BEHAVIOURAL ACTIVATION THERAPY FOR DEPRESSION AFTER STROKE (BEADS): A FEASIBILITY RANDOMISED CONTROLLED PILOT TRIAL OF A PSYCHOLOGICAL INTERVENTION FOR POST-STROKE DEPRESSION

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Protocol amendments since version 1.0:

Version and date	Section(s)	Edit
2.0 (22.01.2015)	3.5.7	Detail added on notification of GPs following ethical review by NRES East Midlands – Leicester.
2.1 (19.06.2015)	3.5.1 / 3.5.2	Additional options added to the recruitment process following early feedback from participating sites. That is, to include the option of a streamlined recruitment process whereby the therapist can contact the patient directly by phone following consent to contact, and to broaden the recruitment routes to include potential participants on acute outpatient caseloads.
2.2 (29.07.2015	3.5.4 / 3.5.6 / 4.2	Additional exclusion criteria to the effect that patients are not eligible to be recruited to BEADS if they are currently receiving psychological intervention; that they will be withdrawn from the intervention arm if it is subsequently agreed that the patient needs immediate clinical psychology input and to clarify that usual care can include

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		psychological input post-randomisation.

SYNOPSIS

Title	Behavioural Activation Therapy for Depression after Stroke (BEADS): A feasibility randomised controlled pilot trial of a psychological intervention for post-stroke depression
Acronym	BEADS
Short title	The BEADS Feasibility Pilot Trial
Chief Investigator	Dr Shirley Thomas, Lecturer in Rehabilitation Psychology, University of Nottingham
Objectives	This is a pilot trial to assess the feasibility of undertaking a randomised controlled trial to investigate the clinical and cost-effectiveness of behavioural activation (BA) therapy for people with post-stroke depression.
Trial Configuration	Parallel group feasibility multicentre randomised controlled trial with nested qualitative research and economic evaluation, comparing BA to usual stroke care for patients with post-stroke depression.
Setting	Three community stroke services. Intervention delivered in participants' own homes.
Sample size estimate	A sample size of 60 patients allows SD for continuous outcomes, such as the Patient Health Questionnaire-9 (PHQ-9) and Visual Analogue Mood Scales (VAMS) Sad, to be estimated to within precision of approximately ±19% of its true value (with 95% confidence). Allocation ratio 1:1 to either usual care or BA.
Number of participants	72 participants – allowing for 15% attrition by 6 months post-randomisation follow-up. In addition to this, we aim to recruit an estimated 65 carers and 3 therapists – a total of 140 participants across the whole study.
Eligibility criteria	Inclusion criteria: Stroke; over 18 years old; community dwelling; between 3 months to 5 years post stroke; depressed (identified by scoring ≥10 on PHQ-9 or ≥50 on VAMS Sad, as appropriate) Exclusions: diagnosis of dementia, were receiving medical or psychological treatment for depression at the time of their stroke; are currently receiving psychological intervention; communication difficulties, visual or hearing difficulties that would impact on capacity to take part in intervention; unable to speak English or lack mental capacity to consent. Carers – are eligible to take part in the study on the basis that they provide informal care to the trial participant. Family members, spouses and friends are all eligible to participate as carers in this study (for outcome assessment and qualitative interview). Therapists – the trial therapist from each participating site will be invited to take part in a qualitative interview about their experience of working on the trial and delivering the intervention.
Description of interventions	Intervention group will receive BA in addition to usual care. Up to maximum 15 (average 10) one-hour sessions over 4 months. The control group will receive usual care.
Duration of study	32 months overall. 6 months per participant.

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Randomisation and blinding	Participants will be randomised after consent and baseline assessments. Randomisation will be conducted using a computer generated pseudo-random list with random permuted blocks of varying sizes, and will be held on a secure server. It is not possible for the participant or therapist to be blind to the group allocation, but the researcher completing outcome assessments will be blinded.
Outcome measures	A series of feasibility outcomes are being measured, and the primary clinical outcome measure is PHQ-9. Additional qualitative analysis of intervention fidelity and feasibility.
Statistical methods	As a feasibility pilot trial the main analysis will be descriptive and focus on confidence interval estimation and not formal hypothesis testing. Rates of consent, recruitment and follow-up by centre and by randomized group will be reported.

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ABBREVIATIONS

AE Adverse Event

AP Assistant Psychologist

BA Behavioural Activation

CI Chief Investigator overall

CRF Case Report Form

CTRU Sheffield Clinical Trials Research Unit

DMEC Data Monitoring and Ethics Committee

GCP Good Clinical Practice

IAPT Improving Access to Psychological Therapies

ICF Informed Consent Form

NHS National Health Service

SOP Standard Operating Procedure

PI Principal Investigator at a local centre

PIS Participant Information Sheet

PSD Post Stroke Depression

REC Research Ethics Committee

R&D Research and Development department

SAE Serious Adverse Event

TMG Trial Management Group

TSC Trial Steering Committee

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1 Trial background information and rationale

1.1 Background

Depression is the most commonly investigated emotional consequence of stroke [1] with an average prevalence of 29%, which remains consistent up to 10 years post-stroke [2]. Effective treatment of depression is important because depression is associated with increased healthcare utilisation [3], worse rehabilitation outcomes [4-7], increased carer strain [8] and increased mortality [2,9]. Co-morbid long term physical health conditions and mental health problems have been found to increase health care costs [10]. Stroke patients who are depressed may engage less in rehabilitation, which in turn can lead to decreased functional recovery [7]. Post-stroke depression (PSD) is also associated with lower quality of life [2,11]. Thus in addition to improving mood, effective treatment of post-stroke depression is important as this has the potential to improve patients' functional outcomes and quality of life and also reduce strain on their carers.

About one third of stroke patients have aphasia (communication disability) and up to 75% will have significant cognitive impairment. Aphasia can affect all communication modalities including speaking, understanding, reading and writing. Stroke survivors with aphasia may be susceptible to post-stroke depression [12,13]. Cognitive problems include difficulties with attention, perception, memory and executive abilities.

There is currently insufficient evidence for the clinical and cost-effectiveness of psychological therapies for treating post-stroke depression [14]. Trials of brief psychosocial behavioural intervention plus antidepressant [15] and motivational interviewing [16,17] reduced post-stroke depression but these studies recruited patients early after stroke and excluded those with severe communication or cognitive problems, so these interventions may not be applicable to all patients with post-stroke depression. There is evidence from single case design studies that some patients with post-stroke depression improve following Cognitive Behavioural Therapy (CBT) [18,19]. However, in the only randomised controlled trial of CBT for post-stroke depression, no significant difference in depression was found between those patients who received CBT, an attention placebo or usual care [20].

A psychological intervention which may be suitable for stroke patients is behavioural activation (BA) therapy. BA is based on the behavioural model of depression, where depression is believed to result from a lack of response-contingent positive reinforcement [21]. Positive reinforcement is dependent on the person's actions [22] and reduction in activity can lead to loss of reinforcement. Stroke can result in a loss or restriction of rewarding activities and interactions (such as everyday activities, hobbies and social interactions) and this loss may lead to depression. BA aims to increase activity level, particularly the frequency of pleasant events, to improve mood. BA is effective at treating depression in adults, older adults and patient-carer dyads with dementia, and has comparable effectiveness to CBT [23-28].

The Chief Investigator (CI) has previously led a Stroke Association-funded multicentre randomised controlled trial (n=105) evaluating BA, delivered by an Assistant Psychologist, for treating depression in stroke patients with aphasia: Communication and Low Mood; CALM trial [29]. This found that mood was significantly better at 6 months follow-up in those who received BA compared to usual clinical care. The transferability of BA to hard-to-reach populations, such as those with aphasia and severe cognitive problems [30,31] adds to its potential as a psychological intervention. Given that CALM demonstrated that it was possible to deliver BA to a group of patients usually excluded from psychological interventions, there is significant potential for using BA for treating all stroke patients with depression.

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1.2 Rationale
There is evidence that BA is effective at treating depression in primary care settings, with older adults and patient-carer dyads with dementia. The CALM trial results were encouraging and if benefits can be demonstrated in those with aphasia, this intervention has real potential to help those without communication problems [29]. Accordingly, a feasibility pilot trial evaluating BA for post-stroke depression is proposed. As the CALM trial was not conducted with the wider stroke population and did not evaluate incremental cost effectiveness, a more robust feasibility study is now required.

1.3 Summary of risks and benefits
This study is not an investigation of a medicinal product (IMP) and entails no invasive procedures. The benefits of BA suggested by the CALM trial include improved mood. No participants will have any existing treatments withdrawn. There is a risk that participants may experience some distress from being asked about their mood, but all researchers and therapists will be trained to deal with these situations. If at any point during the baseline assessment, intervention or outcome assessment the researcher or therapist[1] is concerned about a participant, for example severe distress or reporting feeling suicidal, then the necessary referrals will be made. This process is explained in more detail in section 6 below.

1.4 Importance of the research to future clinical practice
This study will provide information on feasibility and clinical outcomes of BA for treating PSD, and its acceptability to patients, carers and therapists. The results of this study will also provide data on the feasibility of delivering the BA intervention in the NHS as part of routine clinical practice. Such feasibility work is required to provide the data needed to support an application to fund an adequately powered and definitive multicentre RCT evaluating the clinical and cost-effectiveness of BA for treating post-stroke depression for those with and without communication difficulties. The definitive (Phase III) RCT would provide level A evidence for clinical guidelines (the highest level of evidence) and would therefore have potential to change clinical practice nationally and worldwide.

As a feasibility study, this research is not powered to explore any factors that may modify the effects of treatment. This trial will be conducted in compliance with the protocol, GCP and regulatory requirements.

2 Trial objectives and purpose

2.1 Purpose
This is a multicentre pilot trial to assess the feasibility of a study to investigate the clinical and cost-effectiveness of behavioural activation therapy for people with post-stroke depression. This study will provide the necessary parameters and information to plan a definitive Phase III trial to evaluate the clinical and cost-effectiveness of BA for people with post-stroke depression.

[1] Please note: the role of the recruiting researcher and local therapist will be merged in this trial and is referred to as the 'therapist' throughout. In two sites, this work will be completed by an Assistant Psychologist and in the third site, this work will be completed by a Psychological Wellbeing Practitioner from the local IAPT (Increasing Access to Psychological Therapies) service. Other researchers will be responsible for collecting the 6 month outcome data and completing the qualitative interviews – they are referred to as 'researcher' throughout.

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2.2 Primary objective
The primary objective is to determine the feasibility of proceeding to a definitive trial.

2.3 Secondary objectives
The secondary objective is to determine the feasibility of the delivery of the behavioural activation therapy intervention with people with post-stroke depression.

3 Trial design

3.1 Trial configuration
This study will use a parallel group feasibility multicentre randomised controlled trial design, with nested qualitative research, comparing behavioural activation therapy to usual stroke care for patients with post-stroke depression.

3.1.1 Primary endpoint
The primary outcome measures in this study relate to the feasibility of a) proceeding to a definitive trial and b) delivering the behavioural activation therapy intervention with patients with post-stroke depression.

The primary endpoints are based on:

a. Feasibility of recruitment to the main trial
b. Acceptability of the research procedures and measures
c. Appropriateness of the baseline and outcome measures for assessing impact
d. Retention of participants at outcome
e. Potential value of conducting the definitive trial, based upon value of information analysis

3.1.2 Secondary endpoint
The secondary endpoints are related to the feasibility of the behavioural activation therapy intervention, based on:

a. Acceptability of behavioural activation therapy to participants, carers and therapists
b. Feasibility of delivering the intervention by Assistant Psychologists or IAPT therapist under supervision of an experienced mental health practitioner
c. Documentation of 'usual care' using healthcare resource use questionnaire
d. Treatment fidelity of the behavioural activation therapy
e. Feasibility of delivery of behavioural activation therapy within current services and within a definitive trial

In addition to this, the primary clinical outcome measure at 6 months is the Patient Health Questionnaire-9 (PHQ-9) [32]. For those participants with moderate to severe language problems who are unable to complete the PHQ-9, the Visual Analog Mood Scales (VAMS) Sad item [33] will be used – this is a single item visual analogue mood measure. The number of participants unable to complete the PHQ-9 will be recorded, and the VAMS Sad will be completed with all participants so the relationship between the measures can be explored. This is a pragmatic approach, based on self-completion at baseline.

The following measures will also be used to assess outcomes at 6 months:

- Stroke Aphasic Depression Questionnaire - Hospital version (observer-rated depression) [34]
- Nottingham Leisure Questionnaire (leisure activities) [35]
- Nottingham Extended Activities of Daily Living (functional outcome) [36]

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- Carer Strain Index (carer-rated level of strain) [37]
- EuroQol EQ-5D (health related quality of life) – standard version [38] and version for people with cognitive problems [39] for patients and carers
- Healthcare resource use questionnaire

3.1.3 Safety endpoints

Safety will be assessed by recording adverse events (as detailed in section 6 below). As a feasibility study, the trial is not powered to explore efficacy and the primary and secondary endpoints relate to feasibility. The sample size allows estimation of the SD for continuous outcomes, such as the PHQ-9 and VAMS Sad, to within precision of approximately ±19% of its true value (with 95% confidence).

3.1.4 Stopping rules and discontinuation

The study maybe stopped as a whole because of safety concerns or issues with study conduct at the discretion of the sponsor. There are no formal statistical criteria for stopping the trial early. Decisions to stop the trial early on grounds of safety or futility will be made by the Trial Steering Committee (TSC) on the basis of advice from the Data Monitoring and Ethics Committee.

3.2 Randomisation and blinding

Participants will be randomised at baseline (after consent and baseline assessments) in equal proportions to BA or usual stroke care. It is not possible pragmatically for the participant or therapist to be blind to the group allocation, but the researcher completing 6 month outcome assessments will be blinded and will also have had no involvement in any other aspects of the trial. The researcher will be asked to record whether or not they think they were unblinded and will also be asked to guess the group allocation. We will follow guidelines to minimise unblinding during randomised controlled trials of rehabilitation [40,41].

Randomisation will be conducted using a computer generated pseudo-random list with random permuted blocks of varying sizes, created and hosted by the Sheffield CTRU in accordance with their Standard Operating Procedures (SOPs) and will be held on a secure server. Study researchers will access the allocation for each participant by logging in to the remote, secure internet-based randomisation system. Once a participant has consented to the study, the researcher will log into the randomisation system and enter basic demographic information. After this information has been entered the allocation for that participant will then be revealed to the researcher. Access to the allocation sequence will be restricted to those with authorisation. The sequence of treatment allocations will be concealed until interventions have been assigned and recruitment, data collection, and analyses are complete.

3.2.1 Maintenance of randomisation codes and procedures for breaking code

Neither the participants nor the therapists will be blind to which treatment the participants will be receiving. The outcome assessor (researcher) will be blind to the treatment received but there is no requirement for them to know the treatment allocation at any stage. As a result a procedure for breaking the code is not necessary.

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3.3 Trial management

The University of Nottingham will act as sponsor for the trial. University of Nottingham SOPs will be used to govern the conduct of all aspects of the study, except where the sponsor has stipulated that adherence to Sheffield SOPs is permissible.

Three committees will be established to govern the conduct of the study: the Trial Steering Committee (TSC), Data Monitoring and Ethics Committee (DMEC) and the Trial Management Group (TMG).

The TSC will consist of an independent chair with clinical and research expertise in the topic area, and three 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.

The DMEC will consist of an independent chair with clinical and research expertise in the topic area, and two other topic experts, plus an independent medical statistician, as the sponsor sees fit and as agreed by the grant awarding body. The role of the DMEC is to review serious adverse events thought to be treatment-related and look at outcome data regularly during data collection. They will meet at least annually.

A part-time CTRU Trial Manager will contact the Chief Investigator and consult with the Director of CTRU regularly (and at weekly intervals in the first few months) whilst co-ordinating the trial. The TMG will meet at least at three-month intervals and will consist of: the Chief Investigator, Trial Manager, Trial Statistician, Trial Data Manager, the Director of CTRU and all co-applicants. Site contacts will be asked to meet with the TMG to address specific tasks, as appropriate. The TMG is accountable to the TSC for the implementation of the trial and therefore will monitor recruitment, data management, randomisation, patient safety, delivery of the intervention, adherence to protocol, timescales and budget management.

The Chief Investigator has overall responsibility for the study and shall oversee all study management. The data custodian will be the Chief Investigator.

3.4 Duration of the trial and participant involvement

Duration of the trial: Enrolment to the study will last for 12 months and data will be collected over an 18 month period in total. The entire study duration is 32 months from award of funding.

Duration of participant involvement: Participants are in the study for approximately 6 months from recruitment to the trial.

3.4.1 End of the trial

The end of the study will be the last qualitative interview or 6 month outcome assessment of the last participant (whichever occurs last).

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3.5 Selection and withdrawal of participants

3.5.1 Recruitment

Participants will be recruited from three centres[2]. The process for recruitment will vary depending on the specifics of where the participant is recruited from:

(i) Hospital stroke database and community stroke team database

At each site the clinical teams will send invitation letters to those on the hospital or community stroke databases of discharged patients to identify those who may be interested in taking part. Patients will be sent a postal pack containing a covering letter, participant information sheet, reply slip, PHQ-9, VAMS Sad and prepaid envelope. Patients who are interested in taking part will return the reply slip and completed PHQ-9 and VAMS Sad to the therapist. Return of completed questionnaires will be taken as implied consent to be contacted by the therapist, i.e. for potential recruitment into the trial. Those patients who do not reply will be contacted by the clinical team by telephone to remind them about the study. The PHQ-9 and VAMS Sad are used to assess the inclusion criterion of depression; and patients who return the reply slip with the completed PHQ-9 and VAMS Sad will be contacted by the therapist. Those who are identified as not being depressed will be thanked for their interest and will be informed that they are not eligible. The therapist will contact patients classified as depressed to arrange a visit. The purpose of the visit will be to check the participant meets the remainder of the inclusion criteria, to explain the study and formally invite those who are eligible to take part, obtain signed consent and complete baseline assessments. If a patient returns the reply slip to express interest in the study but does not return the completed PHQ-9 and VAMS then the therapist will offer to visit and support the patient to complete these assessments.

(ii) Patients currently on acute hospital stroke wards

At each site, Research Nurses will visit hospital stroke wards to provide information about the research to potential participants and seek their permission to be contacted by the research team in the future (and therefore, permission for their contact details to be passed on to the research team). This will be completed at times that are convenient and when they are able to discuss potential future participation in the research. A screening form will be used to collect key demographic and contact information from all willing, consented patients, who will then be contacted by the local therapist three months from the date of consent to be contacted. Mortality for all patients will be checked with the local Research Nurse or GP prior to further contact with the patient at this stage.

Patients will then be contacted by phone to tell them more about the research and arrange a home visit during which the patient will complete the screening measures. During the home visit, those patients who are identified as not being depressed will be thanked for their interest, and will be informed that they are not eligible. For patients who are classified as depressed, the therapist will either a) arrange a subsequent home visit or b) continue with potential recruitment of the participant as per the steps at (i) above.

Alternatively, the patient can be sent a pack containing a covering letter, participant information sheet, reply slip, PHQ-9, VAMS Sad and a prepaid envelope addressed to the therapist for that site. The same steps outlined above at (i) will then be followed.

(iii) Patients currently on the active caseload of community and acute stroke teams

[2] All references to participants relate to people with post-stroke depression, unless otherwise indicated. Carers of trial participants will also be invited to participate in the outcome assessment, and both they and the therapists will be invited to participate in the qualitative interviews.

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The study will be presented to the community and acute stroke teams at each of the study sites. The clinical care teams will be asked to explain the study to potential participants at the end of therapy or outpatient appointments or between appointments, as appropriate to the individual patient. For patients who are interested in taking part, the clinician will ask permission for their contact details to be passed on to the therapist. Following this, the therapist can then send a pack to the patients and follow the steps outlined at (i) above, or arrange a home visit and follow the steps at (ii) above.

(iv) Voluntary sector (stroke and aphasia groups)

The therapist at each site will seek permission to attend stroke and aphasia groups in each site to explain the study to group members. Those who are interested in taking part will be invited to provide their contact details to the therapist who will then either arrange a home visit and follow the steps at (ii) above, or send them a pack and follow the steps at (i) above. It will be explained to the potential participant that entry into the trial is entirely voluntary and that their treatment and care will not be affected by their decision. It will also be explained that they can withdraw at any time but attempts will be made to avoid this occurrence. In the event of their withdrawal it will be explained that their data collected so far cannot be erased and we will seek consent to use the data in the final analyses where appropriate.

Carers of trial participants will be recruited via the trial participants and asked to complete the baseline and 6 month outcome assessment questionnaires during the initial home visit. The presence of a carer will be established by the therapist during the telephone call to establish the initial home meeting. A smaller sample of carers will also be invited to participate in the qualitative interviews. Similarly, therapists in each of the three participating sites will be invited to take part in qualitative interviews. Informed consent will be taken from all carer and staff participants. As above, it will be explained to them that their participation is voluntary and that they can withdraw at any time.

3.5.2 Eligibility criteria

Participants will be identified from hospital and community stroke databases at three stroke services, as well as the corresponding acute hospital stroke wards, and from voluntary support groups. Participants will be approached by letter or by clinicians in community and acute stroke teams, or by voluntary group leaders. Self-referrals will be facilitated by advertising the study in newsletters of relevant charities and societies. Posters will also be displayed in local voluntary sector groups, libraries and local community centres so that potential participants unknown to local hospital and community stroke teams can self-present to the local research team. The methods of identifying potential participants have been kept broad to allow assessment of the optimum recruitment strategy for the definitive study. This will also enable recruitment of a representative cross-section of the population.

Carer participants are eligible to take part in the study on the basis that they provide informal care to the trial participant. Family members, spouses and friends are all eligible to participate as carers in this study.

The eligibility criterion for the therapists is also straightforward – only the trial therapist from each participating site will be invited to take part in a qualitative interview about their experience of working on the trial and delivering the intervention.

3.5.3 Inclusion criteria

The criteria are designed to identify those who would be suitable for the intervention were it to be offered within clinical practice. Participants will be included in the study if they:

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1. Have a diagnosis of ischaemic or haemorrhagic stroke
2. Are age 18 years or over
3. Are living in community settings, including home or nursing home
4. Are a minimum of three months and a maximum of five years post-stroke
5. Are identified as depressed, defined as:
    a. For participants who are able to complete the Patient Health Questionnaire-9 (PHQ-9 [32]): A score of ≥10 on the PHQ-9, or;
    b. For participants with communication difficulties or severe cognitive difficulties who are unable to complete the PHQ-9: A score of at least 50/100 on Visual Analog Mood Scales (VAMS) Sad item [33][3].

3.5.4 Exclusion criteria

Participants will be excluded from the study if they:

1. Had a diagnosis of dementia prior to the stroke (based on self-report by patient/carer)
2. Were receiving medical or psychological treatment for depression at the time at which they had their stroke (based on self-report by patient/carer)
3. Are currently receiving psychological intervention
4. Have communication difficulties that would impact on their capacity to take part in the intervention (based on assessment with the Consent Support Tool [42] for people with aphasia)
5. Have visual or hearing impairments that would impact on their capacity to take part in the intervention (based on the therapist's discretion at baseline assessment)
6. Were unable to communicate in English prior to the stroke
7. Do not have mental capacity to consent to take part in the trial.

All reasons for patient exclusion will be recorded.

3.5.5 Expected duration of participant participation

Study participants will be participating in the study for approximately 6 months.

3.5.6 Participant withdrawal

Participants have the right to withdraw from the study at any time. The reasons for leaving the study will be recorded on a CRF where given. Participants who withdraw will still be invited to complete the six month outcome assessments unless they have specified that they wish to have no further involvement in the trial. Individuals removed from active participation in the intervention will not be replaced. Reason for withdrawal from the intervention, if known, will be recorded.

Participants may be withdrawn from the trial either at their own request or at the discretion of the Investigator. The investigator may withdraw a participant in the interest of the participant (e.g. if continuation in the trial was considered to be causing undue stress) or due to a deviation from the protocol (e.g. where, following review, it transpires that a participant was incorrectly deemed eligible at the time of consent). Participants may discontinue their allocated intervention or withdraw from the study for the following reasons:

- withdrawal of consent,
- changes to their health status preventing their continued participation,
- failure to adhere to protocol requirements.

[3] For clarity, should there be any inconsistency between level of depression measured by PHQ-9 and VAMS Sad; if the patient completes the PHQ-9, this will be used as the measure of depression.

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More specifically, if during the trial there is a patient allocated to the BEADS intervention who subsequently needs clinical psychology input (as per the protocol of the local service) then the BEADS therapist (AP/PWP) will discuss this with clinical psychologist or clinical lead and the patient and will agree what is best for the patient. If it is agreed that the patient needs immediate clinical psychology input then they would be withdrawn from the BEADS intervention and they will see the clinical psychologist, or be referred to alternative provision, as appropriate to that patient. The patient will be withdrawn from the intervention but not the overall trial, i.e. we will still be able to collect outcome data from them. We will record the number of patients who we withdraw from the BEADS intervention because of a conflict with clinical services.

The participants will be made aware that this will not affect their current or future care. Participation in the study does not mean that access to other services, which are part of usual care, will be compromised. Participants will be informed (via the information sheet and consent form) that should they withdraw, the data collected up to that point cannot be erased and may still be used in the final analysis. Data should not be erased as it should be possible to recreate a participant's participation up to their point of withdrawal. Also once data has been entered onto the University of Sheffield trial database it cannot easily be erased as data has been backed up and cannot be destroyed.

3.5.7 Informed consent

Written informed consent will be obtained from all participants who are able to give it. Those who lack the mental capacity to give consent are excluded from the trial (see exclusion criteria at 3.5.4 above). The therapists will explain the details of the trial and provide a Participant Information Sheet, ensuring that the participant has sufficient time to consider participating or not. The Investigator will answer any questions that the participant has concerning study participation. One copy of the signed and dated consent form will be kept by the participant, one will be kept by the Investigator, and a third will be retained in the patient's records. Informed consent to participate in the trial will be taken before participants undergo any interventions relating to the study. For patients who are physically unable to sign the form (e.g. weakness in dominant hand due to stroke) then consent will be given using a mark or line in the presence of an independent witness (who has no involvement in the trial) who will then corroborate by signing the consent form.

A significant proportion (up to 50-80%) of the stroke population have some degree of cognitive or language impairment – aphasia. 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) [42] 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 a Patient and Public Involvement (PPI) advisory group during the Computerised Aphasia Therapy pilot study and has been validated in a further piece of work [42]. The therapist will request verbal consent from the potential participant to carry out part A of the CST (10 minutes). The result will indicate how appropriate it is to provide the accessible information sheet. If the CST indicates that the potential participant understands less than two key written or spoken words in a sentence, they are likely to find it difficult to understand all the information required to provide informed consent. These participants will be thanked for their time but are not eligible for the study as, despite the intervention using techniques to support the inclusion of those people with reduced language or cognition, the intervention does rely on achieving understanding with support and actively participating in therapeutic communication.

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The accessible information sheet will be provided to those who understand at least two key written and spoken words. This follows standard aphasia-friendly principles with one idea presented per page in short simple sentences in large font. Key words are emboldened and each idea is represented by a pictorial image to support understanding of what the study is about. The therapists will be trained to support understanding further by reading parts of the information aloud and using supportive gestures/actions (as described for information level 3 of the CST and consistent with the types of support offered in the intervention under study).

Once the potential participant has been given the information and had sufficient to time to ask questions and discuss with family or friends, the therapist will check the individual has capacity to provide informed consent by checking that they understand the information, that they can remember what the study is about and clearly express their decision in the way in which they usually communicate (speaking, writing, using a communication aid). The CST provides information on ways people with aphasia might choose to express their intentions. If capacity if not demonstrated, the therapist will go over the information again and discuss it further.

Participants with capacity to provide informed consent who have used the accessible information provision will be provided with an aphasia-friendly consent form and asked to initial all boxes before signing. Where stroke symptoms prevent initialling of boxes or providing written consent, the patient will use a mark or line and a relative/friend should be asked to witness the fact that the participant is consenting to the study, and sign and date the consent form to confirm this on behalf of the participant.

As participants may become distressed during the study, and as such, may be advised to consult their GPs, contact to notify the GP will be sough t from all participants. Participants' GPs will be notified by letter that their patient is taking part in the research and will be sent a copy of the Participant Information Sheet for information.

Written informed consent will also be taken from carer and therapist participants for the outcome assessments and qualitative interviews.

Should there be any subsequent amendment to the final protocol, which might affect a participant's participation in the trial, continuing consent will be obtained using an amended consent form that will be signed by the participant.

4 Trial treatment and regimen

4.1 Intervention arm – Behavioural Activation Therapy

Behavioural Activation (BA) Therapy is a structured and individualised treatment which aims to increase people's level of activity, particularly the frequency of pleasant or enjoyable events, in order to improve mood. Participants randomised to receive BA will be treated at their place of residence by an assistant psychologist at two sites or IAPT Psychological Wellbeing Practitioner (PWP) at one site. They will be offered a maximum of 15 sessions of BA over four months, with an expected average of 10 sessions. Therapy sessions will be delivered face to face on an individual basis, at the participants' residences and will last about one hour.

The intensity and duration of therapy is based on a study of CBT with stroke patients [20] and is informed by the CALM study in which participants received an average of nine one-

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hour sessions over three months [29]. Experience and criticism of the CBT trial [20] was that therapy was too short. The trial of BA for treating depression in primary care provided 12 sessions over three months [43] but this was not in a stroke sample and patients with communication and/or cognitive difficulties may require a longer duration of therapy. The duration of therapy has been increased from three months to four months because the CALM study showed that it was difficult to complete sessions in three months due to non-availability of the participant, short-term illness, etc. Extending therapy to four months will also allow flexibility to provide therapy visits to support maintenance, as might be provided in clinical practice. However, the number of therapy sessions will vary according to the needs of the individual and their progress in therapy. The intensity of treatment will be negotiated between the therapist and the participant, based on their progress in achieving their therapy goals, as this is a pragmatic trial and is designed to reflect clinical practice.

A BA treatment manual was developed for CALM based on the behavioural component of CBT for depression in stroke patients [18, 20], behavioural therapy with older people [44] and guidelines on conducting therapy with people who have aphasia [44-46]. For this trial, this therapy manual will be further revised to cover BA with stroke patients who do not have aphasia and will provide examples and practical guidance relevant to all stroke patients. The overall structure of the therapy programme will remain the same and the therapy manual will contain session content for 10 sessions using the same behavioural approaches as the CALM study.

Goals set during treatment to increase enjoyable activities will be tailored to the individual. BA also includes 'homework' tasks to be completed between sessions to practice exercises and increase activity levels. Behavioural treatment strategies focus on maximising mood-elevating activities. The process of BA involves identifying how the person currently spends their time, identifying activities that they would enjoy doing (this may include resuming previous activities, increasing current activity levels or introducing new activities) and setting goals to increase the number of enjoyable activities.

Behavioural therapy techniques include:
Activity monitoring: Identifying how participants spend their time to assess current activity level, what activities they enjoy and when activities could be carried out. Participants are given an activity diary or timetable to complete as a homework task. The complexity of the diary will vary according to the cognitive and communication abilities of the patient. The activity diaries are available in a range of formats including the use of word cards, picture cards and photographs.

Activity scheduling: Planning in advance realistic activities and goals for the participant to complete each day, which increases the likelihood that activities will be carried out. The intention is to gradually increase activities, and therefore the amount of positive reinforcement received, in order to improve mood. Activities will be set according to the abilities and goals of the individual.

Graded task assignment: Breaking a large task into smaller, manageable steps provides the opportunity to practise tasks participants find difficult. This increases the frequency of self-reward and reduces the chances of failure. For example, for someone who wants to go shopping, they would start by going to a familiar local shop where they know people already; this would then be extended to going to a larger shop which is further away.

4.2 Control arm – Usual care

Stroke survivors are admitted to hospital, usually to a stroke unit. On discharge they may

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receive input from an Early Supported Discharge team or input from a community stroke/rehabilitation team. Availability of psychological support in the community is inconsistent and likely to vary widely across the country (for example, possible pathways are detailed in the Stroke Improvement Programme [47]). The CALM trial [29] found that at the three month follow-up only 14% of participants had received mental health treatment in the past 3 months (from a mental health nurse, counsellor, psychologist, or psychiatrist) and this decreased to 10% at the 6 month follow-up. Although IAPT have extended their remit to include people with physical health problems [48,49] the current rate of uptake by stroke patients is unknown. Participants in the usual care group will follow the current care pathway. Participants will receive all other services routinely available to them as local practice but will have no contact with the trial therapist. This group is the control arm and their care will be recorded to document usual care to inform the design of the definitive trial. Only patients not currently receiving psychological intervention are eligible to be recruited to BEADS. The provision of Clinical Psychology varies. Some sites have a full-time clinical psychologist providing input to both hospital and community services and other sites can access this service but do not have dedicated provision. IAPT services will consider treating stroke patients if referred, but this rarely occurs. GPs may prescribe anti-depressants. Only those with severe mental health problems are referred to psychiatrists. The content of usual care is decided locally by the clinical team as to what this will be, as per local services.

Concomitant treatment

Those being treated for depression at the time of stroke onset will be excluded as we are interested in those who develop depression following stroke (as per exclusion criteria in section 3.5.4 above). However, patients currently receiving antidepressants are included so that we can assess appropriateness of including them in a later definitive trial. Previous research [50] indicates that a high proportion are likely to be taking antidepressants and if they still have scores high enough to indicate they are depressed, it suggests that the antidepressants have not resolved the mood problem. Those currently receiving psychological treatment will be included so we can record how commonly this occurs. Again, previous research suggests that few patients will be receiving on-going psychological treatment [29,51]. Receipt of antidepressant medication or other psychological intervention for depression will be recorded in the CRF.

4.3 Compliance

Compliance with BA is regarded as an endpoint not as a covariate and will be measured by recording whether participants allocated to the BA intervention attend and participate in every therapy session. The completion rates of follow-up questionnaires will also be recorded.

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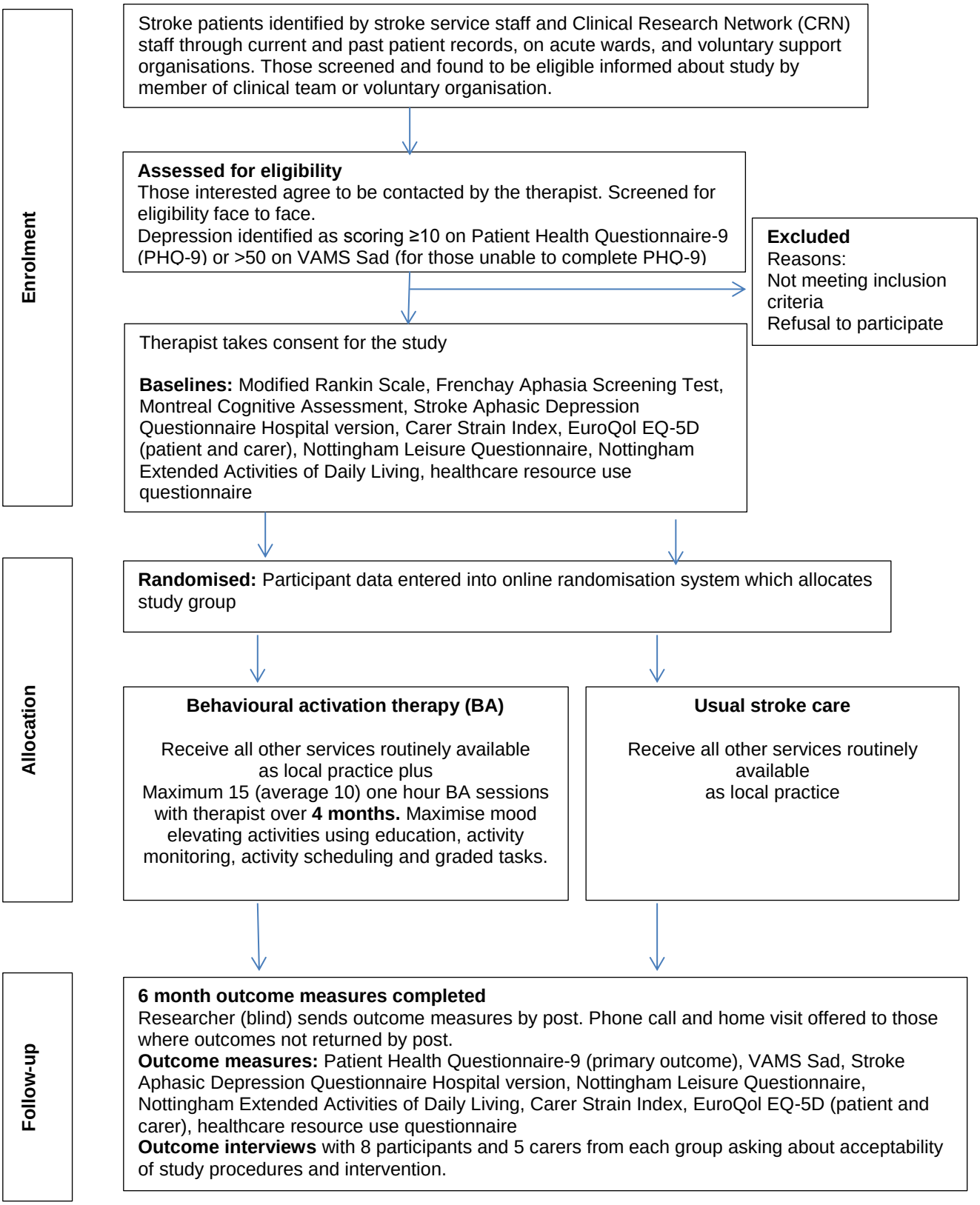
Figure 1: Flow of participants through the trial



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4.3.1 Intervention fidelity

A training manual will be developed, in addition to the treatment manual, to ensure the therapists receive standardised training. The therapists will attend a two-day workshop led by an NHS Consultant Clinical Psychologist and the Chief Investigator. The workshop will cover the rationale of therapy for treating depression, application of behavioural techniques for treating post-stroke depression, and explanation of the therapy manual. The workshop will include fictional case examples and role play exercises. The workshop will also include training from a Speech and Language Therapist on communicating with stroke patients with cognitive and/or communication difficulties. The training workshop will be recorded, as a potential training resource for future use, but also to ensure the same training is delivered again in the event there is a change to study personnel. Communication resources were developed during the CALM study (such as picture cards and activity schedules) and will be provided for each of the therapists. To support homework activities, worksheets/information appropriate sheets will be developed for varying levels of cognitive difficulties or aphasia.

It is important that the therapists deliver the intervention consistently in accordance with the therapy manual. Weekly clinical supervision for the therapists will be provided by a local Clinical Psychologist at each site. In addition, therapists delivering the intervention will have a monthly teleconference to discuss the content of the intervention, share examples of practice and any difficulties with the Chief Investigator and NHS Consultant Clinical Psychologist. To ensure the fidelity of the intervention, the content of treatment will be described and analysed. This will be achieved by video recording 24 intervention sessions, eight at each of the three sites. This will enable the checking of whether the treatment is being delivered according to the manual and the videos may be used for future training. The video recordings will be transferred to a secure encrypted device and deleted from the video recorder prior to transportation and stored in a secure area on the University of Nottingham server.

Participants and sessions will be selected iteratively using purposive sampling to represent the range of severity of depression (mild, moderate, severe from baseline scores) and across the phases of therapy (beginning, middle and end). The proposed sampling of sessions is outlined in table 1 below. It is anticipated that more sessions will be recorded in the middle phase of therapy because this covers more of the therapy sessions and is where the majority of the BA intervention occurs. The sampling strategy and the content of videos will be regularly reviewed and this will feed into the monthly supervision teleconference with the study therapists. The videos, record forms and monthly supervision will be used to check for the consistency of delivery of BA against the BA therapy manual.

Table 1: Sampling strategy for recording therapy sessions over time

	Mild depression	Moderate depression	Severe depression
Beginning of therapy	2 sessions	2	2
Middle of therapy	4	4	4
End of therapy	2	2	2

Video recordings are required to ensure that non-verbal communication is captured, especially for those with communication difficulties. Practices for video recording will draw upon guidance on minimizing intrusiveness of the recording [52, 53]. The assessors analysing the videos will apply a customized therapy record form designed to capture a variety of key elements spanning all aspects of the intervention. At consent for recruitment into the trial, participants will opt in or opt out of future invitations to be video recorded Should

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a participant decline video recording, they will be offered audio recording instead. Participants will not be excluded from the study if they do not want to be video or audio recorded. We will document the proportion of participants who agree to be video (or audio) recorded.

The therapists will also keep treatment notes for each session to summarise the content of the intervention, and to record goals set during BA and whether these were achieved. Therapists will also complete a record form of therapy content per session. The record form will quantify the content of the intervention (for example, how much time in each session was spent on different components). The record form will be based on a time sampling sheet adapted from that used in the CALM study and based on the content of the BA manual for this study. There will be triangulation between the videos, therapy record form and manual. Comparison between the videos and record form will allow analysis of whether the therapy record form alone is sufficient for recording and monitoring the content of the intervention in a definitive trial. Therapists will be able to add to the record form anything not covered by the defined questions. Those analysing the videos will also be able to add any additional strategies used by therapists not covered by the form. This will enable checking of whether the therapists are using BA consistently and also that they are not using non-BA approaches.

A series of qualitative interviews with 16 participants (eight per arm) and 10 carers (five per arm), as well as all three therapists will be completed by an independent researcher to provide a description of the acceptability of the design and procedures used in the trial and the BA intervention. The participant and carer interviews will be completed in their homes (or agreed convenient private location) and the therapist interviews will be completed in private locations, as agreed with the researcher. All participants will provide informed consent to participate in the interview, which will also be audio recorded on an encrypted digital recorder and transferred to a secure area on the University of Nottingham server. The researcher will transcribe all of the interviews, the transcripts will not include any personal identifiers and the recordings will be deleted upon completion of the transcription.

4.4 Criteria for terminating trial

The study may be stopped as a whole because of safety concerns or issues with study conduct at the discretion of the sponsor. There are no formal statistical criteria for stopping the trial early. Decisions to stop the trial early on grounds of safety or futility will be made by the TSC on the basis of advice from the DMEC.

As stated in 3.1.4 no early stopping is planned, but the study may terminate early if, in the view of the TSC, no useful information is likely to be obtained by continuing. The criteria for assessing this will primarily be the feasibility outcomes listed in section 3.1.1. The Steering Committee may also recommend the closure of a centre but that the trial as a whole continues, on the same grounds. Unblinded adverse event data will be reviewed by the DMEC, who may recommend to the TSC that the trial stops if in their opinion there is evidence of harm in the intervention group. The intervention is low-risk to the trial participants however, and stopping on grounds of patient safety is not anticipated. As this is a feasibility trial, it will not stop early for efficacy.

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5 Statistics

5.1 Quantitative Analysis

As the trial is a pragmatic parallel group, RCT data will be reported and presented according to the CONSORT 2010 statement [54]. As a feasibility study the main analysis will be descriptive and focus on confidence interval estimation and not formal hypothesis testing. Rates of consent, recruitment and follow-up by centre and by randomized group will be reported. Outcome measures will be summarised overall and by randomized group, to inform sample size estimation for the definitive trial. The data from this feasibility study will be used to estimate the consent rate, attrition rate, and the variability of the continuous outcomes (e.g. PHQ-9 (primary outcome), VAMS Sad item, Stroke Aphasic Depression Questionnaire – Hospital version, Nottingham Leisure Questionnaire, Nottingham Extended Activities of Daily Living, Carer Strain Index, EuroQol EQ-5D) in the trial population and use this information to inform the sample size calculation for the definitive RCT. Since the intervention is therapist led, the data will be used to estimate the intra cluster correlation (ICC) for patients treated by the same therapist using a marginal or random effects model for the 6-month post-randomisation PHQ-9 outcome.

As part of the feasibility analysis, the effect size for the 6-month PHQ-9 outcome (the probable primary endpoint for the definitive study), the difference in mean scores between the BA and control groups will be estimated, along with its associated 95% confidence interval estimate [55], using marginal or random effects models with baseline PHQ-9 as a covariate to check that the likely effect is within a clinically relevant range as confirmation that it is worth progressing with the definitive trial. The accuracy of the cut-off of the VAMS Sad in comparison with the PHQ-9 will also be checked. This information along with the acceptability of the study design and protocol to patients and carers; the safety of the intervention; patient recruitment and consent/retention rates will enable us to determine whether or not the definitive RCT is feasible.

5.2 Health economic analysis

For the health economic analysis a cost-utility analysis will be undertaken from the NHS and personal social service perspective. Due to the importance of carers for patients with post-stroke depression, a supplementary analysis will be undertaken, taking into account a societal perspective. Costs and utilities will be estimated for individual patients using data collected at baseline and follow-up, based upon responses to EQ5D and resource use questionnaires, combined with standard cost and valuation sources [56,57]. Patient-level costs and outcomes will be assessed over the full length of the feasibility study, and this will be supplemented with the construction of a simple economic model to examine the longer-term cost-effectiveness of treatment and priorities for future research. Costs will include intervention costs (such as assistant and clinical psychologist time), and health care resource use. Questionnaires will be tested as a method for collecting resource use data and information on carer time. Resource use data will be combined with unit cost data from standard sources using their most up-to-date versions in order to calculate costs for inclusion in the economic analysis [56,57].

Participants who do not have moderate or severe language problems will be asked to complete the standard version of the EQ5D as well as an amended accessible version (based upon pictures). Participants who do have moderate to severe language problems will be asked to complete the accessible version of the EQ5D. In addition, for participants who have carers, the carer will be asked to complete a standard EQ5D by proxy [39]. This will allow us to test alternative methods for collecting data from which to calculate quality

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adjusted life years (QALYs) relevant for the patients included in the study. Utility scores based upon EQ5D responses will be calculated for patients at baseline and follow-up and QALYs will be calculated using the area under the curve defined by the scores and straight line interpolation.

Differences between costs and QALYs in the two groups will be described and the incremental cost effectiveness ratio (ICER) will be calculated. A trial-based analysis will be supplemented by an analysis using a simple decision analytic model, which will be used to estimate the cost-effectiveness of the intervention over the lifetime of the patients. This will be populated using the trial data plus information from the literature where required. While this analysis will allow the estimation of lifetime cost-effectiveness and associated cost-effectiveness acceptability curves through the use of probabilistic sensitivity analysis, it is recognised that this will represent only a provisional estimate of the potential cost-effectiveness of the intervention, due to the nature of the feasibility study. The key outcome from the economic evaluation will be provided by a value of information analysis which will allow us to identify those model parameters that are the best candidates for further research [59]. This will be done by estimating expected values of perfect information for each parameter, which in essence identifies the maximum return for additional research [60].

5.3 Sample size and justification

As a feasibility study, this is not powered for efficacy and no formal interim analyses of efficacy are planned. Rather, the sample size for a feasibility study should be adequate to estimate the uncertain critical parameters (SD for continuous outcomes; consent rates, event rates, attrition rates for binary outcomes) needed to inform the design of the definitive RCT with sufficient precision. The sample size of 60 patients allows SD for continuous outcomes, such as the PHQ-9 and VAMS Sad, to be estimated to within precision of approximately ±19% of its true value (with 95% confidence). Allowing for 15% attrition by 6 months post-randomisation follow-up, 72 participants need to be recruited.

To achieve the target sample size of 72, over the 12 month recruitment period, with three centres we need to randomise 2 participants per centre per month. The sample size estimate of 60 will be synthesised with standard deviations observed in other published studies and on-going trials to provide a robust estimate for use in the sample size calculation for the definitive. Preliminary estimates suggest the definitive RCT would need to include 350 patients, in total, with valid outcome data, to detect a small standardised effect size of 0.35 at conventional levels of power (90%) and significance (5% two-sided).

In addition to this, we estimate that we will recruit a total of 65 carers to the study and three therapists to the study. The carer estimate is based on the CALM study [29] where approximately 90% of people with stroke had an informal carer present who completed the study outcome assessments. As such, the total sample size for the study as a whole is 140.

Further information on both the quantitative and health economic analysis will be provided in the detailed Statistical Analysis Plan. This will cover both the procedures for missing, unused and spurious data and definitions of populations whose data will be analysed.

6 Adverse events

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6.1 Definition of adverse events

If adverse events occur, this will be recorded by the therapist or researcher on the CRF and database. For the purposes of this study, adverse events are defined as suicidal intentions.

6.2 Monitoring of adverse events

Researchers will ask participants about any adverse events at the 6 month follow-up. This information will be collected on outcome questionnaires, or recorded in person for those participants who require help at a home visit. Any adverse events that are self-reported by participants in the intervention group during the delivery of the therapy sessions will also be recorded by the therapist on the CRF and database.

All adverse events will be assessed for seriousness, expectedness and causality. In addition, for additional events that are classed as serious, including death; suicide; a life-threatening adverse event; inpatient hospitalization or prolongation of existing hospitalization; disability or incapacity, the therapists and researchers will complete a Serious Adverse Event (SAE) form. For other adverse events, the researcher will complete an Adverse Event form. Further stroke related events will not be reported as SAEs because these are expected within this population.

6.3 Reporting procedures

The local Principal Investigator, therapist or researcher should immediately report all SAEs to the Trial Manager or other members of the CTRU study team (if the Trial Manager is unavailable) by telephone. The SAE form should be faxed to the Trial Manager within 24 hours of discovering the SAE. All SAE forms will be stored in the Site File.

The Trial Manager or other member of the CTRU study team (if the Trial Manager is unavailable) will then inform the Chief Investigator and at least two members of the TMG who will decide whether the event is related to the trial treatment. The DMEC and the TSC will immediately see all SAEs thought by the TMG to be treatment-related. SAEs should be reported by the CTRU to the Head of Department, using the Sponsor's SAE 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 Sponsor.

If a SAE is categorized as related and unexpected, the REC must be informed within 15 days of the Chief Investigator being alerted. This is the responsibility of the Trial Manager at CTRU, or delegated person in their absence. This should be reported to the REC using the Safety Report Form for non-CTIMPs.

The local therapist or the researcher should inform the Trial Manager of any NSAEs within 5 days of becoming aware of the event. He or she should also complete a NSAE form which should be sent to the Trial Manager and a copy held in the Site File. The CI and Trial Manager will review NSAE forms to check the assessment of seriousness and relatedness to the treatment.

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.

The DMEC and TSC will review the following at their next scheduled meeting:

- SAEs not thought to be treatment related
- NSAEs thought to be related to the treatment

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- NSAEs thought to be unrelated to the treatment

6.4 Suicide
The risk of suicide is inherent in the nature of the condition under scrutiny (depression). We will follow good clinical practice in monitoring for suicide risk during all encounters with trial participants. Where any risk to patients due to expressed thoughts of suicide is encountered, we will follow local suicide protocols for each participating site.

6.5 Participant removal from the study due to adverse events
Any participant who experiences an adverse event may be withdrawn from the study at the discretion of the Investigator.

7 Ethical and regulatory aspects

7.1 Ethics Committee and regulatory approvals
The trial will not be initiated before the protocol, informed consent forms and participant information sheets have received approval from the Research Ethics Committee (REC), and the respective National Health Service (NHS) Research & Development (R&D) departments. Should a protocol amendment be made that requires REC approval, the changes in the protocol will not be instituted until the amendment and revised informed consent forms and participant information sheets (if appropriate) have been reviewed and received approval / favourable opinion from the REC and R&D departments. A protocol amendment intended to eliminate an apparent immediate hazard to participants may be implemented immediately providing that the REC are notified as soon as possible and an approval is requested. Minor protocol amendments only for logistical or administrative changes may be implemented immediately; and the REC will be informed.

The trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, 1996; the principles of Good Clinical Practice, and the Department of Health Research Governance Framework for Health and Social Care, 2005.

7.2 Informed consent and participant information
The process for obtaining participant informed consent will be in accordance with the REC guidance, and Good Clinical Practice (GCP) and any other regulatory requirements that might be introduced. The therapist and the participant shall both sign and date the Informed Consent Form before the person can participate in the study.

The participant will receive a copy of the signed and dated forms and the original will be retained in site files. A second copy will be filed in the patient's notes and a signed and dated note made in the notes that informed consent was obtained for the trial.

As detailed in section 3.5.7, the decision regarding participation in the study is entirely voluntary and consent regarding study participation may be withdrawn at any time without affecting the quality or quantity of future medical care. No trial-specific interventions will be done before informed consent has been obtained. The investigator will inform the participant of any relevant information that becomes available during the course of the study, and will discuss with them whether they wish to continue with the study. If applicable they will be asked to sign revised consent forms. If the Informed Consent Form is amended during the study, the investigator shall follow all applicable regulatory requirements pertaining to approval of the amended Informed Consent Form by the REC and use of the amended form (including for ongoing participants).

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7.3 Records

7.3.1 Case Report Forms

Each participant will be assigned a trial identity code number, allocated at randomisation if appropriate, for use on CRFs, other trial documents and the electronic database. The documents and database will also use their trial identity code.

CRFs will be treated as confidential documents and held securely in accordance with regulations. The investigator will make a separate confidential record of the participant's name, date of birth, local hospital number or NHS number, and Participant Trial Number (the Trial Recruitment Log), to permit identification of all participants enrolled in the trial, in accordance with regulatory requirements and for follow-up as required. CRFs shall be restricted to those personnel approved by the Chief or local Principal Investigator and recorded on the 'Trial Delegation Log.'

All paper forms shall be filled in using black ballpoint pen. Errors shall be lined out but not obliterated by using correction fluid and the correction inserted, initialled and dated.
The Chief or local Principal Investigator shall sign a declaration ensuring accuracy of data recorded in the CRF.

7.3.2 Source documents

Source documents shall be filed at the investigator's site and may include but are not limited to, consent forms, current medical records, laboratory results and records. A CRF may also completely serve as its own source data. Only trial staff as listed on the Delegation Log shall have access to trial documentation other than the regulatory requirements listed below.

7.3.3 Direct access to source data / documents

The CRF and all source documents, including progress notes and copies of laboratory and medical test results shall made be available at all times for review by the Chief Investigator, Sponsor's designee and inspection by relevant regulatory authorities (e.g. Department of Health, Human Tissue Authority).

7.4 Data protection

All trial staff and investigators will endeavour to protect the rights of the trial's participants to privacy and informed consent, and will adhere to the Data Protection Act, 1998. The CRF will only collect the minimum required information for the purposes of the trial. CRFs will be held securely, in a locked room, or locked cupboard or cabinet. Access to the information will be limited to the trial staff and investigators and relevant regulatory authorities (see above). Computer held data including the trial database will be held securely and password protected. Information about the trial in the participant's medical records / hospital notes will be treated confidentially in the same way as all other confidential medical information.

Electronic data will be backed up every 24 hours to both local and remote media in encrypted format.

The study will use the CTRU's web-based 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 at the University of Sheffield. All data transmissions are over HTTPS (and thus encrypted using SSL/TLS. Access to the system is controlled by usernames and passwords, and a comprehensive

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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.

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 Data Management Plan. Error reports will be generated where data clarification is required.

8 Quality assurance and audit

8.1 Insurance and indemnity

Insurance and indemnity for trial participants and trial staff is covered within the NHS Indemnity Arrangements for clinical negligence claims in the NHS, issued under cover of HSG (96)48. There are no special compensation arrangements, but trial participants may have recourse through the NHS complaints procedures.

The University of Nottingham as research Sponsor indemnifies its staff, research participants and research protocols with both public liability insurance and clinical trials insurance. These policies include provision for indemnity in the event of a successful litigious claim for proven non-negligent harm.

8.2 Trial conduct

Trial conduct may be subject to systems audit of the Trial Master File for inclusion of essential documents; permissions to conduct the trial; Trial Delegation Log; CVs of trial staff and training received; local document control procedures; consent procedures and recruitment logs; adherence to procedures defined in the protocol (e.g. inclusion / exclusion criteria, correct randomisation, timeliness of visits); adverse event recording and reporting; accountability of trial materials and equipment calibration logs.

The Trial Coordinator, or where required, a nominated designee of the Sponsor, shall carry out a site systems audit at least yearly and an audit report shall be made to the Trial Steering Committee.

8.3 Trial data

Monitoring of trial data shall include confirmation of informed consent; source data verification; data storage and data transfer procedures; local quality control checks and procedures, back-up and disaster recovery of any local databases and validation of data manipulation. The Trial Coordinator, or where required, a nominated designee of the Sponsor, shall carry out monitoring of trial data as an ongoing activity.

Entries on CRFs will be verified by inspection against the source data. A sample of CRFs (10% or as per the study risk assessment) will be checked on a regular basis for verification of all entries made. In addition the subsequent capture of the data on the trial database will be checked. Where corrections are required these will carry a full audit trail and justification.

Trial data and evidence of monitoring and systems audits will be made available for inspection by REC as required.

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8.4 Record retention and archiving
In compliance with the ICH/GCP guidelines, regulations and in accordance with the University of Nottingham Research Code of Conduct and Research Ethics, the Chief or local Principal Investigator will maintain all records and documents regarding the conduct of the study. These will be retained for at least 7 years or for longer if required. If the responsible investigator is no longer able to maintain the study records, a second person will be nominated to take over this responsibility.

The Trial Master File and trial documents held by the Chief Investigator on behalf of the Sponsor shall be finally archived at secure archive facilities at the University of Nottingham. This archive shall include all trial databases and associated meta-data encryption codes.

8.5 Discontinuation of the trial by the sponsor
The Sponsor reserves the right to discontinue this trial at any time for failure to meet expected enrolment goals, for safety or any other administrative reasons. The Sponsor shall take advice from the Trial Steering Committee and Data Monitoring and Ethics Committee as appropriate in making this decision.

8.6 Statement of confidentiality
Individual participant medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited with the exceptions noted above. Participant confidentiality will be further ensured by utilising identification code numbers to correspond to treatment data in the computer files.

Such medical information may be given to the participant's medical team and all appropriate medical personnel responsible for the participant's welfare.

If information is disclosed during the study that could pose a risk of harm to the participant or others, the researcher will discuss this with the CI and where appropriate report accordingly.

Data generated as a result of this trial will be available for inspection on request by the participating physicians, the University of Nottingham and University of Sheffield representatives, the REC, local R&D departments and the regulatory authorities.

9 Publication and dissemination policy
Dissemination will be undertaken through peer-reviewed scientific journals and clinical and academic conferences, both national and international. A final report and monograph will be produced for the HTA. We will also ensure regular dissemination to interested parties via the study website or mailing lists.

A lay summary of findings for participants, service users and carers that is accessible to stroke survivors will be produced in consultation with local consumer groups. Findings will be disseminated nationally to stroke survivors and carers through free publications such as Stroke News (published by The Stroke Association). Organisations such as The Stroke Association, Connect and local stroke groups will be used as a medium for accessing stroke survivors. An executive summary will be prepared for the Trusts where the research was conducted and for the NHS authorities and stakeholders. The findings will be presented at the Nottingham stroke lay conference for stroke survivors and carers.

The study team is 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

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in a journal. This also applies to public oral and poster presentations. The Trial Steering Committee will also be notified of publications which report the final output of the study.

10 User and public involvement

The Chief Investigator attended the Nottingham Stroke Research Partnership Group to discuss the proposal for this study. They stated that this proposal receives their "strong support". In particular they commented that they "cannot stress to strongly how important I think it is to have a strong qualitative element to the study, so that patients' and carers' experiences of the intervention can be captured and taken into account" and this has informed the qualitative component of the study.

Representatives from the Sheffield Aphasia Research Advisory Group will be invited to join a PPI (group for the study and will have input at the planning, conduct, analysis and dissemination stages of the study. A plain English summary of study progress will be provided to the group every six months and they will meet at regular intervals throughout the study. Information materials for participants will be developed in consultation with the group to ensure they are appropriate and accessible. This is particularly important as some participants will have communication or cognitive difficulties. Involvement will also include advice on considerations of how best to deliver the intervention to the stroke population, from the service users' perspective; contributing to ideas on recruitment strategies. This group will also advise on the dissemination materials to ensure the results are accessible to a lay audience, in particular, stroke patients with communication or cognitive difficulties.

Study finances

Funding source

This study is funded by NIHR Health Technology Assessment programme.

Participant stipends and payments

Participants will not be paid to participate in the trial.

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Signature pages

Signatories to Protocol:

Chief Investigator: (name)_____

Signature:_____

Date: _____

Co- investigator: (name) _____

Signature:_____

Date: _____

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