Trials

STUDY PROTOCOL

Open Access

The effectiveness of a motivational interviewing-based intervention for reducing depressive symptoms after stroke compared to an attention control and usual care: study protocol for a multi-centre randomised controlled trial (COMMITS)

Kulsum Patel[1*], Caroline Watkins[1], Valerio Benedetto[1], Amelia Blow[1], Audrey Bowen[2], Robin Cant[1], Andrew Clegg[1], Leanne Daniels[3], Samantha Eccles[1], Jennifer Edwards[1], Richard Emsley[4], Michael Farrell[1], Mark Gabbay[5], Maree Hackett[6], Stephanie Jones[1], Gary Lamph[7], Deb Lowe[8], Gordon Prescott[1], Christopher Sutton[1], Shirley Thomas[9], Svetlana Tishkovskaya[1] and Catherine Elizabeth Lightbody[1]

Abstract

Background Depression affects almost 60% of stroke survivors, impacting on recovery and quality-of-life. Depression may be treated with medication or talk-based therapies. One randomised controlled trial showed a talk-based therapy called motivational interviewing-based intervention (MIBI) delivered early after stroke reduced depressive symptoms at 3 and 12 months post-stroke compared with receiving usual care alone. However, it was unclear if the benefit was due to the specific MIBI components or simply the additional attention received. This trial aims to determine the effect of MIBI plus usual care on reducing depressive symptoms post-stroke, relative to usual care (UC), and to an attention control (AC) (social attention without therapeutic content, i.e. general conversation).

Methods Patients admitted following acute stroke meeting the study eligibility criteria (not currently receiving talk-based therapy and not currently having severe depression) will be recruited across 18 UK hospitals within 28 days of stroke. A total of 1287 participants will be randomised on a 1:1:1 ratio into three groups: MIBI + UC; AC + UC; UC. Participants in MIBI + UC and AC + UC will additionally have remote (telephone/online) sessions with MIBI therapists or AC providers respectively, for four 45-min weekly sessions, beginning within 6 weeks of randomisation. Participant self-report measures of depression (primary outcome, Patient Health Questionnaire (PHQ-9) at 3 months) and quality-of-life will be collected at baseline, 6 weeks and 3 months post-randomisation. The proposed mechanism of effect, via participants' self-efficacy and confidence, and the impact of MIBI dose and/or therapeutic alliance on outcome will also be explored. If benefit of MIBI + UC over UC is demonstrated, mixed effects regression will be fitted to outcome data from all three arms, and appropriate parametrisation with MIBI + UC as the reference group. A mixed-methods

*Correspondence:
Kulsum Patel
kpatel@uclan.ac.uk
Full list of author information is available at the end of the article

process evaluation comprising quantitative assessment of intervention adherence and fidelity and semi-structured interviews with a purposive sample of study participants ($n \sim 18$) and MIBI/AC staff ($n \sim 15$) will explore participation, acceptability, and considerations for implementation. An economic evaluation will explore cost-effectiveness.

Discussion The results will inform whether any observed improvements in mood are a natural change over time, due to attention, or a therapeutic change attributable to MIBI. If MIBI is shown to effectively reduce depressive symptoms, the process evaluation will inform implementation of the intervention into clinical care.

Trial registration ISRCTN, ISRCTN17065351. Registered 01/02/2022, https://www.isrctn.com/ISRCTN17065351.

Keywords Protocol, Randomised controlled trial, Motivational interviewing, Depression, Adjustment, Stroke, Effectiveness, Mechanism, Attention control

Administrative information

Title {1}	The effect of a motivational interviewing-based intervention on reducing depressive symptoms after stroke compared to an attention control and usual care: study protocol for a multi-centre randomised controlled trial (COMMITS)
Trial registration {2a and 2b}	Trial registration: ISRCTN17065351. Date of registration: 01/02/2022
Protocol version {3}	Version 6.0 Date: 23/04/2025
Funding {4}	National Institute for Health and Care Research (NIHR) Applied Research Collaboration North West Coast (ARC NWC) NIHR Senior Investigator Award University of Lancashire NHS England Stroke Quality Improvement for Rehabilitation (SQuIRe) North West Catalyst Funding
Author details {5a}	Kulsum Patel, University of Lancashire * Caroline Watkins, University of Lancashire Valerio Benedetto, University of Lancashire Amelia Blow, University of Lancashire Audrey Bowen, University of Manchester Robin Cant, Patient Representative Andrew Clegg, University of Lancashire Leanne Daniels, True Rehabilitation Samantha Eccles, University of Lancashire Jennifer Edwards, University of Lancashire Richard Emsley, King's College London Michael Farrell, University of Lancashire Mark Gabbay, University of Liverpool Maree Hackett, The George Institute for Global Health Stephanie Jones, University of Lancashire Gary Lamph, Keele University Deb Lowe, Stroke Association Gordon Prescott, University of Lancashire Christopher Sutton, University of Lancashire Shirley Thomas, University of Nottingham Svetlana Tishkovskaya, University of Lancashire Catherine Elizabeth Lightbody, University of Lancashire * corresponding author, email: kpatel@uclan.ac.uk
Name and contact information for the trial sponsor {5b}	University of Lancashire Sponsor's representative: Professor Stjohn Crean Pro Vice Chancellor (Clinical, Health & Research) Vice Chancellor's Office University of Lancashire PR1 2HE 01772 893,393 irassponsor@uclan.ac.uk
Role of sponsor {5c}	The sponsor, separate to the funder, has overall responsibility for the trial

Introduction

Background and rationale {6a}

Assessment of the impact of the psychological effects of stroke and interventions to reduce them were identified by patients, clinicians, and carers as the leading priority in stroke rehabilitation and long-term care [1]. Stroke affects over 100,000 people in the UK each year [2], and almost 60% of stroke survivors experience depression [3]. Depression is a natural response to significant life changes, particularly if life-threatening, and may result in ongoing disability and dependence. Depression and depressive symptoms lead to poorer outcomes: increased disability, longer hospital stay, reduced quality of life, higher levels of tobacco and alcohol use, and higher rates of suicide and premature mortality [4–6]. Depression impacts on the management of stroke symptoms and treatment, reducing adherence to secondary prevention, lowering physical activity, and increasing cardiovascular-related morbidity and mortality [7, 8]. Compared with patients without depression [9–11] or with other mental health problems [12, 13], post-stroke depression is associated with increased health care resource use and costs, which could be reduced by providing adequate care [14].

In the first year post-stroke, 50% of survivors experience depression and/or low mood [3], yet these are inadequately managed, with a UK survey reporting that two-thirds of stroke survivors felt they did not receive the psychological support they believed was needed [15]. Lack of support received may be explained by staff not

identifying or screening for depression, the lack of definitive evidence for management of post-stroke depression [16], and insufficient staff trained in mental health care.

Systematic reviews have shown that antidepressants can benefit people with major depression following stroke [16], although alternative treatments should be available for those with less severe depressive symptoms as antidepressant side effects may reduce quality of life and subsequently adherence [17]. However, we should aim to prevent depression. Early intervention with talk-based therapies may support recovery and reduce, and in some cases prevent, increasing severity of depressive symptoms; and prevent psychological difficulties post-stroke.

We have preliminary evidence that psychological or 'talking' therapies may prevent and treat depression after stroke; however, this evidence is of low certainty [16, 18]. Many studies exclude those with cognitive problems, or include only those with aphasia; as such, the generalisability of these interventions to those with different levels of impairment remains unknown.

As well as stroke-related issues, health inequality issues may also impact on stroke survivors' participation in effective management of mood disorders. There is an increased risk of stroke among older people and among those living with socioeconomic disadvantage [19]. These factors might make accessing psychological support more difficult, particularly if interventions are delivered in settings outside the individual's home, or without flexibility in appointment times, or are costly. A lack of funding in general for the provision of psychological support or talk-based interventions post-stroke limits the accessibility of services for all stroke survivors. Extra funding has recently been provided for NHS Talking Therapies (previously Improving Access to Psychological Therapies (IAPT)) to support people with long-term conditions in the UK [20]. However, these services mainly focus on cognitive behavioural therapy [21], and are not part of standard stroke care.

Effective psychological services could be added to stroke care in practical and affordable ways by training the existing stroke workforce. Given the current staffing challenges, it is necessary to identify innovative ways to work coherently with all stakeholders to provide early effective stroke rehabilitation. This might include re-organising and upskilling existing service staff, and using the capacity and expertise of community and voluntary sector organisations. This has the potential to ease pressure on the NHS and offer patients more flexible access to services and interventions. Ideally, depression could be prevented or treated using simple and affordable interventions. Our motivational interviewing-based intervention (MIBI) is a brief psychological intervention that can be delivered by trained non-specialist staff to help prevent and treat mild to moderate depression [22, 23]. It fits within a matched-care model, freeing specialist mental health staff to focus on people with more severe depression [24].

MIBI was adapted from traditional motivational interviewing, a talk-based therapy for changing problematic behaviour through highlighting cognitive dissonance (where a person holds contradictory thoughts simultaneously). Using person-centred techniques, the therapist increases awareness and the importance of change through sensitively amplifying the discrepancy between current issues and the person's goals or personal values. Confidence is then built through supporting self-efficacy, enabling the person to develop motivation and readiness for change [25, 26]. MIBI applies these therapy techniques early after stroke, to develop motivation to promote self-efficacy in managing life after stroke and to facilitate psychological adjustment to having had a stroke [22, 23]. For example, MIBI may help someone who sets overly optimistic short-term recovery goals after a stroke adjust their expectations, build confidence, and develop the self-efficacy to set more realistic recovery goals.

In our single-centre RCT of MIBI plus usual care (MIBI + UC) delivered by trained research staff versus usual care (UC), MIBI + UC was effective in reducing depressive symptoms at 3 and 12 months post-stroke [22], and premature mortality by 12 months post-stroke [23]. There was also some evidence that those with mild or moderate communication problems may have benefitted more than those without communication problems. Our RCT strengthened the findings of a systematic review that psychotherapy may prevent the development of depression post-stroke [18]; however, our trial design did not allow us to determine whether MIBI, as opposed to the additional attention received during MIBI delivery, was the effective component. In our subsequent single-centre feasibility, RCT of MIBI + UC delivered by clinical staff versus an attention control (AC), delivery of AC, and MIBI by clinical staff (and their training and use of a MIBI manual to support delivery of MIBI) was shown to be achievable [27]. We now aim to test our MIBI, delivered by clinical staff in the acute or rehabilitation setting, or support coordinators in a community setting, and remote methods (telephone/online), in an adequately powered, multi-centre, parallel-group randomised attention and usual care controlled trial.

Objectives {7}

The primary aim of this study is to determine whether a motivational interviewing-based intervention (MIBI) with usual care (UC) reduces depressive symptoms 3 months after stroke better than UC plus matched attention (AC + UC) and/or UC alone.

Our secondary objectives are to:

1. Evaluate the effectiveness of MIBI + UC post-stroke, compared with AC + UC and UC alone, for reducing depressive symptoms;
2. If the intervention is effective, explore the mechanism of action of MIBI, examining self-efficacy and confidence as mediating factors;
3. Explore moderators of treatment effectiveness, including gender, stroke severity, communication problems, and past psychological problems;
4. Explore the impact of post-randomisation effect modifiers (dose, and therapeutic alliance) on the effect of MIBI on reducing depressive symptoms;
5. Conduct a process evaluation to determine whether MIBI and AC were delivered as intended (fidelity), and how those delivering and receiving the interventions responded to it (acceptability), including the potential impact of health inequalities;
6. Explore the feasibility of MIBI delivered in the community by a relevant community group (i.e. the Stroke Association);
7. Investigate the economic consequences of adopting MIBI for reducing post-stroke depressive symptoms.

Trial design {8}

COMMITS is a randomised controlled multi-centre superiority trial with three parallel groups and randomisation performed with a 1:1:1 allocation. It incorporates a mixed-methods process evaluation, and an economic evaluation. Research ethics approval has been granted (19/WA/0337 02 January 2020).

Methods: participants, interventions, and outcomes

Study setting {9}

Up to 22 NHS Trusts' acute stroke units in the UK. A list of study sites will be available on the ISRCTN record (ISRCTN17065351).

Eligibility criteria {10}

Patients will be approached for consent if they meet all the following inclusion criteria: aged 18 years and above; admitted to a participating stroke unit and eligible for consent within 12 weeks of acute stroke onset; able to provide informed consent; no, mild, or moderate speech difficulties (i.e. score of 0, 1, 2, or 3 on the Communication Observational Assessment Tool (COAT) [28]); PHQ-9 total score ≤ 14 and Q9 score = 0; able to converse in English; access to online video calling or a telephone to participate in interventions via remote means; willing to adhere to follow-up procedures. Patients will be ineligible if they meet any of the following exclusion criteria: receiving active treatment for a psychiatric disorder; receiving a talk-based therapy; current alcohol/drug misuse or dependency; life-threatening/terminal illness.

If trial assessments indicate that a participant may be severely depressed, the clinician in charge of their care will be notified and appropriate and usual action taken. These participants will not be randomised (as it may not be suitable, either for themselves or for the AC providers, to be potentially randomised to AC + UC) and will be informed of this, but they may still participate in follow-up data collection, if they are willing.

All participants randomised to receive MIBI or AC and with continued capacity to provide informed consent will be eligible to participate in process evaluation interviews.

Who will take informed consent? {26a}

Eligible patients will be approached by the research practitioner (e.g. research nurse) in the participating hospital, who will discuss the study and provide a participant information sheet. The patient will have as much time as they deem necessary to consider participating in the study. If the patient agrees to participate, the research practitioner will obtain written informed consent from the patient, or where necessary use a witnessed consent process (i.e. if the patient has functional difficulty in providing a signature, such as if the dominant hand is on the side affected by the stroke, or an impairment such that reading/writing is difficult), or telephone consent process (i.e. when patient has been discharged from hospital before consent can be obtained).

Additional consent provisions for collection and use of participant data and biological specimens {26b}

Participants will consent to their anonymised data being used in reports, publications, and to support other research and training in the future.

For eligible patients who decline to participate, core demographic details which are routinely recorded on admission will be collected, including gender; age in years; time and date of stroke; NIHSS [29] score at admission; and pre-stroke mRS [30]. The research practitioner will collect these data from patients' case notes and enter them on a screening log with an accompanying screening number to ensure these data are pseudo-anonymised from this point.

Little is known about why patients decline to participate in research; knowing more would inform the design

of studies and participant-facing materials. All potential participants who consider participation will be asked to complete an anonymous feedback form regarding their decision to participate or not. A pre-paid envelope addressed to Lancashire CTU will be provided for self-return. If we identify common reasons for refusal, we will use this to inform any changes required to maximise accessibility and participation.

Interventions

Intervention description {11a}

MIBI will be delivered by trained MIBI therapists. Two different delivery models will be used at different sites, referred to as group A and group B sites. In group A sites ($n \sim 18$), two NHS band 5 or above clinical staff members from the stroke hospital multidisciplinary team will be selected, based on a person specification indicating the need for empathy, good interpersonal, and active listening skills, to undertake the role of MIBI therapist at their site. In group B sites ($n \sim 4$), Stroke Association Support Coordinators will be selected to undertake the role of MIBI therapist as required, providing cohesive community delivery. In the event of site capacity issues, e.g. site critical incident, trained MIBI therapists from the stroke research team at the University of Lancashire will be allocated to deliver MIBI to participants. All MIBI therapists will receive the same MIBI training, delivered by the researchers who have previously been trained as MIBI therapists and have experience of delivering MIBI for people with stroke. MIBI training will incorporate four 1-day workshops, delivered remotely, incorporating the theory behind MIBI, psychological mechanisms that effect change, familiarisation with the MIBI manual (developed previously by the study team), and practising MIBI. Training will also include ten remotely delivered practice MIBI sessions: two sessions each with five consented volunteer patients with stroke. Threshold competency will be determined by the trainers who will review the audio-recordings of all the practice sessions and assess them with the Motivational Interviewing Treatment Integrity code (MITI) [31] to check fidelity to the MIBI approach. The MITI is a coding system that provides an indication of how well a therapist is using MI. It comprises two components: global scores and behaviour counts. Global scores are based on the rater's overall impression of the entire session and are rated on five dimensions (evocation, collaboration, autonomy/support, direction, and empathy), each on a five-point scale. Higher scores indicate greater fidelity to MI. Scores of 3.5 and higher indicate beginner proficiency; scores of 4 and higher indicate competency. Behaviour counts record the number of instances a particular behaviour is exhibited by the therapist during the session. Ninety percent and above MI-adherent behaviours indicate beginning proficiency; 100% MI-adherent behaviours indicate competency. MIBI therapists will need to achieve global score of 4 and 100% MI-adherent behaviours this to be considered competent for this trial.

Participants in the MIBI + UC group will receive four 45-min weekly individual sessions of MIBI, delivered by the same MIBI therapist (as far as practicable). MIBI sessions will normally commence within 2 weeks, but no later than 6 weeks, from randomisation and will be held via remote means such as online video call (e.g. Microsoft Teams, Attend Anywhere) or telephone, depending on accessibility and participant preference. All sessions will be recorded.

The four MIBI sessions are structured and sequential. The first is an introductory session during which the therapist sets the agenda and the participant talks about their stroke and current concerns. The second and third sessions involve working through the participant's concerns about their mental and physical health and associated issues. The final session is used to resolve unexplored issues from previous sessions and end the therapy in a mutually safe and satisfactory manner.

MIBI therapists will complete record sheets and record all sessions (video or audio) for reflection and preparation for subsequent sessions and transfer these to the study team as they are completed. Ongoing supervision will be provided by the MIBI trainers, remotely via video-call or telephone. Monthly individual supervision sessions will be scheduled with the MIBI trainers, but MIBI therapists will be able to contact the trainers at any point in between scheduled supervision contact for support. MIBI therapists will also receive group supervision every 2 months with a clinical psychologist.

Replicating the amount of 'attention' given to the MIBI + UC group, participants in the AC + UC group will receive four 45-min weekly individual sessions of AC, delivered by the same AC provider (as far as possible). AC sessions will commence within 2 weeks, and no later than 6 weeks, from randomisation and will be held via remote means such as online video call (e.g. Microsoft Teams, Attend Anywhere) or telephone, depending on accessibility and participant preference. All sessions will be recorded.

The AC will mirror the MIBI as far as possible, except for the active component of MIBI, and will involve social attention (general conversation) absent of intuitive psychological support. The AC will be delivered by trained AC providers. Staff members from the research team's institution will be selected to undertake the role of AC provider based on a person specification indicating the need for good interpersonal skills. All AC providers will receive the same AC training, delivered by the

trial research team. AC training will be based on the AC intervention used in our feasibility study [27], and in the Assessing Communication Therapy in the North West (ACTNoW) [32] study. AC training will involve workshops, delivered remotely, incorporating familiarisation with the AC manual (adapted from the ACTNoW AC manual), and strategies for engaging in neutral conversation with participants, and avoiding conversation related to mood. Training will also include ten remotely delivered practice AC sessions: two sessions each with five consented volunteer patients with stroke. AC provider competency will be determined by the AC trainers who will review the audio-recordings of these practice sessions and assess competency based on a checklist adapted from the MITI. AC providers will need to achieve global scores of 4 and above and 100% AC-adherence to be considered competent for this trial. As with the MIBI therapists, AC providers will receive ongoing individual and group supervision from the trainers throughout the study.

Mirroring the MIBI, the four AC sessions are structured so that the first is an introductory session where the provider gets to know the participant, their likes and dislikes, and together decide how to spend the sessions. The second, third, and fourth sessions consist of the AC provider spending time with the participant in general conversation, whilst avoiding talking about the participant's mood or emotional issues. If such topics arise, the AC provider does not offer any advice or therapy and restricts the exchange to a lay conversation. The end of the final session is used to prepare the participant for sessions coming to an end and winding-down the sessions in a mutually safe and satisfactory manner.

Participants in the UC group (and in MIBI + UC and AC + UC groups) will receive the usual care and access to usual services available at their admitting site. Participants will not be denied any treatment. Commonly, UC post-stroke includes no psychological support, even for people with low mood, and is unlikely to include MIBI.

Explanation for the choice of comparators {6b}

We need to be able to understand the differences between MIBI + UC, AC + UC, and UC. If the effectiveness of MIBI + UC is compared relative to UC alone, it would be unclear if the MIBI-specific components were important, or whether any benefits were due to the additional attention received, so MIBI + UC must be compared with AC + UC, to control for non-specific elements of treatment. If MIBI + UC is compared to AC + UC alone and both groups improve, it would be unknown whether either might offer a benefit over UC alone; by using a three-arm design, it is possible to identify whether any benefits to mood are a natural change over time, are due to attention, or are a therapeutic change directly attributable to MIBI.

Criteria for discontinuing or modifying allocated interventions {11b}

Participants may withdraw from receipt of either the MIBI or AC without providing a reason. A member of the clinical team may identify a change in the participant's physical or mental status that raises concerns for the participant's welfare and withdraw the participant from either intervention in the interests of a participant's care.

If a MIBI therapist leaves the trial or becomes unavailable after completing with a participant, 1 session, the participant will begin therapy again with the next available MIBI therapist; 2 sessions, another therapist will continue therapy after a review of notes; 3 sessions, another therapist will carry out a short call to check that the participant is safe and happy to end the intervention. A similar pattern will be adopted for AC providers. Any change to MIBI therapist/AC provider will be documented.

Strategies to improve adherence to interventions {11c}

MIBI therapists and AC providers will be monitored by the research team throughout the study to check that delivery of MIBI and AC is as intended. Trainers will review the audio-recordings of one randomly selected MIBI/AC session for each therapist/provider every 3 months (approximately one in every 12 sessions for each therapist/provider) throughout the study. The random selection will ensure that it cannot be predicted which session will be reviewed, and will ensure diversity of session numbers 1–4 being reviewed. If competency reduces during the study (i.e. for MIBI, MITI global scores fall below 4; for AC, non-avoidance of mood or emotional issues), the trainers will reinforce strategies with the therapist/provider through additional training and supervision will continue until competence is regained, with more frequent review of session audio-recordings.

It will be the participant's choice whether they continue to receive the intervention. Should participants cancel or miss arranged sessions, the MIBI therapist/AC provider will contact them to rearrange the session, attempting contact on at least three occasions (at different times on different days) over a 4-week period, to continue the intervention.

Relevant concomitant care permitted or prohibited during the trial {11d}

All participants will continue to receive usual care and will not be denied any treatment.

Provisions for post-trial care {30}

During the trial, if participants are identified as suffering very low mood or depression (through baseline/6 weeks/3 months post-randomisation assessments (PHQ-9 [33]), or during MIBI/AC sessions (observed distress)), Lancashire CTU will report this to the treating clinician (hospital clinician if participant is inpatient, or GP if post-discharge). After the 3-month follow-up, it will not be possible for the research team to provide any care post-trial.

Outcomes {12}

The primary outcome is depressive symptoms at 3 months post-randomisation, measured with the PHQ-9 and summarised as mean PHQ-9 score (within treatment group).

Secondary outcomes are as follows: status (alive/dead); depression (Yale single item [34], self-reported antidepressant use, or external (outside of trial) psychological input); anxiety disorder (GAD-7 [35]); quality of life (SIS [36], EQ-5D-5L [37]); dependence (mRS [30]); function (Barthel [38]); further stroke (yes/no); patients' health care resource use. All secondary outcomes will be assessed at 3 months post-randomisation and will be summarised as proportions or mean scores within each group at 3 months.

Other outcomes include potential mediating factors possibly relating to the mechanism of action of MIBI: self-efficacy (SSEQ [39]); and confidence (CaSM [40]). These will be assessed at 6 weeks and 3 months post-randomisation, and summarised as mean scores.

Table 1 shows the study outcomes and time points.

Participant timeline {13}

Table 2 shows the flow of the trial's recruitment, intervention, and assessments.

Sample size {14}

Initially sample size calculations were performed for 10 sites. We assumed a relatively conservative therapist ICC = 0.02 in each of the MIBI and AC arms based on trials of similar interventions, e.g. ICC = 0.015 for Hamilton Depression Rating Scale scores in a previous therapy trial [41]. To further justify the choice of ICC, a Bayesian modelling exercise was conducted, following the method described in [42] and combining 43 ICC from 10 relevant studies. The estimated ICC was close to 0.02. With the ICC = 0.02, outcome data from 320 participants (16 per MIBI therapist/AC provider with 10 centres and 2 MIBI therapists/AC providers per centre) per arm would provide 90% power (alpha = 5%) to detect a clinically important between-groups difference of 1.8 (SD = 6.0 [43]) in mean PHQ-9 scores at 3 months post-randomisation. To simplify trial processes, we plan to randomise equal numbers to the three arms, which would provide 94% power to detect a 1.8 difference in mean PHQ-9 scores between the MIBI and UC arms as there is no therapist clustering in the UC arm. Assuming 20% attrition by 3 months (our previous trial had 18% missing mood score at 3 months post-stroke), we would need 1200 participants (400 per arm).

At a later stage, a number of changes in the design were introduced, which resulted in revision of the sample size calculations. The following is a summary of the changes incorporated into the design:

- The number of sites increased to 15 centres, with 2 MIBI therapists in each of 15 sites, so the total number of MIBI therapists increased to 30.
- Six Stroke Association MIBI therapists were introduced to the study which led to adding three additional sites (these therapists are shared between these sites). This increased the number of sites to 18 and the number of MIBI therapists to 36.
- Instead of having 2 AC volunteers in each of 15 sites, the design was changed to have 10 centrally located (University of Lancashire based) AC providers.

Assuming the same relatively conservative therapist ICC = 0.02 for 36 therapists in the MIBI arm, changes to the design would suggest that a smaller ICC = 0.01 can be assumed for 10 centrally located (University of Lancashire) AC providers expected to interact with 3.6 times as many participants. The reduction of the ICC for AC providers is also linked to the expectation that the mean AC effect (if it exists) will be smaller than the mean MIBI effect (also, if that exists) and so the variability in AC effect will be smaller than the variability in the MIBI effect. Under the assumptions described, outcome data from 320 (~ 8.89 per MIBI therapist and ~ 32 per AC provider) participants in those arms would provide 90.6% power (alpha = 5%) to detect a clinically important between-groups difference of 1.8 (SD = 6.0) in mean PHQ-9 scores at 3 months post-randomisation. As we will randomise equal numbers to the three arms, this will provide just over 90% power to detect a 1.8 difference in mean PHQ-9 scores between the MIBI and UC arms.

With 20% attrition by 3 months, the target total number to be randomised remained at 1200 (400 per arm, ~ 11.1 per MIBI therapist, and ~ 40 per AC provider). We further assumed that up to 10% of consented patients might fail to complete the baseline, withdraw, or die before randomisation. The pre-randomisation attrition of 10% was guided by previous research and was rather conservative. Under the parameters stated, the total number approached and consented was set at 1334.

Table 1 Primary and secondary outcomes and measures across baseline, 6-week, and 3-month follow-ups

Measure	Primary	Secondary	Baseline	6 weeks	3 months
Demographics and clinical characteristics					
Sex, age, ethnicity, post code			x		
Pre-stroke function (mRS), stroke location, cognitive function (MoCA), physical function (Barthel)			x		
Mood					
Depressive symptoms (PHQ-9)	x		x	x	x
Depression (Yale)		x	x		x
Self-reported clinical depression		x	x		x
Antidepressant use, psychological input		x	x		x
Anxiety symptoms (GAD-7)		x	x		x
Other health outcomes					
Status (alive/dead)		x			x
Further stroke		x			x
Quality of life (SIS)		x			x
Function (mRS, Barthel)		x			x
Resource use		x	x		x
Health-related quality of life (EQ-5D-5L)		x	x		x
Mediating factors					
Self-efficacy (SSEQ)		x		x	x
Confidence (CaSM)		x		x	x
Moderating factors					
Stroke severity (NIHSS)			x		
Communication (FAST)			x		
History of/current psychological problems			x		
Post-randomisation effect modifiers (intervention only)					
Dose		x			
Therapeutic alliance (WAI)		x			
Fidelity to MIBI		x			

Table 2 Schedule of enrolment, allocation, interventions, and assessments for participants

	Enrolment	Allocation	Treatment (4 weeks)				Follow-up
Time point	$-t_1$	***0***	***1***	***2***	***3***	***4***	
Recruitment:							
Eligibility screen	x						
Informed consent	x						
Randomisation		x					
Interventions:							
Motivational interviewing-based intervention + usual care			x	x	x	x	
Attention control + usual care			x	x	x	x	
Usual care			x	x	x	x	
Assessments:							
Baseline	x						
Post-treatment						x	
6 weeks post-randomisation							x
3 months post-randomisation							x

However, the proportion of participants providing the primary outcome at 3 months was found to be lower than expected—70%, and the variation in the number of participants seen by therapists and AC providers was much greater than expected. Both factors reduce the power for any fixed number of randomisations. There were also 14 AC providers rather than 10 assumed previously, increasing power. Under the revised assumptions, outcome data from 300 (8.33 per MIBI therapist and 21.4 per AC provider) participants in each of those arms will provide 84% power (alpha = 5%) to detect a clinically important between-groups difference of 1.8 (SD = 6.0) in mean PHQ-9 scores at 3 months post-randomisation, assuming variation in the number of participants seen by MIBI therapists and AC providers that is 21.7 and 16.0 times the mean number seen, respectively (as estimated from the current distribution of patients seen by therapists and AC providers). The targets for the numbers consented and randomised have been revised upwards to 1430 and 1287, respectively, to allow for 10% loss between consent and randomisation and 70% retention to primary outcome. Calculations were performed using command 'clsampsi' in STATA 17.

Recruitment {15}

Fifteen to eighteen sites will admit up to 6000 people with acute stroke annually. Assuming at least 4500 (75%) survive to week 2, that 2700 (60%) are eligible (no severe cognitive, communication, or psychological problems), and 40% of those eligible consent, we can recruit 1080 participants per year (6 per month per site). If the estimate is within 5%, we will recruit 5 participants per site per month, meeting the recruitment target if each site recruits for 18 months, even allowing for only 90% to be randomised. Staggering the start of recruitment across sites to allow all MIBI and AC staff to be trained in all sites, and for adequate support from Lancashire CTU to be provided during start-up and early recruitment, will result in a 36-month recruitment period.

Process evaluation interviews will be conducted with 18 study participants from the MIBI + UC ($n = 12$) and AC + UC ($n = 6$) arms, and 15–20 study staff. Eligible study participants (those indicating willingness to be contacted for interview) will be purposively sampled to include maximum variation in the following characteristics: age (< 65/65+), sex, stroke severity, communication difficulties, study site, mode of MIBI/AC delivery, number of sessions completed, and allocated study arm, with greater weighting given to the MIBI arm. Staff will be purposively sampled to include maximum variation in the following characteristics: study role (MIBI therapist/AC provider), study site. Eligible individuals will be contacted by a member of the study team, via telephone or email, to see if they would like to take part in an interview. Those that agree will provide informed consent.

Assignment of interventions: allocation

Sequence generation {16a}

Participants will be allocated to one of three arms: MIBI + UC, AC + UC, or UC in a 1:1:1 ratio. Allocation will be via a computer-generated stochastic minimisation algorithm over four factors: age (< 65, 65 +), baseline mood category (PHQ-9 score of 10–14, < 10), participant preference/ability to receive an intervention via video call or by telephone (audio-only), and site using computer-generated minimisation. The weighting of 'site' in the minimisation algorithm has been increased relative to the other minimisation factors to improve balance between numbers of participants allocated to each arm by site to reduce the possibility of having more allocations of participants to MIBI therapists than there is capacity to support within a reasonable timeframe. A participant allocated to MIBI + UC will be assigned to the next available therapist at that site. Similarly, a participant allocated to the AC + UC will be assigned to the next available AC provider.

Concealment mechanism {16b}

Randomisation will be conducted independently using the secure remote web-based system called Sealed Envelope™ (sealed envelopes are not actually used), which ensures that allocation remains concealed until recruitment is completed.

Implementation {16c}

Each participant will be allocated to one of the three arms: MIBI + UC, AC + UC, or UC, by the research practitioner using the secure remote web-based system provided by Sealed Envelope™. Based on the allocation, the appropriate site staff will be informed as to allocation. The research practitioner will inform patients as to their allocated group. For participants allocated to MIBI + UC or AC + UC, the allocated MIBI therapist/AC provider will be informed of their participant by the research team at site/Lancashire CTU via telephone and/or encrypted email.

Assignment of interventions: blinding

Who will be blinded {17a}

This study is not blinded for either participants or therapists/providers due to the nature of the therapeutic interventions. Most outcomes will be reported by the participant through postal or online questionnaires. Where no response has been returned, a telephone call

may be made to request key outcomes by a member of the Lancashire CTU data management team, who will not be blinded to treatment allocation. The statisticians performing and overseeing the analysis cannot be blind to specific treatment allocation due to the structural changes in MIBI therapist and AC provider assignment, in particular after introducing Stroke Association MIBI therapists. Details of the analysis will identify the treatment group to the statistician. In addition, analysis for objectives 4, 5 (where requiring statistical input), and 6 requires the statistician to be unblinded, as the presence of a therapeutic alliance questionnaire responses will identify the MIBI group in objective 4, and knowledge of MIBI group assignment is required to fulfil objectives 5 and 6.

Procedure for unblinding if needed {17b}

This study is not blinded for participants, MIBI therapists/AC providers, Lancashire CTU data management and trial management teams, or statisticians.

Data collection and management

Plans for assessment and collection of outcomes {18a}

The following baseline data will be collected from participants face-to-face with the research practitioner after informed consent has been provided, and prior to randomisation: demographic and clinical characteristics; depressive symptoms (PHQ-9); stroke severity (NIHSS); communication (FAST/COAT); cognition (MoCA [44]); anxiety symptoms (GAD-7); quality of life (EQ-5D-5L); patients' resource use; and history of/current psychological problems.

The research practitioner will collect the following data at hospital discharge from participants' medical records: mRS score, medications, discharge status (alive/dead), and discharge destination.

Participants in the MIBI + UC and AC + UC arms will be sent a questionnaire to complete and return by post after their final MIBI/AC session: the Working Alliance Inventory (WAI-S) [45] for MIBI + UC, and an alliance questionnaire, adapted from the WAI-S for the AC used in this study, for AC + UC.

Data collection at 6 weeks and 3 months post-randomisation will be via postal or electronic questionnaire (depending on participant preference) for self-completion and return, with telephone assistance from Lancashire CTU data management team when required. The following data will be collected at 6 weeks post-randomisation: depressive symptoms (PHQ-9, Yale); anxiety symptoms (GAD-7); self-efficacy (SSEQ); confidence (CaSM); dependence (Barthel). At 3 months post-randomisation, the following data will be collected: depression symptoms (PHQ-9, Yale, self-reported clinical depression, current antidepressant use); anxiety symptoms (GAD-7); further stroke; quality of life (SIS and EQ-5D-5L); function and dependence (mRS, Barthel); self-efficacy (SSEQ); confidence (CaSM); and patient's resource use.

Process evaluation interviews will be completed with study participants within 6 months of them reaching end of study, and staff participants (MIBI therapists, AC providers, managers) at the end of the study. Participants will have the option to hold interviews by video call or telephone. Interviews will explore the experience of participating in the study, experiences of receiving or delivering MIBI and AC, study processes, acceptability of staff training and supervision received, practical issues, considerations for implementing MIBI in practice, what was felt to have worked well, and what could be improved. Interviews will be recorded and transcribed.

Plans to promote participant retention and complete follow-up {18b}

Outcome data will be collected for all participants, unless they withdraw fully from the trial prior to data collection. In advance of 6 weeks and 3 months post-randomisation questionnaires, all participants will be posted a brief communication keeping them informed of study progress and thanking them for their continued participation. Lancashire CTU will offer telephone assistance if required by participants to complete follow-up. If follow-up questionnaires are not returned by participants within 2 weeks of being sent, they will receive reminders via telephone, then email, and then post if necessary. Up to three reminders will be sent for up to 4 weeks after the 6-week follow-up due date, and for up to 6 weeks after the 3-month follow-up due date. If participants are reluctant or unable to complete the full questionnaire, collection of a reduced core set of outcomes will be attempted over the phone. This will comprise the PHQ-9 for the 6-week follow-up; and the PHQ-9, mRS, EQ-5D-5L, other psychological input, and further stroke for the 3-month follow-up.

Data management {19}

Data management will be carried out by Lancashire CTU in accordance with the trial Data Management Plan and Lancashire CTU Data Management SOPs. Where data is to be collected by trial site staff, this will be carried out following their site-specific data management SOPs.

Access to REDCap and Sealed Envelope™ databases will be granted only to site staff who are listed on the delegation log for data entry or randomisation, with each user having a unique username and password. Site staff will be granted permissions to allow them to complete data entry and randomisation tasks, while Lancashire

CTU staff will be granted these permissions in addition to data exports, reports, monitoring, and audit activities.

Data will initially be collected by the research practitioner at each site on paper CRFs, which will be considered source documents. CRFs containing patient-identifiable data, e.g. registration forms, will be stored at site in a secure cabinet in a secure room accessible only to members of the clinical research team. CRFs containing pseudo-anonymised data will be kept securely at site, in a separate location to patient-identifiable data.

Follow-up data is to be collected by Lancashire CTU via post, telephone, or online link. Postal follow-up questionnaires will be sent to participants by the Lancashire CTU data management team, along with a prepaid return envelope for the participant to complete and return the CRF. The data will then be reviewed and entered on REDCap by the data management team. If a participant would like to complete the questionnaire over the phone, a member of the data management team will contact the participant and complete a paper CRF with them over the phone. This CRF will then be entered into REDCap and stored with other pseudo-anonymised CRFs as described below. For participants who would like to complete the questionnaires online, a REDCap link will be sent by the data management team to the participant's email address, to allow the participant to enter their responses directly into the database.

Copies of site documentation will be transferred to Lancashire CTU via secure email, with separate email addresses to be used for identifiable and pseudo-anonymised data. For sites where secure email is not available, documents will be transferred via an encrypted Microsoft Teams Group, with access given only to specific trial staff at site and Lancashire CTU. Digital copies of CRFs will be stored on a secure shared drive within the Lancashire CTU network, with identifiable documents being password-protected, and access to the shared drive given only to trial staff at Lancashire CTU. Paper CRFs will be stored in secure cabinets within secure offices at the CTU, with patient-identifiable data being stored separately to pseudo-anonymised data. Access to these offices will only be granted to the necessary CTU trial staff.

REDCap will contain field- and form-level validation rules to ensure the validity of data, which will be built into the database by Lancashire CTU. For example, automated checks will be carried out on date fields to confirm they are in line with the trial inclusion and exclusion criteria (so as to highlight a date of birth where the participant would be under 18 years of age), as well as other CRFs applicable for the participant (to ensure, e.g. a date of follow-up questionnaire completion cannot be before the date of randomisation). There will also be data-type restrictions to limit the responses that can be given, such as a number or currency field. Form-level validation will be in place where branching logic applies to a CRF, to hide any fields which should not be entered based on a response to a previous question.

A total of 100% of CRFs will be checked for completeness by the Lancashire CTU data management team upon receipt, with any missing data to be queried with site via email or with the participant via telephone. In addition, 10% of participants will be selected via a random number generator, by the data management team, for quality assurance purposes to verify that paper CRFs have been entered into the database correctly.

Lancashire CTU will keep a Participant Information Tracker Database which will act as the data key for pseudo-anonymised clinical data CRFs. This tracker will be password-protected and stored on a secure shared drive within the Lancashire CTU network, accessible only to the CTU trial management and data management teams.

Confidentiality {27}

Sites will be provided with a bespoke password-protected electronic screening log. All patients admitted to the stroke unit will be screened for eligibility and entered onto the screening log which will allocate the next sequential screening log number to that patient. Key anonymised demographic data will be collected for all admissions. This is important to understand how many patients are eligible, why patients are not eligible (e.g. severely depressed, cognitive impairment, severe speech difficulties) to fully understand the stroke population group, what percentage have different needs, and what percentage of the stroke population as a whole may benefit if this intervention is proven to be beneficial and becomes a standard of care. For all eligible patients, we will collect key data to describe the eligible group as a whole (see Sect. Statistical methods).

Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

This study will not collect any biological samples.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

Randomised participants will be analysed using all available outcome data, according to the group to which they were randomised, regardless of deviation from the protocol. The level of significance will be 5%. Point estimates will be presented with 95% confidence interval estimates. No adjustment for multiple testing between the three

groups will be performed: instead, a hierarchical testing procedure will be applied. MIBI + UC will firstly be tested against UC; only if this test is statistically significant will a test of MIBI + UC vs. AC + UC be performed. This is because the latter comparison is relevant only if the effectiveness of the latter is demonstrated, as it is assumed that any effect of MIBI will be greater than any effect of AC.

For AC + UC and MIBI + UC vs. UC groups, a mixed effects linear regression will be fitted to outcome data from all three arms, and appropriate parameterisation with MIBI + UC as the reference group. For the intervention to be considered successful, both MIBI + UC vs. AC + UC and MIBI + UC vs. UC comparisons must be statistically significant. The former comparison will only be performed if the effectiveness of the latter is demonstrated.

Though it is assumed that implementing MIBI intervention in group A and B will be same, we will explore the possibility of difference in implementation of MIBI between group A and B sites. As an additional analysis, for the primary outcome, 'intervention specification' will be added to the model as an additional site-type adjustment factor (group A or B) and as a group-by-treatment interaction term to account for a potential difference in effect. If there are non-convergence issues, site will instead be fitted as fixed within group.

Secondary outcomes measured at 3 months only will be analysed similarly, using a random effects linear regression model adjusting for site and therapist (as random effects), age, the corresponding baseline assessment, and baseline mood, if the outcome is continuous and meets the required distributional assumptions. If the assumptions are not met, bootstrapping methods will be applied to continuous primary or secondary outcomes where appropriate. Binary secondary outcomes (status (alive/dead), self-reported clinical depression, antidepressant use, history of psychological input, and further stroke) will be analysed using a random effects logistic regression model adjusting for site and therapist (as random effects), baseline mood, and age.

To investigate the mechanistic effect of MIBI in comparison with UC, we will use a parametric regression approach, with baseline factors to minimise confounding, to estimate direct (via intervention exposure) and indirect (via mediators and post-randomisation effect modifier) effects of MIBI. Post-randomisation effect moderators will include therapeutic alliance and dose. Dose will be measured using a proxy of number of sessions attended. Therapeutic alliance will be estimated for all participants based on WAI scores of the MIBI group.

A detailed statistical analysis plan, describing further details of the analysis, including sensitivity analyses, has been developed by the statistical team and approved by the trial steering committee.

An economic evaluation, including a within-trial analysis and subsequent economic modelling beyond the trial, will investigate the economic consequences of adopting the MIBI in preventing post-stroke depression, complementing the investigation on the clinical effectiveness. The economic evaluation will adopt an NHS and Personal Social Services perspective and follow the National Institute for Health and Care Excellence 'reference case' [46].

A cost-consequence analysis (CCA), developed as part of the economic modelling, will present the disaggregated costs and outcomes associated with the trial arms and (where feasible) any additional relevant comparators. Although consideration will be given to developing a de novo model, a scoping review has highlighted that the adaptation of an existing model appears likely [47–51].

These analyses will investigate the comparators in terms of the primary outcomes:

- For the comparators assessed in the trial, two trial-based analyses will be undertaken:
  - A cost-effectiveness analysis (CEA) will estimate, using a decision tree, the differences in cost per minimal clinically important gain on the severity of depressive symptoms, measured by the change in the PHQ-9 scores from baseline to 3 months.

    The minimal important gain will be based on the clinically important between-groups difference of 1.8 in mean PHQ-9 scores used in the sample size calculation, which reflects a 'Good response' to the interventions.
  - A cost-utility analysis (CUA) will estimate, using seemingly unrelated regressions [50, 52], the differences in costs and quality-adjusted life-years (QALYs), measured by the change in the EQ-5D-5L scores from baseline to 3 months.

- For all relevant comparators (or where not possible, for the comparators assessed in the trial only), a model-based CUA will estimate, using a probabilistic Markov model [47, 53], the differences in cost per QALY gained over the patients' lifetime, extrapolating trial data in the future discounting costs and QALYs appropriately [46].

For the base case, the CEA and CUA results will be presented as incremental cost-effectiveness ratios and, using multivariable probabilistic analyses, cost-effectiveness acceptability curves will estimate the probability of the comparators being cost-effective at different

willingness-to-pay thresholds. The underlying model assumptions will be scrutinised through sensitivity analyses of different scenarios and impacts of the parameters (e.g. using univariable deterministic analyses). Where feasible, a value of information analysis [54] will be undertaken, to estimate the benefit of conducting further research to reduce the parameters' uncertainty.

Secondary outcomes measured in the trial will be reported as part of the CCA, such as mental and physical complications, captured by the GAD-7 and the Barthel Index functional questionnaires, and health service resource use by the patients.

Data for the trial comparators will primarily come from the trial, with literature sources filling any gap. Data for the other comparators identified by the systematic review will come from the literature. Unit cost data for staff, drugs, and complications will come from appropriate published sources [55–57], with inflation applied as necessary. Life expectancy data will be sourced from the literature and estimated as a combination of long-term stroke survival and mortality rates [58, 59].

Interim analyses {21b}

No formal interim analysis will be performed. No stopping rules were in place at the time of writing the protocol.

Methods for additional analyses (e.g. subgroup analyses) {20b}

For the moderator (subgroup) analysis of MIBI therapist type, primary outcome data from the group A sites with site-based clinical staff MIBI therapists will be compared with data from the group B sites with Stroke Association MIBI therapists. The methods applied will be the same as for the analysis of all sites, with the addition of an interaction term between site-type and intervention group. No formal testing will be performed due to the low power, with the result that this subgroup analysis will be mainly descriptive, although the estimates and 95% confidence intervals for the effects of MIBI (relative to AC and, if appropriate, UC) in each of the subgroups will be extracted from the model.

To explore the putative mechanisms of action of MIBI, a mediation analysis will be performed. Initially a linear regression analysis will be conducted to demonstrate the treatment effect on outcome, adjusting for baseline value of the outcome. Then, further linear regression analyses will be conducted to confirm an effect of treatment on both putative mediators (self-efficacy and confidence), represented by SSEQ and CaSM, adjusting for the PHQ-9 at baseline and other baseline mediators.

Secondary analyses will test post-randomisation effect modifiers including process/adherence effects using modern causal inference methods using data from all sites.

A structural equation model will be created to perform a moderated mediation analyses to evaluate the mechanisms of action and how they interact with the varying baseline covariates and post-randomisation moderators. This will allow for an evaluation of how different post-randomisation moderators interact with the direct and indirect causal pathways of the mediation model. The fit of this model will be assessed using the appropriate indices, as well as the direct and indirect relationships within the model.

Process evaluation interviews will be analysed thematically using framework analysis based on an implementation framework. Two researchers will code the transcripts in qualitative analysis software, NVivo. Initially, nine (approximately 20% of total) interviews will each be coded independently by both coders to agree codes and check interpretation. Once codes have been agreed and there is good agreement between the coders, the remaining interviews will be coded by one researcher only. Themes will then be derived by multiple researchers using a consensus-based approach.

The qualitative elements of process evaluation will be integrated with quantitative data about MIBI/AC usage, e.g. number and duration of sessions. The quantitative aspects of the process evaluation will use descriptive statistics to describe the data (frequencies with percentages, means and standard deviations, medians, and IQR as appropriate) and will be triangulated with the findings from the qualitative study to draw overall conclusions. The variables describing MIBI/AC usage will be presented in the descriptive analysis as part of process evaluation including number of sessions attended and duration of sessions, by arm.

Responses to the additional question for participants in the MIBI + UC group exploring health inequalities will also be analysed qualitatively by the researchers. Open text responses regarding anything that has impacted on participants' ability to participate in sessions will be coded and categorised. Participant deprivation scores (post-code-based deprivation index score (English Indices of Deprivation 2019)) will be analysed by the statistical team to explore associations between deprivation scores and primary outcome, and deprivation scores and session attendance. Deprivation scores of patients who were screened will also be analysed to explore differences in study participation.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

The main analyses will be conducted on the intention-to-treat population (i.e. all participants randomised

regardless of non-compliance with protocol or withdrawal). However, a per-protocol analysis on the primary outcome will be also conducted: this will be performed by repeating the primary analysis using data from only the participants who received 100% of their sessions (four MIBI/AC sessions).

Percentages of missing data among participants for individual measurements and categorical variables will be presented. Where appropriate, 95% confidence intervals will be provided. Patterns of missingness will be reported using the methods of Sterne [60]. Missing data will be allowed for, using the MAR (missing at random) assumption.

In scales where the treatment of small amounts of missing data is explicitly proscribed, scales total will be imputed as recommended. After doing this:

- If no more than 10% of primary outcome data are missing overall and there is no more than a 10 percentage point differential percentage of missing data across the three treatment groups, then the primary analysis will simply use all available outcomes;
- If there is more than 10% of primary outcome data missing overall or there more than a 10 percentage point differential percentage of missing data across the three treatment groups, then the primary analysis will be performed using multiple imputation by chained equations, assuming that missing outcome data are MAR (missing at random). As sensitivity analyses, under plausible MNAR (missing not at random) assumptions, a threshold approach will be applied to missing outcomes in which we assume several different quantiles of the relevant outcome distribution.

For the economic evaluation, standard guidance for handling missing trial data will be followed [61]. Evidence will be reviewed systematically or as exhaustively as possible, which may indicate alternative data sources (e.g. for QALYs [62]). If no published data are available, the advice of COMMITS clinical experts will be sought.

Plans to give access to the full protocol, participant-level data, and statistical code {31c}

An aggregated anonymised study data set will be kept and added to the University of Lancashire data repository, with open access as appropriate. Statistical code and the participant-level dataset can be shared on request.

Oversight and monitoring

Composition of the coordinating centre and trial steering committee {5d}

The trial will be operationalised by Lancashire CTU, who will provide supervision of all aspects of trial management and oversight including, but not limited to, the following: site selection, site set-up, training related to participant recruitment and data collection, data management (including screening, consent, clinical data in paper and electronic forms, interview recordings), centralised and site monitoring, information governance, information services infrastructure (with bespoke databases), and statistical analysis. Trial oversight will be supported by a principal investigator (PI) and a research practitioner at each site.

The study team will be responsible for the training and supervision of staff selected to deliver the MIBI and AC.

The trial steering committee (consisting of members of the study team, independent stroke researchers, independent statistician, and lay representatives), with an independent Chair, will be responsible for overall study supervision, the execution of the study design and protocol, monitoring progress, and ensuring appropriate ethical and other approvals are in place to protect the rights, well-being, and safety of participants.

A patient, carer, and public involvement (PCPI) group, comprising stroke survivors ($n=5$) and carers ($n=2$) with an interest in the study, contributed to the design of the study and study documents. The PCPI group will continue an active role throughout the study: suggesting ways of increasing participant recruitment and retention; developing process evaluation interview schedules; interpreting emergent findings (particularly qualitative data); producing summaries of, and disseminating, findings.

Composition of the data monitoring committee, its role, and reporting structure {21a}

A separate data monitoring committee was deemed unnecessary by the study sponsor due to the interventions being deemed low risk. As such, as the trial steering committee will monitor patient safety throughout the trial.

Adverse event reporting and harms {22}

There are no anticipated harms. Any harms that do occur may be identified during MIBI and AC sessions, or via questionnaires as all participants' PHQ-9 will be systematically checked for suicidal ideation (PHQ-9). As a non-CTIMP with no IMP involvement, safety will be recorded using standard CTU safety reporting processes. As part of the analysis plan, assigned statisticians will collate safety events and code appropriately using common terms with the guidance of the CI.

The Serious Adverse Event Reporting Guidance (V1.1 18.04.2024) will give advice and guidance as to recognition and classification of SAE incidences for this patient group (taking into account study procedures) and reporting timelines and procedures. SAE will be identified by clinical staff at study sites, or upon receipt of follow-up questionnaires by the CTU's data management team.

For all clinically significant adverse events, as determined by clinical staff at sites and/or the CI (e.g. attendance at A&E; suspected epilepsy), sufficient information will be pursued and/or obtained to allow by the CI and trial steering committee: (i) an adequate determination of the outcome of the event (i.e. whether the event should be classified as a serious adverse event); and (ii) an assessment of the causal relationship between the adverse event and the study treatment. Serious adverse events felt to be associated with the study treatment will be followed until the event resolves or stabilises at a level acceptable to the study sponsor.

Safety reporting will be done as per the institutional ethics committee standard operating procedures and reporting timeline in accordance with ICH Good Clinical Practices.

Frequency and plans for monitoring and auditing trial conduct {23}

Risk-based adapted approaches are encouraged when designing monitoring and other quality assurance activities in the management of a trial, with the emphasis being on clearly identifying and mitigating the likelihood of a potential hazard occurring and resulting in harm to participant or organisation or the reliability of the results [63, 64]. The overall level of risk for the COMMITS trial is assessed as being low, and accordingly planned monitoring activities will reflect this assessment.

Lancashire CTU trial management, under delegated authority from the trial sponsor, will have responsibility for the development of the monitoring plan. Application of required monitoring procedures and collection will be primarily managed by the trial management team, with some input from the data management team for reviewing some aspects of monitoring such as checking completeness and accuracy of data items received against source data.

While methods of continuous central and remote monitoring will be in place for all participating sites during active recruitment, it is envisaged that the main element of monitoring review will be as participating sites have completed recruitment and are moving towards site closure. All sites will receive a site closure visit.

Monitoring checks will be made to ensure the required sampling assurance thresholds have been met, such as all participants have a completed informed consent form, met the study eligibility criteria, and any cases of adverse effects seen have been reported and managed as set out within the research protocol. Accuracy checks of paper case report forms against electronic case reports for primary and secondary endpoints will be undertaken, whilst currency and accuracy of investigator site research involvement delegation and training logs will also be continuously monitored.

Triggered on-site monitoring visits may occur should there be evidence of persistent or significant non-compliances, or serious breaches or a quality concern has been generated which requires review of any source data in person. This will be considered on a case-by-case basis.

The trial management team will seek to engage effectively with participating sites to advise and support them in meeting any monitoring requirements, whilst seeking to minimise the overall burden.

Monthly internal trial meetings within Lancashire CTU will include review of progress and monitoring trial conduct. Lancashire CTU will, through the internal independent quality assurance function, periodically audit trial processes in line with their SOPs. Any audit findings arising from any audit activity will be shared with the sponsor. The trial steering committee will provide overall supervision of the trial to ensure it is conducted to rigorous standards, including progress of the trial and adherence to protocol.

Plans for communicating important protocol amendments to relevant parties (e.g. trial participants, ethical committees) {25}

Any minor amendments (e.g. changes in the documentation used by the research team for recording study data), once authorised, will be advised to the research and development (R&D) office and to the PI at each participating site, who will be required to confirm acknowledgement to the study sponsor. Any substantial amendments (change to the terms of the ethics application or the protocol) will be referred to the relevant REC, with a notification to the R&D office and PI at each site.

Dissemination plans {31a}

Results will be published in a peer-reviewed open-access journal, and a short summary will be communicated with participants who requested this and the public, once agreed with the PCPI group; this will be available in various formats including in writing, audio, and infographics. Findings will also be presented at relevant conferences.

Discussion

Initial recruitment was deemed to be slower than anticipated; as such, a review of the number of sites to be included in the study was carried out, increasing from 18 to 22, and the target sample is expected to be achieved.

This study will determine whether any effects on depressive symptoms after stroke are a natural change over time, are due to the additional attention of talking to someone, or are a therapeutic change directly attributable to MIBI. If MIBI is shown to be effective for reducing depressive symptoms, the process evaluation will help us to propose how best the intervention can be delivered as part of routine clinical stroke care. Such care would then have the potential to reduce the psychological and economic burden associated with stroke, with benefits to patients and their families, and reduction in costs to the NHS. The study results would enable national and international clinical guidelines to recommend evidence-based care.

Trial status

Protocol version number and date: Version 6.0 23/04/2025.

Recruitment commenced in July 2022 and will be completed in September 2025.

The protocol has been submitted close to the end of recruitment as the protocol underwent several revisions throughout the trial and the authors wished to submit the most up-to-date version of the protocol. The date of the last participant visit and final data collection will be 31 st January 2026.

Abbreviations

AC	Attention control
ACTNoW	Accessing Communication Therapy in the North West
BIA	Budget impact analysis
CaSM	Confidence after Stroke Measure
COAT	Communication observational assessment tool
CBT	Cognitive behavioural therapy
CCA	Cost-consequence analysis
CEA	Cost-effectiveness analysis
CUA	Cost-utility analysis
CTU	Clinical trials unit
EQ-5D-5L	EuroQoL-5 Dimensions, Five-Level
FAST	Frenchay Aphasia Screening Test
GAD-7	General Anxiety Disorder-7
MIBI	Motivational interviewing-based intervention
mRS	Modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
PCPI	Patient, carer, and public involvement
PHQ-9	Patient Health Questionnaire-9
QALY	Quality-adjusted life-year
RCT	Randomised controlled trial
SD	Standard deviation
SIS	Stroke Impact Scale
SSEQ	Stroke Self-Efficacy Questionnaire
UC	Usual care
WAI-S	Working Alliance Inventory

Acknowledgements

Not applicable.

Authors' contributions {31b}

KP contributed to the conception and design of the work, and drafting and revising the manuscript. CW, ABo, RC, MG, MH, DL, CJS, STh, and CEL contributed to the conception and design of the work, and revising the manuscript. VB, ABl, AC, LD, SE, JE, MF, SJ, GL, GP, and STi contributed to the design of the work, and revising the manuscript. RE contributed to the conception and design of the work. All authors read and approved the final manuscript. Authorship for future trial publications will be determined by using standard criteria: substantial contributions to conception/design or data analysis, drafting/critically revising the work, and approving the final version. Those meeting these criteria will be included in the authorship.

Funding {4}

Funding for the COMMITS research study was received from the following: National Institute for Health and Care Research (NIHR) Applied Research Collaboration North West Coast (ARC NWC); NIHR Senior Investigator Award; University of Lancashire; NHS England Stroke Quality Improvement for Rehabilitation (SQuIRe) North West Catalyst Funding. The research team at the University of Lancashire conducted the design of the study, data collection, analysis, interpretation, and writing the manuscript. This research was partly funded by the National Institute for Health and Care Research Applied Research Collaboration North West Coast (NIHR ARC NWC). The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

Data availability {29}

Not applicable.

Declarations

Ethics approval and consent to participate {24}

Ethical approval granted (19/WA/0337 02/01/2020).

Consent for publication {32}

Written informed consent will be provided by all study participants. The model consent form can be requested from the corresponding author.

Competing interests {28}

The authors declare no competing interests.

Author details

[1]University of Lancashire, Preston, UK. [2]University of Manchester, Manchester, UK. [3]True Rehabilitation, St Helens, UK. [4]King's College London, London, UK. [5]University of Liverpool, Liverpool, UK. [6]The George Institute for Global Health, Sydney, Australia. [7]Keele University, Keele, UK. [8]Stroke Association, London, UK. [9]University of Nottingham, Nottingham, UK.

Received: 25 September 2025 Accepted: 2 January 2026
Published online: 28 January 2026

References

1. Hill G, Regan S, Francis R on behalf of the Stroke Priority Setting Partnership Group. Research priorities to improve stroke outcomes. The Lancet. 2022;21(4):312–313.
2. Sentinel Stroke National Audit Programme (SSNAP) on behalf of the Intercollegiate Stroke Working Party. State of the Nation Report 2024: Stroke care received between April 2023 and March 2024. London: Health Quality Improvement Partnership; 2024.
3. Hackett M, Pickles K. Part I: frequency of depression after stroke: an updated systematic review and meta-analysis of observational studies. Int J Stroke. 2014;9(8):1017–25.
4. Donnellan C, Hickey A, Hevey D, O'Neill D. Effect of mood symptoms on recovery one year after stroke. Int J Geriatr Psychiatry. 2010;25(12):1288–95.

5. Bartoli F, Lillia N, Lax A, et al. Depression after stroke and risk of mortality: a systematic review and meta-analysis. Stroke Res Treat. 2013;2013:862978.
6. Stenager EN, Madsen C, Stenager E, Boldsen J. Suicide in patients with stroke: epidemiological study. BMJ. 1998;316(7139):1206–10.
7. Hackett ML, Glozier NS, House AO. Moving the ambulance to the top of the cliff: reducing the burden of depressive symptoms after stroke. Int J Stroke. 2009;4(3):180–2.
8. Ayerbe L, Ayis S, Crichton S, Wolfe CD, Rudd AG. The long-term outcomes of depression up to 10 years after stroke; the South London Stroke Register. J Neurol Neurosurg Psychiatry. 2014;85(5):514–21.
9. Bhattarai N, Charlton J, Rudisill C, Gulliford MC. Prevalence of depression and utilization of health care in single and multiple morbidity: a population-based cohort study. Psychol Med. 2013;43(7):1423–31.
10. Sicras Mainar A, Navarro Artieda R, Blanca Tamayo M, Rejas Gutiérrez J, de Fernánz Bobadilla J. Morbidity and costs associated with depressive syndrome in stroke sufferers in a population. Farmacia Hospitalaria (English Edition). 2008;32(6):309–14.
11. Dohl O, Halsteinli V, Askim T, et al. Factors contributing to post-stroke health care utilization and costs, secondary results from the life after stroke (LAST) study. BMC Health Serv Res. 2020;20(1):288.
12. Ghose SS, Williams LS, Swindle RW. Depression and other mental health diagnoses after stroke increase inpatient and outpatient medical utilization three years poststroke. Med Care. 2005;43(12):1259–64.
13. Husaini B, Levine R, Sharp L, et al. Depression increases stroke hospitalization cost: an analysis of 17,010 stroke patients in 2008 by race and gender. Stroke Res Treat. 2013;2013:846732.
14. Bangalore S, Shah R, Gao X, et al. Economic burden associated with inadequate antidepressant medication management among patients with depression and known cardiovascular diseases: insights from a United States–based retrospective claims database analysis. J Med Econ. 2020;23(3):262–70.
15. Stroke Association. Feeling overwhelmed: the emotional impact of stroke. The Stroke Association. 2013.
16. Allida S, Cox K, Hsieh C, Lang H, House A, Hackett ML. Pharmacological, psychological, and brain stimulation treatments for depression after stroke. Cochrane Database Syst Rev. 2020;1:CD003437.
17. Sansone RA, Sansone LA. Antidepressant adherence: are patients taking their medications? Innov Clin Neurosci. 2012;9(5–6):41–6.
18. Allida S, Cox KL, Hsieh CF, House A, Hackett ML. Pharmacological, psychological and non-invasive brain stimulation interventions for preventing depression after stroke. Cochrane Database Syst Rev. 2020;5:CD003689.
19. Marshall IJ, Wang Y, Crichton S, McKevitt C, Rudd AG, Wolfe CDA. The effects of socioeconomic status on stroke risk and outcomes. Lancet Neurol. 2015;14:1206–18.
20. National Collaborating Centre for Mental Health. The Improving Access to Psychological Therapies (IAPT) pathway for people with long-term physical health conditions and medically unexplained symptoms: full implementation guidance. London: National Collaborating Centre for Mental Health; 2018.
21. Clark DM. Realizing the mass public benefit of evidence-based psychological therapies: the IAPT program. Annu Rev Clin Psychol. 2018;14:159–83.
22. Watkins CL, Auton MF, Deans CF, et al. Motivational interviewing early after acute stroke: a randomized, controlled trial. Stroke. 2007;38:1004–9.
23. Watkins CL, Wathan JV, Leathley MJ, et al. The 12-month effects of early motivational interviewing after acute stroke: a randomized controlled trial. Stroke. 2011;42(7):1956–61.
24. Gillham S, Clarke L. Psychological care after stroke – improving stroke services for people with cognitive and mood disorders. 2011; Leicester: NHS Improvement. http://www.improvement.nhs.uk/stroke/Psychologicalcareafterstroke/Stepped.aspx.
25. Miller WR, Rollnick S. Motivational interviewing, third edition: helping people change. New York, London: The Guilford Press; 2012.
26. Auton MF, Patel K, Carter B, et al. Motivational interviewing post-stroke: an analysis of stroke survivors' concerns and adjustment. Qual Health Res. 2016;26(2):264–72.
27. Patel K, Watkins CL, Sutton CJ, et al. Motivational interviewing for low mood and adjustment early after stroke: a feasibility randomised trial. Pilot Feasibility Stud. 2018;4:152.
28. Holland EJ. The feasibility of delivering motivational interviewing those with communication difficulties following a stroke. [Unpublished PhD thesis.] University of Lancashire. 2009.
29. National Institute of Neurological Disorders and Stroke (U.S.). NIH stroke scale. Bethesda, Md.? National Institute of Neurological Disorders and Stroke, Dept. of Health and Human Services, USA; 2011.
30. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van GJ. Interobserver agreement for the assessment of handicap in stroke patients. Stroke. 1988;19:604–607.
31. Moyers TB, Manuel JK, Ernst D. Motivational interviewing treatment integrity coding manual 4.1. Unpublished manual. 2014.
32. Bowen A, Hesketh A, Patchick E, et al. Clinical effectiveness, cost-effectiveness and service users' perceptions of early, well-resourced communication therapy following a stroke: a randomised controlled trial (the ACTNoW study). Health Technol Assess. 2012;16(26):1–159.
33. de Man- Ginkel JM, Gooskens F, Schepers VP, Schuurmans MJ, Lindeman E, Hafsteinsdóttir TB. Screening for post stroke depression using the patient health questionnaire. Nurs Res. 2012;61(5):333–41.
34. Watkins CL, Lightbody CE, Sutton CJ, et al. Evaluation of a single-item screening tool for depression after stroke: a cohort study. Clin Rehabil. 2007;21(9):846–52.
35. Spitzer RL, Kroenke K, Williams JBW, Lowe B. A brief measure for assessing generalized anxiety disorder. Arch Intern Med. 2006;166:1092–7.
36. Jenkinson C, Fitzpatrick R, Crocker H, Peters M. The stroke impact scale: validation in a UK setting and development of a SIS short form and SIS index. Stroke. 2013;44:2532–5.
37. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011;20(10):1727–36.
38. Wade DT, Collin C. The barthel ADL index: a standard measure of physical disability? Int Disabil Stud. 1988;10(2):64–7.
39. Riazi A, Aspden T, Jones F. Stroke self-efficacy questionnaire: a Rasch-refined measure of confidence post stroke. J Rehabil Med. 2014;46(5):406–12.
40. Horne JC, Lincoln NB, Logan PA. Measurement of confidence: the development of psychometric evaluation of a stroke-specific, measure of confidence. Clin Rehabil. 2017;31(11):1529–37.
41. Kim DM, Wampold BE, Bold DM. Therapist effects in psychotherapy: a random-effects modelling of the National Institute of Mental Health Treatment of Depression Collaborative Research Program data. Psychother Res. 2006;16(02):161–72.
42. Tishkovskaya SV, Sutton CJ, Thomas LH, Watkins CL. Determining the sample size for a cluster-randomised trial using knowledge elicitation: bayesian hierarchical modelling of the intracluster correlation coefficient. Clin Trials. 2023;20(3):293–306. https://doi.org/10.1177/17407745231164569.
43. Turner A, Hambridge J, White J, et al. Depression screening in stroke: a comparison of alternative measures with the structured diagnostic interview for the diagnostic and statistical manual of mental disorders, fourth edition (major depressive episode) as criterion standard. Stroke. 2012;43:1000–5.
44. Montreal Cognitive Assessment (MoCA). Available at: https://mocacognition.com/. Accessed 10 March 2023.
45. Tracey TJ, Kokotovic AM. Factor structure of the working alliance inventory. Psychol Assess. 1989;1(3):207–10.
46. National Institute for Health and Care Excellence (NICE). NICE health technology evaluations: the manual. Process and Methods [PMG36]. London: NICE; 2022.
47. Thomas SA, et al. Behavioural activation therapy for post-stroke depression: the BEADS feasibility RCT. Health Technol Assess. 2019;23(47):1–176.
48. van Eeden M, et al. An economic evaluation of an augmented cognitive behavioural intervention vs. computerized cognitive training for post-stroke depressive symptoms. BMC Neurol. 2015;15:266.
49. Koeser L, et al. Modelling the cost-effectiveness of pharmacotherapy compared with cognitive–behavioural therapy and combination therapy for the treatment of moderate to severe depression in the UK. Psychol Med. 2015;45(14):3019–31.
50. Haji Ali Afzali H, et al. A proposed model for economic evaluations of major depressive disorder. Eur J Health Econ. 2012;13(4):501–10.

51. Chambers MG, Koch P, Hutton J. Development of a decision-analytic model of stroke care in the United States and Europe. Value Health. 2002;5(2):82–97.
52. Mutubuki EN, El Alili M, Bosmans JE, et al. The statistical approach in trial-based economic evaluations matters: get your statistics together! BMC Health Serv Res. 2021;21(1):475.
53. Löwe B, Unützer J, Callahan CM, Perkins AJ, Kroenke K. Monitoring depression treatment outcomes with the patient health questionnaire-9. Med Care. 2004;42:1194–201.
54. Claxton K, Sculpher M, Drummond M. A rational framework for decision making by the National Institute for Clinical Excellence (NICE). Lancet. 2002;360:711–5.
55. Jones K, Weatherley H, Birch S, et al. Unit costs of health and social care 2024 manual. Technical report. Personal Social Services Research Unit, University of Kent, Canterbury. 2025; https://doi.org/10.22024/UniKent/01.02.109563.
56. NHS England. 2023/24 National Cost Collection data. https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/.
57. Joint Formulary Committee. British National Formulary (BNF) 90. London: BMJ Group and Pharmaceutical Press; 2025.
58. Brønnum-Hansen H, Davidsen M, Thorvaldsen P, Danish MONICA Study Group. Long-term survival and causes of death after stroke. Stroke. 2001;32:2131–6.
59. Office for National Statistics (2025). National life tables: United Kingdom. Newport: Office for National Statistics. URL: www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesunitedkingdomreferencetables.
60. Sterne JA, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ. 2009;338:2393.
61. Faria R, Gomes M, Epstein D, White IR. A guide to handling missing data in cost-effectiveness analysis conducted within randomised controlled trials. Pharmacoeconomics. 2014;32(12):1157–70.
62. Post PN, et al. The utility of health states after stroke: a systematic review of the literature. Stroke. 2001;32(6):1425–9.
63. MRC/DH/MHRA Joint Project Risk-adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products 2011 @ https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/343677/Risk-adapted_approaches_to_the_management_of_clinical_trials_of_investigational_medicinal_products.pdf.
64. International Council for Harmonisation (ICH). ICH E6(R3) Guideline for Good Clinical Practice. ICH. 2025.

Publisher's Note