Trials

STUDY PROTOCOL

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The clinical and cost-effectiveness of sertraline in preventing depression in adults following a traumatic brain injury (STOP-D): study protocol for a multi-centre randomised controlled trial

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Abstract

Background Traumatic brain injury (TBI) is a common presentation in emergency departments worldwide. Approximately 1.4 million adults present with TBI in England and Wales annually. Post-TBI depression (PTD) is a common neuropsychiatric consequence, affecting up to 50% of patients within two years, and is associated with adverse functional outcomes. PTD remains underdiagnosed and undertreated. Sertraline, a selective serotonin reuptake inhibitor (SSRI), has shown potential in reducing PTD incidence, yet evidence of its effectiveness in preventing depression from adequately powered trials is lacking. This randomised controlled trial aims to compare the clinical and cost-effectiveness of sertraline in reducing the risk of PTD in adults compared to usual care.

Methods The design is a multi-centre, double-blind, placebo-controlled, randomised controlled trial (RCT) aiming to recruit 514 participants. Eligible adults (aged ≥ 18 years) with possible, mild or moderate-severe TBI within eight weeks of injury and without current major depressive disorder (MDD) are randomly assigned to receive sertraline (100 mg daily) or placebo for 12 months. The primary outcome is depressive symptom severity at 12 months, measured using the Patient Health Questionnaire-9. Secondary outcomes include incidence rates of major depressive disorder, psychiatric comorbidities, cognitive impairment, substance use, carer burden, productivity and cost-effectiveness at 6, 12 and 18 months.

Discussion This is the first adequately powered RCT to investigate sertraline as a preventive intervention for PTD. Findings will help inform whether prescribing an SSRI soon after a TBI may reduce the risk of depression and improve functional outcomes.

Trial registration This study is registered in the European Union Drug Regulating Authorities Clinical Trials Database (EudraCT no. 2022–000072-18, date: 7 January 2022) and the ISRCTN – The UK's Clinical Study Registry (ISRCTN no. 17518945, date: 23 December 2022, https://www.isrctn.com/ISRCTN17518945).

Keywords Traumatic brain injury, Depression, Prevention, Antidepressant, Sertraline

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Administrative information

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Introduction

Background and rationale {6a}

Traumatic brain injury (TBI) is one of the most common presentations in accident and emergency (A&E) departments worldwide [1]. In England and Wales, around 1.4 million adults per year present with a TBI and approximately 80% of TBI cases are of mild severity [2, 3].

The consequences of TBI are multi-dimensional [1, 4, 5]. Post-TBI depression (PTD) is the most common psychiatric consequence. The core features of depression (in this proposal refers to depressive symptoms and depressive disorders) are pervasive low mood and loss of pleasure in everyday activities lasting for at least 2 weeks [6].

There are consistent observations that around half of patients either develop or have PTD in the first 12–24 months following their TBI [7], with the range varying from 6 to 77% [8] which is between 5 and 10 times higher than the prevalence of depression in the general population. There is marked heterogeneity in study populations (young people, older adults, military personnel, severity and mechanism of TBI, health care setting, hospital admission status), the duration of follow up, attrition bias and lack of distinction between prevalence and incidence parameters. The risk for PTD emerges soon after the injury; a prospective cohort of inpatients with TBI ($n = 827$) observed a prevalence rate of 56% with caseness for depression (defined using the Hospital Anxiety and Depression Scale Depression score > 8) at 3 months [9]. In a secondary analysis of a medical insurance dataset of adults with and without TBI, the incidence of depression was almost double (adjusted hazard ratio for PTD of 1.83 (95% confidence interval 1.79 to 1.86)) [10].

The course of PTD is chronic with the majority of patients remaining depressed 2 years post-TBI and beyond [11], with a cumulative prevalence rate of 50% over 5 years [12, 13]. In a well-conducted systematic

review and meta-analysis, those with concussion and/or mild TBI compared to those without had a significant twofold increased risk of suicide, and in non-military samples, the relative risk for suicidal ideation or suicide attempt was 2.36 [14, 15]). The relative prevalence rates for other common psychiatric comorbidities, in particular anxiety disorders, substance use disorders and aggression are also increased [16–18].

The strongest predictor for PTD is pre-existing psychiatric morbidity [19]. Those who become unemployed, have early onset of post-TBI neuropsychiatric symptoms, are of ethnic minority and low socioeconomic status and of older age are also at increased risk for PTD [19]. Patients with normal neuroimaging and mild TBI are at higher risk for PTD than those with abnormal neuroimaging [9, 20]. Yet depression is not routinely screened for at TBI presentation [2], and rarely treated optimally based on national guidelines [7].

Serotonin is an indolamine neurotransmitter with cell bodies located primarily in the caudal raphe nuclei in the brainstem. Serotonin modulates mood, appetite and sleep as well as more complex functions such as cognition, reward, learning and memory. Serotonin must be synthesized in the brain as it cannot cross the blood–brain barrier. SSRIs are a class of antidepressants that inhibit the reuptake of serotonin by monoamine transporters in the presynaptic cell, allowing for increased availability of serotonin in the synaptic cleft, which in turn increases stimulation of serotonergic postsynaptic receptors. They are effective in the treatment of disorders on the depression spectrum through the modulation of neuronal cell survival and neuroplasticity. The theoretical application of selective serotonin reuptake inhibitors (SSRIs) to PTD is that they may have a role in neuronal recovery following TBI, which may have led to disruption of the production and metabolism of serotonin. There is good evidence from meta-analyses of randomised control trials (RCTs) conducted in people with stroke that early initiation of SSRIs, preferably for at least 12 months, is associated with a significant reduction by around 30% in the risk of post stroke depression [21].

There have already been several systemic reviews of RCTs of the effectiveness of pharmacological and non-pharmacological interventions for PTD [22–25]. Considering its extraordinarily high rates and adverse outcomes, the primary prevention of PTD has received even less attention than treatment of PTD. There are only 2 RCTs published to date. One RCT of 94 patients hospitalised with mild, moderate or severe TBI and no PTD found that sertraline (a licensed antidepressant) 100 mg once a day (od) for 24 weeks reduced the incidence rate of major depressive disorder (MDD) at 6 months and was well tolerated by patients [26]. A second RCT of 99 outpatients with moderate to severe TBI and no PTD recruited within 3 weeks of injury found that of those treated with sertraline 50 mg od for 3 months, 0% had a Hamilton Depression Rating Scale (HDRS) score > 6 at 3 months compared to 10% of the placebo group, but this difference disappeared at 12 months [27]. This study had a shorter treatment duration and a lower dose of sertraline compared to the first RCT. Both RCTs were single centre sites and were based in the United States, where usual care differs from the National Health Service (NHS). These preliminary findings support the case for early initiation of sertraline as a prophylaxis for PTD and justification for this full-scale efficacy study.

Objectives {7}

The overall objective is to identify whether sertraline 100 mg od is more effective, cost effective and acceptable (as assessed by adherence) in reducing the risk of PTD over 18 months compared to placebo.

Primary objective: To test the primary hypothesis that in patients with a traumatic brain injury, sertraline 100 mg od prescribed for 12 months following presentation is more effective than placebo in reducing depressive symptoms.

Secondary objectives:

1. To test the hypothesis that in patients with a traumatic brain injury sertraline 100 mg od prescribed for 12 months following presentation is more effective than placebo in reducing the incident rate of MDD by 12 months from baseline.
2. To test the hypotheses that sertraline 100 mg od prescribed for 12 months is more effective than placebo in people with post-TBI over 18 months in:
    i. Reducing depressive symptoms
    ii. Reducing incident rate of MDD
    iii. Reducing psychiatric symptoms of anxiety disorder, cognitive impairment and post-traumatic stress disorder
    iv. Reducing alcohol and substance use
    v. Reducing carer burden
    vi. Reducing aggressive behaviours
    vii. Improving productivity
    viii. Improving cost effectiveness
    ix. Having improved patient and carer reported outcomes.
3. Assess whether sertraline is associated with greater incidence rate of adverse events (AEs) than placebo.
4. Assess the proportion who give consent to contact (CtC) for future study, and consent to collect data

from medical records and hospital episode statistics (HES) for 10 years from recruitment.
5. To collect the blood and saliva for future biomarker profiling.
6. Describe the patient and carer experience of the antidepressant in terms of a) acceptability b) changes in their mental health and their social functioning.

Trial design {8}

This is a multi-centre, two-arm, double-blind (patient and researcher), placebo-controlled, parallel RCT, with Stage 1 (internal pilot) to test recruitment and randomisation followed by Stage 2 (substantive study) if the progression criteria are met. Randomisation will be stratified by severity of TBI (possible versus mild versus moderate/severe) and by site. Due to post-Covid-19 delays in the set-up, the pilot was extended by 18 months. Despite this extension, not all sites completed the set-up process, and the rate of recruitment was insufficient to meet the stop–go criteria.

Methods: participants, interventions and outcomes

Study setting {9}

The A&E departments and trauma wards of 10 Major Trauma Centres (MTCs) across England will be the sampling frame [28]. The strengths of this collaboration include the following: it constitutes a third of all MTCs in England and yet collectively captures 40–50% of all TBIs; it is representative of the socioeconomic, ethnic, cultural, and geographical diversity across England; it captures the heterogeneity in the social settings and mechanisms by which TBI occurs; many of the local authorities within these MTCs have the greatest markers of health inequalities, such as Blackpool, which has the lowest male life expectancy at birth of 74 years [29]. The list of study sites can be obtained from the trial's entry in the ISRCTN Registry.

Eligibility criteria {10}

Eligibility checks will be performed by the PI or medical doctor delegated to complete the informed consent process.

Inclusion criteria

1. Adults aged 18 years and above.
2. UK residents.
3a. Participants consented before implementation of protocol version 4.1 (24/04/2024): Mild or moderate-severe TBI that occurred less than 4 weeks before time of consent defined as probable and definite TBIs by the Mayo Classification System (MYS) [30]. MYS for TBI severity will be used as it is a gold standard for research. MYS categorises all available positive evidence into moderate-severe (definite), mild (probable) and symptomatic (possible).
3b. Participants consented on or after implementation of protocol version 4.1 (24/04/2024): Possible, mild or moderate-severe TBI that occurred less than 8 weeks before time of consent defined as possible, probable, and definite TBIs by the Mayo Classification System (MYS) [30].
4. No current MDD. Modified Structured Clinical Interview (SCID) [31], a brief structured clinical interview, will be used to exclude those with Diagnostic and Statistical Manual-5 (DSM-5) MDD [6]. Self-report questionnaires cannot easily be used to diagnose MDD in TBI because patients have a much wider range of neuropsychiatric symptoms as false positives such as irritability, anger, aggression, rumination, self-criticism, and suicidality, apathy, anxiety and emotional dysregulation, and emotional lability. Clinical judgement via a clinical interview conducted by a trained clinician is required to diagnose MDD in this context [8].

Exclusion criteria

1. Participants consented before implementation of protocol version 4.1 (24/04/2024): Possible TBI according to the MYS classification.
2. Concurrent antidepressant medication at British National Formulary (BNF) recommended therapeutic doses for treatment of depression [32]
3. Other causes of acquired brain injury such as stroke.
4a. Participants consented before implementation of protocol version 4.1 (24/04/2024): Known psychotic or bipolar disorders, known dementia, actively suicidal, other acute or chronic neurological conditions except post-traumatic epilepsy, terminal or advanced medical illness such as end-stage kidney failure, heart failure, severe hepatic impairment.
4b. Participants consented on or after implementation of protocol version 4.1 (24/04/2024): known psychotic or bipolar disorders (except for mild cognitive impairment), known dementia (except for mild), actively suicidal, other acute or chronic neurological conditions except post-traumatic epilepsy, terminal or advanced medical illness such as end-stage kidney failure, heart failure, severe hepatic impairment.
5. Pregnant or planning pregnancy.
6. Women of childbearing age unless acceptable effective methods of contraception are being used.

7. Lactating.
8. Medical causes of depression such as pituitary failure.
9. Known allergy to sertraline.
10a. Participants consented before implementation of protocol version 4.1 (24/04/2024): Current hyponatraemia (sodium less than 135 mmol/L based on discussion with hospital endocrinologist).
10b. Participants consented on or after implementation of protocol version 4.1 (24/04/2024): Current hyponatraemia (sodium < 135 mmol/L based on discussion with the local PI or their treating physician to confirm it is safe for the patient to be enrolled).
11. Taking medications absolutely contraindicated with sertraline as stated in the Summary of Product Characteristics (SmPC).
12. Participating in another Clinical Trial of an Investigational Medicinal Product (CTIMP) study or participated < = 30 days from consent.
13. Participants will be excluded if they are not able to complete self-administered questionnaires in English. (English proficiency in comatose patients will be assessed through next of kin and to the best of the ability of the clinician with the available information. Participants who come out of a coma will be reassessed for eligibility regarding English proficiency criterion. If non-proficient in English, they will be withdrawn).

Who will take informed consent? {26a}

Informed consent will be obtained by the Principal Investigator (PI) or a delegated medical doctor. We will invite people who have capacity to consent to research plus people who do not. Capacity to consent to participate in this study will be assessed using the principles of the Mental Capacity Act 2005 [33].

In potential participants lacking capacity, we will wait for two weeks to wait for capacity to return. If this does not occur, the medical doctor who is taking consent will seek a personal legal representative. A personal legal representative is defined as a person who is engaged in caring for the participant (not professionally or for payment) or is interested in his/her welfare and is prepared to give consent. If towards the end of the 4th week we are not able to identify a personal legal representative, we advocate enrolment with written agreement from an independent clinician who is defined here as the professional legal representative (an Independent Healthcare Professional (IHP) who is not connected with the conduct of the trial), typically the patient's consultant in charge. Participants' capacity will be regularly monitored so that participants who regain capacity are invited to give informed consent to continue in the trial.

We will be involving adult carers in this study. A carer is anyone who looks after a family member, partner or friend who needs help because of their illness, frailty, disability, a mental health problem or an addiction and cannot cope without their support. The data collected from carers will be used to assess secondary outcomes. Further information is available in the study protocol which is available upon request.

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

Consent for optional use of samples for future research (including genetic research) subject to ethical approval is sought and recorded on the Informed Consent Form.

Interventions

Explanation for the choice of comparators {6b}

Currently in the UK, no therapies to reduce the risk of PTD are offered, as there is a lack of high-quality evidence for this indication. Given that no other effective medications or treatments are available, a placebo tablet, an inactive treatment, is the most appropriate comparator in order to control for the placebo effect (a temporary positive psychological response when we think we are receiving a treatment that will help us).

Intervention description {11a}

Investigational Medicinal Product (IMP)

The IMP and placebo will be manufactured, packaged and labelled by The Royal Free Hospital Pharmacy Manufacturing Unit and then transferred to the pharmacy at each of the MTCs. A Qualified Person (QP) release certificate will be provided by The Royal Free Hospital Pharmacy Manufacturing Unit. Sertraline is licensed and has a marketing authorisation (MA) in the UK, but it will be repackaged and relabelled for the trial. The Royal Free Hospital Pharmacy Manufacturing Unit will procure active Milpharm Limited branded (PL 16363/0584) 50 mg sertraline tablets and provide a matching placebo tablet, both identical in colour, shape, and size—white capsule-shaped, film-coated tablets debossed with ' A' on one side and a score line in between ' 8' and '1' on the other side. The tablets will be packaged in high-density polyethylene bottles with tamper-evident closure. Labelling will be fully Annex 13 compliant. The MTC pharmacies will be unblinded. The Royal Free Hospital Pharmacy Manufacturing Unit will act as a central pharmacy and distribute to the intended sites.

Group 1 Treatment as usual (TAU) for the TBI: routine clinical management and follow-up as per local MTC guidance for the management of TBI plus placebo for 12

months. The placebo regimen will be prescribed exactly as sertraline. TAU will consist of the local MTC pathway for TBI.

Group 2 TAU plus sertraline. We have selected sertraline because of the following: it has the strongest evidence for effectiveness of treating depression; it is well tolerated in the elderly; it has the lowest epileptogenic risk [34].

Dosing regimen

Participants will be prescribed sertraline 50 mg or placebo as an oral dose od for two weeks then increased to 100 mg or placebo as od for the next 46 weeks, consistent with evidence on optimal dosages for efficacy and acceptability [35]. This duration was chosen as literature suggests that it can take up to 12 months for MDD to emerge [7]. This will be followed by a four-week discontinuation protocol to minimise potential withdrawal symptoms: at 48 weeks, the dose will be reduced to sertraline 50 mg or placebo as od for 2 weeks and at 50 weeks, the dose will be reduced to 25 mg od for two weeks and then stopped. The IMP will be dispensed after randomisation at specified time intervals.

Criteria for discontinuing or modifying allocated interventions {11b}

Site PIs will decide if it is necessary to stop treatment for an individual participant if they develop any of the following:

1. Active suicidal thoughts. Specifically, any participant who scores more than 0 on item 9 (suicidal thoughts) of the Patient Health Questionnaire-9 (PHQ-9) [36] at any of the assessment points in the study will undergo a clinical assessment of suicide risk by a study doctor. If such a participant is assessed as having active suicidal thoughts according to clinical assessment, the site study psychiatrist will make a decision as to whether to stop the trial medication and escalate psychiatric care.
2. Development of depression. The PIs will inform the participant's General Practitioner for the follow-up and then decide on withdrawal/unblinding based on severity and clinical case-by-case judgement.
3. Pregnancy
4. Any Serious Adverse Event (SAE), Serious Adverse Reaction (SAR) or Unexpected Serious Adverse Reaction (SUSAR), which, in the view of the investigators, necessitates treatment cessation.
5. If the participant does not collect the First prescription after 4 attempts to dispense up to 4 weeks from time of TBI.
6. If the sodium is less than 135 mmol/L the measure will be repeated at the timepoints specified and the patient will be withdrawn if clinically indicated and by the judgement of PI.

If a patient wishes to withdraw from taking the study drug, this will be discontinued. We will follow reduction of the IMP as described previously.

Strategies to improve adherence to interventions {11c}

To minimize attrition rates, we will have patient reviews to match the dispensing of the IMP, which aims to match usual care for the management of depression in primary care. In addition, we will seek permission during the informed consent process to be able to contact the next of kin and one other close contact if the patient is not contactable. Participants' compliance will be monitored by filling in the patient diaries. We will also check compliance during the sodium measurement visits with the participants at weeks 2 and 4 and 3 months. We will check adherence at the clinical visits 6, 9 and 12 months.

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

For management of concomitant therapies, please refer to the SmPC. A complete listing of all concomitant medication received during the treatment phase will be recorded in the source data of the trial and eCRF (electronic case report form database).

Provisions for post-trial care {30}

During the study, the Clinical Negligence Scheme for Trusts (CNST) provides indemnity that covers clinical negligence and harm caused at each of the MTC which are set in NHS Trusts. For PIs employed by a university, the university insurance applies. Participants will return to their usual clinical care after completing trial follow-up.

Outcomes {12}

Primary endpoint by 12 months:

1) Depressive symptoms as measured by PHQ-9 [36] score.

Secondary endpoints at:
6 and 18 months:

1) Depressive symptoms as measured by PHQ-9 [36] score,

12 and 18 months:

1) DSM-5 major depressive disorder [6] as measured by the modified SCID [31]
2) Anxiety symptoms as measured by Generalised Anxiety Disorder-7 (GAD-7) [37]
3) Cognitive assessment as measured by Montreal Cognitive Assessment (MOCA) [38]
4) Post-traumatic symptoms as measured by Post-Traumatic Stress Disorder Checklist (PCL-5) [39]
5) Alcohol intake as measured by Alcohol Use Disorders Identification Test (AUDIT) [40]
6) Substance use as measured by Drug Abuse Screening Test-10 (DAST-10) [41]
7) Care burden of neuropsychiatric symptoms as measured by the Neuropsychiatric Inventory Questionnaire (NPI-Q) (only measured in participants with a carer) [42]
8) EQ-5D-5L [43]
9) Adult Service Use Schedule (AD-SUS) [44]
10) Blood and saliva will be collected and stored within a protocol to be established pending further funding. Biomarkers (optional) analysed as part of this trial will likely include a range of inflammatory and other markers to identify those most at risk of long-term problems after TBI.
11) Aggression as measured by the Modified Overt Aggression Scale (MOAS) [45].

Participant timeline {13}

The scheduled times for enrolment, assessments, visits and IMP dose alterations are represented in Fig. 1 Schedule of Events.

Sample size {14}

At 12 months, we estimate a 50% incidence rate of MDD in the control group. For instance, in one cohort of patients hospitalized for TBI, 53% met caseness for MDD at any one point during the first year after TBI [7]. Therefore, assuming a 50:50 split of scores of PHQ 9 > =10 (caseness) and PHQ-9 = 10 and PHQ-9 < 10 respectively with a total mean PHQ-9 score of 5.0, this minimal clinically important difference (MCID) of 5 points, 72 with an SD at endpoint of 15, represents a standardised between-group effect size of 0.33.

For 90% power with 5% significance based on a *t*-test, this requires 386 participants in the analysis set and 514 participants to be recruited at baseline, allowing for a 25% attrition rate. This sample size is also sufficient to perform a *t*-test for between-group effect size in the secondary psychiatric outcomes (MCID for GAD-7 [46] estimated at around 4 points).

This sample size is also sufficient to detect a 33% relative reduction in the incidence rate of DSM-5 MDD in the sertraline arm (0.33) compared to the control arm (0.5), which would require 374 patients in the analysis set based on a Fisher's exact test. The independent Data Monitoring and Ethics Committee (DMEC) will monitor the outcome rate in the control group during the study and implications for the sample size calculation if the rate is significantly lower than 50%.

In practice, by including all timepoints in the analysis models (see Statistical Analysis) and including baseline stratification variables, we will gain power for an effect size of 0.33, have 90% power for a smaller effect size or protect power if some of the underlying assumptions do not hold.

Recruitment {15}

We conducted an audit of presentation rates for any TBI in A&E and trauma wards from which we derived an estimate of presentation rates for probable to definite TBI, and from which we derived estimates of the number of patients admitted for at least 1 night to each MTC. We used this information to estimate the size of our study population. Each MTC will screen patients attending A&E and admitted to the wards for potential participants. The initial planned recruitment period is 12 months, with a possible extension to 15 months.

Assignment of interventions: allocation

Sequence generation {16a}

Randomisation of participants will be conducted by an online system hosted by the King's Clinical Trials Unit (K-CTU), using computer-generated blocks of random sizes. The sample will be stratified by severity into three categories of TBI (possible versus mild versus moderate-severe) and by MTC location, to minimise disproportionate distribution by chance.

Concealment mechanism {16b}

The random allocation will be generated by the central randomisation system and will be revealed to the pharmacist only.

Implementation {16c}

Randomisation services will be provided by the K-CTU. A Patient Identification Number (PIN) will be generated by registering the patient on the MACRO eCRF system (InferMed Macro) after consent has been signed. Authorised site staff will be allocated a username and password for the MACRO eCRF system and the randomisation system. Delegated site staff will use the randomisation system following informed consent and confirmation of eligibility.

Month (+/- 1 week)		**0**		**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**		**11**		**12**	**13**	**14**	**15**	**16**	**17**	**18**
Week (+/- 3 days)	**-8/0**	**0**	**2**	**4**	**6**	**8**										**48**	**50**	**52**						
Patient consent to contact procedures	x																							
Informed consent		x																						
Inclusion/exclusion criteria		x																						
Randomisation		x																						
Sociodemographic data (age, gender, self-report ethnicity, marital status, socioeconomic status, occupation; Index of Multiple Deprivation; educational attainment)		x																						
Glasgow Coma Scale (GCS)		x																						
Rehab Complexity Scale (RCS)		x																						
Current TBI, cause, severity (TARN and MYS)		x																						
Past history (medical, psychiatric and TBI) incl. Imaging and current medications		x																						
Alcohol Use Disorders Identification Test (AUDIT)		x								x							x							x
Drug Abuse Screening Test (DAST-10)		x								x							x							x
Patient Health Questionnaire (PHQ-9)		x	x	x			x			x							x							x
Depression Intensity Scale Circles (DISCs)		x	x	x			x			x							x							x
Glasgow Outcome Scale (GOS)		x								x							x							x
The Structured Clinical Interview for DSM-5 (SCID)		x								x							x							x
Generalised Anxiety Disorder (GAD-7)		x								x							x							x
Modified Overt Aggression Scale (MOAS)		x								x							x							x
Montreal Cognitive Assessment (MOCA)		x								x							x							x
Post-traumatic Stress Disorder Checklist (PCL-5)		x								x							x							x
Neuropsychiatric Inventory Questionnaire (NPI-Q) (carer)		x								x							x							x
EQ-5D-5L		x								x							x							x
Physical Symptoms/Adverse Effects check			x	x	x	x	x			x							x							x
Adult Service Use Schedule (AD-SUS)		x								x							x							x
Duration of PTA if present using routine clinical data [1]		x					x																	
Blood test for: sodium levels[2]		x	x	x			x																	
Serum for freezing for biomarkers (optional)		x	x	x			x			x							x							x
Saliva collection for markers of TBI injury (optional)		x	x	x			x			x							x							x
Medication dispensing (IMP)		x					x			x			x											
Medication review			x	x			x			x			x			x	x							
Recducing sertraline from 100 to 50 mg																x								
Reducing sertraline from 50 to 25 mg																	x							
STOP IMP/placebo																		x						
Adverse events			x	x	x	x	x			x			x				x	x						x

Fig. 1 Schedule of events

Assignment of interventions: Blinding

Who will be blinded {17a}

Table 1 details information withheld from members of the trial team. Group-level summary measures will only ever be seen by the trial statistician undertaking analysis and providing Data Monitoring Committee (DMC) reports.

Procedure for unblinding if needed {17b}

The trial code will only be broken for valid medical or safety reasons, e.g. in the case of an SAE where it is necessary for the investigator or treating health care professional to know which treatment the patient is receiving before the participant can be treated. Twenty-four-hour Emergency Code Break and Medical Information will be provided by Emergency Scientific and Medical Services. Each randomised participant will be provided with a card detailing code break telephone numbers and emergency contact details. Participants will be requested to carry this card with them at all times whilst participating in the trial.

Data collection and management

Plans for assessment and collection of outcomes {18a}

Informed consent and confirmation of eligibility will be obtained by the site PI or a medical doctor who has been delegated to perform this duty by the PI. Baseline and subsequent assessments will be conducted by the PI, delegated doctors and trained members of the research team. Data will be collected on the paper STOP-D Data Collection Schedule and stored securely at the local site, and the data input to the eCRF.

Demographics, medical and psychiatric history, current medications and clinical details of the TBI will be collected by self-report and from the medical notes. Questionnaires screening for psychiatric disorders will be administered (PHQ-9 [36], Depression Intensity Scale Circles [47], GAD-7 [37], PCL-5 [39], AUDIT [40], DAST-10 [41], MOAS [45]) and the presence of MDD assessed using the SCID. Cognitive impairment will be assessed by administration of the MOCA [38]. Health-related quality of life will be assessed by the self-report EQ-5D-5L [44] and service use by the self-report AD-SUS [44]. Where the participant has a consented carer, the NPI-Q [42] for observable neuropsychiatric symptoms will be administered. Physical symptoms and Adverse Events will be collected at each follow-up assessment by self-report. Aspects of recovery from the TBI will be measured by the clinician-rated Glasgow Outcome Scale [48] and Rehab Complexity Score [49]. Serum sodium will be checked at baseline, Week 2, Week 4 and Month 3 and processed by the site laboratory. Adherence to the IMP will be checked by patient self-report, the patient diary, and IMP returns.

Biomarkers (optional) analysed as part of this trial will likely include a range of inflammatory and other markers to identify those most at risk of long-term problems after TBI such as neurofilament light chain protein (NFL), glial fibrillary acidic protein (GFAP), tau, amyloid and Ubiquitin C-terminal hydrolase -L1 (UCH-L1). Whole blood samples will be collected into 10 ml red top vacutainer tubes and centrifuged at 1200 g for 10 min in a swing-out bucket rotor within 20–60 min. Serum samples will be divided into aliquots (1 ml cryovial tubes) and stored immediately in a −80 degree freezer. Saliva samples of 1–2 ml will be collected over 30 min after the participant has last consumed food using a SpeciMAX Saliva Collection kit, and immediately stored in the −80 degree freezer. Funding for the further processing of these samples will be sought.

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

Whether the PI or the participant wishes to stop the trial medication, the participant will be given the option to remain in the study and will be asked to confirm whether

Table 1 Blinding of team members

Group or individual blinded	Information withheld	Method of blinding
Person assigning participants to groups	Group assignment	Concealed allocation schedule
Participants	Group assignment	Placebo medication
Healthcare professional providing standard care	Group assignment	Not told of group assignment
Research workers, fellows and administrators	Group assignment	Not told of group assignment
Trial manager	Group assignment	Not told of group assignment
Trial statistician (undertaking analyses)	Group identities	Groups given numerical identifiers (e.g. A/B)
	Participant identities	Participants given numerical identifiers
Senior statistician(s)	Group assignment	Not told of group assignment (e.g. no knowledge of A/B)
	Participant identities	Participants given numerical identifiers

they are willing to provide trial-specific data at subsequent visit sites and confirm consent to collect routine clinical data. If a patient wishes to withdraw from the study at any time, we will ask permission for their data collected to date to be retained in the final analysis. If the patient dies before regaining capacity, retrospective agreement from the next of kin for trial entry will be sought. If the next of kin refuses, data already collected will not be included in the analysis. All efforts will be made to report the reason for withdrawals as thoroughly as possible.

Data management {19}

For data collected, source data verification worksheets will be prepared for each patient, and data will be entered onto the MACRO eCRF database. The trial site will retain a copy to ensure that the PI has an independent account from the sponsor as to what has occurred during the trial at his/her site including signed consent forms. The CI will act as a custodian for the data, and any data queries will be raised with the trial manager or CI. King's Health Partners Clinical Trials Office (KHP-CTO) will undertake, on behalf of the Sponsor, independent administrative audits of the trial master file and monitoring at all sites and pharmacies periodically during the trial to ensure compliance with the Medicines for Human Use (Clinical Trials) Regulations 2004 and its subsequent amendments.

Confidentiality {27}

The CI will act as custodian for the trial data. The following guidelines will be strictly adhered to:

1. Participant data will be pseudo-anonymised.
2. All pseudo-anonymised data will be stored on a password protected computer at each NHS site.
3. All trial data will be stored in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006, the General Data Protection Regulation (GDPR) and the Data Protection Act 2018 and archived in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006 as defined in the KHP-CTO Archiving Standard Operating Procedure (SOP).

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

Serum and salivary samples will be stored in − 80 °C freezers at each site for future research studies. Logistics of shipping and analysis for biomarkers will be determined by further funding applications. The laboratory addresses and sample locations will be recorded in the Laboratory Manual.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

We will report data in line with the Consolidated Standards of Reporting Trials (CONSORT) statement showing attrition rates and loss to follow-up (Fig. 2 CONSORT diagram). All analyses will be carried out using the intention-to-treat principle, where possible, incorporating data from all participants including those who do not complete treatment.

Analyses will be conducted in Stata version 16 or later. Descriptive statistics within each randomised group will be presented for baseline values. These will include counts and percentages for binary and categorical variables, and means and standard deviations, or medians with lower and upper quartiles, for continuous variables, along with minimum and maximum values and counts of missing values. There will be no tests of statistical significance or confidence intervals for differences between randomised groups on any baseline variable.

Treatment effects on primary and secondary outcomes will be estimated using linear mixed models fitted to outcome variables at all time points. Fixed effects will be TBI severity, centre, history of depression (yes/no), time since TBI, baseline assessment for the outcome under investigation, treatment, time, and time*treatment interactions. Centre has been included as a model covariate due to its status as a stratification factor; we decided to model this as a fixed effect (rather than a random effect) as ten is just on the threshold for getting reliable estimates for the variation of a random intercept. Participant will be included as a random intercept to account for repeated measures.

Marginal treatment effects will be estimated for primary outcome (PHQ-9 score at 12 months), and for PHQ-9 scores at each other time point (6 m, 18 m), and reported separately as adjusted mean differences in scores between the groups with 95% confidence intervals and 2-sided p-values.

Treatment effects on the incidence rate of MDD at 12 months will be estimated using logistic regression, with fixed effects of TBI severity and centre. For continuous secondary outcomes, the approach will use linear mixed models to estimate and report the treatment effect at each time point. Cohen's D effect sizes will be calculated as the adjusted mean difference of the outcome divided by the sample standard deviation of the outcome at baseline. These will be displayed in a forest plot showing the treatment effects on the primary and secondary outcomes at each time point.

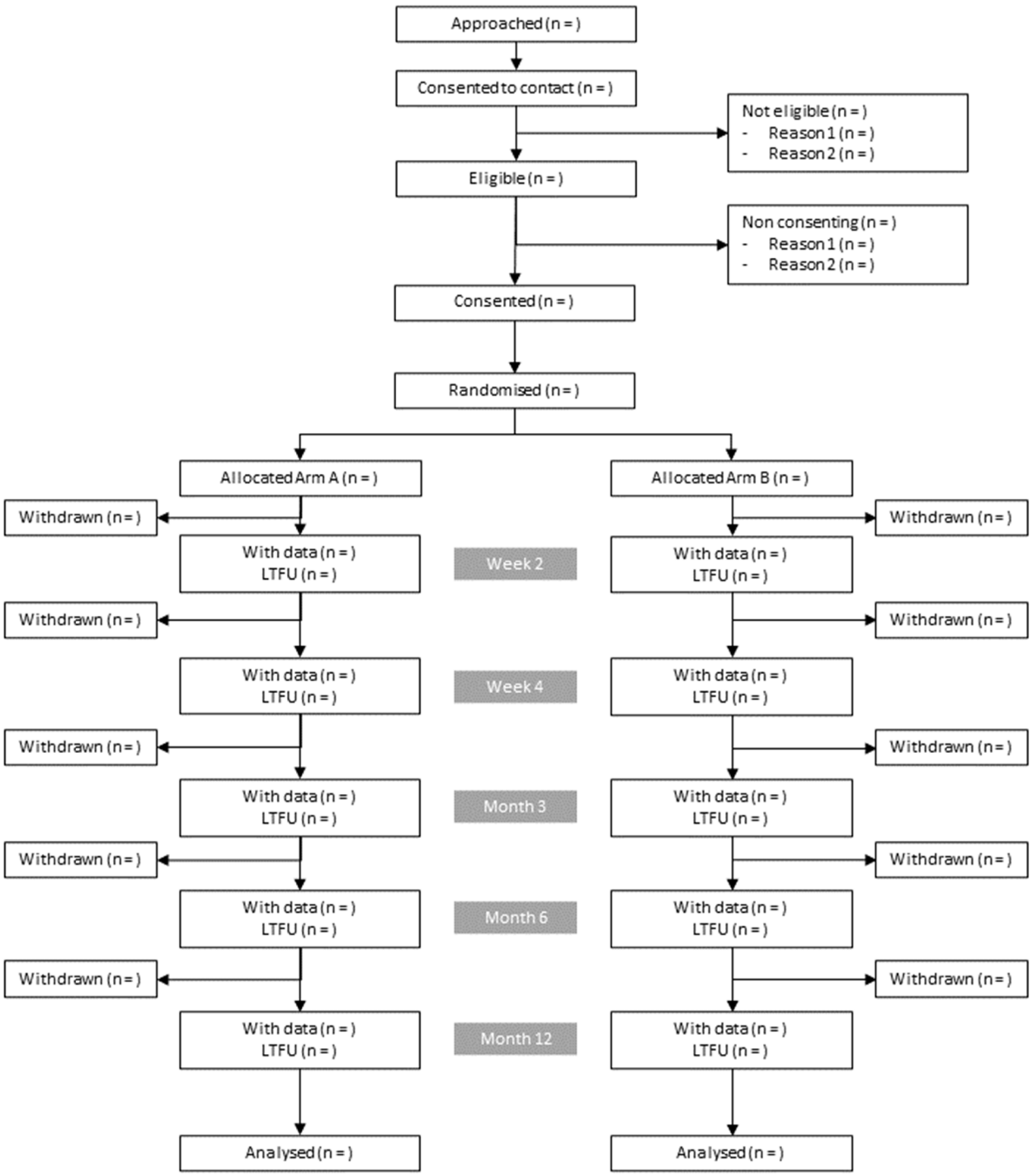

Fig. 2 CONSORT diagram

Interim analyses {21b}

We will conduct an internal pilot using a stop–go system at the end of the 4th month from the start of recruitment as follows:

Green— GO: 7 or more sites open, 100% of participants per Major Trauma Centre (MTC) in months 3 and 4, will continue to full trial.

Amber—WATCH: between 4 and 6 sites open or if we recruit between ≥ 60 but < 100% of participants, will institute our contingency plan:

i) Activate hospitals in each MTC's pathway and identify additional MTC sites using the Clinical Research Network (CRN) sites already identified.
ii) Extensive review and problem-solve site-specific barriers with PPI and clinical co-applicants such as awareness of NHS staff in CtC, skills of CRF, improve screening of trauma and older adult wards, review protocol study criteria (e.g. duration post TBI).
iii) If all sites and participant recruitment is not at ≥ 80% by end of 6th month, we will redistribute Clinical Research Fellows to the more active sites, where possible.
iv) Increase recruitment period to 15 months.
v) Conduct a review of the barriers to compliance and implement changes to optimise uptake of the first prescription.

Red—STOP: If less than 4 sites, or recruitment < 60% plus compliance < 50% by 4th month, will discuss with the Trial Steering Committee (TSC) and Funder (NIHR) whether to terminate the study.

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

A subgroup analysis will be conducted for those participants who have a carer for the NPI-Q outcome, and also for the DAST-10 in those who answer "Yes" to the question "Have you used drugs other than those required for medical reasons?" The primary outcome variable will also be presented descriptively by TBI severity.

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

Missing data on individual measures will be pro-rated if more than 80–90% (depending on questionnaire) of the items are completed; otherwise, the measure will be considered as missing. We will check for differential predictors of missing outcomes by comparing responders to non-responders on key baseline variables. Any significant predictors will be included in the analysis models in a sensitivity analysis. This accounts for missing outcome data under a missing at random assumption, conditional on the covariates included in the model. As a sensitivity analysis, we will assess whether treatment adherence is associated with missing data, and if it is associated, use inverse probability weights or multiple imputation to compare results. Missing PHQ-9 data may be imputed using DISCs data.

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

The full protocol is available on request; the participant-level dataset will be available on request to academics working in TBI following formal collaboration agreements, and the statistical code will be publicly available with the publication of the findings.

Oversight and monitoring

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

The trial is jointly sponsored by King's College London and King's College Hospital NHS Foundation Trust. King's Health Partners Clinical Trials Office (KHP-CTO) assist with regulatory submissions and pharmacovigilance and provide sponsor Quality Assurance (QA) oversight of trial processes.

The TSC meet on a six-monthly basis and DMC on a three-monthly basis throughout the period of the trial (post pilot), and at other times deemed necessary by the CI, the Sponsor or the HTA board. A Senior Investigators' Committee (SIC) was established, including the Co-CIs (rotating Chairs), statisticians and all the PIs and collaborators. The SIC meets monthly to manage the ongoing conduct of the trial. The CI and CI co-lead (Ismail and Raymont) have weekly research meetings with the project manager, research fellows and research workers to discuss the screening logs and recruitment issues.

The role of the TSC is to provide overall supervision for a project on behalf of the Project Sponsor and Project Funder and to ensure that the project is conducted to the rigorous standards set out in the Department of Health's Research Governance Framework for Health and Social Care and the Guidelines for GCP. TSC will operate independently from the Trial Management Group (TMG), the study funder (NIHR) and the Co-sponsors (KCH/KCL). The TSC's key purpose will be to ensure the overall integrity of the study. Committee membership will be documented in the first (joint) minutes of the TSC and DMC.

Composition of the TSC:

- An Independent Chair (UK based and/or holding a substantive UK-based appointment).
- Independent statistician, health economist and clinician(s) and any others with expertise relevant to the project.
- At least one individual who is able to contribute a patient and/or wider public perspective.

- Ideally, the TSC should invite observers, including a representative of the sponsor and a representative from the research network to meetings.
- TSC meetings will be scheduled to follow shortly after DMC meetings so that reports from that group can be considered if appropriate.
- Minutes of meetings will be sent to all members, the sponsor and the funder and will be retained in the study master file. The responsibility for calling and organising TSC meetings lies with the CI, in association with the Chair.

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

The DMCs main role is as follows:

1. It is the only body involved in a trial that has access to the unblinded comparative data
2. The role of its members is to monitor these data and make recommendations to the TSC on whether there are any ethical or safety reasons why the trial should not continue
3. The DMC considers the need for any interim analysis advising the TSC regarding the release of data and/or information
4. The DMC may be asked by the TSC, Project Sponsor or Project Funder to consider data emerging from other related studies
5. There are also rare occasions when the DMC chair might be asked by the Project Funder to provide a confidential interim or futility analysis if serious concerns are raised about the viability of the study or if the research team is requesting significant extensions.

Independence is a key characteristic of a DMC where the committee members are completely uninvolved in the running of the trial.

Composition of the DMC

All DMC members are to be independent (with at least one member being UK based and/or holding a substantive UK based appointment). Membership of the DMC should be small (3–4 members) and comprise experts in the field, e.g. a clinician with experience in the relevant area and expert trial statistician.

The roles will be defined in the DMC charter. Reports to the DMC will be prepared and presented by the Trial Statistician. We will be using DAMOCLES design.

Adverse event reporting and harms {22}

Specification, timing and recording of safety parameters

1 Participants will be provided with a phone number to contact the investigators for urgent queries outside of visits.
2 For the first 12 months, at the time when the trial medication is being dispensed, the patient will be invited to volunteer any adverse effects as free text and by completing the Physical Symptoms/Adverse Effects check [50]. The medication review will also be undertaken by a phone call outside the clinic visits (as per schedule).
3 We will assess for hyponatraemia which is slightly more common post-TBI as per treatment schedule.
4 We will report AEs collected between the period from consent to 30 days post final IMP administration as the active ingredient, sertraline, should be completely washed out at this point. Any AEs after this time will continue to be collected until the end of the trial but not reported as they will not be related to the IMP.

Procedures for recording and reporting adverse events

King's College London and King's College Hospital NHS Foundation Trust as co-sponsors have delegated the delivery of the Sponsor's responsibility for Pharmacovigilance (as defined in Regulation 5 of the Medicines for Human Use (Clinical Trials) Regulations 2004 to the KHP-CTO. All SAEs, SARs and SUSARs as defined by the Medicines for Human Use (Clinical Trials) Regulations 2004 and Amended Regulations (excepting those specified in this protocol as not requiring reporting) will be reported immediately (and certainly no later than 24 h) by the Investigator to the KHP-CTO and CI for review in accordance with the current Pharmacovigilance Policy. The KHP-CTO will report SUSARs to the relevant ethics committee and to the regulatory authorities (Medicines and Healthcare products Regulatory Agency (MHRA)), competent authorities of other European Economic Area states in which the trial is taking place.

Reporting timelines are as follows:

- SUSARS which are fatal or life-threatening must be reported not later than 7 days after the sponsor is First aware of the reaction. Any additional relevant information must be reported within a further 8 days;
- SUSARS that are not fatal or life-threatening must be reported within 15 days of the sponsor first becoming aware of the reaction.

The CI and KHP-CTO (on behalf of the co-sponsors) will submit a Development Safety Update Report (DSUR) relating to this trial IMP to the MHRA and REC annually.

Adverse events that do not require reporting

Very common (≥ 1/10) and common (≥ 1/100) reactions as listed in the SmPC for sertraline will not need to be reported. Death as a result of disease progression (TBI) and other events that are primary or secondary outcome measures are not considered to be SAEs and will be reported in the normal way, on the appropriate CRF.

Frequency and plans for auditing trial conduct {23}

KHP-CTO will undertake, on behalf of the Sponsor, independent administrative audits of the trial master file and monitoring at all sites and pharmacies periodically during the trial to ensure compliance with the Medicines for Human Use (Clinical Trials) Regulations 2004 and its subsequent amendments.

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

The Trial Manager will be responsible for communicating amendments to relevant parties by email or online submission to the party's database where applicable.

Dissemination plans {31a}

It is intended that the results of the study will be reported and disseminated at international conferences and in peer-reviewed scientific journals. No patient identifiable data will be contained in any publication related to this trial.

Discussion

This is the protocol for a full-scale double-blind RCT testing the effectiveness of sertraline with placebo for the primary prevention of depression following TBI. Due to initially unexpectedly low recruitment rates, three changes to the eligibility criteria were made by Substantial Amendment. First, the inclusion criteria were expanded to include possible TBIs, mild cognitive impairment, and mild dementia. In the original protocol, we included only two MYS TBI categories of definite and probable TBI as these are the most widely used in neurosurgery research. However, (a) this classification is not used in routine clinical practice in the NHS and (b) these two categories exclude those who have a head injury but do not require neurosurgical trauma (the category of possible TBI) who are disproportionately most at risk of post-TBI depression (iii) and as the majority of TBIs are possible TBIs, the size and representativeness of the study population were reduced. Second, the recruitment cut-off period was extended to 8 weeks: (a) to give inpatients who have multiple injuries, ongoing symptoms such as nausea or headache and/or on short-term medications such as anticoagulants a longer period to recover so that they do not interact with the sertraline and (b) for patients who are on a subtherapeutic dose or are not adhering to a previously prescribed antidepressant who want to participate, to give them a minimum of 6 weeks' washout period before randomisation. The exclusion criterion of sodium < 135 mmol/L was reviewed and changed, removing the requirement to consult a hospital endocrinologist and replacing it with the PI or their treating physician as this level of scrutiny was not warranted.

Trial status

Recruitment began on 1 February 2023 and ended prematurely on 20 January 2025 (final protocol Version 4.1, date 24.04.2024) following the funder's decision to terminate the study. Due to the complexity of the patient group (TBI) and the nature of the research question (primary prevention of depression), the rate of recruitment was slower than anticipated, and the NIHR decided to stop funding the study as it was unlikely to achieve time to target recruitment. Follow-up of trial participants is ongoing, and the findings will be reported end of 2026.

Abbreviations

A&E	Accident and emergency
AD-SUS	Adult Service Use Schedule
AE	Adverse events
AUDIT	Alcohol Use Disorders Identification Test
BNF	British National Formulary
CtC	Consent to contact
CTIMP	Clinical Trial of an Investigational Medicinal Product
DAST-10	Drug Abuse Screening Test-10
DSM-5	Diagnostic and Statistical Manual of Mental Disorders-5
eCRF	Electronic Case Report Form database
GAD-7	Generalised Anxiety Disorder-7
GCP	Good Clinical Practice
HDRS	Hamilton Depression Rating Scale
HES	Hospital Episode Statistics
HTA	Health Technology Assessment
IMP	Investigational Medicinal Product
K-CTU	King's Clinical Trials Unit
KHP-CTO	King's Health Partners Clinical Trials Office
MCID	Minimal clinically important difference
MDD	Major depressive disorder
MHRA	Medicines and Healthcare products Regulatory Agency
MOAS	Modified Overt Aggression Scale
MOCA	Montreal Cognitive Assessment
MYS	Mayo Classification System
NPI-Q	Neuropsychiatric Inventory Questionnaire
NHS	National Health Service
NIHR	National Institute for Health and Care Research
OD	Once a day
PCL-5	Post-Traumatic Stress Disorder Checklist for DSM-5
PHQ-9	Patient Health Questionnaire-9
PTD	Post-traumatic brain injury depression
PTSD	Post-traumatic stress disorder
RCT	Randomised controlled trial
REC	Research Ethics Committee
SAE	Serious adverse event
SAR	Serious adverse reaction
SCID	Structured Clinical Interview for DSM-5

SSRI	Selective serotonin reuptake inhibitor
SmPC	Summary of Product Characteristics
SUSAR	Unexpected serious adverse reaction
TBI	Traumatic brain injury
TAU	Treatment as usual
TMG	Trial Management Group

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Authors' contributions {31b}
KI, VR, RE, NMH, JW, MD, AA, BB and DL developed the protocol for this trial in response to an NIHR funding call. JB, KI, and NMH prepared the protocol for journal submission. All authors approved the final version of the manuscript.

Funding {4}
The trial is funded by the NIHR HTA- Ref. 131,125. The IMP and placebo will be manufactured, packaged and labelled by the Royal Free Hospital Pharmacy Manufacturing Unit.

Data availability {29}
The Chief Investigator will act as custodian for the trial data. Principal Investigators will have direct access to the datasets collected at their own site; access to other data will be by request. The following guidelines will be strictly adhered to:
1. Participant data will be pseudo-anonymised.
2. All pseudo-anonymised data will be stored on a password protected computer at each NHS site.
3. All trial data will be stored in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006, the General Data Protection Regulation (GDPR) and the Data Protection Act 2018 and archived in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006 as defined in the KHP-CTO Archiving Standard Operating Procedure (SOP).

Declarations

Ethics approval and consent to participate {24}
This study has been reviewed and given a favourable opinion by South Central - Oxford A Research Ethics Committee (IRAS Number: 1004930, REC Reference: 22/SC/0310).

Consent for publication {32}
The authors are willing to provide a model consent form on request.

Competing interests
KI was part funded by the NIHR Maudsley Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. RE is supported by an NIHR Research Professorship (NIHR300051), and the NIHR Maudsley Biomedical Research Centre, part of the NIHR and hosted by South London and Maudsley NHS Foundation Trust in partnership with King's College London. MD is the Co-Medical Director of Brain & Mind Ltd, which is an independent provider of rehabilitation for people with neurological conditions No other competing interests were declared.

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