter will provide an app-based therapy for people with word retrieval difficulties who have had a stroke (naming app for a wide variety of common words and phrases).

What does it do?

The DNI works via mass practice and feedback to the users on a trial-by-trial basis. The DNI is very simple in a way; it just presents a long series of pictures for users to name. The DNI will use speech recognition (SR) software in order to make a binary decision as to whether the user said the correct word or not. This affects what the next trial (object to name) is and what auditory cue (if any) is provided the next time the user has to name the same item (see below):



*The speech will be recorded on the device but no other identifiable information will be stored on it. When the participant finishes the trial, we will delete all information on the device.

What is the clinical trial design?

A small, well-defined sample of patients with the potential to benefit from the DNI will be recruited. The main outcome measure is whether the DNI is effective at improving naming impairments. This comparison is within-subject and is achieved by comparing post-therapy measures to multiple baseline measures. We are also comparing two different versions of the therapy (a between group comparison) to answer our secondary question of whether the therapy can be optimised. Outcome measures will be collected by the research team using a variety of standardized and non-standardized tests of language and cognition. These outcome measures are not built into the DNI at this point.

The DNI will be introduced to the participant when attending a testing session. One of the research team will explain how to use the DNI, provide instructions for the user, and give some time for practice items. When confident that the participant can use the DNI independently, the participant will take the device home and continue their therapy (suggested therapy time is 5-10 hours per week) which will be simultaneously monitored by the research team. The research team will also check in on the participant weekly to trouble shoot any difficulties they may have (whether motivational or technical). When the participant has completed the therapy block, we will invite them in again for testing and they will return the mobile device with the DNI on it. The participants who continue to receive standard care during the therapy block will be asked to record and submit details to the research team.

A.4 Justification for the design of the clinical investigation

Why is the research considered worth doing?

Standard (face to face) Speech and Language Therapy (SALT) has a huge evidence-base but patients in the NHS have unmet therapy needs due to a lack of resources. The evidence from speech-therapy highlights the

amount of time-on-task required to improve patients' ability to communicate. Naming problems are common and impact on the patients' wellbeing and social inclusion. There is also good evidence that current existing therapeutic approaches work.

A Cochrane review of 39 RCT's involving 2518 participants concluded that speech-therapy results in significant benefits to patients' functional communication (Brady, 2012). Many of these studies involve high doses of therapy. A meta-analysis examining dose found that positive therapy studies averaged 98 hours of speech therapy in total, while negative studies averaged 43 (Bhogal, 2003). In the NHS a patient with aphasia can expect a total average of 6-10 hours of SALT (Code, 2003). When the intervention takes place or how intensely seems less relevant to recovery (Moss, 2006). Our solution to the lack of available SALT therapy is to produce digital neuro-interventions that give patients the opportunity to practice scientifically validated, impairment based therapy when and where it suits them which gives them access to optimum therapy dose.

Recent improvements in acute stroke care means that demand for already limited NHS resources will increase. Commissioners will need to address this growing unmet need and innovative relatively cheap interventions like this one will provide necessary rehabilitation.

We know that therapy is effortful for patients who can sometimes be too fatigued when the therapist comes to do their session. This digital neuro-intervention will provide optimum availability of therapy and therefore place the patient in control of how much they do. However, as we recognise it is still effortful we hope to make the therapy engaging through adaptive and exciting software. The adaptiveness will serve to reward the patients for their efforts without ever making them feel like they are failing. This will hopefully boost how long they spend in therapy and therefore make greater gains.

There are therapy 'apps'' available for patients with aphasia but the scientific basis for them is lacking and none are targeted for speech production. By using voice recognition software our intervention will be uniquely designed to be used by patients with word retrieval impairments.

What new information will the research provide?

The concept of the therapy component is based on standard SALT practice and thus has a strong proof of concept basis, as do our proposed outcome measures. The novel component is packaging it in a user- friendly web-app that is designed for and by people with word-retrieval problems. This is ambitious and yet we believe a realistic goal to provide a world-wide evidence-based therapy that can benefit many. This digital neuro-intervention will be in contrast to the plethora of apps available online claiming cognitive training without having scientific proof.

The iTALKbetter research study is a small-scale, randomised, clinical trial for participants with word retrieval impairments post-stroke. The main research question is whether iTALKbetter improves patients' naming ability

for trained items. We test this hypothesis by assessing participants naming abilities on two matched lists of items, half are trained items and half are untrained. A secondary question is whether it matters how the software progresses patients through the therapy. We will test this hypothesis by creating two different versions of iTALKbetter: 'deterministic' and 'reactive'. Participants will be randomised (using minimisastion) to one of two of these versions of the therapy. Participants practice with the therapy for set periods of time (therapy block) following a series of (three) baseline measures split over a single, pre-therapy block (see Trial design section 5). The main outcome measure will be a clinically relevant improvement on the naming ability of the trained items (compared to untrained control items). Secondary outcomes include investigating which therapy version optimises recovery on naming accuracy and also improvements in social activity and participation and participant and/or carer reported outcome measures (PROMS).

We also plan to capture brain-based data (structural MRI) in order to test a series of secondary hypotheses relating to both how and why the therapy may work in some participants but not others. All brain imaging will be outside of standard care for the participants and take place at UCL by trained staff.

A.5 Risks and benefits of the Investigational device and clinical Investigation

The potential clinical benefit to the participants is that they will be receiving more therapy through the DNI that they could ever receive from the NHS. This in turn will provide opportunity for them to improve their word retrieval which can be a distressing impairment.

A full risk assessment and mitigation plan for each risk relating to the investigational device and the clinical investigation is detailed in a separate document entitled: Risk Assessment CTIMP iTALKbetter.

The table below summaries the risks and mitigations of all tests above standard care that are being performed:

Table 1

Intervention	**Potential risk**	**Risk Management**
MRI	Only if any contraindications are missed or not reported. These contraindications may include the presence of any metal in the body.	Performed by trained member of staff. Follow trust standard operational procedures by obtaining surgical history of exposure to metal, metallic dental work and other

	Discomfort or anxiety in the MRI scanner may occur due to the noise and enclosed space.	potential MRI contraindications. These potential risks will be reduced by providing an alarm bulb in the case of any uncertainty discomfort, or distress. Noise from the scanner will be attenuated by the use of earplugs and noise-shielding headphones.
X-Ray	Exposure to ionising radiation	Performed by trained member of staff. Following trust protocols. The standard dose is equivalent to ~0.005% of average annual radiation dose in the UK

The classification of medical devices in the European Union is outlined in Annex IX of the Council Directive 93/42/EEC (as amended). There are four classes, ranging from low risk to high risk.

Class I

Class IIa

Class IIb

Class III

The Medical Device used in this investigation is classified as **Class IIa**

A.6 Objectives and hypotheses of the clinical investigation

A6.1 Hypotheses

H1-Primary: Does iTB improve naming performance on trained items?

This is a within-subject comparison. The criteria for success is a 10% (raw, or unstandardized) relative improvement in performance. This effect size was used in the recent Big Cactus study.

H2-Secondary: Does reactive iTB significantly improve performance compared with deterministic iTB?

This is two factor analysis with both a within-subject factor (trained vs. untrained items) and a between-group factor (reactive iTB vs. deterministic iTB). The criteria for success is a 5% (raw, or unstandardized) relative difference in performance. This is half the effect size used in the recent Big Cactus study, but that was to compare therapy with no therapy, here expected gains may be more marginal as both groups are receiving the therapy items, just in different orders.

A6.2 Primary Objective

Does iTB improve naming performance on trained items?

A6.3 Secondary Objective(s)

We believe that using this DNI will improve word retrieval on trained items by providing a known therapy used by SLT's through a digital app and by enabling an increased dose of therapy. However, we also believe that by using this DNI and practicing every day, there will be changes in participants' brain structure and in the health of the participants and their carers.

- Does reactive iTB significantly improve performance compared with deterministic iTB?
- Are the therapy effects item-specific or do we see generalization to untrained items?
- Are the effects of the DNI therapy limited to the language domain alone or do they improve in other cognitive domains (e.g. sustained attention)?
- Does the DNI improve participant's social activity and participation?
- Is the DNI acceptable to participants (can they use it easily)?
- Is the DNI acceptable to participants' carers?
- Does the DNI improve carer health/well-being?
- Does the DNI have any economic benefits?
- Can baseline structural brain imaging explain participants' responses to the DNI?
- Can baseline structural brain imaging be used to predict incoming participants' response to the DNI?
- Can repeated-measures structural brain imaging identify participants' brain areas that change in response to the DNI?

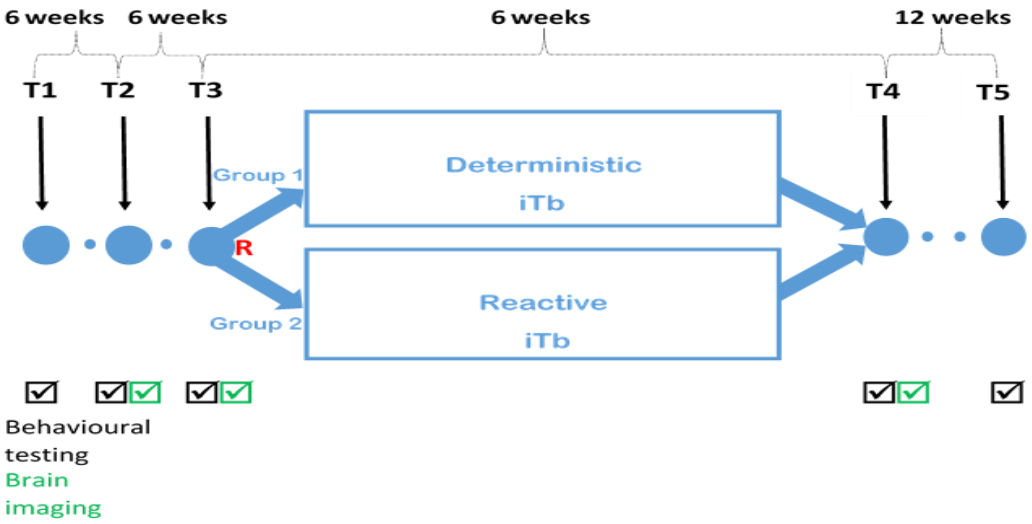
A.7 Design of the clinical investigation

A.7.1 General

iTALKbetter is a small-scale, randomised, clinical trial for participants with word retrieval difficulties who

have had a stroke. Participants will be randomised (using minimisation) to one of two versions of the therapy: 1) deterministic iTALKbetter, 2) reactive iTALKbetter.

Participants will complete 5 assessment sessions (T1-T5) at UCL – they will complete neuropsychological assessments, receive brain imaging scans, and complete a program of therapy using the DNI.



The on-line language battery (Comprehensive Aphasia Test) will be audio and video recorded to ensure accuracy when scoring. Other tests of language will also be recorded.

A.7.2 Investigational device and comparators

The tablets which the DNI will be uploaded onto will be stored in a secure cabinet in the ICN building. After the trial ends, the DNI will be deleted from the app and the devices will be stored or used by Prof Leff as he sees fit. No data will remain on the individual devices.

A.7.3 Subjects

a) Inclusion criteria*

Any type of stroke but at least 6 months after onset.

Evidence of aphasia on the Comprehensive Aphasia Test (Swinburn, 2004).

English as their dominant language

Able to tolerate MRI brain scan

Able to give informed consent

c) Exclusion criteria*

No diagnosis of developmental language disorders

No diagnosis of dementia or primary progressive aphasia

No major co-existing neurological or psychiatric diagnosis

No contraindications to brain scanner (e.g. the presence of ferromagnetic implants or other metallic or electronic objects in the body, weight over 24 stone, claustrophobia or pregnancy).

c) Criteria and procedures for subject withdrawal or discontinuation

A participant may be withdrawn from the trial whenever continued participation is no longer in the participant's best interests, but the reasons for doing so must be recorded. Reasons for discontinuing the trial may include:

- Disease progression whilst in the study
- Intercurrent illness
- Patients withdrawing consent
- Persistent non-compliance to protocol requirements.

d) Point of enrolment.

Participants are enrolled at T1 (first time point) as this is where consent is obtained. They are randomised at T3 (after all three baseline measurements have been collected).

e) Total expected duration of the clinical investigation

3 years

f) Expected duration of each subject's participation

30 weeks

g) Number of subjects included in the clinical investigation

30

h) Estimated time needed to select this number (i.e. enrolment period)

2.5 years

Subject Eligibility

Once written informed consent has been obtained, the Case Report Form will be completed to document adherence to the inclusion and exclusion criteria.

Where a subject fails to fulfil any element of the inclusion and exclusion criteria, this will be documented and the signed consent form and completed inclusion/exclusion criteria will be retained by the Principal Investigator. The subject will not advance any further into this clinical investigation.

Subject Identification

When a subject is identified and considered eligible for entry into this clinical investigation, the subject will be allocated the next available investigation number (subject ID number).

For subjects enrolled, this number will consist of 01 for the first subject, 02 for the second subject and so on. This number will be the unique identifier of the subject and written on each page of the paper/electronic Case Report Form booklet and all other documentation relating to that subject.

Each subject that is enrolled into the study will have their study participation recorded and details of the device recorded in their hospital notes. A copy of their signed consent form and patient information sheet should also be placed on his/her hospitals notes to identify the subject as participating in a Clinical Investigation.

A7.4 Recruitment

Participant recruitment at a site will only commence when the trial has been initiated by the Sponsor (or it's delegated representative), and issued with the 'Open to Recruitment' letter.

Suitable participants will be identified by the clinical care team (Prof Leff, Dr. Crinion) and the study will be advertised in their clinics. If the participant has already consented to be contacted about the research, they will be contacted by telephone by a member of the research team (usually Dr Doogan or a research assistant but may include other members of the team). Participants will be initially identified from UCL and UCLH clinics run by the clinicians on the clinical care team and existing databases that we have permission to use (e.g. the PLORAS

stroke database in London CI: Professor Cathy Price, REC reference number 13/LO/1515). We may also advertise in local community rehab services and support groups. Participants who consent to be contacted by the research team will be consented to take part in the study at time-point 1.

The basic details of our studies will be publicised on other appropriate websites and social media.

A7.5 Randomisation Procedures

Following participant consent, and confirmation of eligibility, the randomisation procedure described below will be carried out.

After consent has been gained and the participants have completed 3 sessions of baseline testing, the CI will randomise the participants using minimisation. This will determine which version of the therapy the participant will use: deterministic or reactive. After time point 2, the participant will also be randomised to which list of words they will be trained on. This will be computer generated.

Participants are considered to be enrolled into the trial following: consent, pre-treatment assessments, confirmation of eligibility, completion of the randomisation process, allocation of the participant trial number and treatment by the central coordinating team/remote system.

A.7.6 Procedures

The intervention which will be an application (DNI) on a tablet will be introduced to the participant when attending a testing session. One of the research team will explain how to use the DNI, provide instructions for the user, and give some time for practice items. When confident that the participant can use it independently then the participant will take the device home and continue their therapy (suggested therapy time is 5-10 hours per week) which will be simultaneously monitored by the research team. However, the research team will also check in on them weekly to trouble shoot any difficulties they may have (whether motivational or technical). When the participant has completed the therapy block, we will invite them in again for testing. The participants who continue to receive standard care during the therapy block will be asked to record and submit details to the research team.

Brain Imaging will also take place. This will happen 3 times, at time-points 2, 3 and 4. The scans will take place in UCL, carried out by trained staff, on the same day as the participants are coming in for behavioural testing and will last approximately 30 minutes.

A.8 Informed Consent Process

We understand it is the responsibility of the Investigator, or a person delegated by the Investigator, to obtain written informed consent from each subject prior to participation in the Investigation, following adequate explanation of the aims, methods, anticipated benefits and potential hazards of the study.

The person taking consent will be GCP trained, suitably qualified and experienced, and have been delegated this duty by the CI/PI on the delegation log.

A week will be given for consideration by the patient before taking part. The PI must record when the patient information sheet (PIS) has been given to the patient. [If the amount of time between the PIS being given and the date of consent are less than 24 hours, the PI will explain the rationale for this]. It must be recorded in the medical notes when the participant information sheet (PIS) has been given to the participant.

The Investigator or designee will explain the patients are under no obligation to enter the Investigation and that they can withdraw at any time during the Investigation, without having to give a reason.

No clinical Investigation procedures will be conducted prior to taking consent from the participant. Consent will not denote enrolment into Investigation. A copy of the signed Informed Consent Document will be given to the participant. The original signed form will be retained at the study site and a copy placed in the medical notes.

If new safety information results in significant changes in the risk/benefit assessment, the consent form will be reviewed and updated if necessary and subjects will be re-consented as appropriate

Informed consent and aphasia

Aphasic patients do require extra care when informed consent is being sought. All information materials will be offered in written and aural forms, and supplemented by pictorial information to ensure that they are comprehensible to all participants. Participants (and, where appropriate, their carers) will be given a minimum of one week to carefully consider the information materials before deciding about participation.

Patients who are incapable of providing informed consent (patients without capacity) will not be recruited. The vast majority of patients with post-stroke aphasia are able to consistently communicate their wishes and desires, including consent to a treatment trial, see:

Stroke and Aphasia Handbook, Parr, S., Pound, C., Byng, S. and Long, B. 2003. Connect Press, UK.

The procedures for consent outlined in the Standard Operating Procedure for informed consent form (UCL) will be adhered to. A written record of the checks made for competence to consent will be kept along with other information in each patient's Case Report Form. The CI will also ensure that written consent is witnessed, preferably by a relation or carer of the patient, or if not, by an independent witness present at the Welcome Trust Centre for Neuroimaging, UCL (WTCN).

Written, informed consent will be obtained for all participants. We plan to follow published guidelines for addressing consent issues in aphasic patients (Penn, Frankel et al. 2009).

Only members of the clinical care team will be identifying and approaching patients.

The research team has considerable experience of working with patients with impaired speech and language abilities (there are four speech and language therapists on the team), and will take the required time and attention to ensure that the requirements and risks of the study are thoroughly understood (by both the participant and, where appropriate, a family member or carer) before consent is obtained.

Procedure of gaining consent

Two of the research team hold weekly clinics for stroke survivors in UCLH/NHHN. They will identify potential participants for iTALKbetter and gain verbal consent to be contacted to discuss the study in more detail.

Potential participants will be telephoned again at least 1 week after initial contact, by Dr Doogan or the research assistant to answer any further questions and, if appropriate, to arrange the first testing appointment at the participating site. When participants come into their first testing appointment, written consent will be obtained.

At the first and subsequent appointments, potential participants will have a further opportunity to ask questions about the study.

If there is any change in capacity as indicated by a carer, the participant or a member of the research team, Dr Doogan, a Clinical Psychologist, will assess this and discontinue if found to be changed.

A.9 Schedule of assessments and interventions by visit

Time-point	**iTALKbetter**

T1	• Baseline neuropsychological testing • Baseline language and cognitive assessment (including Electronic Comprehensive Aphasia Test (eCAT)) • Self-report and carer-report outcome measures
T2	• Language and cognitive assessment (including eCAT) • Self-report and carer-report outcome measures • Brain imaging
T3	• Language and cognitive assessment (including eCAT) • Self-report and carer-report outcome measures • Brain imaging Participants are randomised at this point to one of the two versions of iTALKbetter. Participants receive a mobile device with the DNI on it.
T4	• Language and cognitive assessment (including eCAT) • Self-report and carer-report outcome measures • Brain imaging The mobile device with the DNI is taken away.
T5	• Language and cognitive assessment (including eCAT) • Self-report and carer-report outcome measures.

Some assessments may be audio and video recorded to ensure accuracy when scoring.

We will inform participants' GPs and therapists (if they have one) of their involvement in the study.

A.10 Device accountability

The DNI (software) will be given to each participant to use on hardware (a tablet computer) purchased from the grant and thus belonging to UCL. Because the software uploads data periodically to the database (on the UCL secure virtual server) we are able to tell when participants are using it. At the end of the trial block, the DNI (and tablet computer) are passed back to the research team and will be recycled for a future participant to use.

A.11 Monitoring Plan

Case Report Forms (CRFs) will be completed by the investigator and/or his/her delegates at each timepoint. These will record any potential AEs or ADEs. These data will be collated and passed onto the IDMC for their view on

safety. As each participant has several timepoints when they are not using the DNI, we will be able to perform within-subject analyses for the IDMC to see if rates of AEs or ADEs are higher in the DNI therapy blocks.

a. Confidentiality

All data will be handled in accordance with the UK Data Protection Act 1998. The CRFs will not bear the subject's name or other personal identifiable data. The subject's Investigation identification number, will be used for identification. Subjects will be assigned an Investigation identification number by the study site sequentially starting with 001 upon enrolment into the study. The study site will maintain a master Subject Identification Log.

b. Record keeping and archiving

Archiving will be authorised by the Sponsor following submission of the end of study report. Chief Investigators are responsible for the secure archiving of essential Investigation documents as per their Trust policy. All essential documents will be archived for at least 5 years after completion of Investigation. Destruction of essential documents will require authorisation from the Sponsor.

The Chief Investigator will ensure there are adequate quality and number of monitoring activities conducted by the study team. This will include adherence to the protocol, procedures for consenting and ensuring adequate data quality.

The Chief Investigator will inform the sponsor should he/she have concerns which have arisen from monitoring activities, and/or if there are problems with oversight/monitoring procedures.

An independent data monitoring committee (IDMC) will be set up to deal with patient safety issues related to this project. The IDMC will comprise of three independent researchers at the Institute of Neurology not linked to this project.

The data to be monitored by the IDMC will be taken from the CRFs (which will include all AEs and ADEs), as indicated above.

A.12 Statistical Considerations

Design

A small, well-defined sample of patients with the potential to benefit from the DNI will be recruited. In both cases, the main outcome measure is whether the DNI is effective at improving naming impairments. This comparison is within-subject and is achieved by comparing post-therapy measures to multiple baseline measures. We also compare two different versions of the therapy in order to answer our secondary question of whether the therapy can

be optimised (a between-groups comparison).

Sample size calculation

Sample-size calculation based on data from a more recent trial: The Big Cactus trial using step-by-step software: https://www.sheffield.ac.uk/scharr/sections/dts/ctru/bigcactus.

Therapy group improved by 14.4% compared with a control group (no therapy) on word finding ability (95% CI = 10.8-18.1%). There was no use of control items, but using this data to model the trained items (14% improvement) and the untrained items (0% improvement) we entered the data into a sample size calculator as before (DSS one on percentages) we find the calculation to be in each iTB group (see screenshot) to be 13. In total this means 26 total but with an expected 15% drop out this means we recruit 30.

Planned recruitment rate

We will begin recruitment prior to the start of the trial and hope to have 50% of patients enrolled by the time the first patient enters the trial.

Randomisation methods

After iTALKbetter participants complete baseline testing (time-point 3) they will be randomised using minimisation to make sure the groups do not become unbalanced on key baseline variables. This will determine which version of the therapies participants will use and which of the word lists they are allocated (computer generated).

Participants will be randomised on the following variables: aphasia severity and time since stroke. Multivariate analyses that adjust for all factors used in the minimisation algorithm will be performed as will the appropriate sensitivity analyses.

Statistical analysis

Behavioural baseline data will be used to ensure that the two therapy groups are not unbalanced on key demographic variables, including baseline performance during the randomisation procedure. This process of randomisation is called minimisation (Altman, BMJ 2005).

Data from all timepoints will be analysed using a repeated-measures ANOVA to determine whether there is an

interaction between time (therapy block vs baseline) and item (trained vs untrained). The effect of the between-group factor (therapy type) is a secondary outcome measure which will also be analysed using a repeated measure ANOVA but with this extra factor added in: more formally, a three-way interaction between time (therapy block vs baseline), item (trained vs untrained) and therapy type (iTB: deterministic vs reactive).

Neuroimaging data, collected at three of the time points: Structural magnetic resonance imaging (MRI) data will be used to identify the lesion location. Brain structure at the three time points will be analysed using Voxel-Based Morphometry (Ashburner and Friston 2000) within the Statistical Parametric Mapping software (SPM12) to identify whether these therapies induce any structural brain changes over time. We will employ multi- parameter mapping MRI methodology for the structural brain scans (Callaghan et al, 2014). Structural MRI scans will be analysed using Voxel Based Morphometry (VBM, Ashburner & Friston, 2000) to test for therapy-induced changes in brain structure.

Missing Data

We expect a 15% drop out rate (see sample size correlation above). If the drop out rate is less than 5% then we will remove these cases and proceed with a per-protocol analysis. For drop out rates over 5% we will assess the impact of any potential missing data on our study by conducting the following sensitivity analyses:

1) Categorise the missing data – Missing completely at random (MCAR), Missing at random (MAR) or Missing not at random (MNAR).

If any patients drop out of this study details as to why will be collected from the patient at the time of dropout. The reasons given will be used to categorise the missing data and justify subsequent handling of the missing data.

2) Handling missing data –
    a) MCAR:

In this case the relevant cases will be deleted using listwise or pairwise deletion as appropriate using SPSS.

    b) MAR and MNAR:

We will use multiple imputation methods to generate multiple copies of the original dataset by replacing missing values using an appropriate model. Analyse as complete data sets and combine the different parameter estimates across the data sets to produce a unique point estimate and standard error taking into account the uncertainty of the imputation process.

3) Sensitivity Analyses

We will compare the results of the full dataset analysis (dataset with imputed values) to those of the complete case analysis (dataset with observed data only) on a case-by-case basis. To assess the impact of any missing data on the conclusions of the study.

A.13 Data Management

The handling of all data on the CRFs will be the responsibility of UCL.
It will be the responsibility of the investigator to ensure the accuracy of all data entered in the CRFs. The delegation log will identify all those personnel with responsibilities for data collection and handling, including those who have access to the trial database.

We believe that the DNI will be easy to use and that participants will want to do their therapy as the experience of it being a digital game will be pleasurable. However, therapy is difficult and tiring so in order to minimise possible distress or frustration, the research team will systematically call the participants if they are struggling to meet their targets of therapy week by week. This will enable the participant to discuss any barriers to doing the therapy and researchers can check in with participants to solve any possible, but unlikely, technical issues.

A13.1 Procedures for data review, database cleaning, and issuing and resolving data queries.

Data entered on the CRFs will be source verified by a sponsor representative trained on the CIP and who has current GCP training. Data Clarification Forms (DCF) will be issued to the Investigator should a discrepancy be found between the source and CRF. The Investigator will be required to verify and correct all errors or provide an explanation for the discrepant data. Sponsor representatives will re-verify the corrected data and mark the clarification as resolved at the next monitoring visit.

A13.2 Procedures for verification, validation and securing of electronic clinical data systems

All data from the examinations and investigations listed in Appendix A will be transferred to media provided by the sponsor and collected at the time of CRF collection.

The CI will manage and maintain the study database throughout the Investigation. At the conclusion of the Investigation, the database will then be locked and data transferred for analysis. A final copy of the database will be provided to the study site. Where data is transferred electronically, this will be in accordance with the UK Data Protection Act 1998 as well as Trust Information Governance Policy. There will be a documented record of data transfer and measures in place for the recovery of original information after transfer.

The database maintained by the CI shall be validated and secured according to the UCL standard operating procedures. Access to the data shall be limited to sponsor representatives directly involved in the collection, analysis, maintenance or safety monitoring of the data. Any study data released shall be done according to the publication policy and in accordance with the UK Data Protection Act 1998.

A13.3 Data retention

Archiving will be authorised by the Sponsor following submission of the end of study report. Chief Investigators are responsible for the secure archiving of essential Investigation documents and the Investigation database as per their trust policy. All essential documents will be archived for at least 20 years after completion of Investigation. Destruction of essential documents will require authorisation from the Sponsor.

A13.4 Clinical quality assurance

The Clinical Investigators will meet monthly, to discuss any issues with data quality and any concerns will be discussed with the Sponsor.

A13.5 Completion of Case Report Forms

The Principal investigator will be responsible for the timing, accuracy and completeness of a CRF for each individual subject. All entries are to be made in black ink and are to be legible. All corrections made are to be completed by placing a single line through the incorrect data and the individual making the correction must initial and date the correction. Typing correction fluid must not be used. The personal data recorded on all documents will be regarded as confidential.

The Principal investigator must record the subject's participation in this clinical investigation in the subject's hospital notes. In addition, the Principal investigator must keep a separate list of all subjects entered into the clinical investigation showing each subject's name, date of birth and assigned subject number (for identification

purposes). A Subject Identification Log will also be provided in the Investigation Site File to record the subject's initials and assigned subject number.

All data will be handled in accordance with the UK Data Protection Act 1998.
The CRFs will not bear the subject's name or other personal identifiable data. The subject's initials, date of birth and trial identification number, will be used for identification.

A13.6 Review and Return of Completed Documentation

The Principal investigator will make the original Case Report Forms available to the Sponsor's designated monitor at each visit. At the conclusion of the clinical investigation, completed Case Report Forms will be signed by the Principal investigator, collected (the original left with the Principal investigator) and a copy returned to the Sponsor.

A13.7 Retention of Documentation

The Principal investigator will retain all copies of the records for a period of 20 years from the discontinuation of the clinical investigation. In all cases, the Principal investigator must contact the Sponsor prior to disposing of any records related to the clinical investigation. Included in records to be maintained are signed Clinical Investigation Plan, copies of the CRFs, signed consent forms, ethics committee approval letters, product accountability records, correspondence concerning the clinical and any other documents to identify the subjects.

In addition, if the Principal investigator moves/retires, etc., he should provide University College London with the name and address of the person who will look after and be responsible for the clinical investigation related records.

A13.8 Training

During the initiation of the investigation site, the sponsor will ensure the investigators and the site study staff are trained on the device. The investigator is then responsible for ensuring that the investigation staff uses the device in the same way. All training will be documented in a Site Training Log.

The monitor will also ensure that the investigator and investigation site team have received and understood the requirements and content of:

* CIP (Clinical Investigation Plan)

* IB (Investigators Brochure)
* The informed consent forms
* CRFs (Case Report Forms)
* IFUs (Instructions For Use)
* All written clinical investigation agreements as appropriate

A.14 Amendments to the CIP

Amendments to this CIP may be necessary to protect the safety of the patients and integrity of the data. In collaboration with the Investigator(s), the CIP amendments will be documented and submitted for ethical and regulatory approval (as required) prior to implementation. All changes will be evaluated for impact per sponsor SOPs. Amendments will be considered implemented after all ethical and regulatory approvals (as required) are received and all key sponsor and site staff have been trained. This process does not affect the individual clinician's responsibility to take immediate action if thought necessary to protect the health and interest of individual patients.

A.15 Deviations from clinical investigation plan

A deviation is considered a departure from the conditions and principles of GCP in connection with that Investigation; or the CIP relating to that Investigation, as amended from time to time.

The Investigator shall not deviate from this CIP except in situations that affect the subject's rights, safety and well-being, or the scientific integrity of the clinical investigation.

A.15.1 Procedures for recording, reporting and analysing CIP deviations

If possible, prior approval from the sponsor and REC, if appropriate, shall be obtained by the investigator. All spontaneous CIP deviations shall be recorded and reported to the sponsor as agreed. A deviation log shall be maintained by the study site. Deviations shall be reported to the REC and the regulatory authorities if required by national regulations. All deviations will be included, as required in the final study report.

Notification requirements and time frames.

Requests for deviations by the investigator will be responded to within 48 hours of receipt.

Corrective and preventive actions and principal investigator disqualification criteria.

Refer to the Monitoring Plan (as applicable) for corrective and preventative actions and principal investigator disqualification criteria.

A.15.2 Procedure for reporting any protocol deviations

Any deviation from the protocol that has not been previously approved by the sponsor (JRO at University College London), must be reported to the sponsor within 2 working days of the deviation occurrence. Any deviations from the clinical investigation plan that are identified during routine monitoring visits will be reported to the sponsor (JRO, University College London) within 24 hours of being identified.

A.16 Statements of compliance

The clinical investigation shall be conducted in accordance with the ethical principles of the Declaration of Helsinki, ISO standard 14155 and all other applicable device and UK regulations.

The clinical investigation shall not commence recruitment until all REC, regulatory (if applicable) and local (NHS permission) is received. All additional requirements imposed by the REC or regulatory authority will be followed.

A.17 Insurance

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

Participants may also be able to claim compensation for injury caused by participation in this clinical trial without the need to prove negligence on the part of University College London or another party. Participants who sustain injury and wish to make a claim for compensation should do so in writing in the first instance to the Chief Investigator, who will pass the claim to the Sponsor's Insurers, via the Sponsor's office.

Hospitals selected to participate in this clinical trial shall provide clinical negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary shall be provided to University College London, upon request.

There must also be indemnity arrangements in place, with the manufacturer, to cover the malfunction and breakdown of the device. N/A

A.18 Adverse events, adverse device effects and device deficiencies

a-c) Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device. **Note 1:** This definition includes events related to the investigational medical device or the comparator **Note 2:** This definition includes events related to the procedures involved **Note 3:** For users or other persons, this definition is restricted to events related to investigational medical devices
Adverse Device Effect (ADE)	Adverse Event related to the use of an investigational device. **Note 1:** This definition includes AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational device **Note 2:** This definition includes any event resulting from use error or from intentional misuse of the investigational medical device

Serious Adverse Event (SAE)	Any adverse event that:
	• Led to death,
	• Led to serious deterioration in the health of the subject, that either resulted in
	  • a life-threatening illness or injury, or
	  • a permanent impairment of a body structure or a body function, or
	  • in-patient or prolonged hospitalisation, or
	  • medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
	• Led to foetal distress, foetal death or a congenital anomaly or birth defect

Serious Adverse Device Effect (SADE)	An ADE that has resulted in any of the consequences characteristic of an SAE
Unanticipated Serious Adverse Device Effect (USADE)	An SADE, which by its nature, incidence, severity or outcome, has not been identified in the current version of the risk analysis report.
Device Deficiency (DD)	Inadequately of a medical device with respect to its identity, quality, durability, reliability, safety or performance. **Note 1:** this includes malfunctions, use errors, and inadequate labeling

An adverse event does not include:

- Medical or surgical procedures; the condition that leads to the procedure is an adverse event.
- Pre-existing disease, conditions, or laboratory abnormalities present at the start of the study that do not worsen in frequency or intensity.
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalizations for cosmetic or elective surgery or social/convenience admissions);
- The disease being studied or signs/symptoms associated with the disease unless more severe than expected for the subject's condition.

d) Reporting requirements and timelines

AEs and ADEs are not considered reportable.

Term	Reporter	Reported to	Reporting Timeline from awareness of the event
Adverse Event (AE)	Investigator	Sponsor	As agreed with sponsor. CI to record fully all AEs.
Adverse Device Effect (ADE)	Investigator	Sponsor/Manufacturer	As agreed with sponsor. CI to record fully all ADEs.

The following events are considered reportable events in accordance with Annex 7, section 2.3.5 and Annex X, section 2.3.5 of DIRECTIVES 90/385/EEC AND 93/42/EEC respectively.

Term	Reporter	Reported to	Reporting Timeline from awareness of the event
Serious Adverse Event (SAE)**/ Serious Adverse Device Effect (SADE)	Investigator	Sponsor	Immediately, but no more than 3 calendar days after becoming aware of the event
	CI	MHRA aic@mhra.gsi.gov.uk	Immediately, but not later than 2* calendar days after awareness *For SAEs which indicate an imminent risk of death, serious injury, or serious illness and that require prompt remedial action for other patients/subjects, users or other persons All other events immediately but not later than 7 calendar days following date of awareness.
	CI	REC	N/A
Unanticipated Serious	Investigator	Sponsor	Immediately, but no more than 3

Adverse Device Effect (USADE)			calendar days after becoming aware of the event
	CI	MHRA	Immediately, but not later than 2* calendar days after awareness *For SAEs which indicate an imminent risk of death, serious injury, or serious illness and that require prompt remedial action for other patients/subjects, users or other persons. All other events immediately but not later than 7 calendar days following date of awareness.
	CI	REC	Within 15 days of the chief investigator becoming aware of the event. Only reports of <u>related and unexpected</u> Serious Adverse Events (SAEs) should be submitted to the REC.

Term	Reporter	Reported to	Reporting Timeline from awareness of the event
Device Deficiency (DD)	Investigator	Sponsor	Immediately, no more than 24 hours of becoming aware of the event
	CI	MHRA	7 calendar days Only reportable if the event may have led to an SAE if; • suitable action had not taken • intervention had not been made • if circumstances had been less fortunate
Urgent Safety Measures	CI	REC	(i) Immediately-By telephone (ii) Within 3 days-Notice in writing setting out reasons for the USM and plan for further action

** **Note** Planned hospitalisation for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event

e) Assessments of adverse events

Each adverse event will be assessed for the following criteria:

Severity

Category	Definition
Mild	The adverse event does not interfere with the subjects daily routine, and does not require intervention; it causes slight discomfort
Moderate	The adverse event interferes with some aspects of the subjects routine, or requires intervention, but is not damaging to health; it causes moderate discomfort
Severe	The adverse event results in alteration, discomfort or disability which is clearly damaging to health Note: A severity rating of severe does not necessarily categorise the event as an SAE.

Seriousness

Seriousness as defined for an SAE in section a) above.

Causality

The assessment of relationship of adverse events to the study procedure and the investigational device will be a clinical decision based on all available information at the time of the completion of the case report form. The following categories will be used to define the causality of the adverse event:

Category	Definition
Yes	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely
Possibly	There is some evidence to suggest a causal relationship (e.g. the event occurred within a reasonable time after procedure). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant events).
No	There is no evidence of any causal relationship.

Expectedness

Category	Definition
Expected	An adverse event that is consistent with the information about the device listed in the Investigator Brochure or clearly defined in this CIP.

Unexpected	An adverse event that is not consistent with the information about the device listed in the Investigator Brochure

The reference document to be used to assess expectedness against the intervention is the IB. The CIP will be used as the reference document to assess disease related and/or procedural expected events.

f) Procedures for recording and reporting Adverse Events and Device Deficiencies

Investigator responsibilities:

All adverse events and SAEs will be recorded in the medical records and CRF following consent.

All serious adverse events will need to be reported to the sponsor on a SAE form (using MEDDEV form 2.7/3) unless stated in the CIP that some expected SAEs will not be reported to the sponsor, with a justification as to why they will not be reported.

The Chief or Principal Investigator will complete the serious adverse event form and the form will be emailed to the sponsor UCL, within 3 working day of his/her becoming aware of the event. The Chief or Principal Investigator will respond to any SAE queries raised by the sponsor as soon as possible.

The Investigator will report to the MHRA and REC (as applicable) all reportable events within the specified timeframes as per section d above.

All deaths will be reported to the sponsor irrespective of whether the death is related to disease progression, the device, or an unrelated event.

All serious adverse events will be recorded in the medical records and the CRF, and the sponsor's AE log.

All SAEs (except those specified in section d as not requiring reporting to the Sponsor) must be recorded on a serious adverse event (SAE) form. The CI/PI or designated individual will complete the sponsor's SAE form and the form will be preferably emailed to the Sponsor within 5 working days of becoming aware of the event. The Chief or Principal Investigator will respond to any SAE queries raised by the sponsor as soon as possible. Where the event is unexpected and thought to be related to the intervention, this must be reported by the Investigator to the Health Research Authority within 15 days.

All SAEs and UADEs should be reported to the following; [insert REC and MHRA]

Reporting of all Adverse Events and Device Deficiencies: Investigator and Sponsor responsibilities

Investigator responsibilities shall be as per section d). The sponsor shall keep detailed records of all adverse events and device deficiencies relating to the clinical Investigation, which are reported to them by the Investigation investigators. The sponsor shall ensure that all relevant information about a reportable event, which occurs during the course of this clinical Investigation in the United Kingdom, is reported as soon as possible to the MHRA, and the relevant ethics committees per their reporting requirements and according to the timelines in section d. Any additional relevant information should be sent within the same time frame as the initial report. The CI is responsible for informing the appropriate regulatory authorities, ethics committees and other investigators of any reportable events that have occurred with the study device in any clinical investigation according to the guidelines set forth by either the REC of record or regulatory authority in the country where the clinical investigation is taking place.

Progress reports

Progress reports will be submitted to the REC as per the REC requirements. The chief investigator will prepare the annual progress reports.

Foreseeable adverse events and anticipated adverse device effects

a) Anticipated adverse events and adverse device effects (ADEs), together with their likely incidence, mitigation or treatment.

Adverse events

Patients with stroke are at risk for both further strokes and morbidity and mortality associated with co-existing cardiovascular disease.

1) Further strokes.

2) Myocardial infarction.

3) Angina.

4) Peripheral vascular disease.

If any brain abnormality is found on the MRI scans during the study the following procedure will be adhered to:

All abnormal structural scans will be shown to a Consultant Neuroradiologist from the National Hospital for Neurology and Neurosurgery, as soon as possible.

Prof Alex Leff, Consultant Neurologist will have responsibility for reporting the finding to the participant's GP and discussing it with the participant as soon as possible.

A record of events will be kept in the research log, however, they will not be reported to REC and MHRA as they are anticipated events that patients are at risk of due to the nature of the underlying condition being studied. The records of these events will be discussed by the IDMC.

Adverse device effects and events

Below is a table summarizing the anticipated adverse device effects and events.

Adverse event/effect	**Likelihood (low, medium, high)**	**Mitigation Strategy**
Despite the user and simulation testing carried out on development. There is still risk of unanticipated bugs in the software that may arise due to differences in patient usage from the recommended usage.	Medium	During the clinical trial, all bugs will be tracked and logged using the Project Locker bug tracking tools) and all bugs will be given a unique reference code, an associated record for that reference code is captured, by the clinical team, detailing what caused the bug to occur, each bug is then prioritized and a fix is implemented (The clinical team will have access to the bug tracking code reports). Once a bug

		is fixed by the engineering team a standard formal automated verification test (again a test prior approved by the clinical team) is run on the compiled software to verify that the bug has been fixed.
Speech recogniser gives an incorrect binary decision. There is a risk that the speech recognition system may provide incorrect decisions to patient input i.e false positive or false negative decisions on a patient's naming attempt.	Medium	During the trial the performance of the speech recognizer will be monitored by the research team via the backend. The speech recognizer is expected to work at 80% accuracy. Thus these types of risks are considered an expected adverse device event and as such, a record of these types of events will be kept and reviewed by the relevant auditing committee and the IDMC for the trial.
Patient fatigue, headache, eyestrain from using the tablet device during the therapy and from prolonged screen time.	Low	The device can be supported by the user or can be used with table to prevent any patient fatigue if holding the tablet. Participants will also be encouraged to take regular beaks and to avoid prolonged screen time.

A.19 Oversight Committees

Trial Management Group (TMG)

The TMG will include the Chief and Principal Investigators and experts from relevant specialties. The TMG will be responsible for overseeing the trial. The group will meet at least twice per year and all members will sign a TMG charter. The TMG will review substantial amendments to the protocol prior to submission to the REC and MHRA.

Trial Steering Committee (TSC)

As this is not a multicenter trial, the TMG and TSC are one and the same.

Independent Data Monitoring Committee (IDMC)

The role of the IDMC is to provide independent advice on data and safety aspects of the trial. Meetings of the Committee will be held annually to review the safety data generated by the study or as necessary to address any issues. Information about adverse events and device effects will be gathered at each of the clinical trial time-points per patient. If the IDMC deems any adverse event or device effect is excessively high (i.e. statistically and clinically significant) then they can recommend premature closure of the trial.

The IDMC is advisory to the TSC and can recommend premature closure of the trial to the TSC. All IDMC members will sign an IDMC charter.

A.20 Vulnerable population

a) Description of the vulnerable population.

Stroke

Some stroke survivors may be considered vulnerable as they may have significant communication and cognitive difficulties. However, as part of this clinical trial we will not be recruiting anyone with significant cognitive impairment and therefore on an individual basis may not be considered as vulnerable.

There may be some support with travelling to appointments by family members which we will encourage.

b) Description of the specific informed consent process.

However, due to the difficulties with communication that aphasic patients do have they require extra care when informed consent is being sought. All information materials will be offered in written and aural forms, and supplemented by pictorial information to ensure that they are comprehensible to all participants. Participants (and, where appropriate, their carers) will be given a minimum of one week to carefully consider the information materials before deciding about participation.

Patients who are incapable of providing informed consent (patients without capacity) will not be recruited. The vast majority of patients with post-stroke aphasia are able to consistently communicate their wishes and desires, including consent to a treatment trial, see:

Stroke and Aphasia Handbook, Parr, S., Pound, C., Byng, S. and Long, B. 2003. Connect Press, UK.

c) Description of the EC's specific responsibility.

N/A

d) Description of what medical care, if any, will be provided for subjects after the clinical investigation has been completed.

N/A

A.21 Suspension or premature termination of the clinical investigation

Both the Sponsor and the Principal investigator reserve the right to terminate the clinical investigation at any time. Should this be necessary, the procedures will be arranged on an individual basis after review and consultation by both parties. In terminating the clinical investigation, the JRO at University College London and the Principal investigator will assure that adequate consideration is given to the protection of the subject's interests.

A21.1 Subject Withdrawals and Discontinuation

A participant may be withdrawn from the trial whenever continued participation is no longer in the participant's best interests, but the reasons for doing so must be recorded. Reasons for discontinuing the trial may include:

- Subject's rescission of consent.
- Any unexpected adverse device effect which is, in the opinion of the Principal investigator, related to the device and will endanger the wellbeing of the subject if the treatment is continued.

- The development of any undercurrent illness(es), infection or condition(s) that might interfere with the Clinical Investigation Plan.
- Any problem deemed by the Principal investigator and/or the JRO at University College London to be sufficient to cause discontinuation.
- Disease progression whilst in the study
- Intercurrent illness
- Patients withdrawing consent
- Persistent non-compliance to protocol requirements.

All subjects discontinued from the clinical investigation due to an unexpected adverse device effect, directly related to the clinical investigation, will be treated until the effect resolves. The Principal investigator will clearly document the date and reason(s) for subject withdrawal in his/her CRF and the monitor must be notified.

Subjects who are withdrawn will not be replaced if they have received the investigational device. If possible, any procedures or assessments planned for the subject on withdrawal from the clinical investigation should be performed when intention to withdraw the subject is announced.

Subjects who are withdrawn prior to receiving investigational device will be replaced.

A.22 Definition of End of Trial

The expected duration of the trial is 3 years from recruitment of the first participant. The end of the trial (phase 2) is the date of the last visit of the last participant.

A.23 Publication policy

Yes we plan to publish the findings.

As we are NIHR funded, the NIHR need to be sent a draft at the time of submission. The rules are here:
"The NIHR actively encourages the dissemination of research. Investigators and their research teams funded under an NIHR programme should provide advance notice of research outputs. A copy of the proposed publication should be sent to the funding programme at the same time as submission for publication or at least 28 days before the date intended for publication whichever is earlier. Please note this also applies to press releases to be issued by your host institution, e.g. university, NHS Trust or hospital. (Please see 4.1 on Press Releases)"
https://www.nihr.ac.uk/funding-and-support/documents/funding-for-research-studies/manage-my-study/outputs-guidance-notes-2.pdf (page 2).

All proposed publications will be discussed with and reviewed by the Sponsor prior to publishing other than those presented at scientific forums/meetings. Please refer to UCL publication policy.

The results of the study will be reported in the following ways: peer reviewed scientific journals; internal report; conference presentation; written feedback to research participants.
Please refer to UCL publication policy.

Intellectual Property

All background intellectual property rights (including licences) and know-how used in connection with the study shall remain the property of the party introducing the same and the exercise of such rights for purposes of the study shall not infringe any third party's rights.

All intellectual property rights and know-how in the protocol and in the results arising directly from the study, but excluding all improvements thereto or clinical procedures developed or used by each participating site, shall belong to UCLH. Each participating site agrees that by giving approval to conduct the study at its respective site, it is also agreeing to effectively assign all such intellectual property rights ("IPR") to UCL and to disclose all such know-how to UCL.

Each participating site agrees to, at the request and expense of UCL execute all such documents and do all acts necessary to fully vest the IPR in UCL.

Nothing in this section shall be construed so as to prevent or hinder the participating site from using know-how gained during the performance of the study in the furtherance of its normal activities of providing or commissioning clinical services, teaching and research to the extent that such use does not result in the disclosure or misuse of confidential information or the infringement of an intellectual property right of UCL. This does not permit the disclosure of any of the results of the study, all of which remain confidential.

A.24 Bibliography

List of the literature and data that are relevant to the trial, and that provide background for the trial. Please ensure the text contains appropriate cross references to this list

Ashburner, J. and K.J. Friston (2000). "Voxel-based morphometry-the methods". Neuroimage, **11** (6 Pt 1): 805-821.

Bhogal, S.K., R. Teasell, and M. Speechley (2003). "Intensity of aphasia therapy, impact on recovery". Stroke, **34**(4): 987-93.

Brady, M.C., H. Kelly, J. Godwin, and P. Enderby (2013). "Speech and language therapy for aphasia following stroke". Cochrane Database of Systematic Reviews, **12**(5).

Callaghan, J., J. Wells, S. Richardson, H. Holmes, Y. Yichao, S. Walker-Samuel, B. Siow, and M.F. Lythgoe (2014). "Is Your System Calibrated? MRI Gradient System Calibration for Pre-Clinical, High-Resolution Imaging". Plos one: https://doi.org/10.1371/journal.pone.0096568.

Code, C. and C. Heron (2003). "Services for aphasia, other acquired adult neurogenic communication and swallowing disorders in the United Kingdom, 2000." Disability Rehabilitation **25**(21): 1231- 1237.

Craig P., P. Dieppe, S. Macintyre, S. Michie, I. Nazareth, and M. Petticrew (2008). "Developing and evaluating complex interventions: the new Medical Research Council guidance". British Medical Journal, **33**(7): a 1655.

Moss A., and M. Nicholas (2006). "Langauge Rehabilitation in chronic aphasia and time postonset". Stroke, **37**(12): 3043-3051.

Palmer, R., Enderby, P., Cooper, C., Latimer, N., Julious, S., Paterson, G. & Delaney, A. (2012). Computer therapy compared with usual care for people with long-standing aphasia poststroke: a pilot randomized controlled trial. *Stroke*, *43*(7), 1904-1911.

Swinburn, K., G. Porter, and D. Howard (2004). "Comprenhensive Aphasia Test". Psychology Press.

Werner, P. (2004). "Beliefs about memory problems and help seeking in elderly persons". Clinical Gerontologist, **27**(4): 19-30.

Appendix A:	**iTALKbetter**	

iTALKbetter	***Baseline 1***	***Baseline 2***	***Baseline 3***	*Treatment*	**Time-point 4**	**Final Time-point**
Visit #	*1*	*2*	*3*		*4*	*5*
	Week 0	*Week 6*	*Week 12*	*6 weeks duration*	*Week 18*	*Week 30*
Informed Consent	*X*					
Medical History	*X*					
Baseline neuropsych tests	*X*	*X*	*X*	*X*	*X*	*X*
Language Tests	*X*	*X*	*X*	*X*	*X*	*X*
Proms	*X*	*X*	*X*	*X*	*X*	*X*
Randomisation [d]			***X***			
Brain Scans		*X*	*X*		*X*	
Device/Treatment				*X*		
Adverse Events review (CRF)	*X*	*X*	*X*	*X*	*X*	*X*
Concomitant Medication review	*X*					