PROTOCOL FULL TITLE: A multi-centre randomised controlled trial of the clinical and cost-effectiveness of sertraline in preventing depression in adults following a traumatic brain injury

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Protocol Short Title/ Acronym: Trial of sertraline to prevent post-TBI depression

Version 2 dated 14.10.2022

Trial Identifiers

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(Co) Sponsor(s)

Name of organisation(s): Lead Sponsor: Co-sponsor:	King's College London Professor Reza Razavi Director of Research at King's Health Partners 1 Lambeth Palace Rd, South Bank, London, SE1 7EU +44 (0) 20 7848 3224 reza.razavi@kcl.ac.uk King's College Hospital NHS Foundation Trust
(Co)Sponsor(s') contact:	Rebecca Newton
Address:	King's Health Partners Clinical Trials Office, Floor 16, Tower Wing, Guy's Hospital, Great Maze Pond, London, SE1 9RT
Telephone:	07515 190089
Fax:	020 71888330
Email:	rebecca.newton@kcl.ac.uk

Chief Investigator

Name:	Professor Khalida Ismail
Address:	Department of Psychological Medicine Weston Education Centre, King's College London 10 Cutcombe Road , London, SE5 9RJ
Telephone:	+44 (0)20 7848 5131
Email:	Khalida.2.ismail@kcl.ac.uk

Co-Investigator

Name:	Dr Vanessa Raymont
Address:	University of Oxford, Department of Psychiatry, Warneford Hospital, Oxford, OX3 7JX
Telephone:	+44 (0)1865 613147
Email:	Vanessa.raymont@psych.ox.ac.uk

Statisticians

Name:	Professor Richard Emsley
Address:	King's College London, Institute of Psychiatry, Psychology & Neuroscience, 16 De Crespigny Park, London, SE5 8AF
Telephone:	+44 (0)207 848 0724

Email:	richard.emsley@kcl.ac.uk

Name:	Dr Nicholas Beckley-Hoelscher
Address:	King’s College London
Email:	Nicholas.beckley-hoelscher@kcl.ac.uk

CONTENTS

1. Study Synopsis

Title of clinical trial	A multi-centre, placebo controlled, double blind, randomised controlled trial of the clinical and cost-effectiveness of sertraline in preventing depression in adults following a traumatic brain injury (TBI)
Protocol Short Title/Acronym	Trial of sertraline to prevent post-TBI depression
Trial Phase if not mentioned in title	Clinical Phase III
Co-Sponsors name	King's College London and King's College Hospital NHS Foundation Trust
Chief Investigator	Professor Khalida Ismail
EudraCT number	2022-000072-18
IRAS number	1004930
Medical condition or disease under investigation	Post-Traumatic Brain Injury Depression
Purpose of clinical trial	To study the effectiveness of sertraline compared to placebo in the prevention of depression following a traumatic brain injury
Primary objective	To test the primary hypothesis that in patients with a traumatic brain injury sertraline 100mg od prescribed for 12 months following presentation in accident and emergency department is more effective than placebo in reducing depressive symptoms.
Secondary objective (s)	1. To test the secondary hypotheses that sertraline 100 mg od prescribed for 12 months is more effective than placebo in people with post-traumatic brain injury over 18 months in: i) incident rate of major depressive disorder at 12 months from baseline ii) reducing depressive symptoms iii) reducing incident rate of major depressive disorder iv) reducing psychiatric symptoms of anxiety disorder, cognitive impairment and post-traumatic stress disorder v) reducing alcohol and substance use vi) reducing carer burden vii) reducing aggressive behaviours viii) improving productivity ix) improving cost effectiveness x) having improved patient and carer reported outcomes

	2. Assess whether sertraline is associated with greater incidence rate of adverse events than placebo 3. Assess the proportion who give consent to contact for future studies, and consent to collect data from medical records and hospital episode statistics for 10 years from recruitment. 4. To collect the blood and saliva for future biomarker profiling. 5. 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	Multi-centre, placebo controlled, double blind, randomised controlled trial
Endpoints	Primary endpoint at 12 months: 1) Depressive symptoms as measured by Patient Health Questionnaire-9 score. Secondary endpoints at: <u>6 and 18 months:</u> 1) Depressive symptoms as measured by Patient Health Questionnaire-9 score <u>6, 12 and 18 months</u>: 1) DSM (Diagnostic and Statistical Manual)-5 major depressive disorder as measured by the modified Structured Clinical Interview (SCID) 2) Anxiety disorder as measured by Generalised Anxiety Disorder-7 3) Cognitive assessment as measured by Montreal Cognitive Assessment; 4) Post-traumatic symptoms as measured by Post-Traumatic Stress Disorder Checklist; 5) Alcohol intake as measured by Alcohol Use Disorders Identification Test; 6) Substance use as measured by Drug Abuse Screening Test-10; 7) Care burden of neuropsychiatric symptoms as measured by the Neuropsychiatric Inventory Questionnaire (only measured in participants with a carer) 8) EQ-5D-5L and the Adult Service Use Schedule 9) Blood and saliva will be collected and stored within a protocol to be established pending further funding. Biomarkers 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 Traumatic Brain Injury (TBI) such as neurofilament light chain protein (NFL), glial fibrillary acidic protein (GFAP), tau, amyloid and Ubiquitin C-terminal hydrolase -L1 (UCH-L1).
Sample size	514

Summary of eligibility criteria	**Inclusion criteria** 1. Adults aged 18 years and above 2. UK residents 3. 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 4. No current major depressive disorder as measured by the modified Structured Clinical Interview (SCID). **Exclusion criteria** 1. Possible TBI according to the Mayo Classification System. 2. Concurrent antidepressant medication at British National Formulary recommended therapeutic doses for treatment of depression 3. Other causes of acquired brain injury such as stroke 4. 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 5. Pregnant or planning pregnancy 6. Women of childbearing potential if they are not using acceptable effective methods of contraception as defined by the Clinical Trials Facilitation Group (CTFG) (*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. 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, a single FSH measurement is insufficient. For the purpose of this document, a man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.*) *Female subjects must agree to one of the following during the duration of the study:* *• Complete abstinence from intercourse of reproductive potential. Abstinence is an acceptable method of contraception only when it is in line with the subject's preferred and usual lifestyle.* *• Consistent and correct use of 1 of the following methods of birth control: a) intrauterine device (IUD) with a failure rate of <1% per year; b) tubal sterilization; c) vasectomy in the male partner; d) hormonal methods (oral contraceptives, injectable progesterone, implants of levonorgestrel, transdermal contraceptive patch, contraceptive vaginal ring). In case of essure micro-insert system, this will need to be used in association with another method of contraception; Male subjects with female partners of childbearing potential must use condoms during the trial.* 7. Lactating 8. Medical causes of depression such as pituitary failure 9. Known allergy to sertraline 10. Current hyponatraemia (if participant's sodium is <130 mmol/L it will be discussed with a local hospital endocrinologist to confirm it is safe for the patient to be enrolled) 11. Taking medications contraindicated with sertraline as stated in the SmPC including concomitant treatment with irreversible monoamine oxidase inhibitors and pimozide

	12. Participating in another 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.
IMP, dosage and route of administration	Sertraline, 100mg once a day orally or placebo, prescribed for 12 months.
Active comparator product(s)	N/A
Maximum duration of treatment of a participant	12 months
Version and date of protocol amendments	Version 1 01.07.2022 Version 2 29.09.2022

2. Glossary of Terms

AE	Adverse Event
A&E	Accident and Emergency
AR	Adverse Reaction
ASEC	Antidepressants Side Effects Checklist
AD-SUS	Adult Service Use Schedule
AUDIT	Alcohol Use Disorders Identification Test
BNF	British National Formulary
CA	Competent Authority
CI	Chief Investigator
CIRS	Cumulative Illness Rating Scale
CNST	Clinical Negligence Scheme for Trusts
CONSORT	Consolidated Standards of Reporting Trials
CRA	Clinical Research Associate
CRF	Case Report Form
CRN	Clinical Research Network
CSRI	Client Services Receipt Inventory
CTA	Clinical Trial Authorisation
CtC	Consent to contact
CTIMP	Clinical Trial of an Investigational Medicinal Product
CTU	Clinical Trials Unit
DAST	Drug Abuse Screening Test
DISCs	Depression Intensity Scale Circles
DMC	Data Monitoring Committee
DMEC	Data Monitoring and Ethics Committee
DSM	Diagnostic and Statistical Manual
DSUR	Development Safety Update Report
EEA	European Economic Area
ESMS	Emergency Scientific and Medical Services
Eudract	European Clinical Trials Database
GAD	Generalised Anxiety Disorder
GCP	Good Clinical Practice
GCS	Glasgow Coma Scale
GFAP	Glial fibrillary acidic protein
GOS	Glasgow Outcome Scale
HDPE	High Density Poly Ethene
HDRS	Hamilton Depression Rating Scale
HES	Hospital Episode Statistics
HCP	Healthcare Professional
ICER	Incremental Cost-Effectiveness Ratio
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use.
IME	Important Medical Event
IMP	Investigational Medicinal Product
ISRCTN	International Standard Randomised Controlled Trials Number
KHP-CTO	King's Health Partners – Clinical Trials Office

MA	Marketing Authorisation
MAOI	Monoamine Oxidise Inhibitor
MCID	Minimal Clinically Important Difference
MDD	Major Depressive Disorder
MHRA	Medicines and Healthcare products Regulatory Agency
MOCA	Montreal Cognitive Assessment
MTC	Major Trauma Centre
MYS	Mayo Classification System
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NPI-Q	NeuroPsychiatric Inventory Questionnaire
NFL	neurofilament light chain protein
od	once daily
PCL	Post-Traumatic Stress Disorder CheckList
PHQ	Patient Health Questionnaire
PI	Principal Investigator
PIN	Patient Identification Number
PIS	Participant Information Sheet
PTA	Post-Traumatic Amnesia
PTD	Post-TBI Depression
QA	Quality Assurance
QALY	Quality Adjusted Life Year
QP	Qualified Person
RCT	Randomised Control Trial
REC	Research Ethics Committee
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SCID	Structured Clinical Interview
SDV	Source Data Verification
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SSRI	Selective Serotonin Reuptake Inhibitor
SUSAR	Suspected Unexpected Serious Adverse Reaction
TARN	Trauma Audit and Research Network
TAU	Treatment As Usual
tau	tau protein
TBI	Traumatic Brain Injury
TSC	Trial Steering Committee
UAR	Unexpected Adverse Reaction
UCH-L1	Ubiquitin C-terminal hydrolase -L1
USAR	Unexpected Serious Adverse Reaction
WCBA	Women of Child-Bearing Age
WOCBP	Women of Child-Bearing Potential

3. Background & Rationale

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 [2]. It has a bimodal distribution in adults, with the most common TBI presentations being falls in the elderly and road traffic collisions in young adults [3]. Approximately 80% of TBI cases are of mild severity; while the majority of these resolve within 3 months, in around a third of patients, neuropsychiatric symptoms can persist for months or years, especially in older age and in those with past or current depressive and anxiety symptoms [4, 5].

The consequences of TBI are multi-dimensional [1]. Post-TBI depression (PTD) is the most common psychiatric consequence. The core features of depression are pervasive low mood and loss of pleasure in everyday activities lasting for at least 2 weeks [6]. It is both a continuous and a categorical construct, measured as severity of depressive symptoms on rating scales and as diagnostic criteria for depressive disorder respectively. As researchers have used both constructs, in this proposal the term depression and PTD refers to depressive symptoms and depressive disorders.

The epidemiology of PTD has been reviewed extensively by others [7, 8, 9]. Taking into account the marked heterogeneity of the study population (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, there are consistent observations that around half of patients either develop or have PTD in the first 12-24 months following their TBI [10] with the range varying from 6 to 77% [11]. This is up to 10 times higher than the prevalence of depression in the general population and this risk emerges very soon after the injury. One large prospective cohort of inpatients with TBI (n=827) observed a prevalence rate of 56% with caseness for depressive disorder (defined using the Hospital Anxiety and Depression Scale-Depression score > 8) at 3 months [12]. The estimates for incidence rates appear to be similar to the prevalence rates, although the distinction between prevalence and incidence is not always transparent. 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)) [13]. The course of PTD is chronic with the majority of patients remaining depressed 2 years post-TBI [14], with a cumulative prevalence rate of 50% over 5 years, and this risk persists for decades [15, 16].

There are multiple consequences of PTD. Suicide and suicidal ideation is twice as common than in the general population [17] as are psychiatric comorbidities, in particular anxiety disorders, substance use disorders and aggression [18, 19, 20].

The strongest predictor for PTD is pre-existing psychiatric morbidity [7]. 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 [7]. Patients with normal neuroimaging and mild TBI are at higher risk for PTD than those with abnormal neuroimaging [12, 21]. Importantly, these are similar to the risk factors observed in those with persistent neuropsychiatric symptoms in mild TBI, potentially suggesting shared mechanisms secondary to multifactorial interactions between pre-existing psychiatric vulnerability, subtle structural and functional changes of neural circuits and the subjective (or contextual) experience of the TBI. Neuro-inflammation post-TBI is well recognised and there are very early findings that this may also be a contributory mechanism for PTD [22]. Yet depression is not routinely screened for at TBI presentation, and rarely treated optimally.

The theoretical application of selective serotonin reuptake inhibitors (SSRIs) to PTD is that following TBI there is disruption or shearing of the axons, which disrupts the production and metabolism of serotonin. 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. Thus in PTD, they may also have a role in neuronal recovery through optimization of the serotoninergic metabolism. 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, was associated with a significant reduction by around 30% in the risk of post stroke depression [32].

There have already been several systemic reviews of RCTs of the effectiveness of pharmacological and nonpharmacological interventions for PTD [33, 34, 35, 36]. One review focused only on sertraline in the treatment of PTD [35]. There is a stark paucity in the number of high-quality RCTs, taking this into account SSRIs do appear to be at least partially effective for PTD. Considering its extraordinarily high rates and adverse outcomes, the primary prevention of PTD has received even less attention than secondary prevention 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 100mg once a day (od) for 24 weeks reduced the incidence rate of major depressive disorder (MDD) [6] at 6 months and was well tolerated by patients [37]. 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 50mg od for 3 months, 0% had a Hamilton Depression Rating Scale (HDRS) score >6 at 3 months compared to 10% of placebo group, but this difference disappeared at 12 months [38]. This study had a shorter treatment duration and a lower dose of sertraline (a licensed antidepressant) compared to the first RCT. Both RCTs were single centre sites and were based in the US, where usual care differs from the 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.

4. Trial Objectives and Design

4.1 Trial Objectives

The main objective is to identify whether sertraline 100mg od is more effective, cost-effective and acceptable in reducing the risk of PTD over 18 months compared to placebo. The specific aims are to:

Primary objective

To test the primary hypothesis that in patients with a traumatic brain injury sertraline 100mg od prescribed for 12 months following presentation in A&E department 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 100mg od prescribed for 12 months following presentation in A&E department is more effective than placebo in reducing incident rate of MDD at 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

4.2. Primary endpoints

Depressive symptoms as measured by Patient Health Questionnaire-9 (PHQ-9) [40] score.

4.3. Secondary endpoints

<u>Secondary endpoints at 6 and 18 months:</u>

1) depressive symptoms as measured by Patient Health Questionnaire-9 score (PHQ-9) [40];

<u>Secondary endpoints at 6, 12 and 18 months:</u>

1) DSM-5 MDD [6] as measured by the modified Structured Clinical Interview (SCID) [42];
2) anxiety disorder as measured by Generalised Anxiety Disorder-7 (GAD-7) [43];
3) cognitive assessment as measured by Montreal Cognitive Assessment (MOCA) [44];
4) post-traumatic symptoms as measured by Post-Traumatic Stress Disorder Checklist (PCL-5) [45];
5) alcohol intake as measured by Alcohol Use Disorders Identification Test (AUDIT) [46];

6) substance use as measured by Drug Abuse Screening Test-10 (DAST-10) [47];

7) care burden of neuropsychiatric symptoms as measured by the Neuropsychiatric Inventory Questionnaire (NPI-Q) (only in participants with a carer) [48];

8) EQ-5D-5L [51] and the Adult Service Use Schedule (AD-SUS) [52];

9) Blood and saliva will be collected and stored within a protocol to be established pending further funding. Biomarkers will likely include a range of inflammatory and other markers to identify those most at risk of long-term problems after TBI, such NFL, GFAP, tau, amyloid and UCH-L1.

4.4. Trial Design

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 the Stage 2 (substantive study) if the progression criteria are met. The design is a placebo controlled double blind multi-centre RCT stratified by severity of TBI (mild versus moderate/severe) and by site.

Table 2: Feasibility pilot progression criteria at 4 months

	Red	Amber	Green
Trial Recruitment rate	<60%	≥60% but <100%	100%
Recruitment rate/site/month	<4	4-6	5-8
Number of sites opened	<4	4-6	7-9
Total number of participants recruited	<102	102-170	171
AND			
Prescription collection	<50%	≥50% but <80%	≥80%

We will conduct an internal pilot using 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 4-6 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 (eg duration post TBI).

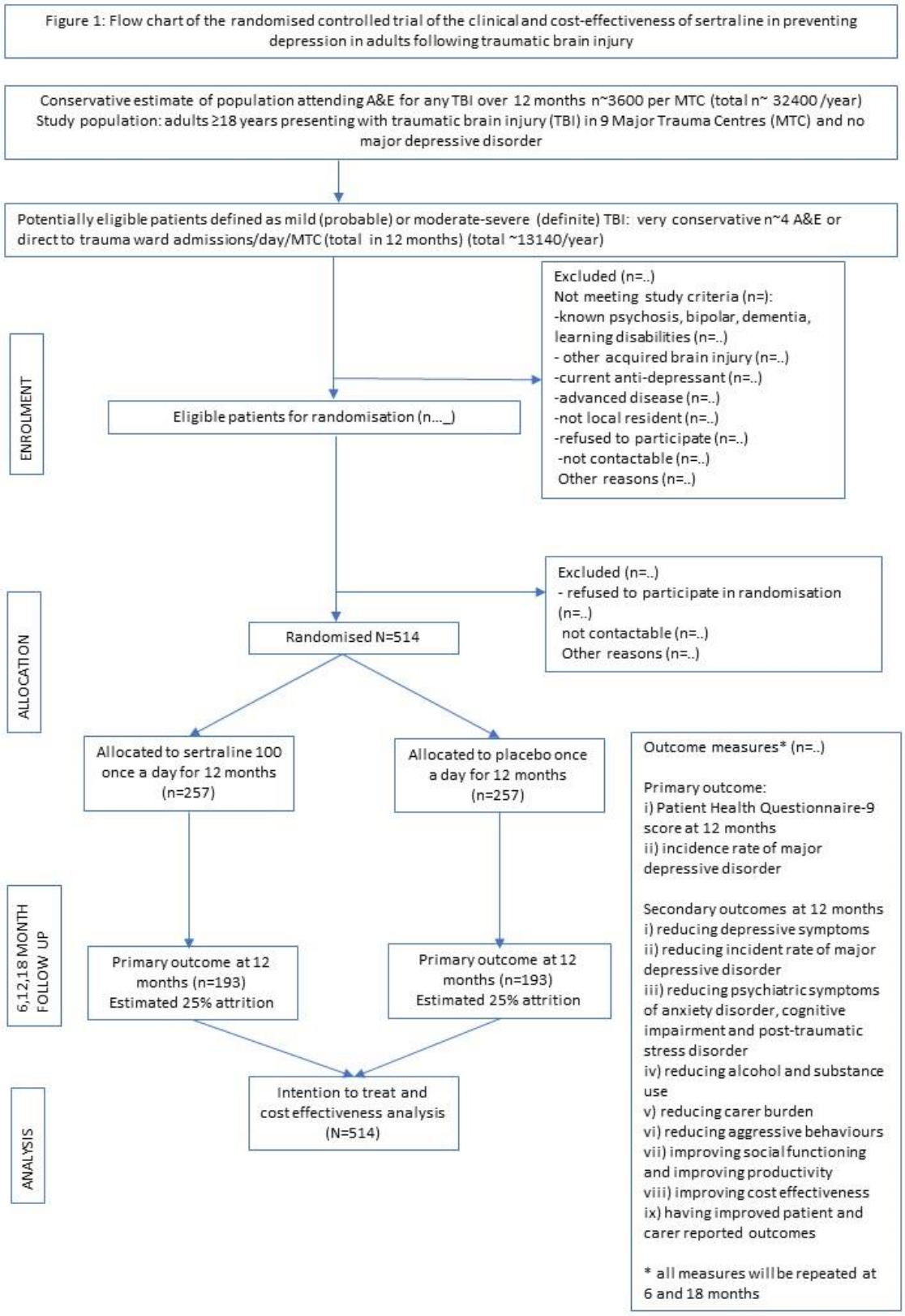
iii) If all sites and participant recruitment is not at ≥80% by end of 6th month we will redistribute Clinical Research Fellows to the more active sites, where possible.

iv) Increase recruitment period to 15 months

v) Conduct a review of the barriers to compliance and implement changes to optimizing uptake of 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.

4.5. Trial Flowchart



5. Trial Medication

5.1. Investigational Medicinal Product (IMP)

This will be sertraline or placebo, manufactured and packaged specifically for the trial. The IMP will be packaged to maintain blinding. Sertraline is licensed and has a marketing authorisation (MA) in the UK but it will repackaged and relabelled for the trial. This will be completed by The Royal Free Hospital Pharmacy Manufacturing Unit.

The active IMP consists of 50 mg sertraline tablets (as sertraline hydrochloride). The placebo tablets will visually match the active 50 mg sertraline tablets. Tablets will be packed in High-density polyethylene (HDPE) bottles with tamper evident closure.

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.

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 score line in between '8' and '1' on the other side. The tablets will be packaged in HDPE bottles and dispensed according to the randomisation schedule. Labelling will be fully Annex 13 compliant and in a blinded fashion.

The Royal Free Hospital Pharmacy Manufacturing Unit will act as a central pharmacy and distribute to the intended sites.

5.2. Dosing Regimen

Participants will be prescribed sertraline 50mg or placebo as oral dose (once daily (od)) daily for two weeks then increased to 100mg or placebo as od daily for the next 46 weeks, consistent with evidence on optimal dosages for efficacy and acceptability [54]. At 48 weeks, the dose will be reduced to sertraline 50mg or placebo as od daily for 2 weeks. At 50 weeks, the dose will be reduced to 25mg od for two weeks and then stopped. The IMP will be dispensed after randomisation at the specified time intervals as per table 1.

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: it has the strongest evidence for effectiveness of treating depression; it is well tolerated in the elderly; it has the lowest epileptogenic risk [55]. The regimen will consist of sertraline 50mg od for 2 weeks, then increased and maintained at 100mg od. In older adults (aged 75 years and above), we will review tolerability before increasing to 100mg. At 48 weeks, the dose will be reduced to sertraline 50mg or placebo as od daily for 2 weeks. At 50 weeks, the dose will be reduced to 25mg od for two weeks and then stopped.

Follow-up patient safety assessments will be conducted at baseline, 2, 4 and 12 weeks after randomisation to monitor hyponatraemia (below 135mmol/L) [55], and capacity for those who did not have mental capacity at recruitment. A standardised checklist of AEs and the Antidepressant Side-Effect Checklist (ASEC) [56] scale will be conducted at each IMP dispensing.

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.

5.3. IMP Risks

Summary of Product Characteristics (SmPC) for sertraline is in the reference safety information (RSI) document which details the IMP risks. Specifically, section 4.8 will be used to assess the relativeness and expectedness of an AE with the IMP.

The risks stated in the SmPC are mitigated by excluding patients on pimozide, Monoamine Oxidase Inhibitors (MAOIs), and patients with severe hepatic impairment. The IMP dose will be reduced over 2 weeks instead of being stopped suddenly.

Should the research team have any concerns about any new symptoms when taking the IMP, they should follow their local guidance and contact the investigator.

5.4. Drug Accountability

The Chief Investigator (CI) will arrange transfer of active IMP/placebo from The Royal Free Pharmacy Manufacturing Unit to the participating sites' pharmacies. It will be transported below 30 degrees Celsius. The Principal Investigator (PI) will then take responsibility for IMP accountability by ensuring that: the IMP is stored in a secure location, segregated from other medicines, used and returned medication is kept separate from unused medication, IMP is dispensed to participants in accordance with the trial protocol and any randomization list.

Any unused IMP will be returned to the trial pharmacy where it will be destroyed in accordance with good clinical practise (GCP) guidelines after verification by the sponsor Clinical Research Associate (CRA). Authorization for destruction will be given by the CI and Sponsor.

5.5. Storage of IMP

The SmPC for sertraline states 'no special storage conditions required'. It will therefore be stored below 30 degrees Celsius.

5.6. Participant Compliance

Participant's 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 the adherence at the clinical visits 6, 9 and 12 months. We will request consent to send calendar notifications to collect prescriptions and follow up appointments using e-calendars such as Google calendar to facilitate compliance.
In case of missed clinic visits we will be contacting the patient by phone within a week. In addition, we will seek permission during the informed consent process to be able to contact the next of kin if the patient is not contactable.

5.7. Concomitant Medication

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).

6. Selection and Withdrawal of Participants

6.1. Inclusion Criteria

1. Adults aged 18 years and above
2. UK residents
3. 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) [58]. 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).
4. No current MDD. Modified Structured Clinical Interview (SCID) [42], 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 [11].

6.2. Exclusion Criteria

1. Possible TBI according to the MYS classification [59]
2. Concurrent antidepressant medication at British National Formulary (BNF) recommended therapeutic doses for treatment of depression [60]
3. Other causes of acquired brain injury such as stroke
4. 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
5. Pregnant or planning pregnancy
6. Women of childbearing age (WCBA) unless acceptable effective methods of contraception are being used (*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. 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, a single FSH measurement is insufficient. For the purpose of this document, a man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy*.)
Female subjects must agree to one of the following during the duration of the study:
• Complete abstinence from intercourse of reproductive potential. Abstinence is an acceptable method of contraception only when it is in line with the subject's preferred and usual lifestyle.
• Consistent and correct use of 1 of the following methods of birth control: a) intrauterine device (IUD) with a failure rate of <1% per year; b) tubal sterilization; c) vasectomy in the male partner; d) hormonal methods (oral contraceptives, injectable progesterone, implants of levonorgestrel, transdermal contraceptive patch, contraceptive vaginal ring). In case of essure micro-insert system, this will need to be used in association with another method of contraception; Male subjects with female partners of childbearing potential must use condoms during the trial.

7. Lactating
8. Medical causes of depression such as pituitary failure
9. Known allergy to sertraline
10. Current hyponatraemia (sodium <135 mmol/L based on discussion with hospital endocrinologist)
11. Taking medications absolutely contraindicated with sertraline as stated in the 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.

6.3. Selection of Participants

The A&E departments and trauma wards of 10 MTCs across England will be the sampling frame [61].

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 [62]. The target population are adults age over 18 years who present with TBI and do not have MDD.

6.4. Consent

The Principal Investigator (PI) retains overall responsibility for the conduct of research at their site; this includes the taking of informed consent of participants at their site. They must ensure that any person-delegated responsibility to participate in the informed consent process is duly authorised, trained and competent to participate according to the ethically approved protocol, principles of Good Clinical Practice (GCP) and Declaration of Helsinki. If delegation of consent is acceptable then details should be provided.

Informed consent must be obtained prior to the participant undergoing procedures that are specifically for the purposes of the trial and are out-with standard routine care at the participating site.
We will invite people who have capacity to consent to research plus people who do not have this capacity temporarily. The rationale is that PTD is a painful, disabling, chronic condition associated with significant adverse outcomes including higher rates of suicide, and that it appears within days and weeks of the TBI. It is estimated that 10% of patients will not have capacity to consent to participate in the trial for many reasons including being in traumatic or iatrogenic induced coma, sedating medications such as opiates and benzodiazepines, substance and alcohol intoxication and undiagnosed dementia. This group are likely to be at high risk of PTD.

The consent process will involve the following steps and processes:
1. Discussion between the potential participant or their legally acceptable representative and an individual knowledgeable about the research, the nature and objectives of the trial and the possible risks associated with their participation.
2. The presentation of written material (e.g., patient information sheet (PIS) and informed consent form (ICF), which must be approved by the research ethics committee

(REC) and be in compliance with GCP, local regulatory requirements and legal requirements).
3. The opportunity for potential participants and their representative to ask questions.
4. Assessment of capacity. For consent to be ethical and valid in law, participants must be capable of giving consent for themselves. A capable person will:
i) understand the purpose and nature of the research;
ii) understand what the research involves, its benefits (or lack of benefits), risks and burdens;
iii) understand the alternatives to taking part;
iv) be able to retain the information long enough to make an effective decision;
v) be able to make a free choice;
vi) be capable of making this particular decision at the time it needs to be made (though their capacity may fluctuate, and they may be capable of making some decisions but not others depending on their complexity).

Capacity will be assessed using normal clinical assessment and will be documented in patients' notes and the source data.

Patient legal representative available in the hospital

In potential participants lacking capacity, a legal representative will be sought. If the legal representative is available in the hospital, is contactable, or is due to visit the potential participant within a reasonable timescale, then they will be provided with information about the trial and asked if they will provide consent for the potential participant before enrolment. This will take place during their visit to the patient.
We will seek informed consent from a personal legal representative who is engaged in caring for the participant (not professionally or for payment) or is interested in his/her welfare, and is prepared to be giving consent.
For the purposes of sites in England, Wales and Northern Ireland, a legal representative is defined as:
A person not connected with the conduct of the trial who is:
(a) Suitable to act as the legal representative by virtue of their relationship with the adult, and
(b) Available and willing to do so.

Patient legal representative not available in the hospital

Due to the condition of these patients, there will be those who will have no registered legal representative or where the legal representative is not contactable or able to visit the hospital within 2 to 3 weeks to be able to enrol the potential participant in a timely manner. In such cases we advocate enrolment would be possible with written agreement from an independent clinician. If no legal representative is available for discussion then an independent clinician will be approached. If a legal representative visits the hospital at a later date, then the trial will be discussed with them and their consent sought at that time point to continue in the trial.

Independent healthcare professional (IHP) definition

'For the purposes of this trial, the Independent Healthcare Professional (IHP) is defined as:
A person* who is NOT connected with the conduct of the trial, specifically:
a) The sponsor of the trial;
b) A person who undertakes activities connected with the management of the trial;

c) An investigator of the trial or;
d) A health care professional who is a member of the investigator's delegated team for the purposes of the trial.'
*(a-d CANNOT be the Independent Healthcare Professional)

Participants who regain capacity whilst in hospital will be informed about the clinical trial and consent to continue will be sought. If at any stage either the legal representative or the participant chose to withhold consent then the participant will be withdrawn from the trial.
Participant's capacity will be regularly monitored so that participants who regain capacity can be invited to give informed consent to continue in the trial. It will be monitored at baseline, 2 and 4 weeks and if still not capacious, the date at which capacity did return, if at all, will be derived from the medical records.

Participants who regain capacity following discharge will be contacted by phone and posted a patient information sheet and consent form as soon as possible.

Any new information which becomes available, which might affect the participant's willingness to continue participating in the trial will be communicated to the participant as soon as possible, verbally if the participant is in hospital, by post or phone if they have been discharged.

For participants who do not regain capacity for the duration of the study, follow-up will continue to be conducted.

We will be involving 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. When we refer to carers in this document, this only concerns adult carers. The data collected from carers will be used in the overall trial data analysis.

6.5. Randomisation Procedure / Code Break

Randomisation services will be provided by King's College London Clinical Trials Unit (KCTU).

6.6. Randomisation

Randomisation of participants will be conducted by an online system hosted by the King's CTU, using computer generated blocks of random sizes. A Patient Identification Number (PIN) will be generated by registering the patient on the MACRO eCRF system (InferMed Macro), after consent has been signed. This unique PIN will be recorded on all source data worksheets and used to identify the patient throughout the study. Authorised site staff will be allocated a username and password for the randomization system.

The sample will be stratified by severity into two categories of TBI (moderate-severe versus mild) and by MTC location, to minimise disproportionate distribution by chance. The experimental and placebo drugs will look the same and the random allocations will not be revealed to the pharmacist.

6.7. Emergency Code Break

The list of trial team members roles and the information they are blind to can be found in the table below:

Group or individual blinded	Information withheld	Method of blinding
Person assigning participants to groups	Group assignment	Concealed allocation schedule
Participants	Group assignment	Placebo medication
Health care professional providing standard care	Group assignment	Not told of group assignment
Research workers, fellows and administrators	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

Group-level summary measures will only ever be seen by the trial statistician undertaking analysis and providing DMEC reports.

The trial code will only be broken for valid medical or safety reasons e.g. in the case of a serious adverse event (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.

24hr Emergency Code Break and Medical Information will be provided by Emergency Scientific and Medical Services (ESMS). 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.

6.8. Withdrawal of Participants

Withdrawal by medical team:

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 PHQ-9 [40] 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 GP 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 in section 5.2.

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 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, they will be given the option of having their data collected to date being retained for future analysis or not used 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.

6.9. Expected Duration of Trial

Recruitment over 12 months:
Date of recruitment start 01.03.2022
Date of recruitment end 28.02.2023

18 month follow up:
Date of 18 month follow up start 01.09.2023
Date of 18 month follow up end 28.02.25

6.10 The End of Trial Definition

The end of the trial will be deemed to occur after database lock (following completion of monitoring of the last patient last visit undergoing the TBI trial).end of the trail will be defined by the database lock.

7. Trial Procedures

The trial questionnaires will be administered by research fellows and research nurses. Physical examinations will be completed by a research fellow.

7.1 By Visit

The trial procedures can be found in the Schedule of Events below.

7.1.1 Admission/Screening (Week -4/0)

When the patient presents in A&E with a TBI after they have received the standard of care, the health care professional (HCP) will give them the consent to contact form on discharge or following admission, which will have the following options:

1. The patient can agree to sign the consent to be contacted by the research team. The HCP will forward the consents to the research team.
2. Meet the inclusion criteria for the age (18 and above) and the TBI (mild/moderate).

7.1.2 Baseline (Week 0):

1. Informed consent
2. Inclusion/exclusion criteria review
3. Questionnaires as per Schedule of Events (1-15 below)
4. Medication (IMP) dispensing
5. Blood test for sodium levels
6. Serum for biomarkers
7. Saliva for TBI markers
8. Randomisation
9. Dispensing of IMP (+/- 3 days)

Several other measures will be collected at baseline, that are not direct efficacy parameters for primary and secondary outcomes, that will be used to characterise the trial cohort:

1. Sociodemographic including age, gender, self-report ethnicity, marital status, socioeconomic status, occupation; Index of Multiple Deprivation [64]; educational attainment
2. Medical, psychiatric and trauma history (including recent neuroimaging); current medications
3. TBI characteristics: mechanism of TBI using the Trauma Audit and Research Network (TARN) classification [65]; MYS severity score [59]; Glasgow Coma Scale (GCS) [66]; Rehabilitation needs using the Rehab Complexity Scale (RCS) [68]. If Post-Traumatic Amnesia (PTA) is present, the routine medical records will be reviewed daily for the first 3 months to record the date in which it resolved, if at all in this time period.
4. Cumulative Illness Rating Scale (CIRS) [69]
5. Patient Health Questionnaire-9 (PHQ-9) [40]
6. Depression Intensity Scale Circles (DISCS) [70]
7. Glasgow Outcome Scale (GOS) [71]
8. Alcohol Use Disorders Identification Test (AUDIT) [46]
9. Drug Screening Questionnaire (DAST-10) [47]
10. Modified Structured Clinical Interview (SCID) [42]
11. Generalised Anxiety Scale (GAD-7) [43]
12. Montreal Cognitive Assessment (MOCA) [44]
13. Post-traumatic Stress Disorder Checklist (PCL) [45]
14. Neuropsychiatric Inventory Questionnaire (NPI-Q) (only in participants with a carer) [48]
15. EQ-5D-5L [51] (There are 3 versions that will be administered according to circumstances: self-completed, Proxy 1 and Interviewer).
16. Adult Service Use Schedule (AD-SUS) [52]

7.1.2 Week 2

1. Blood test for sodium levels
2. Concomitant Medication review (incl. patient diary of IMP administration)

3. Dispensing of IMP
4. AE collection (The adverse event log will be reviewed at each trial assessment clinic visit and at all follow-ups and following any occurrences in between study visits and follow-ups)
5. The Antidepressant Side-Effect Checklist (ASEC) [56]

7.1.3 Week 4

1. Blood test for sodium levels
2. Medication review (incl. patient diary of IMP administration)
3. AE collection
4. The Antidepressant Side-Effect Checklist (ASEC)

7.1.4 Week 6

1. AE collection
2. The Antidepressant Side-Effect Checklist (ASEC)

7.1.5 Week 8

1. AE collection
2. The Antidepressant Side-Effect Checklist (ASEC)

7.1.6 Month 3

1. Record duration of PTA if was present at baseline using routine clinical data
2. Blood test for sodium levels
3. Medication review (incl. patient diary of IMP administration)
4. AE collection
5. The Antidepressant Side-Effect Checklist (ASEC)
6. Dispensing of IMP

7.1.7 Month 6

1. Questionnaires as in Baseline (no. 4-16):
    - Cumulative Illness Rating Scale (CIRS) [69]
    - Patient Health Questionnaire-9 (PHQ-9) [40]
    - Depression Intensity Scale Circles (DISCS) [70]
    - Glasgow Outcome Scale (GOS) [71]
    - Drug Screening Questionnaire (DAST-10) [47]
    - Modified Structured Clinical Interview (SCID) [42]
    - Generalised Anxiety Scale (GAD-7) [43]
    - Montreal Cognitive Assessment (MOCA) [44]
    - Post-traumatic Stress Disorder Checklist (PCL) [45]
    - Neuropsychiatric Inventory Questionnaire (NPI-Q) (only in participants with a carer) [48]
    - EQ-5D-5L [51] (There are 3 version that will be administered according to circumstances: self-completed, Proxy 1 and Interviewer)
    - Adult Service Use Schedule (AD-SUS) [52]
2. Antidepressant Side-Effect Checklist (ASEC)

3. Serum for biomarkers
4. Saliva for TBI markers
5. Medication review (incl. patient diary of IMP administration)
6. AE collection
7. IMP dispensing

7.1.8 Month 9

1. IMP dispensing
2. Medication review (incl. patient diary of IMP administration)

7.1.9 Month 11 (Week 48)

1. Reducing sertraline from 100 to 50 mg
2. Medication review (incl. patient diary of IMP administration)

7.1.10 Month 12 (Week 50)

1. Questionnaires as in Baseline (no. 4-16):
   - Cumulative Illness Rating Scale (CIRS) [69]
   - Patient Health Questionnaire-9 (PHQ-9) [40]
   - Depression Intensity Scale Circles (DISCS) [70]
   - Glasgow Outcome Scale (GOS) [71]
   - Alcohol Use Disorders Identification Test (AUDIT) [46]
   - Drug Screening Questionnaire (DAST-10) [47]
   - Modified Structured Clinical Interview (SCID) [42]
   - Generalised Anxiety Scale (GAD-7) [43]
   - Montreal Cognitive Assessment (MOCA) [44]
   - Post-traumatic Stress Disorder Checklist (PCL) [45]
   - Neuropsychiatric Inventory Questionnaire (NPI-Q) (only in participants with a carer) [48]
   - EQ-5D-5L [51] (There are 4 versions that will be administered according to circumstances: self-completed, Proxy 1 and Interviewer)
   - Adult Service Use Schedule (AD-SUS) [52]
2. Antidepressant Side-Effect Checklist (ASEC)
3. Serum for biomarkers
4. Saliva for TBI markers
5. AE collection
6. Medication review (incl. patient diary of IMP administration)
7. Reducing sertraline from 50 to 25 mg

7.1.11 Month 18

1. Questionnaires as in Baseline (no. 4-16):
   - Cumulative Illness Rating Scale (CIRS) [69]
   - Patient Health Questionnaire-9 (PHQ-9) [40]
   - Depression Intensity Scale Circles (DISCS) [70]
   - Glasgow Outcome Scale (GOS) [71]
   - Alcohol Use Disorders Identification Test (AUDIT) [46]

- Drug Screening Questionnaire (DAST-10) [47]
- Modified Structured Clinical Interview (SCID) [42]
- Generalised Anxiety Scale (GAD-7) [43]
- Montreal Cognitive Assessment (MOCA) [44]
- Post-traumatic Stress Disorder Checklist (PCL) [45]
- Neuropsychiatric Inventory Questionnaire (NPI-Q) (only in participants with a carer) [48]
- EQ-5D-5L [51] (There are 3 versions that will be administered according to circumstances: self-completed, Proxy 1 and Interviewer)
- Adult Service Use Schedule (AD-SUS) [52]

2. Serum for biomarkers
3. Saliva for TBI markers
4. AE collection

7.3 Laboratory Tests

The Major Trauma Centre (MTC) laboratories will be used for the routine bloods at baseline, 2 and 4 weeks and 3 months.

Serum and salivary samples will be stored in -80 degrees Celsius 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.

7.3 Schedule of Events

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)	**-4/0**	**0**	**2**	**4**	**6**	**8**										**48**	**50**							
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
Drug Abuse Screening Test (DAST-10)		x								x							x							x
Cumulative Illness Rating Scale (CIRS)		x								x							x							x
Patient Health Questionnaire (PHQ-9)		x								x							x							x
Depression Intensity Scale Circles (DISCs)		x								x							x							x
Glasgow Outcome Scale (GOS)		x								x							x							x
SCID		x								x							x							x
Generalised Anxiety Disorder (GAD-7)		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
Antidepressant Side-Effect Checklist (ASEC)			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		x								x							x							x
Saliva collection for markers of TBI injury		x								x							x							x
Medication dispensing (IMP)		x	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							
Adverse events			x	x	x	x	x			x			x				x	x						x

1. If PTA is present, the routine medical records will be reviewed daily for the first 3 months to record the date in which it resolved, if at all in this time period
2. [74]

Missed tests or assessments will be recorded as a protocol deviation.

8. Assessment of Efficacy

8.1. Efficacy Parameters

8.1.1 Primary outcome at 12 months:

i) PHQ-9 [40] score

8.1.2 Secondary outcomes at 6, 12 and 18 months:

i) incidence rate of DSM-5 MDD [6].
ii) anxiety disorder (GAD-7) [43];
iii) cognitive assessment (MOCA) [44];
iv) Post-traumatic Stress Disorder Checklist (PCL) [45];
v) alcohol intake (AUDIT) [46];
vi) substance use (DAST-10) [47];
vii) carer; neuropsychiatric symptoms (NPI-Q) (only in participants with a carer) [48];
viii) productivity
ix) EQ-5D-5L [51] and AD-SUS [52] to calculate unit costs
x) patient reported outcomes

8.2. Procedures for Assessing Efficacy Parameters

These will be combination of clinician interviews and self-report questionnaires conducted either face-to-face or conducted as remote assessments.

9. Assessment of Safety

9. 1 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 ASEC [56]. 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.

9.2 Procedures for Recording and Reporting Adverse Events

The Medicines for Human Use (Clinical Trials) Regulations 2004 and Amended Regulations 2006 gives the following definitions:

- **Adverse Event (AE)**: Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not

necessarily caused by or related to that product.

- **Adverse Reaction (AR):** Any untoward and unintended response in a participant to an IMP which is related to any dose administered to that participant.
- **Unexpected Adverse Reaction (UAR)**: An adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out in the SmPC for that product (for products with a MA)
- **Serious adverse Event (SAE), Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR):** Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that**:**
    - Results in death;
    - Is life-threatening;
    - Required hospitalisation or prolongation of existing hospitalisation;
    - Results in persistent or significant disability or incapacity;
    - Consists of a congenital anomaly or birth defect.
- **Important Medical Events (IME) & Pregnancy:** Events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious. Although not a serious AE, any unplanned pregnancy will also be reported via the SAE reporting system.

Reporting Responsibilities

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 King's Health Partners Clinical Trials Office (KHP-CTO).

All SAEs, SARs and SUSARs (excepting those specified in this protocol as not requiring reporting) will be reported immediately (and certainly no later than 24hrs) 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 regulatory authorities (Medicines and Healthcare products Regulatory Agency (MHRA), competent authorities (CAs) of other EEA (European Economic Area) states in which the trial is taking place).

The CI will report to the relevant REC. 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.

9.3 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 should be reported in the normal way, on the appropriate CRF.

9.4 Premature Termination of the Trial

The trial may be prematurely discontinued by the Funder, Sponsor, CI or Regulatory Authority on the basis of new safety information or for other reasons given by the Data Monitoring Committee (DMC) / TSC, regulatory authority or ethics committee concerned.

If the trial is prematurely discontinued, active participants will be informed and no further participant data will be collected. The CA and REC will be informed within 15 days of the early termination of the trial.

10. Statistics

10.1 Sample Size

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 number of patients admitted for at least 1 night to each MTC. We used this information to estimate the size of our study population.

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 [10]. Therefore, assuming a 50:50 split of scores of PHQ-9>=10 (caseness) and PHQ-9 <10 with a total mean PHQ-9 score of 10; and a 25:75 percentage split in the sertraline group with 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, 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 test for between group effect size in the secondary psychiatric outcomes (MCID for GAD [72] 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. 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.

10.2 Randomisation

Please see section 6.6.

10.3 Analysis

A detailed statistical analysis plan (SAP) for the primary and secondary outcomes, including the economic analysis, will be approved by the DMC and TSC before analysis of unblinded data.

We will report data in line with the Consolidated Standards of Reporting Trials (CONSORT) statement showing attrition rates and loss to follow-up (Figure 1: flow diagram). All analyses will be carried out using the intention-to-treat principle, incorporating data from all participants including those who do not complete therapy. Every effort will be made to follow up all participants in both arms for research assessments.

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, baseline assessment for the outcome under investigation, treatment, time and time*treatment interactions. 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 (6m, 18m), 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 center.

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 the secondary outcomes at 12 months.

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 baseline PHQ-9 data may be imputed using baseline DISCS or GOS scores.

Economic Evaluation

The cost-utility of sertraline will be evaluated over a time horizon of 18 months. The primary analysis will take a health and social care perspective as recommended by the National Institute of Health and Care Excellence (NICE). In sensitivity analysis we will include productivity costs. Resource use data on primary health care and social care will be collected from patients using a bespoke questionnaire and valued using appropriate national unit costs (e.g., Unit Costs of Health & Social Care). Secondary health care resource use will be quantified through access to administrative records in HES, and valued using the relevant Payment by Results tariff for the associated Healthcare Resource Group code. Sertraline costs will be estimated using appropriate national sources and a consideration of routine prescribing costs. Quality adjusted life-years (QALYs) accrued over 18 months will be quantified by linear interpolation between measurements of quality of life using the EQ-5D-5L [51]. We will follow the relevant guidance at the point of analysis regarding the appropriate tariff set to apply to EQ-5D-5L responses. Missing data will be imputed using Multiple Imputation, provided assumptions of Missing at Random are considered reasonable.

We will report mean costs and QALYs at 18 months by trial arm, both raw and after adjusting for pre-specified covariates. Cost-effectiveness will be reported as the incremental cost-effectiveness ratio (ICER) of sertraline, assuming sertraline is both more expensive and more effective. We will also report the net monetary benefit for sertraline and placebo after valuing a QALY at £20,000. Uncertainty will be captured by bootstrapping the trial data. The data will be bootstrapped prior to imputation of missing data in each bootstrap replicate and estimation of the treatment effect on costs and QALYs using a regression model to adjust for baseline covariates. We will investigate the most appropriate regression models to apply after investigation of the relationship between covariates and the dependent variables. The impact of uncertainty will be reported as the cost-effectiveness acceptability curve across a range of values for a QALY from zero to £50,000. Subgroup analysis will be undertaken to report cost-effectiveness for patient with milder and more severe TBI severity.

11. Trial Steering Committee

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 (add funder), and the Co-sponsors (add sponsors). 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.

12. Data Monitoring Committee

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

4. The DMC considers the need for any interim analysis advising the TSC regarding the release of data and/or information

5. The DMC may be asked by the TSC, Project Sponsor or Project Funder to consider data emerging from other related studies

6. 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 are 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.

13. Direct Access to Source Data and Documents

The Investigator(s) will permit trial-related monitoring, audits, REC review, and regulatory inspections by providing the Sponsor(s), Regulators and REC direct access to source data and other documents (e.g. Participants' case sheets, blood test reports, X-ray reports, histology reports etc.).

14. Ethics & Regulatory Approvals

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of GCP and in accordance with all applicable regulatory requirements including UK Policy Framework for Health and Social Care v3.3 07/11/17 and any subsequent amendments.

This protocol and related documents will be submitted for review to Health Research Authority (HRA), REC, and to the MHRA for Clinical Trial Authorisation (CTA).

The CI will submit a final report at conclusion of the trial to the KHP-CTO (on behalf of the Sponsor) and the REC within the timelines defined in the Regulations. The KHP-CTO or delegate will upload the final report to a publicly registered database on behalf of the Sponsor.

15. Quality Assurance (QA)

Monitoring of this trial will be to ensure compliance with GCP and scientific integrity will be managed and oversight retained, by the KHP-CTO Quality Team.

16. Data Handling

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).

17. Data Management

For data collected, source data verification (SDV) worksheets will be prepared for each patient and data will be entered onto the MACRO eCRF database. The CI will act as a custodian for the data and any data queries will be raised with the trial manager or CI.

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.

Worksheets as Source Documents

Data will be entered directly onto the paper worksheets which will be considered the source document. Patients' electronic records will also be considered a source document. The source documents will be transcribed into MACRO 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 in signed consent forms. Additional information can be found in ICH E6, section 6.4.9.

The worksheets will consist of multisource data including a standardised self-report or clinician rated tools, procedure (venepuncture and saliva collection) and data extraction from routine medical records.

18. Publication Policy

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.

19. Insurance / Indemnity

Co-Sponsors insurance and indemnity schemes apply.

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.

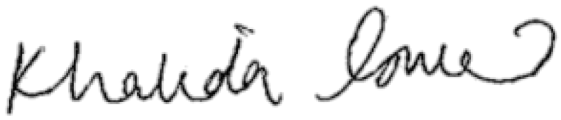
20. Financial Aspects

Funding to conduct the trial is provided by NIHR Project number 131125.

21. Archiving

At the end of this trial, all trial data will be stored in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006 and the 2018 Data Protection Act and archived in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006 as defined in the (Co)-Sponsor(s) Archiving SOP.

22. Signatures



Chief Investigator: Date: 17 Oct 2022

Print name KHALIDA ISMAIL

Trial Statistician……. Date

Print name NICK BECKLEY-HOELSCHER

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