Evaluating Antidepressants for
Emotionalism after Stroke

EASE: Evaluating Antidepressants for emotionaliSm after strokE

A multi-centre, randomised, double-blind, placebo-controlled trial to establish the effect(s) of administration of Sertraline (50 mg once daily for six months) in people with a recent stroke and post-stroke emotionalism

Version	Version 1.2
Date	05.08.24
Sponsor	Norfolk and Norwich University Hospitals NHS Foundation Trust
Trial registration	ISRCTN: 67104216
IRAS	1008638
CTA #	13630/0016/001-0001
NRES #	24/NE/0074

Signature Page

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

For and on behalf of the Trial Sponsor: -

Julie Dawson	Sponsor Representative	DocuSigned by: Julie Dawson 4CBAB360CF534A2...	16 September 2024

Chief Investigator(s): -

Prof Niall Broomfield	Lead Investigator	Signed by: Niall Broomfield 5F720B8F48FB414...	16 September 2024
Dr Kneale Metcalf	Clinical Chief Investigator	Signed by: AKMetcalfe 42B87F548FB3442...	19 September 2024

Norwich Clinical Trials Unit: -

Matt Hammond	CTU Deputy Director	Signed by: Matthew Hammond 7153BBAFE90F42E...	13 September 2024
Prof Lee Shepstone	Statistician	Signed by: Lee Shepstone 8CA029CAB1304E8...	19 September 2024
David Turner	Health Economist	Signed by: David Turner 3B6053A632D34E6...	24 September 2024
Martin Pond	Head of Data Management	DocuSigned by: Martin Pond B811081D49AE4DC...	13 September 2024

Table of Contents

1 Administrative information

This document was constructed using the Norwich Clinical Trials Unit (NCTU) Protocol template Version 4.1. It describes the EASE trial, sponsored by NNUH and co-ordinated by NCTU.

It provides information about procedures for entering participants into the trial, and provides sufficient detail to enable: an understanding of the background, rationale, objectives, trial population, intervention, methods, statistical analyses, ethical considerations, dissemination plans and administration of the trial; replication of key aspects of trial methods and conduct; and appraisal of the trial's scientific and ethical rigour from the time of ethics approval through to dissemination of the results. The protocol should not be used as an aide-memoire or guide for the treatment of other patients. Every care has been taken in drafting this protocol, but corrections or amendments may be necessary. Version control will be maintained throughout the project with most up to date version (and previous drafts) stored in the Trial Master File. These will be circulated to registered site investigators in the trial. Sites entering participants for the first time should confirm they have the correct version through a member of the trial team at NCTU.

NCTU supports the commitment that its trials adhere to the SPIRIT guidelines. As such, the protocol template is based on the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2012 Statement for protocols of clinical trials [1]. The SPIRIT Statement Explanation and Elaboration document [2] can be referred to, or a member of NCTU Protocol Review Committee can be contacted for further detail about specific items.

1.1 Compliance

The trial will be conducted in compliance with the approved protocol, the Declaration of Helsinki (2008), the principles of Good Clinical Practice (GCP) as laid down by the Commission Directive 2005/28/EC with implementation in national legislation in the UK by Statutory Instrument 2004/1031 and subsequent amendments, the UK Data Protection Act 2018, and the UK Policy Framework for Health and Social Care Research, the Mental Capacity Act 2005, Adults with Incapacity (Scotland) Act 2000, and other national and local applicable regulations. Agreements that include detailed roles and responsibilities will be in place between participating sites and NCTU.

Participating sites will inform NCTU as soon as they are aware of a possible serious breach of compliance, so that NCTU can fulfil its requirement to report the breach, if necessary, within the timelines specified in the UK Clinical Trials Regulations (currently 7 days). For the purposes of this regulation a 'serious breach' is one that is likely to affect to a significant degree:

- The safety or physical or mental integrity of the subjects in the trial, or
- The scientific value of the trial.

1.2 Sponsor

Norfolk and Norwich University Hospitals NHS Foundation Trust is the trial sponsor and has delegated responsibility for the overall management of the EASE trial to the Chief Investigator and NCTU. Queries relating to sponsorship of this trial should be addressed to the Chief Investigator or via the trial team.

1.3 Structured trial summary

Primary Registry and Trial Identifying Number	ISRCTN 67104246
Date of Registration in Primary Registry	2nd August 2024
Secondary Identifying Numbers	• IRAS number 1008638 • REC Reference 24/NE/0074 • CTA 13630/0016/001-0001
Source of Monetary or Material Support	NIHR Health Technology Assessment (HTA) Programme: NIHR152423
Sponsor	Norfolk and Norwich University Hospitals NHS Foundation Trust
Contact for Public Queries	easetrial@uea.ac.uk
Contact for Scientific Queries	Prof Niall M Broomfield Deputy Dean, Norwich Medical School Head, Department of Clinical Psychology and Psychological Therapies (CPPT) University of East Anglia Norwich Research Park Norwich, NR4 7TJ N.Broomfield@uea.ac.uk Tel: 01603 591217
Short Title or Acronym	Evaluating Antidepressants for emotionaliSm after strokE (EASE)
Scientific Title	**E**valuating **A**ntidepressants for emotionali**S**m after strok**E**: A multi-centre, randomised, double-blind, placebo-controlled trial to establish the effect(s) of administration of Sertraline (50 mg once daily for six months) in people with a recent stroke and post-stroke emotionalism
Countries of Recruitment	UK
Health Condition(s) or Problem(s) Studied	Post-Stroke Emotionalism (PSE)

Randomisation	Online, permuted block, participant level randomisation across three strata: recruitment centre, time since stroke, and use of anti-depressants within a year of screening.
Intervention(s)	50mg Oral Sertraline, Once Daily for 6-months versus matched placebo
Key Inclusion and Exclusion Criteria	Inclusion: • 18 years or older • Clinical diagnosis of first or repeat acute stroke in past one year with imaging compatible with ischaemic or haemorrhagic stroke (including those with normal CT if clinical history strongly suggestive of stroke.) • Any PSE sub-type (crying, laughter, combined) defined by CNS-LS score ≥13 • Capacity, as assessed by the patient's attending physician, to consent and complete trial assessments Exclusion: • Significant medical condition that in the opinion of the patient's attending physician would affect subject safety or influence the study outcomes • Allergy to Sertraline • Contraindication to Sertraline - known hepatic impairment, known long QT syndrome, close angle glaucoma, History of Chronic Kidney Disease (CKD) or Chronic Obstruction Pulmonary Disease (COPD), using a medication that could interact seriously with Sertraline e.g. pimozide, monoamine oxidase inhibitors and other serotonergic drugs (amphetamines, triptans and fentanyl) • Current or recent (within 1 month) treatment with any SSRI antidepressant or irreversible monoamine oxidase inhibitors (MAOIs) • Recent (within 1 month) change in non-SSRI antidepressants. Those on a stable dose for 1 month or more will still be eligible, including those having psychological therapies for anxiety/depression • Current or known history of hyponatraemia • Enrolment in another CTIMP interventional study or not available for full follow-up duration

	• a known history of a drug overdose, self-harm or attempted suicide in the last three months • pregnant or breast-feeding • Women of Childbearing Potential (WOCBP) and not using a highly effective form of contraception (See section 6.3 for full definitions) • Unable or prefers not to undertake trial assessments remotely. Options to participate will include by post, telephone or video calls or completion of assessments online
Study Type	Phase III, Multi-centre, parallel-group, 1:1 securely randomised, double-blind, placebo-controlled trial with an internal 9 month pilot phase
Setting	Secondary and tertiary stroke care – NHS Trusts/Health Boards
Date of First Enrolment	Anticipated October 2024
Target Sample Size	310
Primary Outcome(s)	Difference between sertraline and placebo groups in change of symptoms of PSE, measured by CNS-LS between baseline and 6 months
Key Secondary Outcomes	The following measures will be captured at 3, 6 and 12 months post randomisation, unless stated otherwise; • CNS-LS (only 3 and 12 months after randomisation) • PSE Symptoms (TEARS-Q) • Symptoms of Depression (PHQ-9) • General Anxiety Disorder 2-item (GAD-2) • Cognitive functioning and Social functioning (WHODAS 2.0) • Health Related Quality of Life (EQ-5D-5L) • Health Related Quality of life (ICECAP-O, at 6 and 12 months only) • Acceptability of Intervention (only at 6 months after randomisation) • Cost-effectiveness • Serious Adverse Reaction • Adherence (only at 6 months after randomisation)

1.4 Roles and responsibilities

These membership lists are correct at the time of writing; please see terms of reference documentation in the TMF for current lists.

1.4.1 Protocol contributors

Name	Affiliation	Role
Prof Niall Broomfield	UEA	Lead Investigator
Dr Kneale Metcalf	NNUH	Clinical Chief Investigator
Matt Hammond	Norwich CTU	CTU Deputy Director
Juliet High	Norwich CTU	CTU Research Lead
Martin Pond	Norwich CTU	Head of Data Management
Prof Lee Shepstone	UEA	Senior Statistician/Co-Applicant
Prof Martin Dennis	Edinburgh	Clinical Trials and Stroke Medicine/Co-Applicant
Prof Robert Howard	UCL	Clinical Trials and Old Age Psychiatry/Co-Applicant
Prof Caroline Watkins	UCLAN	Clinical Trials and Stroke Nursing /Co-Applicant
Prof Maree Hackett	UCLAN	Clinical Trial, Stroke Epidemiology and Stroke Emotionalism/Co-Applicant
Prof Robert West	Leeds	Statistician/Co-Applicant
David Turner	UEA	Health Economist/Co-Applicant
Dr Helen Parretti	UEA	General Practice and PPI/Co-Applicant
Dr Joanna Semlyen	UEA	EDI/Co-Applicant
Jeremy Dearling	UEA	Public Partner/Co-Applicant
Dr Terry Quinn	Glasgow	Stroke Medicine/Co-Applicant
Dr Eirini Kontou	Nottingham	Stroke Neuropsychology/Co-Applicant
Dr Yvonne Chun	Edinburgh	Stroke Medicine/Co-Applicant
Dr Naaheed Mukadam	UCL	PPI and EDI/Co-Applicant
Dr Moïse Roche	UCL	PPI and EDI/Co-Applicant

Prof Osvaldo Almeida	Western Australia	Clinical Trials and Geriatric Psychiatry/Collaborator
Prof Steven Faux	New South Wales, AU	Clinical Trials and Rehabilitation Medicine/Collaborator
Prof Michael Nilsson	Newcastle, AU	Clinical Trials and Rehabilitation Medicine/Collaborator
Brian Beh	George Institute for Global Health, AU	Public Partner/Collaborator

**Sincere thanks and acknowledgements to Professor Gillian Mead and Professor Richard Lindley for their contribution to the conception and design of an earlier iteration of EASE

1.4.2 Role of trial sponsor and funders

Name	Affiliation	Role
Julie Dawson	NNUH	Sponsor: Research Services Manager
Michael Sheridan	NNUH	Sponsor: Research Grants Coordinator
Jasmine Nabarro	NNUH	Sponsor: Research Grants Officer
Rozz Bloom	NIHR EME	Funder: Research Manager

1.4.3 Trial Team

Name	Affiliation	Role and responsibilities
Prof Niall Broomfield	UEA	Lead Investigator
Dr Kneale Metcalf	NNUH	Clinical Chief Investigator
Veronica Bion	Norwich CTU	EASE Trial Manager
Hannah Lewis	Norwich CTU	EASE Trial Assistant
Izobel Clegg	Norwich CTU	EASE Research Associate
Prof Lee Shepstone	UEA	Senior Statistician
Kelly Grant	Norwich CTU	Trial Statistician
Matt Hammond	Norwich CTU	CTU Deputy Director
David Turner	UEA	Health Economist/Co-Applicant
Juliet High	Norwich CTU	CTU Research Lead

Martin Pond	Norwich CTU	Head of Data Management
Cecile Guillard	Norwich CTU	Database Programmer

1.4.4 Trial Management Group

Name	Affiliation	Role and responsibilities
Prof Niall Broomfield	UEA	Lead Investigator
Dr Kneale Metcalf	NNUH	Clinical Chief Investigator
Veronica Bion	Norwich CTU	EASE Trial Manager
Kelly Grant	Norwich CTU	Trial Statistician
Matt Hammond	Norwich CTU	CTU Deputy Director
Juliet High	Norwich CTU	CTU Research Lead
Martin Pond	Norwich CTU	Head of Data Management
Cecile Guillard	Norwich CTU	Data Programmer
Julie Dawson	NNUH	Sponsor: Research Services Manager
Prof Lee Shepstone	UEA	Senior Statistician/Co-Applicant
Prof Martin Dennis	Edinburgh	Clinical Trials and Stroke Medicine/Co-Applicant
Prof Robert Howard	UCL	Clinical Trials/Co-Applicant
Prof Caroline Leigh Watkins	UCLAN	Clinical Trials and Stroke Nursing /Co-Applicant
Prof Maree Hackett	UCLAN	Clinical Trials and Stroke Emotionalism/Co-Applicant
Prof Robert West	Leeds	Statistician/Co-Applicant
David Turner	UEA	Health Economist/Co-Applicant
Dr Helen Parretti	UEA	General Practice and PPI/Co-Applicant
Dr Joanna Semlyen	UEA	EDI/Co-Applicant
Jeremy Dearling	UEA	Public Partner/Co-Applicant
Dr Terry Quinn	Glasgow	Stroke Medicine/Co-Applicant
Dr Eirini Kontou	Nottingham	Stroke Neuropsychology/Co-Applicant

Dr Yvonne Chun	Edinburgh	Stroke Medicine/Co-Applicant
Dr Naaheed Mukadam	UCL	PPI and EDI/Co-Applicant
Dr Moïse Roche	UCL	PPI and EDI/Co-Applicant

1.4.5 Trial Steering Committee

Name	Affiliation	Role and responsibilities
Dr Lisa Shaw	Newcastle	Chair
Dr Susan Tebbs	Birmingham CTU	Independent trialist
Dr Charlie Welch	York	Independent Statistician
Dr Jonathan Hewitt	Cardiff	Independent stroke clinician
Dr Yvonne Chun	Edinburgh	Stroke clinician (non-independent, observer)
Mrs Abi Dennington-Price	UEA	Independent Public Partner

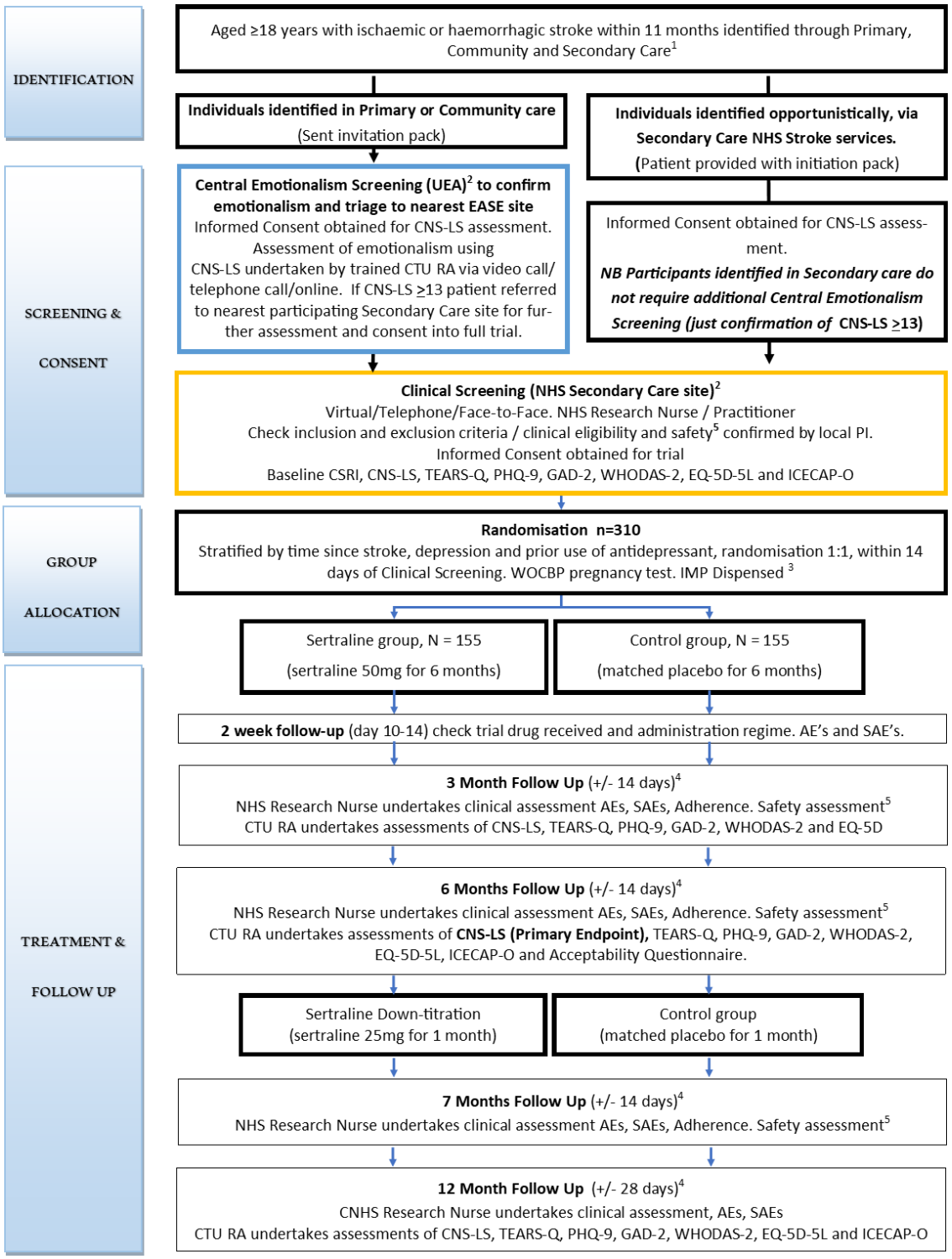
1.4.6 Independent Data Monitoring Committee/Safety Committee

Name	Affiliation	Role and responsibilities
Prof Bart Van Der Worp	Utrecht	Chair
Prof Graeme Hankey	Western Australia	Second independent
Prof Victoria Allgar	Plymouth	Independent Statistician

1.4.7 Lived Experience Advisory Forum (LEAF)

Name	Affiliation	Role and responsibilities
Mr Jeremy Dearling	UEA	Co-Chair
Dr Helen Parretti	UEA	Co-Chair

2 Trial Diagram



[1]As patients with PSE can be under the care of Primary Care (GP), Community Care Teams or within Secondary Care we will aim to screen in all settings; (1) Approx. 100 geographically distributed, large GP practices will be asked to run searches for patients who have had a stroke within the previous 11 months (11 months will give time for patients to be recruited and fulfil inclusion criteria at randomisation, of stroke in past 12 months). These patients will be sent information by their GP practice on the study and PSE and asked if they would like to be considered for the trial and how to

register their interest. (2) Approx. 20 community care trusts will be asked to screen their patients and provide information on the trial for those with suspected emotionalism via mail outs and / or during their routine visits. (3) Approx. 20+ Secondary and Tertiary Care sites (which will also act as recruiting sites—see below) will be asked to screen patients (including those returning for routine 6 month post-stroke visits) with suspected emotionalism.

[2]Potentially eligible patients will be assessed for emotionalism using CNS-LS by a trained CTU RA via telephone call/video call/online. If eligible on CNS-LS, the participant will be referred to their nearest participating NHS site. The NHS Sites will act as the formal recruiting sites and will confirm eligibility, undertake local investigator oversight and sign trial prescriptions. Participants will not need to visit site to participate, unless safety assessments are required at the criteria of the Site Investigator. Recruitment can be undertaken remotely. If participants are identified at a participating NHS Site, then they are permitted to proceed directly to Clinical Screening (which will include a CNS-LS eligibility check)

[3] Participants will have the option to have IMP dispensed direct to their home address on receipt of a signed prescription from the PI (or PI delegate).

[4] To improve participant engagement and accessibility and reduce NHS burden, we will offer participants the option to undergo screening and study visits virtually (via the patient's own device), over the telephone, by post, or by email link to the study database. We will however retain the option to offer face-to face visits in clinic if this is the preference of the participant. Further to this, all research assessments not relating to safety, including CNS-LS, will be undertaken centrally and remotely by the UEA team.

[5] Assessment of participant safety, including: physical examination, vital signs, ECG and safety blood test (haematology, biochemistry and clotting) when required, as clinically indicated at the criteria of the PI or sub-I.

3 Abbreviations

AE	Adverse Event
AR	Adverse Reaction
CI	Chief Investigator
CNS-LS	Center for Neurologic Study-Lability Scale
CRF	Case Report Form
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
DSUR	Development Safety Update Report
ECG	Electrocardiogram
EDI	Equality Diversity and Inclusion
EHR	Electronic Health Records
EQ-5D-5L	EuroQol Group EQ-5D - Health Questionnaire
EU	European Union
FDA	(US) Food and Drug Administration
FWA	Federal Wide Assurance
GAD-2	General Anxiety Disorder 2-item (GAD-2)
GCP	Good Clinical Practice
HRA	Health Research Authority
ICECAP-O	ICEpop CAPability measure for Older people
ICH	International Conference on Harmonisation
IDMC	Independent Data Management Committee
IMP	Investigational Medicinal Product
ITT	Intention to Treat
LEAF	Lived Experience Advisory Forum
MHRA	Medicines and Healthcare products Regulatory Agency
NAE	Notifiable Adverse Event
NCTU	Norwich Clinical Trials Unit
NIHSS	National Institutes of Health Stroke Scale
NNUH	Norfolk and Norwich University Hospitals NHS Foundation Trust
NOK	Next of Kin
PHQ-9	Patient Health Questionnaire-9
PI	Principal Investigator
PID	Participant Identification Number
PIS	Participant Information Sheet
PPIE	Patient and Public Involvement and Engagement
PROMS	Patient Reported Outcome Measures
QA	Quality Assurance
QC	Quality Control
QMMP	Quality Management and Monitoring Plan
R&D	Research and Development
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SIV	Site Initiation Visit
SPC	Summary of Product Characteristics
SSA	Site Specific Approval

SUSAR	Suspected Unexpected Serious Adverse Reaction
TdP	Torsades de pointes
TEARS-Q	Testing for Emotionalism After Recent Stroke-Questionnaire Crying
TMF	Trial Master File
TMG	Trial Management Group
TMT	Trial Management Team
ToR	Terms of Reference
TSC	Trial Steering Committee
UEA	University of East Anglia
WHODAS-2	World Health Organization Disability Assessment Schedule 2.0
WOCBP	Woman of Childbearing Potential

4 Glossary

None

5 Introduction

5.1 Background and Rationale

Post-stroke emotionalism (PSE) is an under researched neurologic sequela of stroke involving sudden onset, uncontrollable crying episodes (occasionally laughter) not under usual social control and which represent a change to pre-stroke functioning (3-5).

Clinically, people with persisting PSE may experience significant distress, embarrassment, negative beliefs, anxiety and social avoidance. This psychological profile is confirmed in recent qualitative research emerging in the literature (6,7) although if and how these variables interplay to influence psychosocial recovery and represent modifiable treatment targets is not known. PSE can also be upsetting and confusing for families and there is a known overlap of PSE with depression (8), so careful assessment is merited.

PSE is common, with the available prevalence data, pooled on systematic review, suggesting 17% of people with stroke meet PSE diagnostic criteria at 1 month and 12% at 6 months or more. (9) A recent longitudinal cohort study noted conditional PSE point prevalence (corrected for case missingness) of 22% at 12 months.(10)

Despite this and a likely association with impaired psychological and social functioning, current knowledge of safe, effective PSE treatments is limited, due to a lack of high-quality treatment research.

There is still no psychological theory or model of PSE and no clinical trial has evaluated a non-pharmaceutical PSE treatment despite survey data indicating UK NHS stroke professionals use reassurance, education and acknowledgement of emotional episodes to help their patents cope.(11)

Equally, whilst current stroke clinical guidelines advocate use of antidepressants as a first-line PSE therapy (12,13), this recommendation rests on limited, low-quality evidence drawn from a small number of clinical trials with inherent methodological weaknesses, as summarised in the recent Cochrane review of pharmaceutical PSE interventions.(14)

In their Cochrane review, Hackett and colleagues identify seven randomised controlled trials which evaluated antidepressants to treat PSE although due to missing data, reliable pre- and post-treatment data could only be extracted from five. Four trials tested an SSRI (Selective Serotonin Uptake Inhibitor), one a Tricyclic antidepressant, with moderate to large effect sizes favouring the antidepressant arm consistently observed. However, all five trials were small scale (N = 213 participants in aggregate), with wide durations of antidepressant treatment (10 to 182 days) and time since stroke (3 days to 13 years), poor monitoring of adverse events and in three instances, non-psychometric (thus not standardised) assessment of PSE outcomes.(14)

Accordingly, the Cochrane review authors concluded that whilst antidepressants may show promise as an effective candidate PSE treatment, because of the low quality of the trial data, definitive, large scale, high quality clinical trials are needed to guide clinical practice regarding likely responders, length of treatment and expected side effects.(14) This uncertainty and unknown balance of benefit and risk facing stroke clinicians seeking to help people with PSE led NIHR Health Technology Assessment to put

out a commissioning call: *Antidepressants for post-stroke emotionalism,* to which this protocol is written in response.

Using a multi-centre, randomised, double-blind, placebo-controlled trial design, EASE will establish whether administering Sertraline 50 mg once daily for 6 months in people with a recent stroke and post-stroke emotionalism is a safe, clinical and cost-effective treatment strategy for use in the UK NHS.

Change in CNS-LS was chosen as the primary outcome as this psychometric measure has been used in clinical trials of emotionalism across a range of neurologic disorders. Secondary outcomes will include a stroke-specific measure of emotionalism (Testing for Emotionalism After Recent Stroke-Questionnaire Crying Questionnaire (TEARS-Q; 21), and a range of other stroke validated psychometrics of mood, cognition, social functioning, quality of life and activities of daily living.

Choice of antidepressant, dosage and duration

The decision to evaluate six-months treatment of Sertraline 50 mg once per day was based on a review of the evidence and consultation with stroke clinicians, psychiatrists, general practitioners, and patient and public involvement and engagement (PPIE) contributors who considered the benefits and risks of sertraline over alternative antidepressants.

Sertraline is a widely used antidepressant with a half-life of one day and non-active metabolites. This makes it safer than other similar compounds such as fluoxetine for use in people with stroke.

50 mg sertraline is the standard starting dose in the treatment of depression.

Per chosen dosage, a six-months treatment duration also mirrors usual clinical practice. There is a further logic in deploying a six-month rather than longer course of treatment, in that emotionalism is more prevalent acutely/post acutely (< 6 months) compared to the longer term. Six-months of treatment thus provides a good test of whether sertraline will work and maximises treatment adherence whilst minimising excess participant burden and likelihood of SAEs.

Risk: Benefit Evaluation

In designing the trial, the risks involved in taking part were carefully evaluated against the potential benefits.

There are several potential risks to participants, especially given that many will be elderly, and all will have sustained stroke and may present with co-occurring long-term conditions.

Although relatively uncommon and most likely to occur early in a course of treatment (< 2 weeks), known side effects of sertraline include nausea, sexual dysfunction, headache and lethargy, hyponatraemia (low sodium electrolyte level) and long QT interval prolongation (electrical abnormality on ECG). There is also a heightened risk of bone fractures in people living with stroke commenced on fluoxetine, a similar SSRI (Selective Serotonin Reuptake Inhibitor) antidepressant medicine.

The potential benefits to taking part would include a 50% chance of receiving the antidepressant sertraline which limited evidence suggests could be a safe and effective treatment of emotionalism

after stroke. Furthermore, during the trial participants will receive medical oversight, and be helping to answer a critical research question pertaining to the future care of stroke patients like them.

Weighing up the potential benefits and risks, it is our evaluation on balance that a carefully conducted clinical trial evaluating sertraline to treat emotionalism in adults after stroke is a safe, timely, clinically important and a scientifically important endeavour.

5.1.1 Explanation for choice of comparators

Sertraline will be compared with matched placebo as this is the most robust way to determine its efficacy. Treatment allocation will be double-blind to reduce potential bias in reporting of the patient reported primary and secondary outcome measures.

5.2 Objectives

The primary objective is to determine whether administration of Sertraline 50mg once daily for 6 months reduces post-stroke emotionalism (PSE) symptoms in adults, with stroke in the previous 12 months, as defined by change in CNS-LS score from baseline.

- Secondary objectives are to investigate the effect of Sertraline at 3, 6 and 12 months post randomisation on PSE symptoms (TEARS-Q), symptoms of depression (PHQ-9), General Anxiety Disorder 2-item (GAD-2), cognitive functioning and social functioning (WHODAS 2.0), Health Related Quality of Life (EQ-5D-5L, ICECAP-O (6 and 12 months only)) and CNS-LS (at 3 and 12 months). We will also investigate acceptability of the intervention, cost-effectiveness, serious adverse reactions and treatment adherence.

5.3 Trial Design

EASE is a Phase III, multi-centre, parallel-group, 1:1 securely randomised, double-blind, placebo-controlled clinical trial of an investigational medicinal product with an internal 9 month pilot phase.

The investigational medicinal product is a type of antidepressant known as a selective serotonin reuptake inhibitor (SSRI), licenced in the UK as an antidepressant. It will be used outside of its licenced indication for this trial.

5.3.1 Progression criteria for the internal pilot

EASE will contain a 9 month internal pilot to assess recruitment, retention and collection of outcome data to allow successful trial delivery. The Independent Data Monitoring Committee (DMC) will scrutinise the first 9 months of participants recruitment to recommend to the Trial Steering Committee (TSC) whether EASE should continue or stop at the pilot stage. Decision will be based upon the thresholds below.

Recruitment targets have been set with the following expectations:

If both targets are GREEN, the trial is on course to recruit to time and target. The trial will progress as planned.

In the case of AMBER, discussion will take place with the TSC to develop a mitigation plan/strategies to deliver the study as originally proposed. The TSC and NIHR will review the plan to determine whether it is considered feasible and acceptable and whether the trial should continue with

amendments. This is likely to involve, at a minimum, opening trial recruitment at additional sites and a close review of screening data to identify existing barriers to recruitment.

If the participant or site recruitment are RED, trial recruitment would not be on course. The funder will be notified and the TSC will meet to discuss whether any other changes to the project can be made to remedy the situation or whether the trial should be terminated.

Internal pilot phase: 9 months

	RED	AMBER	GREEN
PARTICIPANT RECRUITMENT Number recruited to the trial in 9 months	<60	≥60 & <120	≥120
SITE RECRUITMENT Number open to recruitment at 9 months	<20	≥20 & <30	≥30

6 Methods

6.1 Site Selection

The trial sponsor has overall responsibility for site and investigator selection and has delegated this role to the CI and NCTU.

6.1.1 Study Setting

EASE will primarily be set within Stroke clinics within Secondary Care NHS sites throughout the UK. The trial has been designed to allow remote assessments to reduce the burden on participants and sites.

We will also identify potential participants in primary care via GP database searches, and opportunistically, via secondary and community care NHS stroke services. The trial will also be widely publicised through national third sector charitable organisations and social media to support recruitment.

6.1.2 Site/Investigator Eligibility Criteria

Once a site has been assessed as being suitable to participate in the trial, the trial team will provide them with a copy of this protocol.

To participate in the EASE trial, investigators and trial sites must fulfil a set of criteria that have been agreed by the EASE Trial Management Group (TMG) and that are defined below.

Eligibility criteria:

- A named clinician is willing and appropriate to take Principal Investigator responsibility
- Suitably trained staff are available to recruit participants, enter data and undertake trial procedures as detailed in this protocol.
- The site should have a pharmacy that is able to store, prepare and dispense IMP appropriately

- Site team willing and able to take steps to avoid unintentional unblinding through Electronic Health Records (HER) system.
- The site should have sufficient data management resources to allow prompt data return to NCTU.

Trial sites meeting eligibility criteria will be issued with the local information pack needed by the Research and Development Department (R&D) of their Site to enable the Site to provide confirmation of capacity and capability to undertake the study. Upon confirmation of capacity and capability sites will be sent an EASE Investigator Site File. Sites will be sent a link to access an electronic ISF (eISF). This will provide the structure and content of the ISF. Guidance, in the form of a Work Instruction, will be provided to assist sites with setting up their own electronic filing system, or paper copy.

6.1.2.1 Principal Investigator's (PI) Qualifications and Agreements

The investigator(s) must be willing to sign an investigator statement to comply with the trial protocol (confirming their specific roles and responsibilities relating to the trial, and that their site is willing and able to comply with the requirements of the trial). This includes confirmation of appropriate qualifications, familiarity with the appropriate use of any investigational products, agreement to comply with the principles of GCP, to permit monitoring and audit as necessary at the site, and to maintain documented evidence of all staff at the site who have been delegated significant trial related duties.

6.1.2.2 Resourcing at site

The investigator(s) should be able to demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period (i.e. the investigator(s) regularly treat(s) the target population). They should also have an adequate number of qualified staff and facilities available for the foreseen duration of the trial to enable them to conduct the trial properly and safely. The local site team should communicate changes in staff, delegated to undertake activities for the EASE trial, to the Trial Team. Further trial specific training of local site staff will be provided by NCTU as necessary.

Sites will be expected to complete and maintain a delegation of responsibilities log and provide staff contact details.

6.2 Site approval and activation

The Clinical Trial Authorisation (CTA) for the trial requires that the Medicines and Healthcare products Regulatory Agency (MHRA) is supplied with the names and addresses of all participating site Principal Investigators. Trial staff at NCTU will perform this task.

On receipt of the signed investigator statement, approved delegation of responsibilities log and staff contact details, written confirmation will be sent to the site PI. The trial manager or delegate will notify the PI in writing of the plans for site initiation/training. Sites will not be permitted to recruit any participants until a letter for activation has been issued. The Trial Manager or delegate will be responsible for issuing this after the sponsor green light process has been completed.

The site must conduct the trial in compliance with the protocol as agreed by the Sponsor, HRA, and by the regulatory authority(ies) (as appropriate), and which was given favourable opinion by the

Research Ethics Committee (REC). The PI or delegate must document and explain any deviation from the approved protocol and communicate this to the trial team at NCTU.

A list of active sites may be obtained from the EASE Trial Team.

6.3 Participants

6.3.1 Eligibility Criteria

6.3.1.1 Participant selection

There will be **NO EXCEPTIONS** (waivers) to eligibility requirements at the time of randomisation. Questions about eligibility criteria should be addressed PRIOR to attempting to randomise the participant.

The eligibility criteria for this trial have been carefully considered and are the standards used to ensure that only medically appropriate participants are entered. Participants not meeting the criteria should not be entered into the trial for their safety and to ensure that the trial results can be appropriately used to make future treatment decisions for other people with similar diseases or conditions. It is therefore vital that exceptions are not made to these eligibility criteria.

Participants will be considered eligible for enrolment in this trial if they fulfil all the inclusion criteria and none of the exclusion criteria as defined below.

Investigators are encouraged to contact the EASE trial team for guidance in assessing eligibility in relation to exclusion criteria prior to approaching the patient about the trial if required.

6.3.1.2 Participant Inclusion Criteria

- Age ≥18 yrs
- Clinical diagnosis of first or repeat acute stroke (all types) in past one year with imaging compatible with ischaemic or haemorrhagic stroke (including those with normal CT if clinical history strongly suggestive of stroke).
- Any PSE sub-type (crying, laughter, combined) defined by CNS-LS score ≥13
- Capacity, as assessed by the patient's attending physician, to consent and complete trial assessments

Participants can be supported by a study partner, to assist them with completing trial outcomes, if required. Study partners will not be required to provide consent, undertake trial activities themselves or provide their own data.

We will examine any effects of the presence or absence of such a study partner by conducting appropriate sensitivity analyses.

6.3.1.3 Participant Exclusion Criteria

- Significant medical condition that in the opinion of the patient's attending physician would affect subject safety or influence the study outcomes
- Allergy to Sertraline
- Contraindication to Sertraline - including known hepatic impairment, known long QT syndrome, close angle glaucoma, History of Chronic Kidney Disease or Chronic Obstruction

Pulmonary Disease (COPD), using a medication that could interact seriously with Sertraline e.g. Pimozide, monoamine oxidase inhibitors and other serotonergic drugs (amphetamines, triptans and fentanyl)

- Current or recent (within 1 month) treatment with any SSRI antidepressant or irreversible monoamine oxidase inhibitors (MAOIs).
- Recent (within 1 month) change in non-SSRI antidepressants. Those on a stable dose for 1 month or more will still be eligible, including those having psychological therapies for anxiety/depression.
- Current or known history of hyponatraemia
- Enrolment in another CTIMP interventional study or not available for full follow-up duration
- A known history of a drug overdose, self-harm or attempted suicide in the last three months
- Pregnant or breast-feeding
- Women of Childbearing Potential (WOCBP) and not using a highly effective form of contraception. A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. Pregnancy tests will be required before trial treatment starts. Highly effective forms of contraception defined as: Methods of birth control which result in a low failure rate (i.e. less than 1% per year) when used consistently and correctly such, as implants, injectables, combined oral contraceptives, some intrauterine devices (IUDs), sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments) or vasectomized partner. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required. WOCBP must continue to follow contraception requirements, as a minimum, for 30 days after the last dose of trial medication.
- Unable or prefers not to undertake trial assessments remotely. Options to participate will include by post, telephone or video calls or completion of assessments online.

6.3.1.4 Co-enrolment Guidance

Concurrent participation in another CTIMP is not permitted. Concurrent participation is defined as within 4 weeks of the last study drug administration (or at least one half-life if longer than 4 weeks). However, participants may be entered into other observational studies and non-CTIMPs, given prior agreement from the CI of both studies.

6.3.1.5 Screening Procedures and Pre-randomisation Investigations

Written informed consent to enter and be randomised into the trial must be obtained from participants after explanation of the aims, methods, benefits and potential hazards of the trial and **BEFORE** any trial-specific procedures. The only procedures that may be performed in advance of written informed consent being obtained are those that would be performed on all patients in the same situation as a usual standard of care.

Patients who have had a stroke within the previous 11 months (participants inclusion is stroke within last 12 months at randomisation) will be identified via GP practice, secondary care database searches or via participating Secondary Care NHS sites (i.e. attendance at stroke units acutely, or returning for routine post-stroke visits), will be given study invitation packs and asked to register their interest in EASE (web, email, telephone or post) with NCTU. Consent will be obtained for an initial (centralised) pre-screening to determine whether patients have any PSE sub-type (crying, laughter, combined). This initial PSE pre-screen (virtual/telephone/face-to-face) using CNS-LS will be performed online or undertaken by an appropriately trained RA at NCTU prior to clinical screening and consent into the full trial.

Individuals with diagnosed PSE (≥13 on CNS-LS) on the initial centralised CTU screening will then be referred to nearest participating Secondary care NHS site for eligibility check and consent to full trial. To reduce NHS and participant burden, potentially suitable participants presenting at secondary care stroke unit sites do not need to undergo centralised CNS-LS screening via NCTU prior to entry to the trial. Consent to Contact and completion of CNS-LS can be completed at site/clinic. (see Appendix One, Study Flowchart)

6.4 Interventions

50mg Oral Sertraline, Once Daily for 6-months or matched placebo

6.4.1.1 Products

2 x 25mg oral Sertraline once daily

Or

2 x Matched oral placebo once daily

6.4.1.2 Treatment Schedule

Participants will be asked to take 2 x 25mg oral Sertraline tablets or 2 x matched placebo, once daily with or without food for 6 months.

After 6 months, or on discontinuation of treatment, participants should take one Sertraline 25mg or one matched placebo for 1 month to reduce the risk of withdrawal symptoms and protect the blinding of the trial.

6.4.1.3 Dispensing

Following receipt of a trial prescription, the IMP will be dispensed from the recruiting site pharmacy at baseline and 3 months. A resupply at 3 months will include sufficient IMP for the down-titration. 3 bottles containing 70 tablets per bottle will be dispensed at each timepoint.

6.4.1.4 Dose Modifications, Interruptions and Discontinuations

If a participant forgets to take a dose and it is more than 24 hours after their scheduled dose, they should omit the missed dose and take the next dose when it is due. Participants must not take a double dose to make up for a forgotten dose. Interruptions should be avoided where possible, any reported should be recorded on the eCRF.

If any participant is struggling to tolerate the full 2 x 25 mg once daily dosage, then 1 x 25mg dosage would be accepted, with participants staying in the trial. Dose reduction should only be done after PI discussion with the participant about side effects, and any options other than dose reduction. Any such instances should be recorded on the eCRF.

6.4.2 Accountability

The local PI will be responsible for drug accountability at each site. This task will usually be delegated to the site research pharmacist. Accountability will include records of drug and placebo received at site, dispensed to participant, and will ensure batch recall is possible in the event of it being necessary.

6.4.3 Compliance and Adherence

To capture compliance to study treatment data, we will ask participants to report any non-compliance at 3, 6 and 7 months follow-up and provide a tablet count as part of drug accountability at the end of the treatment period.

6.4.4 Concomitant Care

The duty of care for participants remains with the site PI and the participant's GP.

Participants who develop depression during the trial will remain in the trial and are able to receive treatment for their depression. While the trial protocol will not be prescriptive, the protocol and letter sent to participants' GPs will suggest psychological therapy/counselling as the preferred first option for treatment, as indicated in stepped care for depression.

The GP letter will also describe that the active treatment is 50 mg Sertraline daily, and should they prescribe an antidepressant during the trial, they should assume the participant is already receiving Sertraline and choose their antidepressant and its dose accordingly. The GP will manage the mood disorder as they see fit, including provision of information about depression after stroke.

6.4.5 Overdose of Trial Medication

Following randomisation and at three-month follow up, participants will be provided with a supply of study medication, in tablet form.

In the EASE trial, there is a 50% chance that this supply will be Sertraline.

There is therefore a slight risk of Sertraline overdose to participants and to those known to them, whether by accident or due to a deliberate act. This is particularly the case for deliberate overdose risk, given the known overlap between PSE and clinical depression. (23)

Sertraline has a margin of safety dependent on patient population and/or concomitant medication. The risk of unintentional or deliberate overdose is lower than in anti-depressant treatment in usual practice. We have put the following mitigations in place:

- Anyone with a history of a drug overdose, self-harm or attempted suicide in the last three months will be excluded
- Anyone on any recent (within 1 month) SSRI anti-depressant treatment will be excluded
- Anyone on pimozide, monoamine oxidase inhibitors and other serotonergic drugs (amphetamines, triptans and fentanyl), or MAOI within the last 14 days, will be excluded

- Trial medication to be supplied in bottles with tamper-proof lids
- Participants to be supplied with 2 x 3month medication supplies at separate visits, rather than one six-month supply. IMP for the down-titration will be included in this.

Deaths have been reported involving overdoses specifically of Sertraline, alone or in combination with other drugs and/or alcohol. Therefore, any overdosage should be medically treated according to local protocol(s).(22)

Symptoms

Symptoms of overdose include serotonin-mediated side effects such as somnolence, gastrointestinal disturbances (e.g., nausea and vomiting), tachycardia, tremor, agitation, and dizziness. Coma has been reported although less frequently.

Management

In the event of serious overdose patient should be admitted for urgent NHS care. There are no specific antidotes to Sertraline. It is recommended to establish and maintain an airway and, if necessary, ensure adequate oxygenation and ventilation. Activated charcoal, which may be used with a cathartic, may be as, or more effective than lavage, and should be considered in treating overdose. Induction of emesis is not recommended.

QTc prolongation / Torsades de pointes (TdP) has been reported following Sertraline overdose; therefore cardiac (e.g., Electrocardiogram (ECG)) and vital sign monitoring is also recommended, along with general symptomatic and supportive measures.

Due to the large volume of distribution of Sertraline, forced diuresis, dialysis, haemoperfusion and exchange transfusion are unlikely to be of benefit.

6.4.6 Protocol Treatment Discontinuation

In consenting to the trial, participants are consenting to trial treatments, trial follow-up and data collection. However, an individual participant may stop treatment early or be stopped early for any of the following reasons:

- Unacceptable treatment toxicity or adverse event
- Inter-current illness that prevents further treatment
- Any change in the participant's condition that in the clinician's opinion justifies the discontinuation of treatment
- If participant becomes pregnant, they will be advised to stop trial treatment immediately. The participant can and should be encouraged to remain in the trial for follow-up measures as far as possible.
- Withdrawal of consent for treatment or follow-up by the participant

As participation in the trial is entirely voluntary, the participant may choose to discontinue trial treatment at any time without penalty or loss of benefits to which they would otherwise be entitled. Although not obliged to give a reason for discontinuing their trial treatment, a reasonable effort should be made to establish this reason, whilst remaining fully respectful of the participant's rights.

Participants who discontinue protocol treatment, for any of the above reasons, should remain in the trial for the purpose of follow up and data analysis.

On discontinuation of treatment, participants will be provided with Sertraline 25mg or matched placebo for 1 month to reduce the risk of withdrawal symptoms.

6.4.7 Prohibited Medications

Concomitant treatment with irreversible monoamine oxidase inhibitors (MAOIs) is contraindicated due to the risk of serotonin syndrome with symptoms such as agitation, tremor and hyperthermia. Sertraline must not be initiated for at least 14 days after discontinuation of treatment with an irreversible MAOI. Sertraline must be discontinued for at least 7 days before starting treatment with an irreversible MAOI. (22)

Concomitant intake of pimozide is contraindicated. (22)

Increased monitoring is recommended for participants also taking triptans, fentanyl, amphetamines, MAO-B inhibitors, linezolid due to the risk of serotonin syndrome.

Increased monitoring is also recommended for participants on anti-platelet medications, due to the increased risk of bleeding, and drugs that are likely to cause hyponatraemia.

6.5 Outcomes

6.5.1 Primary Outcomes

We will use CNS-LS to screen trial eligibility (≥13) and record symptoms of PSE at baseline, 3, 6 and 12-months post randomisation.

The Primary Outcome is the difference between sertraline and placebo groups in change of symptoms of PSE, measured by CNS-LS between baseline and 6 months. CNS-LS is a 7-item, self-administered questionnaire that has been widely used in large clinical trials of treatment of emotionalism in patients with multiple sclerosis and motor neurone disease and in an open-label trial of PSE. CNS-LS provides a validated measure of the frequency of PSE episodes and is effectively regarded as the “industry standard” to measure emotionalism in clinical trials in neurological disorders. (24,25)

6.5.2 Secondary Outcomes

The following Secondary Outcome Measures will be captured at 3, 6 and 12-months post randomisation.

PSE Symptoms:

TEARS-Q is a 7-item, self-administered questionnaire of PSE crying symptoms, validated using stroke survivors based on PSE diagnostic criteria (26,27), and suited to telephone/video calls.

Symptoms of Depression:

PHQ-9 (28) is a score depression symptom measure. The PHQ-9 is a 9-item measure of depression that scores each of the 9 DSM-IV criteria for depression from "0" (not at all) to "3" (nearly every day) and has been recommended for use in people with stroke. (29,30) People with depression will be included,

so long as they are not already taking, need to take, or have taken any SSRI antidepressant or irreversible monoamine oxidase inhibitors (MAOIs), in the last month.

Depression affects approximately one third of people living with stroke (31) and like with other major health problems, there is also an elevated risk of suicide following stroke, relative to the general population. (32)

We wish to ensure that for any participant presenting with moderate/severe depression or suicide ideation, there are mechanisms which allow the site PI and clinical team to offer immediate care in response, including signposting to mental health services, referral to the GP and checking the participant is receiving appropriate psychological or psychiatric care (see Table 1, below [33]):

Table 1: PHQ-9 score category conversion

PHQ-9 total score	Depression category
0-4	Minimal
5-9	Mild
10-14	Moderate – signposting
15-19	Moderate – signposting/advise to contact GP
20-27	Severe – consent to contact GP, and check on status of ongoing psychological or psychiatric care

Section 6.11.1.2 details procedures to follow if a participant reports moderate depression and / or suicidal ideation or a risk of self-harm on a self-reported PHQ-9 Questionnaire.

Anxiety

We will use General Anxiety Disorder 2-item (GAD-2) to measure change in anxiety.

Cognitive functioning, activities of daily living, social functioning and impact on relationships:

We will use WHODAS 2.0 (World Health Organization Disability Assessment Schedule 2.0)(34) to measure changes in cognitive functioning, activities of daily living, social functioning and impact on relationships. WHODAS 2.0 has been validated for use in stroke for the first year post index event. (35)

Health Related Quality of Life:

We will capture HRQoL via EQ-5D-5L.(36) The EQ-5D-5L is a five dimension, five level routine patient-reported questionnaire which enables the calculation of quality adjusted life years (QALYs). (baseline, 3, 6 and 12 months)

We will also administer the ICEpop CAPability for Older people (ICECAP-O; 37) (baseline, 6 and 12 months only), a measure of capability for older people with focus on wellbeing instead of health. It covers 5 dimensions of wellbeing, with each having 4 levels.

Social functioning:

We will use the participation domain of the WHODAS 2.0(34) to capture social functioning behaviours.

Acceptability of Intervention:

We will measure acceptability of the trial intervention using a structured questionnaire provided to participants at 6-months.

Cost-effectiveness:

This will be determined over twelve months from the perspective of the NHS and social care, with resource use data being collected via a modified CSRI, see Sections 5.13.5 to 5.13.5.2 for full details.

Serious Adverse Reactions:

Sertraline is a widely used and well tolerated antidepressant medication with an excellent safety profile, regularly prescribed in the UK for depression and obsessive-compulsive disorder. We will take a risk-based approach to Adverse Event reporting. We will monitor for Serious Adverse Reactions (SARs) and identify whether frequency is greater than in other populations given Sertraline and sufficiently common to offset benefits. The Summary of Product Characteristics (SmPC) will set out known adverse reactions to Sertraline and common adverse events which occur post-stroke.

We will only analyse SARs as we do not aim to detect occurrence of the many AEs which occur in stroke patients unlikely related to trial participation or the medication.(20) We will record relevant drug/non-drug therapy use and gauge 'treatment as usual' in controls.

Adherence:

IMP adherence will be measured by a tablet count completed at the end of each treatment period.

At each assessment of adherence, we will check that participants have not been prescribed Sertraline, instead of their IMP, or any SSRI as well as the IMP. Patients can often report to their GP that they are taking Sertraline, when in fact they are taking the IMP which may be a placebo.

6.6 Participant Timeline

The EASE trial team based at Norwich CTU (comprising the Chief Investigator, Trial Manager, CTU Research Lead, Study Statistician and Research Assistants) will coordinate collection of the centralised data. The site Principal Investigators and Research Teams will coordinate collection of the local data.

Figure 1. EASE Visit Schedule

TIMEPOINT	PSE Pre-Screening *Only required for participants identified in*	Baseline Visit	Randomisation (UP TO 14 DAYS AFTER BASELINE ASSESSMENTS)	2 week Follow up **(DAY 10-14)**	3 Month Follow up (+/- 14 DAYS)	6 Month Follow Up (+/- 14 DAYS)	7 Month Follow Up (+/- 14 DAYS)	12 Month Follow Up (+/- 28 DAYS)
Consent to Contact	CTU*	**NHS**						
Eligibility check - Full consent informed consent		**NHS**						
Concomitant medication check		**NHS**						
Medication review		**NHS**			**NHS**	**NHS**		**NHS**
demographics, medical history and patient characteristics collected		**NHS**						
Safety Assessments**		**NHS**			**NHS**	**NHS**	**NHS**	
Randomisation			**NHS** / CTU					
Urine Pregnancy test for WOCBP			**NHS**					
IMP dispensed			**NHS** / CTU***		**NHS** / CTU***			
CSRI		**NHS**				CTU		CTU
CNS-LS	CTU*	**NHS**			CTU	CTU		CTU
TEARS-Q		**NHS**			CTU	CTU		CTU
PHQ-9		**NHS**			CTU	CTU		CTU

GAD-2		**NHS**			CTU	CTU		CTU
WHODAS-2		**NHS**			CTU	CTU		CTU
EQ-5D-5L		**NHS**			CTU	CTU		CTU
ICECAP-O		**NHS**				CTU		CTU
AE recording				**NHS****	**NHS**	**NHS**	**NHS**	**NHS**
SAE recording		**NHS**						
Treatment adherence				**NHS**	**NHS**	**NHS**	**NHS**	
Acceptability questionnaire						CTU		

* Participants identified in primary or community care, or who approach CTU about participating in the trial, will provide consent to contact and pre-screening including CNS-LS. Full consent to take part in EASE will be obtained for those passing pre-screening by the NHS site, after which full eligibility will be confirmed and CNS-LS will be repeated.

** Safety Assessments - Physical examination, vital signs, ECG and safety blood tests (haematology, biochemistry and clotting) where clinically indicated at the discretion of the PI, existing results may be used if suitable.

*** At baseline and 3 months, participants will be dispensed an additional supply of trial treatment. The baseline supply will include enough to allow a prescription to be raised and dispensed following 3 month NHS assessment. The 3-month supply will include a 1-month (half dose) supply for down titration at the end of the study.

**** AEs from time of consent will be recorded at the 2-week follow-up.

CNS-LS	Center for Neurologic Study-Lability Scale
TEARS-Q	Testing for Emotionalism After Recent Stroke-Questionnaire Crying
PHQ-9	Patient Health Questionnaire-9
GAD-2	General Anxiety Disorder 2-item
WHODAS-2	World Health Organization Disability Assessment Schedule 2.0
EQ-5D-5L	EuroQol Group EQ-5D - Health Questionnaire
ICECAP-O	ICEpop CAPability measure for Older people

6.6.1 Patient Assessments / IMP Dispensing

1. For individuals identified via GP database searches (and any self-referrals). **Centralised emotionalism pre-screen** using CNS-LS online or undertaken by CTU trial team via video call/telephone, with individuals scoring ≥13 then referred to nearest NHS recruiting site. **Individuals identified opportunistically, via secondary and community care NHS stroke services, are omitted from this initial pre-screen step.**

2. **Trial eligibility check** by site PI or delegated member of site team video call/telephone or face-to-face at NHS recruiting site.
3. **Consent for full trial** by NHS site research nurse video call/telephone or face-to-face at NHS recruiting site, or remotely via post / email link.
4. **Baseline questionnaires** by NHS site research nurse video call/telephone or face-to-face at NHS recruiting site, or remotely via post / email link.
    1. Baseline demographics
    2. Baseline Resource Use (CSRI)
5. **Baseline assessments**, per the below fixed order, by NHS Research nurse, video call/telephone, face-to-face, at NHS recruiting site, or remotely via post / email link:
    - Comorbidities and relevant medical and social history including but not limited to; date of previous diagnosis of PSE, stroke type (ischaemic, haemorrhagic), stroke classification (left, right, anterior or posterior), stroke severity including National Institutes of Health Stroke Scale (NIHSS) total score, functional status, living circumstances, symptoms of aphasia, history of a drug overdose or attempted suicide in the last three months, concomitant medication
    - CNS-LS questionnaire assessment of emotionalism (5 minutes)
    - TEARS-Q questionnaire assessment of emotionalism (5 minutes)
    - PHQ-9 questionnaire assessment of depression (5 minutes)
    - GAD-2 questionnaire assessment for anxiety (1 minute)
    - WHODAS-2 questionnaire assessment of disability (15 minutes)
    - EQ-5D-5L questionnaire assessment of generic quality of life (5 minutes)
    - ICECAP-O questionnaire assessment of capability wellbeing (5 minutes)

    ECG, safety blood and physical examination/vital signs, as clinically indicated at the criteria of the PI or sub-I.
6. **Baseline IMP dispensed**. For WOCBP a highly sensitive urine pregnancy test will be sent prior to dispensing IMP. The participant will conduct the test at home and inform the result on the phone to the NCTU RA. If the test is negative the participant will be sent their IMP dosing, but if the test is positive the participant must be excluded.
7. **2-week follow-up**, by NHS Research Nurse, video call/telephone or face-to-face, at NHS recruiting site to check IMP arrived, patient adhering to regime and AE/SAE recording.
8. **Three month follow up assessments**, by NHS Research nurse, video call/telephone or face-to-face, at NHS recruiting site:
    - AE/SAE recording
    - Safety Assessments if required, as clinically indicated at the criteria of the PI or sub-I.
    - Adherence review
    - Review of all medications
9. Three month IMP dispensed
10. **Three month follow up questionnaire assessment**, by CTU trial team, video call/telephone or remote via post / email link:
    - CNS-LS questionnaire assessment of emotionalism (5 minutes)
    - TEARS-Q questionnaire assessment of emotionalism (5 minutes)
    - PHQ-9 questionnaire assessment of depression (5 minutes)
    - GAD-2 questionnaire assessment for anxiety (1 minute)

- WHODAS-2 questionnaire assessment of disability (15 minutes)
- EQ-5D-5L questionnaire assessment of generic quality of life (5 minutes)

11. **Six month follow up assessments**, by NHS Research nurse, video call/telephone or face-to-face, at NHS recruiting site:
    - AE/SAE recording
    - Safety Assessments if required, as clinically indicated at the criteria of the PI or sub-I.
    - Previous SARs follow up
    - Adherence review
    - Review of all medications
12. **Six month follow up questionnaire assessments**, by CTU trial team, video call/telephone or remote via post / email link:
    - **CNS-LS** questionnaire assessment of emotionalism (5 minutes) **(primary endpoint)**
    - TEARS-Q questionnaire assessment of emotionalism (5 minutes)
    - PHQ-9 questionnaire assessment of depression (5 minutes)
    - GAD-2 questionnaire assessment for anxiety (1 minute)
    - WHODAS-2 questionnaire assessment of disability (15 minutes)
    - EQ-5D-5L questionnaire assessment of generic quality of life (5 minutes)
    - ICECAP- O questionnaire assessment of capability wellbeing (5 minutes)
    - Acceptability Questionnaire (3 minutes)
    - CSRI Resource Use questionnaire (3 minutes)
13. **Seven month follow up assessments**, by NHS Research nurse, video call/telephone or face-to-face, at NHS recruiting site:
    - AE/SAE recording
    - Safety Assessments if required, as clinically indicated at the criteria of the PI or sub-I.
    - Previous SARs follow up
    - Adherence review
14. **Twelve month follow up assessments**, by NHS Research nurse, video call/telephone or face-to-face, at NHS recruiting site:
    - AE/SAE recording
    - Previous SARs follow up
    - Review of all medications
15. **Twelve month follow up questionnaire assessments**, by CTU trial team, video call/telephone or remote via post / email link:
    - CNS-LS questionnaire assessment of emotionalism (5 minutes)
    - TEARS-Q questionnaire assessment of emotionalism (5 minutes)
    - PHQ-9 questionnaire assessment of depression (5 minutes)
    - GAD-2 questionnaire assessment for anxiety (1 minute)
    - WHODAS-2 questionnaire assessment of disability (15 minutes)
    - EQ-5D-5L questionnaire assessment of generic quality of life (5 minutes)
    - ICECAP- O questionnaire assessment of capability wellbeing (5 minutes)
    - CSRI Resource Use questionnaire (3 minutes)

The participants consent form will include an optional section asking the participant to confirm their wishes for remaining in the trial in the event of post-consent fluctuating capacity. If it is the wish of the participant to remain in the trial, they will be asked to provide name and contact details for a Next of Kin (NOK)/appropriate representative. Where possible NOK/representative can support participants, with fluctuating capacity, to complete the assessments. The trial will not use adapted versions of assessments but ask that as many as possible are completed. Completion of assessments must always start with and include responses for the CNS-LS.

6.6.1.1 Bloods, ECG (Electrocardiogram), Physical Examination and Vital Signs

Adequate safety monitoring is the responsibility of the study investigators. Assessment of participant safety should include, when required, physical examination, vital signs, ECG and safety blood test (haematology, biochemistry and clotting). These assessments will be conducted in both arms at baseline and during treatment up to and including the 7-month visit as clinically indicated at the criteria of the PI or sub-I. An authorised clinician will need to review the results to confirm participant safety, to enter the study or continue participation, or to confirm that no additional tests are required.

Where the participant has already had the requisite blood tests or an ECG at a routine care visit, and where there are no other safety concerns relating to past medical history or current physical state, the PI can review these results to decide whether the patient is eligible to be randomised and receive trial medication.

Where AE monitoring at follow-up time points indicates at the criteria of the PI that additional safety assessments are required, these should be progressed without delay to confirm that the participant should remain on the trial medication or not. The investigator must ensure that adequate medical care is provided to anyone experiencing an AE or SAE, according to usual care processes.

Safety bloods (15ml) will include a full blood count, biochemistry (urea and electrolytes) and clotting profile.

If clinically indicated a 12 lead ECG will be required if not recently available.

Physical examination and vital signs will be at the discretion of the PI.

In-person clinical visits will be possible if required to complete these assessments if clinically required.

If a participant refuses the recommended tests during a follow up visit, the PI should use their clinical judgement and usual care processes to decide the most appropriate onward treatment and this may include down titration and stopping of trial medication. The participant should be encouraged to remain in the trial for follow up of all other assessments, providing they are willing.

6.6.2 Early Stopping of Follow-up

Sites must inform NCTU of all forms of early trial discontinuation via the eCRF. In instances where a participant has decided to withdraw consent, it is essential for the site to establish which aspects of the trial the participant is withdrawing consent from.

- If a participant chooses to discontinue their trial treatment, they should continue to be followed up as closely as possible to the follow-up schedule defined in the protocol, providing they are willing. They should be encouraged and facilitated not to leave the whole trial, even though they no longer take the trial treatment.
- If a participant who has discontinued trial treatment no longer wishes to attend any remaining follow-up visits or undertake trial specific assessments, relevant routine data (for example vital status) will continue to be collected from the site during the trial providing the participant is willing for this to continue.
- If, however, the participant exercises the view that they no longer wish to provide any data either through study visits or from existing routine data, this view must be respected, and the participant withdrawn entirely from the trial. Data already collected will be kept and included in analyses according to the intention-to-treat principle for all participants who stop follow up early.

Where participants are unable or unwilling to continue to undertake study measurements/activities, the decision as to whether the participant should continue with trial treatment and/or follow-up assessments will be at the discretion of the local PI and/or CI.

Participants who stop trial follow-up early will not be replaced.

6.6.3 Participant Transfers

If a participant moves from the area making continued follow up by their recruiting site inappropriate, every effort should be made for them to be followed at another participating site. Written consent should be taken at the new centre and then a copy of the participant's CRFs should be provided to the new centre. Responsibility for the participant remains with the original consenting centre until the new consent process is complete. Given that all EASE assessments can be completed via video or telephone call, we do not anticipate participant transfers will create particular problems.

6.6.4 Loss to Follow-up

Sites will be asked to report any hospital admissions that they become aware of, particularly if they meet the definition of a SAR.

Sites will hold contact details for all participants and will follow local policy with regards to number and type of attempts used to contact participants. If there is no response after reasonable attempts to follow up and when the end of study timepoint is reached, a participant will be considered withdrawn.

6.6.5 Trial Closure

The end of the trial is defined as 6 months following the last follow-up visit of the last participant randomised, to allow for data entry and data cleaning activities to be completed.

6.7 Sample Size

We aim to recruit 310 participants (155 per arm). Assuming a drop-out of no more than 15%, this will provide 264 participants with primary outcome data, providing 90% power at the two-side 5% significance level to detect a difference between groups of 0.4 standard deviations.

6.8 Recruitment and Retention

6.8.1 Recruitment

Most stroke survivors living with PSE are not in hyper acute/acute stroke settings and we wish to be maximally inclusive in our recruitment strategy and involve a 'real world' representative sample of people with PSE.

We plan a dual recruitment strategy involving screening of GP databases to identify people with stroke, (all types) and opportunistic sampling in secondary and community care (stroke pathway) settings.

The trial will also be widely publicised through national third sector charitable organisations and social media to support recruitment. Ethical approval for any associated materials and processes will be sought prior to use.

To recruit and follow- up 310 people, we aim to identify and recruit approximately 30 centres.

We will also run searches using GP electronic patient records at approximately 100 geographically distributed, large GP practices for adults (≥18 yrs) who have had a stroke (ischaemic or haemorrhagic, first or repeat) in the last 11 months. (This will allow time to recruit patients in order that they meet randomisation eligibility criteria of stroke within last 12 months). We will include patients whose records show that they have existing depression and/or anxiety, but not if their records indicate that currently, or in the last month, they were prescribed any type of SSRI antidepressant or MAOI. We will exclude anyone from the list of patients potentially eligible to invite if their records indicate an allergy to Sertraline.

In parallel to the above, we will ask up to 20 Community Care trusts to review their lists of potentially eligible patients (using the same criteria as for the GP practices above).

In both GP practice and community care trusts, potentially eligible participants will be provided an invitation pack by post or during a routine visit asking that they contact the Norwich CTU study team if they wish to express an interest in participating. The pack will include details on the study and CNS-LS pre-screening assessment and a consent to contact form which can be returned by post or completed online.

Invitation letters will include a choice for patients to express interest but to defer enrolment in the trial to a later date.

On receipt of a consent to contact form, which will include consent for NCTU trained staff to complete a PSE assessment using CNS-LS, NCTU will contact the individual to arrange a mutually convenient time to complete the centralised emotionalism pre-screen (virtual/telephone/online). Participants who score ≥13 on the CNS-LS will be referred to the most appropriate participating local NHS site for consent into the full trial.

If the EASE research team are unable to contact the participant on the first attempt, there will be two further attempts to contact by phone / email before discontinuing pre-screening.

The EASE trial team based at Norwich CTU will coordinate responses from database searches at sites, and the subsequent PSE pre-screen process.

The site Principal Investigators and Research Teams will coordinate recruitment from within the secondary and community care stroke pathways.

The EASE trial team based at Norwich CTU will closely monitor recruitment rates at site and via database searches on a weekly or more often basis as the trial progresses.

6.8.2 Retention

Whilst we wish to support participants as best as possible, in this clinical trial we need to replicate 'usual care' as best as possible. We do not therefore plan specific retention strategies. However, we provide six trial-specific contacts after randomisation over 12 months (three with the central NCTU team, three with the NHS recruiting site team) which exceeds the number of times participants would usually receive unprompted contact by the NHS asking about their mood and stroke recovery.

6.9 Assignment of Intervention

6.9.1 Allocation

6.9.1.1 Sequence generation -

The allocated treatment for a participant will be generated via computer written code using stratification. Online, permuted block randomisation, across three strata: recruitment centre, time since stroke (0 to 5 months (0-152 days) / 6 - 12months (153-365 days)), and current use of anti-depressants (where permitted within the protocol) will be used.

Full details of the stratification will be documented in a separate document (EASE Allocation Schedule) stored in a shared file accessible to only the study statistician(s) and data management team as appropriate.

6.9.1.2 Allocation concealment mechanism

Allocation will be computer generated by a web-based system ensuring concealment prior to randomisation. Following consent and confirmation of eligibility the PI or delegate will enter data confirming eligibility into the eCRF generating a participant identification number. Blinded notification of randomisation will be sent to the PI and/or delegates, CI and NCTU trial team. A notification of randomisation email containing the blinded kit IDs will be sent to the site clinical trial pharmacy.

6.9.1.3 Allocation Implementation

The PI or delegated sub-investigator is responsible for ensuring only eligible participants are randomised and prescribed study medication. Participants will be allocated to the intervention by a process embedded in the web-based data management system. The randomisation code will be saved in the study database for later decoding and for emergency unblinding purposes.

6.9.2 Blinding

This is a double-blind study. The placebo and active treatments will appear identical and will be dispensed in identical containers. All trial participants, the trial management group and core trial team, care providers and outcome assessors will remain blinded throughout the study.

6.9.3 Unblinding

The decision to unblind a single case should be made when knowledge of an individual's allocated treatment is essential for the clinical management or welfare of the participant.

This will be done via the study database (local PIs and the CI will have special logins which will allow unblinding and which will be closely audited within the database management system). For all instances of unblinding, it is the responsibility of the treating physician to promptly record and report the unblinding to NCTU by the local PI, or delegate, including the identity of all recipients of the unblinding information.

If a suspected unexpected serious adverse event (SUSAR) is reported, delegated members of the NCTU will be able to unblind a participant to enable expedited reporting to the regulatory agencies.

6.10 Data Collection, Management and Analysis

6.10.1 Data Collection Methods

Each participant will be given a unique trial Participant Identification Number (PID). Data will be collected at the time-points indicated in the Trial Schedule.

The preferred method of data collection is direct online entry of data onto the central database, stored on servers based at NCTU, by members of the EASE trial team working within each research site. Data may be entered onto paper Case Record Forms (CRFs) prior to entry onto the database. Staff will receive training on data collection and use of the online system (see Section 6.1.2.2).

Data collection, data entry and queries raised by a member of the EASE trial team will be conducted in line with the NCTU and trial specific Data Management Standard Operating Procedure.

Participant identifiable data may be stored on a Participants Database to enable participants to be contacted by site staff for the purpose of trial delivery. There will be a clear logical separation of participant identifiable data from the trial data. All participant identifiable data will be stored securely, and logically separated from trial database by strict, minimised database permissions, with access only granted to those members of the study team who require it.

Where there is a requirement for study materials to be stored and/or shared electronically outside of the study database (e.g. supporting materials shared via SharePoint or similar), the mechanism for achieving this will be appropriate in terms of governance, regulatory and legal compliance, and resource to administer it will be identified.

Clinical trial team members will receive trial protocol training. All data will be handled in accordance with the Data Protection Act 2018.

6.10.2 Data Management

Participants will be offered the opportunity to complete online questionnaires but there will be provision for completing the questionnaires on paper, or via phone or MS teams call if the participant states a preference for this at baseline. Paper questionnaires will be sent to NCTU (by post or email) where they will be transcribed into the eCRF. Online responses will be stored directly in the eCRF. Virtual responses will be uploaded directly into the eCRF, by the NCTU trained RA.

Data will be entered under the PID number onto the central database stored on the servers based at NCTU. Access to the database will be via unique, individually assigned (i.e. not generic) usernames and passwords, and only accessible to members of the EASE trial team, and external regulators if

requested. The servers are protected by firewalls and are patched and maintained according to best practice. The physical location of the servers is protected physically and environmentally in accordance with the University of East Anglia's General Information Security Policy 3 (GISP3: Physical and environmental security).

The database and associated code have been developed by NCTU Data Management, in conjunction with the EASE trial team. The database software provides a number of features to help maintain data quality, including; maintaining an audit trail, allowing custom validations on all data, allowing users to raise data query requests, and search facilities to identify validation failure/ missing data.

After completion of the trial the database will be retained on the servers of NCTU for on-going analysis of secondary outcomes. It will then be taken offline and archived as per NCTU_DM WI_4_Electronic Archiving. A copy will be provided to Sponsor for facilitating data requests.

The identification and enrolment logs (as appropriate to site tasks), linking participant identifiable data to the pseudonymised PID, will be held locally by the trial site. (PIC sites will only be required to identify patients.) These will either be held in written form in a locked filing cabinet or electronically in password protected form on hospital computers. After completion of the trial the identification, screening and enrolment logs will be stored securely by the sites for 25 years unless otherwise advised by NCTU.

Further information on data collection and management processes are provided in the EASE Data Management Plan.

6.10.3 Non-Adherence and Non-Retention

The consent form will explain that if a participant wishes to withdraw from the study the data acquired prior to that point will be retained. Reason for withdrawal will be recorded, if given, as will loss to follow up.

Non-adherence to trial medication will be assessed through tablet counts of unused drug supplies at 3, 6 and 7 months. A per-protocol study population will also be analysed based upon adherence to study treatment. This population will include those participants using their study medication above a certain threshold. e.g. 80% of tablets dispensed.

This threshold will be discussed, agreed and recorded in the SAP prior to any efficacy analyses. Where participants are unable or unwilling to continue to undertake study measurements/activities, the decision as to whether the participant should continue with trial treatment and/or follow-up assessments will be at the discretion of the local PI and/or CI.

6.10.4 Statistical Methods

6.10.4.1 Efficacy Outcomes Analyses

We will use a general linear model (GLM) to estimate treatment effect on the primary outcome, the change in CNS-LS between baseline and 6 months. This model will include the design variables of 1. recruitment centre, 2. time since stroke (0 to 5 months / 6 - 12 months), and 3. use of anti-depressants within a year of screening (Yes / No). It will include CNS-LS baseline values together with any baseline

variables deemed to be predictive of emotionalism severity. These will be determined in advance of the analysis by the trial team and specified in the statistical analysis plan (SAP). The fixed effect of treatment group will be added to the model. An estimate of this parameter, i.e. mean difference between groups in CNS-LS adjusted for other model variables, will provide the estimate of treatment effect. A 95% confidence interval will be constructed around this point estimate.

The proposed GLM makes the assumption of normally distributed model residuals. This assumption will be tested by graphically examining the residuals and considering distributional statistics such as skewness.

Secondary efficacy outcomes will be analysed using analogous linear models with appropriate link and error terms according to the nature of the data and treatment effects expressed accordingly.

No adjustment for multiple comparisons is planned. Statistical significance will be set at the conventional two-sided 5% level.

6.10.4.2 Statistical Analysis Plan (SAP)

A full SAP will be produced prior to the analysis of any efficacy data and before recruitment is complete. Both the TSC and DMC will be given the opportunity to comment on the SAP prior to it being signed-off by the CI and lead statistician.

6.10.4.3 Additional Analyses

All additional analyses will be prespecified in the SAP. Particularly, ***subgroup analyses***, to consider the effect of Sertraline on ***key subgroups***, will be considered, and specified, prior to the acceptance of the SAP. At present, but to be confirmed, sex and, emotionalism type (crying/laughing/mixed presentation) will be used to define subgroups for analysis of the primary outcome. This analysis will be conducted by adding the subgroup defining factor together with a subgroup-by-treatment interaction term.

Additional analyses to be prespecified will include sensitivity analyses based, for example, upon the exclusion of non-compliant individuals or adjustments to outcome definitions or timings. These will need to be agreed and justified by the trial team and specified in the SAP.

6.10.4.4 Analysis Population

An Intention-to-Treat (ITT) approach will be adopted as the primary analysis strategy. This is the intention to analyse all participants in the study according to the group to which they were randomly allocated rather than with reference to treatment received. A per-protocol study population will also be analysed based upon adherence to study treatment. This population will include all participants receiving 80% of the allocated study intervention.

6.10.4.5 Missing Data

The primary analysis of the primary outcome will be based upon a full-case analysis of those individuals without missing information. If this approach includes more than 95% or less than 50% of all randomised individuals, then no further analyses will be conducted. However, in the likely event that the complete case sample lays within this range, we will seek to use full maximum likelihood as a strategy to mitigate against bias from missing values. If this approach is not possible (most notably from lack of convergence of estimates) then a multiple imputation (MI) approach will be used. Missing data strategies will only be applied to the primary outcome.

6.10.5 Economic evaluation

The use of Sertraline for PSE is likely to have resource implications, and these could be important components of the decision to adopt this drug in the NHS to treat PSE. Sertraline is comparatively low cost, but the resources required to treat stroke can be substantial and hence a treatment has the potential to markedly affect general health care resource use as well as affecting health related quality of life. We therefore feel it is important to include an economic evaluation alongside this trial in order to determine whether the addition of 6-month treatment with Sertraline represents a good use of scarce healthcare resources compared to no treatment with Sertraline. The comparators will therefore be the study groups of Sertraline treatment and placebo.

The economic evaluation will be a 'within trial' analysis conducted for the duration of the randomised trial. The base case perspective will be that of the NHS and social care. Additional information will be sought to enable a broader perspective as a sensitivity analysis, for example costs borne by participants and their families. The base case economic analysis will assess cost-utility using the outcome measure of quality adjusted life year (QALY). QALYs will be assessed by means of the EQ-5D-5L completed at baseline, 3, 6 and 12 months. The analysis will therefore estimate the incremental cost per QALY of Sertraline compared to treatment as usual. The EQ-5D-5L will be scored using a published valuation tariff, the exact tariff chosen will depend on which method is recommended at the time of analysis. Two additional economic analyses will be conducted as sensitivity analyses. Firstly, an additional cost-effectiveness analysis using the ICECAP-O, measured at baseline, 6-months, and 12-months. The ICECAP-O focusses on capabilities and hence will cover different aspects of health to the EQ-5D-5L. The use of the EQ-5D-5L and ICECAP-O will enable judgement of the comparative performance of these two instruments in this population when judged against the CNS-LS. Finally, we will estimate a cost-effectiveness analysis using the primary outcome measure of CNS-LS at 6-months. This will take the form of a cost-per point change in the CNS-LS from baseline to 6-months.

These economic analyses require estimates of the implications of Sertraline use on resource use compared to the placebo group. This includes the cost of the intervention as well as health, social care, and other costs incurred by individuals with PSE.

For the cost of the intervention the REDCAP database will record those allocated to the Sertraline arm and the Sertraline tablets that are issued. The cost of Sertraline will be counted as the cost of tablets issued rather than those actually used as, in practice, unused tablets cannot be used for other individuals. For those who discontinue Sertraline treatment the date will be recorded, and we will calculate the number of complete months used in terms of the estimated cost.

For other resource implications for people with PSE we will use two methods of collecting data. Firstly, a participant completed questionnaire based on a modified version of the client service receipt inventory (CSRI; 56). This will record the use of NHS secondary and primary health care and social care received by participants at baseline, 6 and 12-months, including all relevant participant- and family-borne costs. The full list of resources covered by this questionnaire will be developed in discussion with trial investigators and PPIE/LEAF contributors. The intention will be to make this questionnaire as simple as possible in order to minimise participant burden. The time frame of the questionnaires will cover the last 6 months so questionnaires at 6 months and 12 months will cover the entire period of the study. Additionally, we will ask this information at baseline which will provide information on resource use prior to the study. This information will be used to determine if the two groups are similar

at baseline in terms of their health care resource use. It will also be used as a variable in the economic evaluation analysis. The time frame of the baseline data collection will be the past 3 months. As 6-months is a long time to accurately recall all aspects of service use we will provide participants with a diary sheet to record resource use events to act as a mnemonic. These will not be returned to the team or entered as data in the study, they would only be an aid to participants/carers in complete the modified CSRI.

Secondly, in addition to the modified CSRI, we will also collect data from national routine data sets. Data will be obtained from the medicines dispensed in primary care data set to cover use of medicines. This will obviate the need to ask participants about medicines use in the modified CSRI as these questions can be complex and burdensome to individuals who may be on a number of different medicines. The time period will cover the 1-year of follow-up. We will also collect from the hospital episode statistics (HES) on secondary care use. This will enable more accurate costing of this resource type. Taken together it is anticipated that these sources will enable simplification of the modified CSRI, reducing participant burden and improving data quality.

All resources identified will be costed using appropriate UK sources for unit costs: (i) NHS reference costs; (ii) PSSRU unit costs (University of Kent and the Centre of Health Economics (CHE) at the University of York); and (iii) the BNF for medicines. Costs will be in UK £Sterling and the cost year will be that of the most recent data available at the time of analysis. In economic analyses it is important to allow for the differential timing of costs and benefits. In general costs and effects that occur now will be valued more than those that occur in the future. However, the consensus in UK health economic evaluation is to not discount costs and effects that occur in the first year. As this study has a one-year timeframe, costs and benefits will not be discounted.

6.10.5.1 Health Economic Analysis Plan (HEAP)

Prior to data lock and analysis, the health economics lead will write a health economics analysis plan (HEAP). This has a similar purpose to the SAP in that it pre-specifies the methods and assumptions that will be used in conducting the economic analysis. The HEAP will conform to the NCTU guidelines for HEAPs, which are periodically updated to incorporate current UK best practice, for example recent guidance on HEAPs. (38) Where it is not possible to pre-specify all methods then this will be highlighted and the planned approach for making the final methodological choices will be outlined. For example, the method of handling missing data is contingent on examining patterns of data that are missing before trial unblinding. The HEAP will be shared with the trial CI, trial statistician and the TMG for comment and approval. If during analysis it becomes clear that a divergence from the specified HEAP is required, then this will be noted and recorded in any final reporting.

6.10.5.2 Within-trial analysis

The economic analysis conducted will be limited to the follow-up period of the trial and will constitute a 'within trial analysis'. We will report descriptive data on both costs and outcomes measures for the study time period. Resource use will be reported by study group with means and confidence intervals. We will report usage for each major category of resource use. This will include both the estimated costs as well as numbers of items of resource use. Also, reported will be estimates of total cost by study group. We will also report the health economic outcome measures at each time period for which

they are collected as well as any aggregation of this data, e.g., QALYs. Data on costs and outcomes will be presented in Tables, unadjusted for baseline characteristics.

The level of missing data will be evaluated, and if deemed necessary, appropriate methods of dealing with missing data will be employed, for example multiple imputation. This decision will be taken in consultation with the trial CI and statistician.

For analysis of cost-utility and cost-effectiveness we will use regression-based methods to estimate costs and effects to allow for differences in baseline characteristics between groups. This analysis will be conducted according to accepted best practice at the time of analysis. A priori we would expect to use seemingly unrelated regression (sureg command in stata) to allow for correlation between costs and effects. The analysis will be presented on an incremental basis – i.e., will show the incremental costs and effects of the Sertraline group compared to the placebo group. Uncertainty in the economic analysis will be represented by the use of cost-effectiveness acceptability curves (CEAC), which will show the probability that Sertraline is cost-effective compared to the placebo at different monetary values of a unit of effect. If the Sertraline group is both more effective and more costly than the placebo group, we will provide estimates of the incremental cost-effectiveness ratio (ICER). Whether this represents a cost-effective intervention will be judged based on the cost-effectiveness thresholds used by the National Institute for Health and Clinical Effectiveness (NICE). These thresholds currently deem an intervention to be cost-effective if they generate QALYs at a cost of between £20,000 and £30,000 per QALY or lower. (39)

6.11 Safety reporting

6.11.1 Safety reporting

Sertraline has been prescribed for a number of years and has a well-established drug safety profile. It has been used in similar populations previously.

The stroke population is likely to have a number of underlying medical conditions and many events that would not meet the definition of an AE because they are present prior to baseline assessments.

Recording of all AEs and SAEs in participant notes will commence from signing the consent form, in both arms of the study, and SAEs will be recorded in the trial database. We only plan to analyse Serious Adverse Reactions (SARs), events that in the opinion of the PI meet the definition of serious and at least possibly related to the trial medication.

AEs and SAEs will continue to be collected in the same way at every visit and analysed according to the SAP. Serious Adverse Reactions, by treatment group, will be reviewed regularly by the DMC as described in their Terms of Reference (ToR).

Definitions of harm of the EU Directive 2001/20/EC Article 2 based on the principles of ICH GCP apply to this trial.

Table 2: Adverse Event Definitions

Adverse Event (AE)	Any untoward medical occurrence in a participant or clinical trial participant administered a medicinal product and which does not necessarily have a causal relationship with this product.
Adverse Reaction (AR)	Any untoward and unintended response to an investigational medicinal product related to any dose administered/trial treatment.
Unexpected Adverse Reaction (UAR)	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's Brochure for an unauthorised product or SPC for an authorised product or treatment.
Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)	Any AE or AR that at any dose: • results in death • is life threatening* • requires hospitalisation or prolongs existing hospitalisation** • results in persistent or significant disability or incapacity • is a congenital anomaly or birth defect • or is another important medical condition***

* The term life threatening here refers to an event in which the participant is at risk of death at the time of the event; it does not refer to an event that might hypothetically cause death if it was more severe (e.g. a silent myocardial infarction).

** Hospitalisation is defined as an in-patient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisation for pre-existing conditions (including elective procedures that have not worsened) does not constitute an SAE.

*** Medical judgement should be exercised in deciding whether an AE or AR is serious in other situations. Important AEs or ARs that may not be immediately life threatening or result in death or hospitalisation but may seriously jeopardise the participant by requiring intervention to prevent one of the other outcomes listed in the table (e.g. a secondary malignancy, an allergic bronchospasm requiring intensive emergency treatment, seizures or blood dyscrasias that do not require hospitalisation, or development of drug dependency).

Adverse events include:

- An exacerbation of a pre-existing illness.
- An increase in the frequency or intensity of a pre-existing episodic event or condition.
- A condition (regardless of whether PRESENT prior to the start of the trial) that is DETECTED after trial drug administration. (This does not include pre-existing conditions recorded as such at baseline – as they are not detected after trial drug administration).
- Continuous persistent disease or a symptom present at baseline that worsens following administration of the trial treatment.

Adverse events do NOT include:

- Medical or surgical procedures: the condition that leads to the procedure is the adverse event.
- Pre-existing disease or a condition present before treatment that does not worsen.
- Hospitalisation where no untoward or unintended response has occurred e.g. elective cosmetic surgery.
- Overdose of medication without signs or symptoms.

SAEs will be coded according to the current version of the Medical Dictionary for Regulatory Activities (MedDRA).

6.11.1.1 Investigator responsibilities relating to safety reporting

All non-serious AEs and ARs, whether expected or not, should be recorded in the patient's medical notes within 7 days of report/becoming aware.

All SAEs should be notified to NCTU immediately after the investigator becomes aware of the event (in no circumstance should this notification take longer than 24 hours).

6.11.1.1.1 Seriousness assessment

When an AE or AR occurs, the investigator or delegated sub-investigator responsible for the care of the participant must first assess whether or not the event is serious using the definition given in Table 2.

6.11.1.1.2 Causality

The investigator must assess the causality of all serious events in relation to the trial treatment using the definitions in Table 3.

Table 3: Adverse Event Causality Definitions

Relationship	Description	Event type
Unrelated	There is no evidence of any causal relationship.	Unrelated SAE
Unlikely to be related	There is little evidence to suggest that there is a causal relationship (e.g. the event did not occur within a reasonable time after	Unrelated SAE

	administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition or other concomitant treatment).	
Possibly related	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition or other concomitant treatment).	SAR
Probably related	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.	SAR
Definitely related	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	SAR

If an SAE is considered to be related to trial treatment, and treatment is discontinued, interrupted or the dose modified, refer to section 5.7.1.4 of this protocol. If an event meets the definition of a SAE an expedited reporting form must be completed and sent to NCTU within 24 hours of the Investigator becoming aware of the event. Expedited SAE reporting is required from time of consent until 4 weeks after the participant last took IMP.

6.11.1.1.3 Severity or grading of Serious Adverse Reactions

The severity of all SARs in this trial should be graded mild, moderate or severe, as assessed by the clinician, according to MedDRA criteria.

1 – Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.

2 – Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities.

3 – Severe: An event that prevents normal everyday activities

6.11.1.1.4 Expectedness

If there is at least a possible involvement of the trial IMP (including any comparators), the investigator and NCTU must assess the expectedness of the event. An unexpected adverse reaction is one that is not reported in the approved SmPC, or one that is more frequently reported or more severe than previously reported. See section 4.8 of the SmPC for a list of expected reactions associated with the IMP being used in this trial. If a SAR is assessed as being unexpected, it becomes a suspected, unexpected, serious adverse reaction (SUSAR) and MHRA and REC reporting guidelines apply (see Notifications sections of the protocol section 6.11.1.4.1).

6.11.1.2 Procedures to follow if a participant reports moderate depression and / or suicidal ideation or a risk of self-harm on a self-reported PHQ-9 Questionnaire

The eCRF will be designed to immediately flag the entry of data that indicates moderate depression (a score of 15 or more on PHQ-9) and / or suicidal ideation or a risk of self-harm. The latter will be defined as any participant scoring 2 ('more than half the days') or above on item 9 of PHQ-9 ('How often in the past two weeks have you had thoughts that you would be better off dead or of hurting yourself in some way?),

In the event of the above, an email will be generated by the eCRF and sent to the PI and local site team.

The recruiting site should follow its standard local suicide protocol procedures to ensure the safety and wellbeing of the participant is maintained and will be required to send a template letter, to notify the GP that the participant has reported moderate depression and / or suicidal ideation or a risk of self-harm. For monitoring purposes, a copy of this letter should be sent by the local site to the EASE trial team to ensure that this has occurred.

In parallel, this should be recorded by the site on the eCRF as an AE of special interest.

6.11.1.3 Procedures to follow if a participant becomes pregnant

Pregnancy is a trial exclusion criterion. However, Women of Childbearing Potential (WOCBP) are not excluded. Highly sensitive urine testing prior to IMP will be mandated. Only those who have a negative test result and who use acceptable methods of contraception will be allowed to enter the study.

Pregnancies are unlikely within the trial population. UK NHS advice (40) notes that:

"Sertraline can be taken in pregnancy. Some studies have suggested that Sertraline might occasionally affect the development of a baby's heart. However, if there is any risk, it is small, and the majority of babies born to women taking Sertraline have a normal heart."

As soon as a member of staff is notified of a pregnancy the local PI must be informed and this will be recorded in the eCRF. The participant must be advised to stop taking the IMP immediately and no further dispensing will take place. NCTU must be notified using the REDCap database and where the participant is willing the outcome must be followed up for mother and child. The participant should be encouraged to remain in the study for follow up as far as possible.

Pregnancy itself does not meet the definition of an SAE and does not need to be reported as such. If the outcome of the pregnancy does meet the definition of a SAE, it must be reported in the adverse events section of the trial database.

6.11.1.4 Notifications

6.11.1.4.1 Notifications by the Investigator to NCTU

NCTU must be notified of all SARs immediately and no later than 24 hours of the investigator becoming aware of the event.

Investigators should notify NCTU of any SAEs occurring from the time of randomisation until 30 days after the last protocol treatment administration. SAEs/SARs and SUSARs must be notified to NCTU until trial closure. Any subsequent events that may be attributed to treatment should be reported to the MHRA using the yellow card system (https://yellowcard.mhra.gov.uk/the-yellow-card-scheme/).

The SAE form must be completed by the investigator or sub-investigator (a clinician named on the delegation of responsibilities list who is responsible for the participant's care) with attention paid to the grading and, causality of the event. In the absence of the responsible investigator, the SAE form should be completed and signed by a member of the site trial team and emailed as appropriate within the timeline. The responsible investigator should check the SAE form at the earliest opportunity, make any changes necessary, sign and then email to NCTU. Detailed written reports should be completed as appropriate. Systems will be in place at the site to enable the investigator to check the form for clinical accuracy as soon as possible.

The minimum criteria required for reporting an SAE are the PID and date of birth, name of reporting investigator and sufficient information on the event to confirm seriousness. Any further information regarding the event that is unavailable at the time of the first report should be recorded on NCTU EASE SAE reporting database as soon as it becomes available.

Full details of any SAE must be immediately entered onto the NCTU SAE reporting database, with an accompanying email sent to:

nctu.safety@uea.ac.uk and copy to sponsor: **rdsae@nnuh.nhs.uk**

Participants must be followed up until clinical recovery is complete and laboratory results have returned to normal or baseline values, or until the event has stabilised. Follow-up should continue after completion of protocol treatment and/or trial follow-up if necessary. Follow-up SAE forms (clearly marked as follow-up) should be completed and emailed to NCTU as further information becomes available. Additional information and/or copies of test results etc. may be provided separately. The participant must be identified by PID, date of birth and initials only. The participant's name should not be used on any correspondence and should be redacted and replaced with trial identifiers on any test results.

6.11.1.4.2 NCTU responsibilities

Medically qualified staff at NCTU and/or the Clinical Chief Investigator (KM, or a medically qualified delegate) will review all SAE reports received and the NCTU trial team will notify the Sponsor as appropriate. In the event of disagreement between the causality assessment given by the local

investigator and the CI, both opinions and any justifications will be provided in subsequent reports. The causality attributed to Sertraline by the local investigator cannot be downgraded by other parties.

NCTU is responsible for the reporting of SUSARs to the regulatory authorities (MHRA and competent authorities of other European member states and any other countries in which the trial is taking place) and REC as appropriate. Fatal and life threatening SUSARs must be reported to the competent authorities within 7 days of NCTU becoming aware of the event; other SUSARs must be reported within 15 days.

NCTU will keep investigators informed of any safety issues that arise during the course of the trial.

The trial manager or delegate at NCTU will submit Development Safety Update Reports (DSURs) to competent authorities.

6.12 Data Monitoring

6.12.1 Independent Data Monitoring Committee

Further details of the roles and responsibilities of the Independent Data Monitoring Committee (IDMC), including membership, relationships with other committees, decision making processes, and the timing and frequency of interim analyses (and description of stopping rules and/or guidelines where applicable) are described in detail in the EASE DMC Terms of Reference (ToR).

6.12.2 Interim Analyses

There are no interim analyses planned.

6.12.3 Quality Assurance and Control

6.12.3.1 Risk Assessment

The Quality Assurance (QA) and Quality Control (QC) considerations for the EASE trial are based on the standard NCTU Quality Management Policy that includes a formal Risk Assessment, and that acknowledges the risks associated with the conduct of the trial and proposals of how to mitigate them through appropriate QA and QC processes. Risks are defined in terms of their impact on: the rights and safety of participants; project concept including trial design, reliability of results and institutional risk; project management; and other considerations.

QA is defined as all the planned and systematic actions established to ensure the trial is performed and data generated, documented and/or recorded and reported in compliance with the principles of GCP and applicable regulatory requirements. QC is defined as the operational techniques and activities performed within the QA system to verify that the requirements for quality of the trial related activities are fulfilled.

6.12.3.2 Central Monitoring at NCTU

NCTU staff will review Case Report Form (CRF) data for errors and missing key data points. The trial database may also be programmed to generate reports on errors which will be presented to the Trial Management Group and Oversight Committees. Essential trial issues, events and outputs, including defined key data points, will be detailed in this protocol and the EASE trial Quality Management and Monitoring Plan (QMMP).

6.12.3.3 On-site Monitoring

The frequency, type and intensity of routine and triggered on-site monitoring will be detailed in the EASE QMMP. The QMMP will also detail the procedures for review and sign-off of monitoring reports. In the event of a request for a trial site inspection by any regulatory authority, NCTU must be notified as soon as possible.

6.12.3.3.1 Direct access to participant records

Participating investigators must agree to allow trial related monitoring, including audits, REC review and regulatory inspections, by providing access to source data and other trial related documentation as required. Participant consent for this must be obtained as part of the informed consent process for the trial.

6.12.3.4 Trial Oversight

Trial oversight is intended to preserve the integrity of the trial by independently verifying a variety of processes and prompting corrective action where necessary. The processes reviewed relate to participant enrolment, consent, eligibility, and allocation to trial groups; adherence to trial interventions and policies to protect participants, including reporting of harms; completeness, accuracy and timeliness of data collection; and will verify adherence to applicable policies detailed in the Compliance section of the protocol. Independent trial oversight complies with the NCTU trial oversight policy.

In multi-centre trials this oversight is considered and described both overall and for each recruiting centre by exploring the trial dataset or performing site visits as described in the EASE Quality Management and Monitoring Plan.

6.12.3.4.1 Trial Team

The Trial Team (TT) will be set up to assist with developing the design, co-ordination and day to day operational issues in the management of the trial, including budget management. The membership, frequency of meetings, activity (including trial conduct and data review) and authority will be covered in the TT terms of reference.

6.12.3.4.2 Trial Management Group

A Trial Management Group (TMG) will be set up to assist with developing the design, co-ordination and strategic management of the trial. The membership, frequency of meetings, activity (including trial conduct and data review) and authority will be covered in the TMG terms of reference.

6.12.3.4.3 Independent Trial Steering Committee

The Independent Trial Steering Committee (TSC) is the independent group responsible for oversight of the trial in order to safeguard the interests of trial participants. The TSC provides advice to the CI, NCTU, the funder and sponsor on all aspects of the trial through its independent Chair. The membership, frequency of meetings, activity (including trial conduct and data review) and authority will be covered in the TSC terms of reference.

6.12.3.4.4 Independent Data Monitoring Committee

The Independent Data Monitoring Committee (IDMC) is the only oversight body that has access to unblinded accumulating comparative data. The IDMC is responsible for safeguarding the interests of

trial participants, monitoring the accumulating data and making recommendations to the TSC on whether the trial should continue as planned. The membership, frequency of meetings, activity (including review of trial conduct and data) and authority will be covered in the IDMC terms of reference. The IDMC will consider data in accordance with the statistical analysis plan and will advise the TSC through its Chair.

6.12.3.4.5 Trial Sponsor

The Norfolk and Norwich University Hospitals NHS Foundation Trust is the trial sponsor. The role of the sponsor is to take on responsibility for securing the arrangements to initiate, manage and finance the trial. The Sponsor is responsible for ensuring that the study meets the relevant standards, and makes sure that arrangements are put, and kept, in place for management, monitoring and reporting. A proportion of the Sponsor's activities have been delegated to the CI, UEA and NCTU as outlined on the form for delegated activities agreed and signed by all parties before the start of the trial.

7 Ethics and Dissemination

7.1 Research Ethics and Health Research Authority Approval

Before initiation of the trial at any clinical site, the protocol, all informed consent forms and any material to be given to the prospective participant will be submitted to the relevant REC and to HRA for approval. Any subsequent amendments to these documents will be submitted for further approval.

The rights of the participant to refuse to participate in the trial without giving a reason must be respected. After the participant has entered the trial, the clinician remains free to give alternative treatment to that specified in the protocol, at any stage, if they feel it to be in the best interest of the participant. The reasons for doing so must be recorded. After randomisation the participant must remain within the trial for the purpose of follow up and data analysis according to the treatment option to which they have been allocated. However, the participant remains free to change their mind at any time about the protocol treatment and follow-up without giving a reason and without prejudicing their further treatment.

7.2 Competent Authority Approvals

This protocol will be submitted to the MHRA via the IRAS combined review process.

This is a Clinical Trial of an Investigational Medicinal Product (IMP) as defined by the EU Directive 2001/20/EC. Therefore, a CTA is required in the UK.

The progress of the trial, safety issues and reports, including expedited reporting of SUSARs, will be reported to the MHRA in accordance with relevant requirements and practices.

7.3 Other Approvals

Documentation will need to be submitted to the R&D Department at each NHS Site in order to gain confirmation of capacity and capability prior to the study being initiated at that site. Confirmation from the site will take the form of a site agreement signed by the Sponsor, NCTU and the relevant site as required.

A copy of the local R&D approval and of the Participant Information Sheet (PIS) and consent form on local hospital headed paper must be forwarded to the co-ordinating centre before participants are randomised to the trial.

The protocol has received formal approval and methodological, statistical, clinical and operational input from the NCTU Protocol Review Committee.

7.4 Amendments

Amendments to the Protocol and other documents (e.g. changes to eligibility criteria, outcomes, sample size calculations, analyses) will be agreed by the TMG. Such amendments will be forwarded to the Sponsor for confirmation as to whether it is either substantial or non-substantial and will then be submitted to the MHRA, HRA or Ethics Committee for categorisation and approval as required. Once the amendment has been categorised it will be sent to relevant sites for consideration in accordance with standard MHRA and/or HRA processes and timescales. Amendments must not be implemented until all regulatory approvals are received and sites have either confirmed acceptance or, no objection has been received within the defined timescale(s). Notification will be sent by NCTU to trial personnel to confirm when an amendment can be implemented.

7.5 Consent or Assent

Patients will be provided with a Patient Information Sheet (PIS) and given time to read it fully. Consent will be a two-part process: consent for initial PSE assessment using CNS-LS and referral to NHS site for further assessment for eligibility to the full trial. Where patients meet the pre-screen eligibility criteria, they will be referred to their local NHS participating site. Following a discussion with a medical qualified investigator, or suitable trained and authorised delegate, any questions will be satisfactorily answered and if the participant is eligible and willing to participate, written informed consent will be obtained. Potential participants will be asked how they would like to complete the consent form (and baseline assessments). The preferred option will be by a link, within an email, directly to the study database (REDCap). Other options will include, by post, or via a video call. For any participants giving oral consent, their consent will be managed via a video call in the presence of a witness chosen by the participant. During the consent process it will be made completely and unambiguously clear that the participant is free to refuse to participate in all or any aspect of the trial, at any time and for any reason, without incurring any penalty or affecting their treatment. Consent will also include an optional section for participants to indicate who to contact in the event of fluctuating capacity. Participants will be given an option to confirm whether they wish to remain in the study in such an event, however a final decision will be taken by the site PI, or delegate, following discussions with the person identified by the participant.

At each follow-up time point, 3, 6 and 12 months the participants will receive a call from their participating NHS site to confirm capacity and continued consent, and method of assessment completion (online, paper or oral). (See section 6.6.1 for more details on completion of assessments).

Consent will be re-sought if new information becomes available that affects the participant's consent in any way. This will be documented in a revision to the patient information sheet and the participant will be asked to sign an updated consent form. These will be approved by the ethics committee prior to use.

A copy of the approved consent form is available from the NCTU trial team.

7.6 Confidentiality

Any paper copies of personal trial data will be kept at the participating site or NCTU in a secure location with restricted access. Location of filing will be dependent on where trial data is returned to. Completion of personal trial data managed centrally will the returned to NCTU.

Following consent, identifiable data will be kept on the trial database to allow authorised members of the trial team to contact participants in order to arrange appointments and send out survey links, by email, for the 3, 6 and 12 month assessments, reminders, newsletters and to arrange couriers. Only authorised trial team members will have password access to this part of the database. This information will be securely destroyed twelve months after the end of the trial.

Confidentiality of participant's personal data is ensured by not collecting participants names on CRFs and limiting access to personal information held on the database at NCTU. At trial enrolment the participants will be issued a participant identification number, and this will be the primary identifier for the participant, with secondary identifiers of month and year of birth and initials.

The participant's consent form will carry their name and signature. These will be kept on a database (for example eConsent) or at trial site, with a copy uploaded to REDCap for monitoring purposes. This copy will be destroyed once checks are complete. Consent forms will not be kept with any additional participant data.

7.7 Declaration of Interests

The investigators named on the protocol have no financial or other competing interests that impact on their responsibilities towards the scientific value or potential publishing activities associated with the trial.

7.8 Indemnity

The NHS indemnity scheme will apply to the potential liability of the Sponsor for harm to participants arising from the management and conduct of the research.

7.9 Finance

EASE is fully funded by a NIHR HTA grant (reference NIHR152423). It is not expected that any further external funding will be sought.

7.10 Archiving

The Sponsor agrees to archive and/or arrange for secure storage of EASE trial materials and records for 25 years after the close of the trial unless otherwise advised by the NCTU. Sponsor retains responsibility for confirming when trial materials and records (including data) should be archived.

7.11 Access to Data

Requests for access to trial data will be considered, and approved in writing where appropriate, after formal application to the TMG. Considerations for approving access are documented in the TMG Terms of Reference.

7.12 Ancillary and Post-trial Care

There are no plans to offer trial treatment to individuals participating in this study after its conclusion.

7.13 Publication Policy

7.13.1 Trial Results

The results of the trial will be disseminated regardless of the direction of effect. An EASE Dissemination and Publication Plan will be drafted prior to the end of the trial, with input from LEAF, which will detail the methods and format for informing participants and the public of the results of the trial. We will closely follow the learnings from RECAP and FOCUS.(41-43) When they enrol, participants will be asked whether they (and their NOK) wish to be informed regarding the results of the trial and if participants wish, we will also ensure, if desired, their NOK are informed of the trial if they have died.

7.13.2 Authorship

Ownership of the data arising from the study resides with the trial team. The publication policy for EASE will be in line with rules of the International Committee of Medical Journal Editors with co-authorship granted, basing upon the following four criteria:

1. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
2. Drafting the work or revising it critically for important intellectual content; AND
3. Final approval of the version to be published; AND
4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

We recognise that successful delivery of EASE will be a vast, collaborative, time consuming effort involving the hard work, support and cooperation of a huge number of colleagues nationally and internationally including stroke health professionals, clinical and non-clinical academics, public partners, people living with emotionalism and their relatives, and administration colleagues. We aim in our publication policy for EASE to be as wholly inclusive as possible and we will strive to properly recognise and capture the contributions of all individuals involved. Following helpful advice from co-applicant colleagues experienced in collaboratively publishing large scale stroke clinical trials (e.g. 44), we will publish primary and key secondary outcome data arising from EASE under the EASE Trial Collaboration, and after that any further data arising will be published by named authors on behalf of EASE Trial Collaboration. This collaborative approach seems most democratic and per wording from the authors of FOCUS, AFFINITY and EFFECTS Trial protocols (45), will ensure that:

"the credit for the main results will be given, not to the central trial coordinators, but to all wholehearted collaborators in the study." (45 (p44))

Accordingly, early in trial development, we will convene a writing committee comprising experienced colleagues used to writing main papers for high impact medical journals which we would target at study end. Membership of the writing committee will be agreed by the TMG. Main papers arising from the trial will be published in the name of the EASE Trial Collaboration, with all members of the writing group listed for authorship at the end of the article and all members of the EASE Trial collaboration listed for authorship in the paper appendix. The TMG will decide on authorship with any difficulties being resolved by the TSC.

7.13.3 Reproducible Research

The trial will be registered on the International Standard Randomised Clinical Trials Number (ISRCTN) website granting public access to the trial outcomes. In addition, the clinical study protocol will be submitted for publication. Every effort will be made to grant access to the participant level dataset subject to approval.

7.14 Patient and Public Involvement

Patient and public involvement representatives will assist the EASE trial team in the design, management and undertaking of the study, and in the dissemination of trial results. Representatives will be consulted during the development of trial documents to ensure they are acceptable to participants with amendments made accordingly.

The EASE trial team will identify and appoint patient and public involvement representatives for each of the TMG and TSC. Their input will be used to guide the undertaking of the research as and where appropriate.

The results of the trial will be discussed with the representatives prior to submission of any formal reports.

8 Protocol Amendments

Protocol Version	Date	Summary of Changes
1.0	13.03.24	Initial release
1.1	21.05.24	As request for MHRA – addition of: - • Exclusion criteria - Current or know history of hyponatraemia and Women of Childbearing Potential (WOCBP) and not using a highly effective form of contraception. (Section 6.3.1.3 and other places as required.) • Assessment of participant safety, including: physical examination, vital signs, ECG and safety blood test (haemotology, biochemistry and clotting) when required, as clinically indicated at the criteria of the PI or sub-I. • Additional information on choice of antidepressant, dosage and duration / Risk benefit evaluation provided in section 5.1, Background and Rationale. • Section 6.4.6 –if pt becomes pregnant, advised to stop trial treatment immediately. Also see section 6.11.1.3 for procedure to follow if participant becomes pregnant. • Table updated in section 6.6. • Section 6.6.1 updated to include safety assessments, Pregnancy testing. • Section 6.9.3 update to unblinding process to record that this will be done via the study database. (local PIs and the CI will have special logins to allow unblinding. • Section 6.11, and other sections as required – updated to clarify that recording of all AE's and SAE's in participant notes will commence from signing the consent form, in both arms of the study, and SAE's will be recorded in the trial database. • Section 7.4 updated for clarity on amendment process.
1.2	05.08.24	Inclusion of Trial Registration number and date, CTA and NRES numbers. Anticipated date of first enrolment changed from June to October 2024. Addition of name of Norwich CTU Research Associate. Change of name of TSC Chair.

		Sponsors email for Safety reporting Section 8, updated. Typographical errors throughout.

9 References

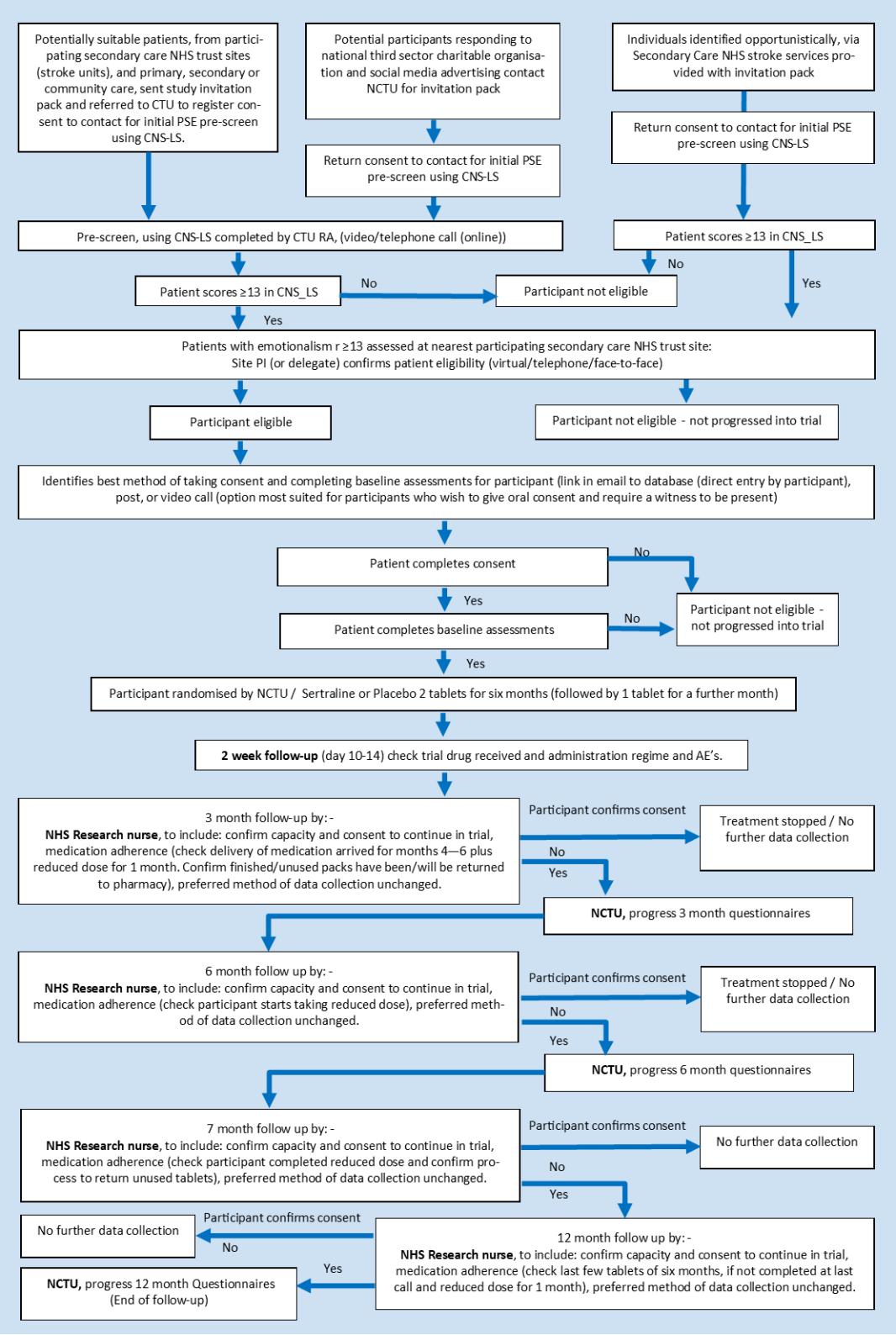
1. Chan AW, Tetzlaff JM, Altman DG et Al. SPIRIT 2013 Statement: Defining Protocol Items for Clinical Trials. *Ann Intern Med* 2013; 158:200-207.
2. Chan AW, Tetzlaff, Gotzsche et Al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013; 346: e7586.
3. House AO, Dennis M, Molyneux A, Warlow C, Hawton K. Emotionalism after stroke. Brit Med J. 1989; 298:991-994
4. Wang G, Teng F, Chen Y, et al. Clinical Features and Related Factors of Poststroke Pathological Laughing and Crying: A Case-Control Study. J Stroke Cerebrovasc Dis. 2016; 25:556-64.
5. Fitzgerald S, Gracey F, Broomfield NM, Trigg E. Predictors and correlates of emotionalism across acquired and progressive neurological conditions: A systematic review. Neuropsychological Rehabilitation 2022, 1-43, 2022. https://doi.org/10.1080/09602011.2022.2052326
6. Fitzgerald S, Gracey F & Broomfield, NM. Post-stroke emotionalism (PSE): a qualitative longitudinal study exploring individuals' experience with PSE. Disability and Rehabilitation, 2021; DOI: 10.1080/09638288.2021.2002439
7. McAleese N, Guzman A, O'Rourke SJ, Gillespie DC. Post-stroke emotionalism: a qualitative investigation. Disabil Rehabil. 2021; 43:192-200.
8. Cummings JL, Arciniegas DB, Brooks BR et al. Defining and diagnosing involuntary emotional expression disorder. CNS spectrums. 2006;11:1-11.
9. Gillespie DC, Cadden AP, Lees R, West RM, Broomfield NM. Prevalence of pseudobulbar affect following stroke: A systematic review and meta-analysis. J Stroke Cerebrovasc Dis. 2016; 25:688-694.
10. Broomfield NM, West R, Barber M, Quinn TJ, Gillespie DC et al. TEARS: a longitudinal investigation of the prevalence, psychological associations and trajectory of poststroke emotionalism. JNNP 2022; Apr 28. DOI: 10.1136/jnnp-2022-329042
11. Gillespie D, Caddens A, Broomfield NM. Non-pharmacological interventions for post-stroke emotionalism within in-patient settings. Topics in Stroke Rehabilitation. 2020; 27:15-24.
12. National Clinical Guideline for Stroke. Fifth Edition, 2016. Royal College of Physicians.
13. Management of patients with stroke: A national clinical guideline. 2010. Scottish Intercollegiate Guidelines Network 118.
14. Allida S, House A, Hackett ML. Pharmaceutical interventions for emotionalism after stroke. Cochrane Database of Systematic Reviews 2022, Issue 11. Art. No.: CD003690. doi: 10.1002/14651858.CD003690.pub5
15. Burns A, Russell E, Stratton-Powell H et al. Sertraline in stroke-associated lability of mood. International Journal of Geriatric Psychiatry. 1999;14:681-5.
16. Murray V, von Arbin M, Bartfai A, et al. Double-blind comparison of Sertraline and placebo in stroke patients with minor depression and less severe major depression. Journal of Clinical Psychiatry 2005;66:708-16.
17. National Institute for Health and Care Excellence. British National Formulary: Sertraline https://bnf.nice.org.uk/drug/sertraline.html#cautions [Accessed 23/06/22].
18. National Institute for Health and Care Excellence. Clinical Knowledge Summaries: Depression https://cks.nice.org.uk/topics/depression/management/new-or-initial-management/ [Accessed 20/11/20].
19. Eccles S, House AO, Knapp P. Psychological adjustment and self-reported coping in stroke survivors with and without emotionalism. J Neurol Neurosurg Psych. 1999; 67:125-126

20. Dennis M, Forbes J, Graham C, Hackett ML, Hankey GJ…Mead GE. Effects of fluoxetine on functional outcomes after acute stroke (FOCUS): a pragmatic, double-blind, randomised, controlled trial. Lancet 2019; 393:265-74.
21. Broomfield NM, West R, House A, et al. Psychometric evaluation of a newly developed measure of emotionalism after stroke (TEARS-Q). Clinical Rehabilitation. 2021;35:894-903. doi:10.1177/0269215520981727
22. Electronic Medicines Compendium, https://www.medicines.org.uk/emc/product/11992/smpc#CONTRAINDICATIONS. Accessed February 9th 2023.
23. Tang, W.K., Chan, S.S.M., Chiu, H.F.K. *et al.* Emotional incontinence in Chinese stroke patients. *J Neurol* **251**, 865–869 (2004). https://doi.org/10.1007/s00415-004-0450-z
24. Moore SR, Gresham LS, Bromberg MB, Kasarkis EJ, Smith RA. A self-report measure of affective lability. J Neurol Neurosurg Psychiatry. 1997;63:89-93.
25. Smith RA, Berg JE, Pope LE & Thisted RA. Measuring pseudobulbar affect in ALS. Amyotrophic Lateral Sclerosis and Other Motor Neuron Disorders. 2009;5:99-102, DOI: 10.1080/17434470410020058
26. Broomfield NM, West R, House A, et al. Psychometric evaluation of a newly developed measure of emotionalism after stroke (TEARS-Q). Clinical Rehabilitation. 2021;35:894-903. doi:10.1177/0269215520981727
27. Broomfield, N. M., West, R., Barber, M., Gillespie, D. C., House, A., & Walters, M. (2021). Practical guidance on use of TEARS-Q to diagnose post-stroke emotionalism. *Clinical Rehabilitation*, *35*(12), 1768-1772. https://doi.org/10.1177/02692155211024801
28. Williams LS, Brizendine EJ, Plue LD, et al. Performance of the PHQ-9 as a Screening Tool for Depression After Stroke. Stroke. 2005; 36:635–638.
29. Turner A, Hambridge J, White J, Carter G, Clover K, Nelson L, 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(4):1000–1005.
30. Meader N, Moe-Byrne T, Llewellyn A, Mitchell A. Screening for poststroke major depression: a meta-analysis of diagnostic validity studies. *J Neurol Neurosurg Psychiatry.* 2014;85:198–206.
31. Hackett ML, Pickles K. Part I: frequency of depression after stroke: an updated systematic review and meta-analysis of observational studies. Int J Stroke. 2014 Dec;9(8):1017-25. doi: 10.1111/ijs.12357. Epub 2014 Aug 12. PMID: 25117911.
32. Vyas MV, Wang JZ, Gao MM, Hackam DG. Association between stroke and subsequent risk of suicide. A systematic review and meta analysis. Stroke. 2021;52:1460–1464
33. Spitzer RL, Williams JB, Kroenke K. Test-review-patient-health-questionnaire-9 (PHQ-9). Rehabil Couns Bull. 2014;57(4):246–8.
34. Measuring Health and Disability: Manual for Who Disability Assessment Schedule Whodas 2.0. Geneva: World Health Organization, 2010.
35. Schlote A, Richter M, Wunderlich MT, Poppendick U, Möller C, Schwelm K, Wallesch CW. WHODAS II with people after stroke and their relatives. Disabil Rehabil. 2009;31:855-64. doi: 10.1080/09638280802355262.
36. 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; 20:1727-1736.
37. Coast J, Flynn TN, Natarajan L, er al. Valuing the ICECAP capability index for older people. Soc Sci Med. 2008; 67:874-82

38. Thorn JC, Davies CF, Brookes ST, Noble SM, Dritsaki M, Gray E, Hughes DA, Mihaylova B, Petrou S, Ridyard C, Sach T, Wilson ECF, Wordsworth S, Hollingworth W. Content of Health Economics Analysis Plans (HEAPs) for Trial-Based Economic Evaluations: Expert Delphi Consensus Survey. Value in Health 2021; 24: 539-547.
39. NICE. Guide to the methods of technology appraisal. *Pharmacoeconomics*. 2013;26(9):1-93. doi:10.2165/00019053-200826090-00002.
40. https://www.nhs.uk/medicines/sertraline/pregnancy-breastfeeding-and-fertility-while-taking-sertraline/#:~:text=Sertraline%20and%20pregnancy,sertraline%20have%20a%20normal%20heart.
41. Bruhn, H., Cowan, EJ., Campbell, M.K. et al. Providing trial results to participants in phase III pragmatic effectiveness RCTs: a scoping review. Trials 22, 361 (2021).
42. Raza MZ, Bruhn H, Gillies K. Dissemination of trial results to participants in phase III pragmatic clinical trials: an audit of trial investigators intentions BMJ Open 2020;10:e035730. doi: 10.1136/bmjopen-2019-035730
43. Mead G, Dennis M. Feasibility of reporting results of large randomised controlled trials to participants: experience from the Fluoxetine Or Control Under Supervision (FOCUS) trial. BMJ Open 2020;10:e040492. doi:10.1136/ bmjopen-2020-040492
44. Focus Trial Collaboration. Lancet 2019; 393: 265–74. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)32823-X/fulltext#%20)
45. Trial protocol for FOCUS – Fluoxetine or control, under supervision (2019). University of Edinburgh. https://www.ed.ac.uk/sites/default/files/atoms/files/focus_trial_full_protocol.pdf

10 Appendices

Appendix 1 Simplified EASE Trial flow chart



11 Principal Investigator compliance statement

Principal Investigator agreement to confirm adherence to the protocol, the UK Policy Framework for Health and Social Care Research and GCP.

EASE: Evaluating Antidepressants for emotionaliSm after stroke

I, [Insert investigator name], confirm:

1. that I am willing and able to comply with the requirements of the EASE trial;
2. that I regularly treat the target population and believe the site has the potential for recruiting the required number of suitable subjects within the agreed recruitment period (figures included in the trial recruitment plan);
3. that I have sufficient time to properly conduct and complete the trial within the agreed trial period;
4. that I have supplied an up-to-date curriculum vitae, GCP certificate and/or other relevant documentation requested by NCTU, to demonstrate that I am qualified by education, training and experience to assume responsibility for the proper conduct of the trial at this study site;
5. that I am thoroughly familiar with the appropriate use of the investigational products as described in the protocol, in the current Investigator Brochure (if applicable), in the product information and in other information sources provided by NCTU;
6. that I have an adequate number of qualified staff and adequate facilities available for the foreseen duration of the trial to conduct the trial properly and safely;
7. that I will maintain a signature and delegation log of appropriately qualified persons to whom I have delegated trial related duties which includes confirmation that each member of staff is appropriately trained (including GCP) for the roles allocated to them, and will ensure this is made available to NCTU in a timely manner on request;
8. a research CV for each member of staff on the delegation log will be stored in the site file according to site policy;
9. that I take responsibility for ensuring all staff delegated trial related duties are adequately informed about the protocol, the investigational product and their trial related duties and functions, and that I will continue to take responsibility for regularly updating them as new information becomes available;
10. that the [insert name of site] site has sufficient resources to manage data generated by the trial to allow prompt and complete data and query return to NCTU;
11. that I am aware of, and will comply with, the principles of GCP as given in the EASE protocol compliance statement and the applicable regulatory requirements, and that a record of my GCP training is accessible and described on my current curriculum vitae;
12. that a record of GCP training is accessible for all staff delegated responsibilities in relation to the EASE trial and who are named and approved on the site signature and delegation of responsibilities log and that individual training evidence will be saved in the site file, for all staff, according to trust policies;

13. that I will permit routine and for-cause monitoring and auditing by NCTU, and inspection by the appropriate regulatory authorities, including the provision of direct access to source data and other participant notes and files as required; and
14. that I agree to archive and/or arrange for secure storage of EASE trial materials and records for a minimum of 25 years after the close of the trial unless otherwise advised by the NCTU.

Agreement: Principal Investigator

Name	[insert name]
Signature	[signature]
Date	[insert date]

(Please return a signed copy of this agreement (only pages 65 and 66) to the EASE Trial Manager at NCTU, at easetrial@uea.ac.uk)