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CLEAR
CLOZAPINE IN EARLY PSYCHOSIS

CLOZAPINE IN EARLY PSYCHOSIS (CLEAR): A MULTI-CENTRE, RANDOMISED CONTROLLED TRIAL OF CLOZAPINE FOR YOUNG PEOPLE WITH TREATMENT RESISTANT PSYCHOSIS IN REAL WORLD SETTINGS

Protocol (Version 6.0 27/08/24)

Trial Identifiers

EudraCT Number:	2021-006248-28
IRAS Number:	1004947
REC Number	22/LO/0723

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Protocol Short Title/Acronym	CLEAR
Trial Phase	Phase IV
Co-Sponsors name	King's College London South London and Maudsley NHS Foundation Trust
Chief Investigator	Professor James MacCabe
EudraCT number	2021-006248-28
IRAS number	1004947
Medical condition or disease under investigation	Treatment-resistant psychosis
Purpose of clinical trial	The trial will assess whether clozapine is more effective than treatment as usual (TAU, i.e. standard antipsychotics) in people < 25 years old, at the level of clinical symptoms, patient rated outcomes, quality of life and cost effectiveness.
Primary objective	To compare the change in total PANSS score at 12 weeks relative to baseline between patients treated with clozapine and TAU.
Secondary objectives	To compare clozapine treatment to TAU, over 1 year: i. Clozapine is associated with greater functional improvement, greater self-assessed improvement, better quality of life, better medication adherence and reduced service use. ii. Clozapine is associated with more severe adverse effects. iii. Clozapine is associated with better patient rated outcomes. iv. Clozapine is more cost-effective when clinical effectiveness, quality of life, service use and costs are combined.

	v. Clozapine has as great an advantage over TAU in people aged under 18 as it is in those aged 18-24. vi. Regarding mechanism of action, clozapine is associated with greater reduction in proinflammatory cytokines, brain glutamate and regional cerebral blood flow, and increase in anti-inflammatory cytokines and glutathione. vii. To evaluate the effectiveness of a decision support intervention for personal legal representatives through a randomised Study Within a Trial (SWAT)
Trial design	Multi-centre, randomised, rater-blinded, controlled clinical trial.
Endpoints	Change in total PANSS score after 12 weeks, relative to baseline.
Sample size	260 patients with treatment-resistant psychosis < 25 years old.
Summary of eligibility criteria	<u>Inclusion Criteria:</u> i. Age ≥12 and <25 years at randomisation. ii. Meets criteria for schizophrenia or related disorder, in the range in the range ICD-10v2016 F20.x, F22.x-F29.x iii. Meets NICE criteria for treatment resistance, defined as: a. Previous trials of at least two different antipsychotic drugs with adequate adherence (estimated <20% missed doses) – both treatment trials to exceed 4 weeks at adequate doses (within the dose range given in the British National Formulary and the British National Formulary for children) b. At least 1 of these trials must be with a second-generation drug. iv. Positive and Negative Syndrome Scale (PANSS) total ≥70, at least 2 items >4 v. Clinician Rating Scale [24] (CRS) ≥3 vi. English or Welsh language sufficient to participate vii. Capacity to give informed consent OR has a legal representative able to give consent to the trial.

	<u>Exclusion Criteria:</u> i. Psychosis predominantly caused by substance misuse. ii. Pregnancy. iii. Breastfeeding. iv. Women of child-bearing potential (WOCBP*) not using at least acceptable methods of contraception** during the trial (see 6.1 for definitions) v. Contra-indications to clozapine as listed in SmPC as follows: a. Hypersensitivity to the active substance or to any of the excipients, listed in section 6.1. b. Patients unable to undergo regular blood tests. c. History of toxic or idiosyncratic granulocytopenia/agranulocytosis (with the exception of granulocytopenia/agranulocytosis from previous chemotherapy). d. History of clozapine-induced agranulocytosis. e. Impaired bone marrow function. f. Uncontrolled epilepsy. g. Alcoholic and other toxic psychoses, drug intoxication, comatose conditions. h. Circulatory collapse and/or CNS depression of any cause. i. Severe renal or cardiac disorders (e.g. myocarditis). j. Active liver disease associated with nausea, anorexia or jaundice; progressive liver disease, hepatic failure. k. Paralytic ileus. l. Clozapine treatment must not be started concurrently with substances known to have a substantial potential for causing agranulocytosis; concomitant use of depot antipsychotics is to be discouraged. vi. Previous adequate trial of clozapine. vii. CNS disorders (ICD-10 G00-26; G40-41, G45-46; G80-94, G97). viii. Concurrent medications with documented interactions with antipsychotics. ix. Participation in a clinical trial involving any investigational medical product (licensed or unlicensed) within the last 3 months. x. Positive test for COVID-19 within the past 10 days.

	xi. For participation in the substudy MRI scan only, standard contraindications to MRI at 3 Tesla such as ferromagnetic or electronic implants.
IMP, dosage and route of administration	Clozapine, as per BNF guidance, oral
Active comparator product(s)	Treatment as usual (non-clozapine antipsychotics)
Maximum duration of treatment of a participant	12 weeks (treatment can be continued even after end of trial upon clinical teams' choice)
Version and date of protocol amendments	2.0 01/12/2022 3.0 01/03/2023 4.0 01/08/2023 5.0 19/02/2024 6.0 27/08/2024

2. Glossary of Terms

AE	Adverse Event
AR	Adverse Reaction
CA	Competent Authority
CGI-S	Clinical Global Impression – Severity
CGI-I	Clinical Global Impression – Improvement
CI	Chief Investigator
CRF	Case Report Form
CRS	Clinician Rating Scale
CRO	Contract Research Organisation
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
CTU	Clinical Trials Unit
DAI-10	Drug Attitude Inventory – 10 items
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
EC	European Commission
EI-AD-SUS	Early Intervention Adult Service Use Schedule
EMEA	European Medicines Agency
EQ5DY	Youth version of the EQ-5D
EU	European Union
EUCTD	European Clinical Trials Directive
EudraCT	European Clinical Trials Database
GASS-C	Glasgow Antipsychotic Side-effects Scale for Clozapine
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GSH	Glutathione
IB	Investigator Brochure
ICF	Informed Consent Form
IL	Interleukin
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
ISF	Investigator Site File (This forms part of the TMF)
ISRCTN	International Standard Randomised Controlled Trials Number
MA	Marketing Authorisation
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	Magnetic Resonance Imaging
NIMP	Non-Investigational Medicinal Product
PI	Principal Investigator
PIC	Participant Identification Centre
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
QP	Qualified Person
PANSS	Positive and Negative Syndrome Scale
RA	Research Assistant
rCBF	Regional Cerebral Blood Flow
RCT	Randomised Control Trial

REC	Research Ethics Committee
ReQoL-10	Recovering Quality of Life Questionnaire
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
SWAT	Study Within a Trial
TAU	Treatment as usual
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee

3. Background & Rationale

3.1. Background

Clozapine is an antipsychotic drug with unique efficacy. It is the only recommended treatment for treatment-resistant schizophrenia (TRS: failure to respond to at least two different antipsychotic drugs). In addition, it is the most effective of all antipsychotics in reducing hospital use, suicide, aggressive behaviour, violent crime, and substance misuse. However, it is also associated with a range of adverse effects which restrict its use, including blood dyscrasias, for which patients require haematological monitoring. As treatment resistance is increasingly recognised earlier during the course of the illness, the question of whether clozapine should be prescribed in children and young people is increasingly important. However, most research to date has been in older, chronic patients, and both the NICE Guideline Development Group and James Lind Alliance have highlighted the lack of evidence about the efficacy and safety of clozapine in people under age 25. At present, most young patients with schizophrenia who meet criteria for treatment resistance are treated with standard antipsychotics, rather than the clozapine that is recommended by NICE. The trial will assess whether clozapine is more effective than treatment as usual (TAU: standard antipsychotics), at the level of clinical symptoms, patient rated outcomes, quality of life and cost effectiveness. This is a multi-centre, open label, blind-rated, randomised controlled effectiveness trial of clozapine vs TAU (i.e. compared with other antipsychotics – clinician's choice) for 12 weeks in 260 children and young people with TRS (12-24 years old). We will recruit from NHS-funded secondary care, both inpatient and community settings, using a hub and spoke model, with 6 academic centres coordinating 20-30 recruitment sites. The primary outcome is the change in total blind-rated PANSS scores at 12 weeks from baseline. Secondary outcomes include blind-rated clinical global impression, patient-rated outcomes, quality of life, adverse effects, treatment adherence and service use. Patients will be followed up for 12 months with the potential for further follow-up using clinical records.

Treatment resistant schizophrenia (TRS), defined by NICE and most other treatment guidelines as non-response to at least two different antipsychotic drugs and a course of psychological treatment [1], affects around one third of people diagnosed with schizophrenia [2]. TRS is associated with severe long-term consequences on social, educational and occupational functioning, with total treatment costs between three and eleven times that of schizophrenia that is responsive to standard treatment [3]. Treatment resistance in schizophrenia is strongly associated with age at illness onset, with onset before age 25 predicting higher risk of subsequent treatment resistance [4]. Clozapine is the only antipsychotic to have superior efficacy in TRS and is the treatment of choice in adults with TRS. This is supported by evidence from randomised controlled trials [5, 6] although some doubt has been cast

on the strength of this evidence [7]. Pharmacoepidemiological studies have demonstrated the superiority of clozapine over other antipsychotics in reducing readmission [8], violent offending [9], self-harm [10] and all cause mortality [11]. Most of the evidence for the superiority of clozapine over other antipsychotics derives from studies in chronic patients; a recent meta-analysis found the median age in trials of clozapine to be 39 years with a median length of illness of 16 years [7]. The evidence for the efficacy of clozapine in younger patients is sparse, although it suggests that clozapine is superior to other antipsychotics in people under 18 with TRS. A recent retrospective study showed that the vast majority of paediatric patients (95%) admitted with or started on clozapine during an acute psychiatric hospitalization remained on clozapine at discharge, suggesting that it was clinically effective [12]. Furthermore, a Danish cohort study on early onset schizophrenia showed that the majority of patients (88.8%) prescribed clozapine had a favourable clinical response [13]. An unpublished secondary analysis from a recent meta analysis of RCTs comparing clozapine versus other antipsychotics [6] showed an effect size of -0.61 [95%CI -1.05 to -0.17] in children versus -0.36 [95%CI -0.60 to -0.11] in adults (Dan Siskind personal communication). However this is based on a meta-analysis of data from only 85 patients in 3 small non-UK RCTs [14–16]. There is thus a clear need for larger scale studies in younger patients. Clozapine is reserved as a third line treatment because of its associated adverse effects, which are more numerous and severe than those of most other antipsychotics [17]. The most problematic is the rare but potentially fatal adverse effect of agranulocytosis [18]. In order to reduce the risk of agranulocytosis, in the UK and most other developed countries, monitoring of the patient's full blood count is mandatory in clozapine-treated patients. There is evidence that psychiatrists unfamiliar with clozapine are reluctant to prescribe it, and that blood testing in particular acts as a barrier [19]. This may particularly apply to child and adolescent psychiatrists, who rarely encounter treatment resistant psychosis. Less than 0.5% of prescriptions for clozapine are in children and adolescents, and a survey of UK psychiatrists showed that only 40% of psychiatrists working in UK CAMHS services have ever prescribed clozapine [20]. The probable superior efficacy of clozapine in younger patients has to be balanced against its potentially inferior tolerability [21]. A recent literature review concludes that the risk-benefit ratio for clozapine use in young TRS patients is unclear, and that the question can only be resolved by conducting well powered studies that simultaneously measure safety and effectiveness [22]. The NICE guidance for schizophrenia and psychosis in adults (CG-178) and children (CG-155) recommend clozapine in patients whose illness has not responded to trials of at least two antipsychotics of adequate dose and duration. Nevertheless, the NICE Guideline Development Group and the James Lind Alliance have both identified the lack of evidence surrounding this recommendation, particularly with regard to overall cost-effectiveness. A well powered randomised controlled effectiveness trial is required to fill this gap.

No such study has been completed to date, probably reflecting the difficulties of recruitment in this patient group. We believe we, as a group, have the clinical reach, expertise and experience to conduct such a study in the UK.

The biological mechanisms that underlie the unique efficacy of clozapine are unclear. Better understanding of the mechanisms that mediate response to clozapine may help identify rationale new targets for drug development. Leading theories of schizophrenia pathogenesis include the linked processes of inflammation and excess glutamate release, leading to increased oxidative stress and brain metabolic demands which perfusion aims to correct. We propose that the efficacy of clozapine is linked to its actions on these pathways. Preclinical research has shown that, compared to most other antipsychotics, clozapine may be particularly effective in reducing expression of proinflammatory cytokines (e.g. IL-6), increasing expression of anti-inflammatory cytokines (e.g. IL-10) [23,24], has greater antioxidant effects [25-27] and can reduce brain glutamate [28-30] In a recent observational study in patients with TRS, we found that during 12 weeks of clozapine treatment glutamate decreases in the striatum and that this is associated with the degree of clinical improvement [31]. However, as there was no comparison group of patients on antipsychotics other than clozapine, we were unable to attribute these effects to clozapine specifically.

Therefore, this trial will include a mechanistic sub-study embedded within the main clinical trial, which will include a subgroup of participants and study sites. In this study we will investigate whether clozapine is better able to reduce proinflammatory cytokines, brain glutamate and rCBF and increase peripheral and central markers of oxidative defence than standard antipsychotic treatment, and if these mechanisms are related to symptom improvement. A secondary aim is to determine whether these variables, measured prior to clozapine initiation, predict subsequent response.

In addition to evaluating the effectiveness and mechanisms of clozapine, CLEAR will also contribute to the trials methodology evidence-base to improve the design and conduct of future trials through embedding a Study Within A Trial (or SWAT). A SWAT is a self-contained research study that is embedded within a host trial or trials with the aim of evaluating alternative ways of delivering or organising a particular trial process [56].

Recruiting adults (over 16 years) who lack capacity into trials can be challenging [57]. This is due in part to the psychological stress and uncertainty that family members or close friends may experience when asked to make what can be complex and challenging decisions, with some experiencing decisional and emotional burden as a result [58]. A decision aid (DA) has been developed to help

personal legal representatives of participants over the age of 16 who lack capacity to consent for themselves, to make informed decisions about participation and to reduce the decisional burden they experience [59]. The aim of the CONSULT SWAT is to evaluate the effectiveness and cost-effectiveness of the DA in approx. 5 host trials, including CLEAR [60].

Personal legal representatives involved in CONSULT will be invited to take part in an optional interview to talk about their experience, alongside interviews with members of the research teams who provided the study information and DA. Consent will be obtained by the CONSULT study team at Cardiff University prior to participation in an optional interview. Interviews and all data-analysis will be undertaken by the CONSULT study team. SWAT processes will be aligned with CLEAR to minimise any additional burden for participants, families, or researchers.

3.2. Rationale for study design

It is established in previous trials and in clinical guidelines that a 12 week timeframe is required in order to determine response to clozapine. The CLEAR trial duration of 12 weeks will allow to identify response to treatment without delaying a switch of medication in case of no response. Follow up for at least 52 weeks is an explicit requirement of the NIHR, who are funding the trial, and this was set out in the funding call. However, we feel it would be unethical to force participants to continue on a treatment for the full 52 weeks without the option of switching to a different treatment if it was clear that they were not responding or were suffering intolerable adverse effects. On the other hand, the trial design will allow participants to continue the allocated treatment if effective. The choice of either stopping or continuing the allocated treatment in the long term will reflect the efficacy of the drug itself. We believe that long-term follow-up is essential in TRS, as it is a chronic and highly disabling condition. Furthermore, some antipsychotic-related adverse events typically develop over time (e.g. weight gain, diabetes). For these reasons, the CLEAR study design will provide a longer follow-up of 52 weeks to identify efficacy and safety of clozapine vs. TAU in the long term without requiring longer than necessary trial of medication.

3.3. Risk and benefit evaluation

The CLEAR trial will contribute to knowledge about the efficacy and safety of clozapine in young people with TRS, providing strong evidence to reinforce clinical guidance.

People with severe mental illness, especially TRS, are often not included in trials due to the impact of their symptoms on capacity, and there is evidence of systemic exclusion from research leading to lack of strong generalisable results in TRS research. This is even more true in young people, especially <16s, whose consent to participate needs additional consideration. The CLEAR trial will allow young people with TRS to participate in research and contribute to more generalisable knowledge on the best management of TRS in this population. Furthermore, the CLEAR study is designed to be as close to real-world settings as possible to reflect everyday clinical practice. This will allow to further improve the generalisability of the results and hopefully facilitate clinicians for the duration of the trial. Additionally, such design will add as little burden as possible to the participants, who will be likely to be already struggling due to their illness.

Another potential benefit of the CLEAR study design is the possibility to switch antipsychotic after the end of the 12 weeks trial if clinically indicated. This will allow participants who have not tolerated or responded to the allocated treatment to switch drug whilst continuing to be part of the study. This will also allow people who have been allocated to TAU to switch to clozapine, which is currently the recommended treatment for TRS, and which will therefore not be substantially delayed by the participation in the trial.

Participants in both arms will be patients who are already taking antipsychotics and participation in the trial will merely determine whether clozapine or another antipsychotic is taken for a 12 week period. All antipsychotics are associated with potentially severe adverse events (SAEs). All participants will be closely monitored for adverse events, and managed by the treating clinicians. SAEs will be promptly reported to the KHP-CTO and CI. As no previous trial has focused on clozapine-related adverse events in young adults, this trial will be of unique importance to add evidence-based data on the safety of clozapine in young people. Participating in the CLEAR study will allow young people with TRS on antipsychotic medications to have a closer and more structured monitoring of the potential adverse events.

The risks of participation include the adverse effects that are unique to clozapine, i.e. not shared with other antipsychotics. These are listed in the SmPC. It should be noted that NICE guideline recommend clozapine treatment for patients with treatment resistant psychosis, so the risks are not unique to participants in the trial.

4. Trial Objectives and Design

4.1. Trial Objectives

The purpose of the trial is to assess whether clozapine is more effective than treatment as usual (TAU: standard antipsychotics) in real-world settings, over a 12-week period. The primary objective is to compare the treatments on the change in total PANSS score from baseline to 12 weeks. The secondary objectives are to compare the treatments on function, side effects, quality of life, subjective improvement and cost effectiveness.

4.2. Primary endpoints

The primary endpoint of the study is the change in total PANSS score assessed after a treatment period of 12 weeks. Participants will be assessed by a centralized blinded experienced rater.

4.3. Secondary endpoints

Secondary endpoints include change in overall clinical impression (CGI) [32], clinician rated level of adherence (CRS) [33], side effects (GASS-C) [34], quality of life (EQ-5D-Y) [35], and subjective experience (DAI-10) [36], psychotropic treatment, service use and readmission rate, (EI-AD-SUS) [37], and change in PANSS sub scale (positive, negative and general) [38]. We will also combine these outcomes (EQ-5D-Y and total PANSS score) with service use data (EI-AD-SUS) to compare treatments on cost effectiveness.

For the mechanistic sub-study, additional endpoints include change in brain glutamate, regional cerebral blood flow (rCBF), and glutathione (GSH) and peripheral cytokines and GSH over the treatment period of 12 weeks.

For the CONSULT SWAT, endpoints include the quality of decision-making by personal legal representatives, CONCORD [61], alongside qualitative data exploring family/close friends' and researchers' experiences, and the costs involved (resource use data).

4.4. Trial Design

4.4.1. Treatment

Intervention: Clozapine, oral, flexible dose within dose range defined by British National Formulary (BNF); (Maximum dose = 900 mg per day), at the discretion of the prescriber, for 12 weeks. Following this, if clozapine is continued, it will no longer be classified as an investigational medicinal product.

Control: Any oral antipsychotic in TAU group ATC code – N05A (other than clozapine ATC code – N05AH02 and Lithium – N05AN), within licensed dose range defined by BNF, for 12 weeks. The choice of antipsychotic will be agreed by the clinical team in collaboration with the participant, and the dose titrated to achieve the best balance between response and adverse effects.

4.4.2. Target population

Children and young people under age 25 with treatment resistant schizophrenia as defined by NICE (CG178, Section 1.5.7.2) as having failed to respond to at least two antipsychotic treatments in adequate doses and having also failed to engage in and/or respond to psychological treatments. The inclusion and exclusion criteria are specified in greater detail in 6.1.

4.4.3. Design

Multi-centre, open label, blind-rated (primary outcome), 1:1 randomised controlled effectiveness trial of clozapine versus treatment as usual in children and young people (<25) with treatment resistant schizophrenia.

4.5. Trial Flowchart

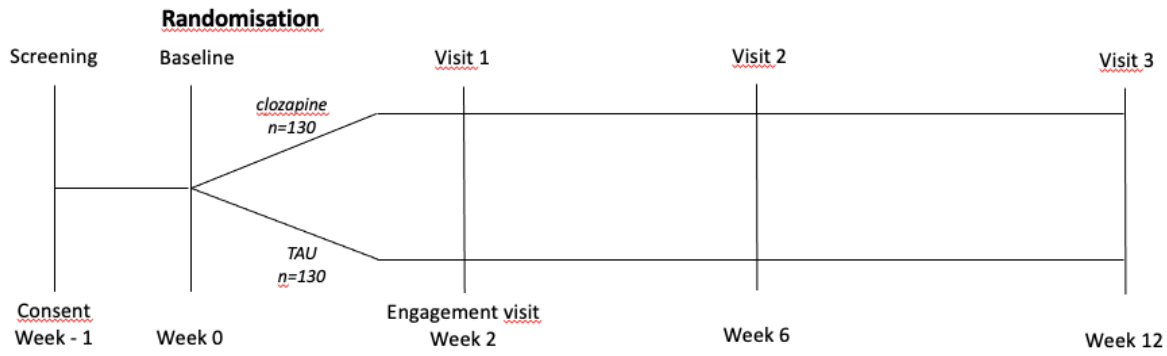


Figure 1. Trial design treatment period (n=260)

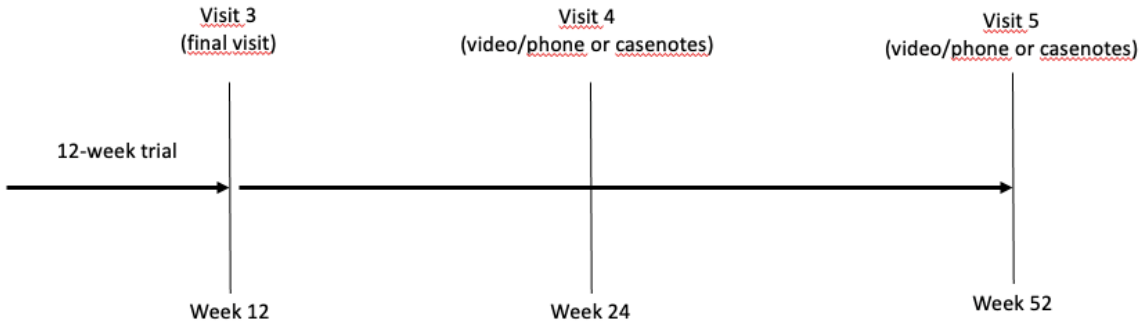


Figure 2. Trial design follow-up period (n=260)

	Screening visit	**Baseline visit**	**Randomisation**	***Treatment with study drug starts***	**Visit 1**	**Visit 2**	**Visit 3** (1^ outcome)	**Visit 4**	**Visit 5**
			Week -1	Day 1	week 2 (+/- 3 days)	week 6 (+/- 3 days)	week 12 (+/- 7 days)	week 24 (+/- 7 days)	week 52 (+/- 7 days)
Informed consent	x								
Inclusion/exclusion criteria review	x	x							
Sociodemographic data	x								
Medical/psychiatric history	x								
Medication use	x	x			x	x	x	x	x
Smoking status	x	x			x	x	x	x	x
Pregnancy Test		x							
Randomisation			x						
Clozapine plasma levels (in clozapine arm only, clinicans to request)					x	x	x		
Lipid, and prolactin, HbA1c and LFTs (clinicians to request)		x					x		
Adverse events (spontaneous)	x	x			x	x	x	x	x
Height		x							
Weight		x			x	x	x	x	
Primary outcome									
PANSS		x				x	x	x	x
Secondary outcomes									
CGI-S		x							
CGI-I						x	x	x	x
GASS-C		x				x	x	x	x
EQ-5D-Y		x				x	x	x	x
CRS	x	x				x	x	x	x
DAI-10		x				x	x	x	x
ReQoL-10		x				x	x	x	x
EI-AD-SUS		x				x	x	x	x
Switch, continue or end antipsychotic (clinical decision)							x		
Mechanistic Sub-Study*									
MRI scan		x					x		

Blood sample		x					X		
CONSULT SWAT**									
Randomisation	x								
CONCORD scale	x								

Table 1: Schedule of assessments
** The mechanistic sub-study will only be conducted at selected study sites (King's College London, Universities of Oxford and Manchester) and is optional for participants recruited at those sites.*
***Personal legal representatives will be approached by CLEAR Research Assistants to take part in CONSULT SWAT; randomised 1:1 ratio to receive the decision aid in addition to standard legal representative CLEAR information sheet and both groups will complete the CONCORD scale.*

5. Trial Medication

5.1. Investigational Medicinal Product

All the drugs being evaluated in the study are licenced in the UK for the treatment of schizophrenia and other psychoses, so they will be prescribed and dispensed using routine NHS systems.

Both Clozapine and all medicines in the TAU comparator control arm are considered IMPs for the purposes of the study. Clozapine is a licenced treatment for treatment-resistant schizophrenia in the UK. It is recommended by NICE guidelines at all ages, including in the NICE guideline CG155 [Psychosis and schizophrenia in children and young people: recognition and management]. It is licenced for age 16 and above, and it is clinically used from 12 years old [39-44]. It is distributed by Britannia Pharmaceuticals Limited (Denzapine), Mylan (Clozaril) and Leyden Delta B.V. (Zaponex).

As this is a Type A trial, with no higher risk to the participant than standard of care, and the trial will use commercially available IMP with no modifications and which will be used in accordance with the SmPC, no additional labelling is required.

5.2. Dosing Regimen

Intervention: Clozapine, oral, flexible dose within dose range defined by BNF, at the discretion of the prescriber, for a minimum of 12 weeks. Clozapine has unpredictable pharmacokinetics with high heterogeneity in plasma concentration, depending on age, sex, smoking status and genetics of the liver enzymes that metabolise clozapine, especially CYP-1A2 and -2D6. It also requires titration over the first 2 weeks up to therapeutic doses to minimise postural hypotension, and the optimal balance between efficacy and adverse effects can only be achieved on an individual basis. Enforcing a fixed dose would reduce the acceptability of the trial to patients and clinicians and affect recruitment.

The previously prescribed antipsychotic can be titrated down during the first 2 weeks of clozapine treatment, but must be stopped within the first two weeks.

Control: Any oral antipsychotic other than clozapine, (ATC code = N05A) within licensed dose range defined by BNF, for a minimum of 12 weeks. The choice of antipsychotic will be agreed by the clinical team in collaboration with the participant, and the dose titrated to achieve the best balance between response and adverse effects. The full list of drugs available to be prescribed in the comparator arm is listed below:

- AMISULPRIDE
- ARIPIPRAZOLE
- ASENAPINE
- BENPERIDOL
- CARIPRAZINE
- CHLORPROMAZINE
- FLUPENTIXOL
- HALOPERIDOL
- LEVOMEPROMAZINE
- LOXAPINE
- LURASIDONE
- OLANZAPINE
- PALIPERIDONE
- PERICYAZINE
- PIMOZIDE
- PROCHLORPERAZINE
- PROMAZINE
- QUETIAPINE
- RISPERIDONE
- SULPIRIDE
- TRIFLUOPERAZINE
- ZUCLOPENTHIXOL

The previously prescribed antipsychotic can be titrated down over the first 2 weeks of the trial antipsychotic treatment but must be stopped within the first 2 weeks.

5.3. IMP Risks

Risks, special precautions and contra-indications to clozapine (ATC code – N05AH02) and TAU (ATC code N05A, except clozapine (N05AH02) and Lithium (N05AN) are listed in the applicable SmPCs for each drug product.

5.4. Drug Accountability

As this is a Type A trial, drug accountability will be according to local pharmacy protocols. Treatments will be prescribed by the participants' psychiatrist using local prescriptions and dispensed by their local pharmacies as it is per standard care.

5.5. Storage of IMP

IMP and TAU to be stored according to the applicable SmPCs and under local pharmacy protocols.

5.6. Participant Compliance

Medication adherence will be determined by clozapine plasma level as in standard care, and via the Clinician Rating Scale (CRS) and the Drug Attitude Inventory-10 (DAI-10).

5.7. Concomitant Medication

Any concurrent medication will be permitted except where documented interaction with antipsychotics exists. A complete listing of all concomitant medication received during the treatment phase will be recorded in the eCRF and source data documents.

6. Selection and Withdrawal of Participants

6.1. Inclusion and Exclusion Criteria

Inclusion Criteria:

i. Age ≥12 and <25 years at randomisation
ii. Meets criteria for schizophrenia or related disorder, in the range ICD-10v2016 F20.x, F22.x-F29.x
iii. Meets NICE criteria for treatment resistance, defined as:
    a. Previous trials of at least two different antipsychotic drugs with adequate adherence (estimated <20% missed doses) – both treatment trials to exceed 4 weeks at adequate doses (within the dose range given in the British National Formulary and the British National Formulary for children).
    b. At least 1 of these trials must be with a second-generation drug.
iv. Positive and Negative Syndrome Scale (PANSS) total ≥70, at least 2 items >4
v. Clinician Rating Scale [24] (CRS) ≥3.
vi. English or Welsh language sufficient to participate.

vii. Capacity to give informed consent OR has a legal representative able to give consent to the trial.

Exclusion Criteria:

i. Psychosis predominantly caused by substance misuse.

ii. Pregnancy.

iii. Breastfeeding.

iv. Women of child-bearing potential (WOCBP*) not using at least acceptable methods of contraception** during the trial

v. Contra-indications to clozapine as listed in SmPC as follows:

   a. Hypersensitivity to the active substance or to any of the excipients, listed in section 6.1.
   b. Patients unable to undergo regular blood tests.
   c. History of toxic or idiosyncratic granulocytopenia/agranulocytosis (with the exception of granulocytopenia/agranulocytosis from previous chemotherapy).
   d. History of clozapine-induced agranulocytosis.
   e. Impaired bone marrow function.
   f. Uncontrolled epilepsy.
   g. Alcoholic and other toxic psychoses, drug intoxication, comatose conditions.
   h. Circulatory collapse and/or CNS depression of any cause.
   i. Severe renal or cardiac disorders (e.g. myocarditis).
   j. Active liver disease associated with nausea, anorexia or jaundice; progressive liver disease, hepatic failure.
   k. Paralytic ileus.
   l. Clozapine treatment must not be started concurrently with substances known to have a substantial potential for causing agranulocytosis; concomitant use of depot antipsychotics is to be discouraged.

vi. Previous adequate trial of clozapine.

vii. CNS disorders (ICD-10 G00-26; G40-41, G45-46; G80-94, G97).

viii. Concurrent medications with documented interactions with antipsychotics.

ix. Participation in a clinical trial involving any investigational medical product (licensed or unlicensed) within the last 3 months.

x. Positive test for COVID-19 within the past 10 days.

xi. For participation in the substudy MRI scan only, standard contraindications to MRI at 3 Tesla such as ferromagnetic or electronic implants.

** WOCBP defined as: 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.

*** acceptable methods of contraception include:*

- *progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action*
- *male or female condom with or without spermicide ****
- *cap, diaphragm or sponge with spermicide ****

**** A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are also considered acceptable, but not highly effective, birth control methods*

Acceptable methods are the <u>minimum requirement.</u> It should be noted that the requirement for 'at least acceptable methods of contraception' would include the above methods but also include all 'highly effective' methods listed below:

- *combined (estrogen and progestogen containing) hormonal*
- *contraception associated with inhibition of ovulation 1:*
    - *oral*
    - *intravaginal*
    - *transdermal*
- *progestogen-only hormonal contraception associated with inhibition of ovulation 1:*
    - *oral*
    - *injectable*
    - *implantable*
- *intrauterine device (IUD)*
- *intrauterine hormone-releasing system (IUS)*
- *bilateral tubal occlusion*
- *vasectomised partner*
- *sexual abstinence (if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments).*

6.2. Selection of Participants

Recruitment will follow a hub and spoke model. Six participating academic centres (KCL, UCL, Oxford, Birmingham, Manchester and Cardiff) will act as a coordinating hub for the surrounding population,

liaising with 20 - 30 local clinical recruiting centres. NIHR LCRNs are involved in the recruitment process.

6.3. Consent

During the screening visit, the patient's capacity to consent to the study will be assessed. Overall responsibility for the taking of informed consent under GCP guidelines will rest with the local PI. They will 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. Moreover, given the particular sensitivities of assessing capacity in minors, capacity to consent will be assessed by the local psychiatrist or via video link by the study psychiatrist following GCP guidelines. If the patient lacks capacity, a legal representative will be sought. During a joint visit with the RA and the clinician, after checking understanding of the participant and clarifying any concerns, the clinician will obtain informed consent, informing the participant of their rights according to GCP.

In addition to the ethical considerations pertaining to any RCT, there are three ethical aspects to this trial that require further consideration:

a) Some of the participants may lack capacity to give informed consent to the trial.
b) Some of the participants may be detained in hospital under the Mental Health Act, which will usually entail a requirement to stay in hospital and may also include a requirement to take treatment. It should be noted that many patients detained patients under the Mental Health Act retain the capacity to consent to research.
c) Some participants will be under 16 and thus prohibited under the Medicines for Human Use (Clinical Trials) Regulations from giving consent to participate in a CTIMP.

All three of these issues can be addressed by the appointment of a legal representative where potential participants lack capacity to consent to the trial. Under the UK Clinical Trials Regulation No 536/2014, a relative or friend may act as legal representative The legal representative must decide whether the person lacking capacity should participate in the trial on the basis of what they would have wanted had they the capacity to choose for themselves, their 'presumed will'. The legal representative will be given the opportunity to understand the objectives, risks, and inconveniences. If a participant is deemed to gain capacity during their time in the study, consent should be re-sought.

For children under 16, a legal representative will consent on their behalf. Young adults over the age of 16 are able to consent for themselves if deemed to have capacity to understand the research and their involvement. If participants reach the age of 16 (with a legal representative e.g. parent or

guardian initially signing on their behalf) whilst in the study and deemed to have capacity, consent should be re-sought. For further information please visit https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/research-involving-children/

Family members or close friends approached to act as a personal legal representative (for CLEAR participants 16 years old and over) will be given the opportunity to take part in CONSULT SWAT and randomised 1:1 ratio to receive the receive the DA in addition to the standard information sheet containing information about CLEAR compared with those who receive the standard information sheet alone. Both groups will be provided with brief information about CONSULT and asked to complete a questionnaire about their experience of making a decision. Responses from those who received the booklet and those who did not will be compared to see if it increased their knowledge and decision-making. Return of the questionnaire will indicate consent to participate in the CONSULT SWAT and for their anonymised data to be shared with the CONSULT study team at Cardiff University. Participants (i.e. CLEAR's personal legal representatives) will be given the option of providing their contact details if they are willing to be contacted about participating in an interview with the CONSULT team.

6.4. Randomisation Procedure / Code Break

This trial is a single-blind, randomised, controlled trial. The raters will be centralised and blinded to minimise observer bias.

A web based randomisation system will be designed, using the bespoke KCTU randomisation system. The randomisation system will be created in collaboration with the trial analyst/s and the CI and maintained by the King's Clinical Trials Unit for the duration of the project. It will be hosted on a dedicated server within KCL.

The CI or delegate will request usernames and passwords from the KCTU. System access will be strictly restricted through user-specific passwords to the authorised research team members. It is a legal requirement that passwords to the randomisation system are not shared, and that only those authorised to access the system are allowed to do so. If new staff members join the study, a user-specific username and password must be requested via the CI or delegate (e.g. Trial Manager) from the KCTU team and a request for access to be revoked must be requested when staff members leave the project. Study site staff experiencing issues with system access or functionality should contact the CI or delegate (e.g. Trial Manager) in the first instance.

Once the participant is registered i.e. has their data entered into the MACRO database, a unique pin will be generated. This will then be entered along with participant initials and date of birth on the randomisation system, and an allocation will be returned. NHS number, email addresses, participant names and addresses and full postcodes will not be entered into the randomisation system or the MACRO database. The unique pin number will be entered onto the trial identification log along with participant identification details, which is kept in the Investigator Site File. No data will be entered onto the randomisation system unless a participant, or their legal representative, has signed a consent form to participate in the trial. Randomisation will be undertaken centrally by the co-ordinating study team, by authorised staff onto the randomisation system by going to www.ctu.co.uk and clicking the link to access the randomisation system. A full audit trail of data entry will be automatically date and time stamped, alongside information about the user making the entry within the system.

The CI team will undertake appropriate reviews of the data entered onto the MACRO database, in consultation with the project analyst, for the purpose of data cleaning. No data can be amended in the randomisation system, however CI or delegate (e.g. Trial Manager) may request King's Clinical Trials Unit to add notes against individual subject entries to clarify data entry errors.

Upon request, KCTU will provide a copy of the final exported randomisation and main trial datasets to the CI and trial statisticians and the CI will onward distribute as appropriate.

Randomisation will be at the level of the individual using the method of block randomisation with randomly varying block sizes stratified by age group (<18 or ≥18) and sex.

There is no emergency code break as the trial is open-label.

6.5. Blinding

There will be four blinded members of the study team: two research psychiatrists, one for adult participants and the other for child participants (each with appropriate training for that age group), the Chief Investigator (Prof MacCabe) and Co-Chief Investigator (Prof Santosh). The research psychiatrists will conduct the blinded assessments where possible, but when unavailable, these will be conducted by the CI and Co-CI. All four blinded raters will be blind to treatment allocation. They will not be informed which treatment arm the participants are in, and will not enquire about the participant's treatment or side effects. The participants will be instructed by the RA not to mention their treatment or side effects to the research psychiatrists. The eCRF will have a blinded section containing only the participant's study ID, and the blind-rated measures which are the PANSS scores and CGI. The blinded raters will not have access to the non-blinded sections of the eCRF.

Levels of blinding are clarified in the below table:

Group or individual blinded	Information withheld	Method of blinding
Person assigning participants to groups	Group assignment	Concealed allocation schedule
Chief investigators	Group assignment	Not told of group assignment (e.g. no knowledge of A/B)
Outcome assessors	Group assignment	Not told of group assignment (e.g. no knowledge of A/B)
Trial manager	Data split by group	No knowledge of accumulating trial data split by group
Research Assistants	Data split by group	No knowledge of accumulating trial data split by group
Site PIs and clinicians	Data split by group	No knowledge of accumulating trial data split by group
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

6.6. Withdrawal of Participants

Participants have the right to withdraw from the study at any time for any reason. Any patient who withdraws consent will be withdrawn from the study. The investigator also has the right to withdraw participants from the study drug in the event of inter-current illness, AEs, SAEs, SUSARs, protocol violations, cure, administrative reasons or other reasons. It is understood by all concerned that an excessive rate of withdrawals can render the study un-interpretable; therefore, unnecessary withdrawal of participants should be avoided. Should a participant decide to withdraw from the study, all efforts will be made to report the reason for withdrawal as thoroughly as possible. Should a participant withdraw from study drug only, efforts will be made to continue to obtain follow-up data, with the permission of the participant. Where a participant withdraws due to a serious adverse event, the study team will conduct appropriate safety follow-up in collaboration with the clinical team.

6.7. Expected Duration of Trial

The end of trial will be defined as the last recruited participant's visit at week 52. Each individual participant will remain on treatment for 12 weeks and will be followed-up for 12 months through clinical notes and, whenever possible, video link assessments (week 24 and 52).

6.8. End of Trial Treatment Period

After the 12-week treatment period, the treatment period will end and the participant and treating team will have complete freedom to decide what treatment, if any, the participant takes. At this point they will have left the trial and will only be followed up, with no further trial interventions. The participants will be followed up at 26 and 52 weeks. No study-specific safety follow-up is required.

7. Trial Procedures

7.1. By Visit

The location of the visits will be determined locally. Visits can be conducted remotely when deemed appropriate. All data will be collected via an electronic case report form (eCRF).

1) Screening visit
    - Inclusion/exclusion criteria review: The RA will visit the potential participant with a member of the clinical team. The clinician will confirm that the participant meets the eligibility criteria. The inclusion/exclusion criteria will be reviewed and eligibility confirmed after PANSS has been completed at Baseline visit.
    - Informed consent: The participant will be given information about the study and encouraged to ask any questions and consult widely with family, friends, clinicians and other advisors. The patient's capacity to consent to the study will be assessed, usually by the treating psychiatrist. If he/she lacks capacity, a legal representative will be sought (see Ethics for more details). Any queries that can not be addressed by the RA will be escalated to the research psychiatrist or the local PI. No clinical trial procedures will be conducted prior to taking consent. Potential participants will be given a written information sheet about the trial and be given sufficient time to read and consider the study information prior to deciding whether to take part. A second joint visit with the RA and a clinician may be required. After checking understanding and clarifying any concerns, the clinician will obtain informed consent, informing the participant of their rights according to GCP.
    - If a personal legal representative is involved, CLEAR RAs will provide the additional CONSULT SWAT envelope with the CONCORD scale for completion and either a DA booklet (if randomised to receive) or a blank notebook.
    - Adverse events (on current medication/treatment)
    - Data collection at this visit will include, sociodemographic data including ethnicity, smoking status, medical/psychiatric history, medication use past/current and the clinician rating scale (CRS).

2) Baseline
    - Inclusion/exclusion criteria review.
    - Medication use past/current.
    - Smoking status
    - A routine clinical blood sample will be taken to measure Lipid, and prolactin, HbA1c and LFTs (this can be up to 28 days before treatment start)
    - Adverse events (on current medication/treatment)
    - Height and weight.
    - Assessments conducted will be PANSS, CGI-S, GASS-C, EQ5DY3L, CRS, DAI-10, ReQoL-10, EI-AD-SUS.
    - PANSS and CGI-S assessment will take place via a 4G-enabled laptop over an encrypted video link by the blinded centralised physician rater. The blinded rater will be the research psychiatrist, or if he/she is unavailable, the Chief Investigator (Adults) or co-CI (under age 18).
    - Urine pregnancy test for females of child bearing potential
    - MRI scan (participants in the optional mechanistic sub study only)
    - Additional blood sample for peripheral biomarkers (participants in the optional mechanistic sub study only)

3) Randomisation – participant will be randomly assigned to one of two arms of the study, to take clozapine or another antipsychotic (TAU). Randomisation occurs using an online system hosted by the King's Clinical Trials Unit.

4) Treatment with clozapine or another antipsychotic will commence (within 2 weeks of randomisation) **and the day treatment starts will be defined as day 1**.

5) Visit 1 at 2 weeks after start of treatment (+/- 3 days).
    - The 2-week visit is an engagement visit to ensure the patient is participating in the study, record any adverse effects and to address any concerns.
    - Medication use current
    - Smoking status
    - Weight

- For those participants taking clozapine a routine clinical blood sample will be taken to measure clozapine plasma levels.
- Treatment with study drug continues.

6) Visit 2 at 6 weeks (+/- 3 days).
   - Medication use current
   - Smoking status
   - Weight
   - For those participants taking clozapine a routine clinical blood sample will be taken to measure clozapine plasma levels.
   - Adverse events
   - Assessments conducted by the RA will include GASS-C, EQ5DY, CRS, DAI-10, ReQoL-10, EI-AD-SUS.
   - PANSS and CGI-I assessment will take place via a 4G-enabled laptop over an encrypted video link by the blinded centralised physician rater. The blinded rater will be the research psychiatrist, or, if he or she is unavailable, the Chief Investigator (Adults) or co-CI (under age 18)
   - Treatment with study drug continues.

7) Visit 3 at 12 weeks (+/- 7 days)
   - Medication use current
   - For those participants taking clozapine a routine clinical blood sample will be taken to measure clozapine plasma levels.
   - All participants will have a routine clinical blood sample to measure Lipid, and prolactin, HbA1c and LFTs
   - Adverse events
   - Smoking status
   - Weight
   - Assessments conducted by the RA will include GASS-C, EQ5DY, CRS, DAI-10, ReQoL-10, EI-AD-SUS.
   - PANSS and CGI-I assessment will take place via a 4G-enabled laptop over an encrypted video link by the blinded centralised physician rater. The blinded rater will be the research psychiatrist, or, if he or she is unavailable, the Chief Investigator (Adults) or co-CI (under age 18)

- Switch, continue or end antipsychotic (clinical decision)
- MRI scan (participants in the optional mechanistic sub study only)
- Additional blood sample for peripheral biomarkers (participants in the optional mechanistic sub study only)

8) Visit 4 at 24 weeks (+/- 7 days)
    - Completed by telephone or video consultation.
    - Medication use current.
    - Smoking status
    - Weight (self -reported)
    - Adverse events.
    - Assessments conducted will include PANSS, CGI-I, GASS-C, EQ5DY, CRS, DAI-10, ReQoL-10, EI-AD-SUS.

9) Visit 5 at 52 weeks (+/- 7 days)
    - Completed by telephone or video consultation.
    - Medication use current.
    - Adverse events
    - Assessments conducted will include PANSS, CGI-I, GASS-C, EQ5DY, CRS, DAI-10, ReQoL-10, EI-AD-SUS.

7.2. Assessments

7.2.1. Centralised, remote, blind assessment by Research Psychiatrists

a) Positive and Negative Syndrome Scale (PANSS) is the primary outcome, the most well validated standardised rating scale in clinical trials of psychosis.
b) Clinical Global Impression Scale (CGI). It is simple and designed to capture the overall clinical judgement of an experienced clinician, hence it will be administered by the research psychiatrist as opposed to the RA.

7.2.2. Data collected by RA

a) Medical history: Full history of antipsychotic use, doses and response.
b) Patient-rated outcome measure (PROM): Drug Attitude Inventory (DAI-10).

c) Adverse events: Glasgow Antipsychotic Side-effect Scale for Clozapine. It is a modification of the GASS, a well validated side effect scale, with additional questions pertaining to common adverse effects of clozapine.
d) Adverse events: Spontaneous report. The RAs will prompt for any other suspected adverse reactions and record these.
e) Adherence: Clinician Rating Scale (CRS).
f) Health-related quality of Life: EQ-5D-Y, a questionnaire recommended by NICE, which may be used to generate QALYs.
g) Service use for economic evaluation: Early Intervention Adult Service Use Schedule (EI-AD-SUS). It is specifically designed for use in children and young adults with psychosis, may be used to derive nationally applicable unit costs for total service use.
h) Recovering Quality of Life-10 items measure (ReQoL-10). It is specifically designed as a participant-rated QoL outcome measure for severe mental illness.

7.3. Laboratory Tests

Laboratory measurements will be collected at baseline (the sample can be taken up to 28 days before treatment start) and at 12 weeks. Blood tests include HbA1c, lipids, prolactin and LFTs. As per standard care, the clozapine arm will undergo weekly blood monitoring to check FBC and clozapine plasma levels as per standard care. As the blood tests required for the study would be performed in standard care at treatment initiation and 12-week follow-up, the local clinical team will perform venepunctures and local labs will conduct the analyses.

7.4. MRI Scans

For participants in the mechanistic sub-study only, MRI brain scans will be acquired at 3 Tesla at baseline and at 12 weeks (+/- 7 days). The MRI scans will take approximately 60 minutes and will include collection of structural brain images, levels of glutamate and GSH using proton magnetic resonance spectroscopy and rCBF using arterial spin labelling.

London participants will be scanned at the Centre Neuroimaging Sciences, King's College London. Participants from the Manchester area will be scanned at the NIHR/Wellcome Trust Manchester Clinical Research Facility, Manchester University NHS Foundation Trust (MFT). Oxford participants will be scanned at the Wellcome Centre for Integrative Neuroimaging (WIN), University of Oxford.

7.5. Blood sampling for biomarkers and sample storage

For participants in the mechanistic sub-study only, an additional blood sample will be acquired at baseline and at 12 weeks. Blood samples will be collected via venous puncture according to the study blood sampling manual. Where practical, these blood samples for biomarkers can be collected at the same time as the blood samples for laboratory tests, to reduce the number of venepunctures (providing they are +/- 7 days from the baseline and visit 3 date). The blood samples can be collected either at the participant's clinical team base / ward or at the relevant University research facility. The participant will give up to 110 mL (about 6 tablespoons) of blood in total during the study (up to 55 ml at baseline and at week 12); this is in line with sampling guidelines. The blood samples will be used to measure levels of: pro- and anti-inflammatory markers (cytokines, immunoglobulins, lymphocytes); oxidative defence (GSH), proteomics, genetics and epigenetics.

While study data collection is ongoing, samples will be stored within -80 freezers owned by University and/or local NHS Trust in London, Oxford and Manchester. Transportation by courier to King's College London laboratories for central storage will be organised when required. Details of sample collection and storage at each site will be recorded. Study SOPs will describe collection and storage specifications to ensure all sites are following the same guidelines.

We are planning for samples to be subsequently transferred by courier for analysis as follows:

- Pro- and anti-inflammatory markers: University of Birmingham and King's College London.
- Proteomics: Stoller Biomarker Discovery Centre, University of Manchester
- Genetics: MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University and King's College London.
- Epigenetics: MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University.

We will store DNA from the samples and plan to keep it for 5 years for genotyping/sequencing or other analyses as part of other projects. Relevant material will not be stored beyond the end of the project.

8. Assessment of Efficacy

8.1. Efficacy Parameters

8.1.1. Primary Efficacy Parameters

The primary outcome is the change in total blind-rated PANSS scores at 12 weeks from baseline.

8.1.2. Secondary Efficacy Parameters

Secondary outcomes include blind-rated clinical global impression (CGI), patient-rated outcomes (DAI-10, ReQoL-10), quality of life (EQ-5D-Y), adverse effects (GASS-C, HbA1C, lipids, LFTs, prolactin), treatment adherence (CRS) and service use (EI-AD-SUS). Patients will be followed up for 12 months with the potential for further follow-up using clinical records.

Secondary outcome	**Range of possible scores**	**Indication**	**Analysis – change or absolute level**
CGI-I	*1-7*	Higher score indicates worsening of symptoms. A score of 4 indicates no change.	The score represents the change from baseline.
DAI-10	-10 - +10	A positive total score indicates a positive subjective response and a negative total score indicates a negative subjective response	Change
ReQoL-10	Range of score for each question: 0-4 (if the answer is missing, we can use 999) Range of total score: 0-40	The higher score relates to higher quality of life	Absolute
EQ-5D-Y	Range of each question: 1-3. Total 15. (if the answer is missing, we can use 999) Range of visual analogue scale: 0-100	The higher the score the higher quality of life.	Absolute
GASS-C	0-48	Higher number indicates worse side effects	Absolute
CRS	1-7	Higher number indicates greater compliance	Absolute
EI-AD-SUS	The plausible range would differ for each question.		Absolute

	0-999 would cover the whole ranges for all questions.		
HbA1C	Individual site reference ranges applied	Higher value indicates greater pathology	Change
Lipids	Individual site reference ranges applied	Higher value indicates greater pathology	Change
LFTs	Individual site reference ranges applied	Higher value indicates greater pathology	Change
Prolactin	Individual site reference ranges applied	Higher value indicates greater pathology	Change

8.2. Procedures for Assessing Efficacy Parameters

Research assistants will administer questionnaires and record patient-rated outcomes according to the schedule, and coordinate PANSS and CGI assessment via a 4G-enabled laptop computer over an encrypted video link by the blinded centralised physician rater.

9. Assessment of Safety

9.1. Specification, Timing and Recording of Safety Parameters

Participants will be asked at each visit from consent onwards to report any suspected adverse reactions. Any suspected adverse events will be recorded from consent visit to end of trial. Any suspected adverse events recorded will be explored again at each visit thereafter. Blood tests will be performed at baseline and end of trial, by the treating team, and the results recorded in the eCRF in order to investigate glucose and lipid profile and prolactin level. BMI will be calculated at baseline and end of trials, and recorded in the eCRF, in order to investigate the treatment effect on weight. Participants from the clozapine arm will also undergo to regular weekly blood monitoring (FBC) as per standard practice, but the results will not be recorded in the eCRF.

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 investigational medicinal product 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 summary of product characteristics (SmPC) for clozapine (clozapine arm) and other antipsychotics (TAU).
- **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 adverse event, any unplanned pregnancy will also be reported via the SAE reporting system.

Reporting Responsibilities

KCL / SLaM 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 (MHRA) and to the relevant ethics committee. 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 Chief Investigator 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

Events or reactions listed in the Summary of Product Characteristics (SmPC) do not need to be reported unless they fulfil seriousness criteria.

9.4. Premature Termination of the Trial

The trial may be prematurely discontinued by the Sponsor, Chief Investigator or Regulatory Authority on the basis of new safety information or for other reasons given by the Data Monitoring & Ethics Committee / Trial Steering Committee 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 Competent Authority and Research Ethics Committee will be informed within 15 days of the early termination of the trial.

10. Statistics

A detailed statistical analysis plan for the primary and secondary objectives will be prepared by the trial statisticians and approved by the DMC and TSC. The statistical analysis plan will be drafted before recruitment starts and will be approved before the junior statistician sees any outcome data split by arm. The senior statistician will remain fully blind throughout the study and any future amendments to the SAP will be made by them.

We will report data in line with the CONSORT 2010 statement [45] showing attrition rates and loss to follow-up. The target estimand is the treatment policy estimand and all primary and secondary analyses will be carried out following the intention to treat principle, incorporating data from all participants including those who do not complete treatment. Every effort will be made to follow up all participants in both arms for research assessments. The trial will be blind-rated to minimise observer bias.

The primary analysis will be conducted after the final 12-week follow-up assessment is completed for the final patient recruited into the study. The study team including CI and trial statisticians will be

aware of the results of the primary analysis from this point. The remaining 24- and 52- week assessments will continue to be conducted blind to individual patient's allocation. We will analyse the 24- and 52- week outcomes in a secondary analysis.

10.1. Sample Size

The standardised mean difference for clozapine versus other antipsychotics in adults is based PANSS total score to at 12 weeks is 0.39 [46]. The standard deviation of the PANSS score at 12 weeks in our similar sample of treatment resistant patients being started on clozapine [32] is 14.2 (60% CI 12.96 – 16.20). Using an upper limit of the 60% confidence interval [47], an effect size of 0.39 corresponds to a between group difference of 6.4 points. In our previous research [32], the 95% CI for the baseline-12 week correlation in the sample was 0.553 to 0.880, and we use a value of 0.5 – this is conservative but realistic since the time points are only 12 weeks apart.

Under these assumptions, a sample size of 208 in the analysis set will have 90% power to detect a standardized effect size of 0.39 with alpha 0.05. A sample size of 204 in the analysis set will have 80% power to detect a standardized effect size of 0.34.

Assuming 20% attrition to 12-week follow-up, this gives a target sample size to recruit at baseline of 260 participants.

In practice, by including all timepoints in the analysis models and including baseline stratification variables, we will gain power for an assumed effect size of 0.39, have 90% power for a smaller effect size or preserve power if the resilience of the underlying assumptions does not hold.

10.2. Randomisation

Participants will be randomised 1:1 using an online system hosted by the King's Clinical Trials Unit, using computer generated blocks of random sizes. The sample will be stratified by sex and age group (<18 years, >=18 years).

10.3. Statistical Analysis

Analyses will be conducted in Stata version 17 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.

For the primary analysis, the treatment effects on primary and secondary outcomes will be estimated using linear mixed models fitted to all outcome variables up to and including the 12-week assessment. Fixed effects will be sex, age (±18) and duration of previous treatment (±3 years), 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 (PANSS score at 12 weeks), and for PANSS scores at each other time point (6w, 12w), and reported separately as adjusted mean differences in scores between the groups with 95% confidence intervals and 2-sided p-values. For secondary outcomes the same approach will be followed using 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 weeks.

For the secondary analysis including 24- and 52- week timepoints, we will repeat the linear mixed model approach with these additional outcomes in the response vector. We will report the estimated marginal treatment effects at 24- and 52- weeks.

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. A pre-specified subgroup analysis will test the treatment effect in children (age<18 years) by estimating the effect in each group separately. If the final proportion of under 18s is low, we may use a Bayesian subgroup analysis to increase precision of the effect in the groups.

There are no planned interim analyses.

11. Economic evaluation

A detailed health economic analysis plan (HEAP) will be prepared by the trial health economists and approved by the DMC and TSC. The HEAP will be drafted before recruitment starts and will be approved before the junior health economist sees any outcome data split by arm. The senior health

economist will remain fully blind throughout the study and any future amendments to the HEAP will be made by them.

A within-trial cost-effectiveness analysis will be carried out, taking the NHS and social services perspective preferred by NICE [48], including relevant education-based health and social care services, given the age group. Service use will be collected in interview at baseline (covering the previous 3 months) and at the 6-,12-, 24- and 52-week follow-up assessments (covering the period since previous interview to ensure coverage of the full 52-week follow up period) using the Early Intervention Adult Service Use Schedule (EI-AD-SUS). The EI-AD-SUS was originally designed and successfully applied in populations of young people and young adults at risk of or with psychosis [37]. Nationally applicable unit costs will be applied to all services (for example, NHS Reference Costs for hospital contacts, British National Formulary for medications, PSSRU Unit Costs of Health & Social Care for community-based services etc.).

The primary economic evaluation will be a cost-utility analysis carried out at the 12-week follow-up, in line with the primary clinical analysis, with outcomes expressed in terms of quality adjusted life years (QALYs) calculated from the EQ-5D-Y [35], as preferred by NICE [48]. Secondary analyses will explore a) cost-effectiveness using the primary clinical measure of outcome (PANSS total score) at 12-weeks and b) cost-utility using QALYs at the 52-week follow-up.

QALYs will be calculated using the recommended area under the curve approach [49]. However, given evidence to suggest the EQ-5D may not be particularly sensitive in psychosis populations [50], we will additionally include the Recovering Quality of Life-10 items measure (ReQoL-10), a new generic self-reported outcome measure for use with people experiencing mental health difficulties [51], which may be more sensitive to change than the EQ-5D. The ReQoL is not appropriate as the main measure of effectiveness for the economic evaluation because it is not yet associated with preference weights to generate QALYs for use in cost effectiveness analyses and it is currently considered suitable for people aged 16 and over. However, the inclusion of this brief measure will support exploration of the sensitivity of the EQ-5D in comparison to the ReQoL and the validity of the measure in young people under the age of 16.

Costs and QALYs will be presented as mean values by trial arm with standard deviations. Mean differences in costs and 95% confidence intervals will be obtained by non-parametric bootstrap regressions to account for the non-normal distribution commonly found in economic data [52]. Cost-effectiveness will be assessed using the net benefit approach and following standard approaches [53]. A joint distribution of incremental mean costs and effects for the two groups will be generated using bootstrapping to explore the probability that clozapine is the optimal choice compared to TAU, subject

to a range of possible maximum values (ceiling ratio) that a decision-maker might be willing to pay for unit improvements in outcomes. Cost-effectiveness acceptability curves will be presented by plotting these probabilities for a range of possible values of the ceiling ratio [54]. These curves are the recommended decision-making approach to dealing with the uncertainty that exists around the estimates of expected costs and expected effects associated with the interventions under investigation and uncertainty regarding the maximum cost-effectiveness ratio that a decision-maker would consider acceptable. To provide more relevant treatment-effect estimates, all economic analyses will include adjustment for the variable(s) of interest and baseline covariates [55], which will be prespecified and in line with the clinical analyses.

Complete case analyses will be carried out with the impact of missing data explored in sensitivity analyses. The pattern of missing data and the plausibility of assuming the data are Missing at Random will be examined for missing cost and EQ-5D-Y tariff values. Any variables predictive of missingness or predictive of response (at $P<0.1$) will be included in the equation to impute missing values.

12. Trial Steering Committee

An independent Trial Steering Committee (TSC) will be established. The roles and constitution of the TSC will be as set out in the NIHR Research Governance Guidelines. The TSC will meet bi-annually, and be responsible for ensuring that the study is conducted in accordance with Good Clinical Practice (GCP). The TSC will have the power to stop the trial prematurely, on grounds of ethics, safety or efficacy.

13. Data Monitoring Committee

A Data Monitoring Committee (DMC) will be established to review accruing data and safety information, reporting to the TSC. Independent membership will include an adult psychiatrist, a CAMHS psychiatrist and a clinical trial statistician.

14. 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.).

15. 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 but not

limited to the Research Governance Framework and the Medicines for Human Use (Clinical Trial) Regulations 2004, as amended in 2006 and any subsequent amendments.

This protocol and related documents will be submitted for review to Health Research Authority (HRA), Research Ethics Committee (REC, details below), and to the Medicines and Healthcare products Regulatory Agency (MHRA) for Clinical Trial Authorisation.

London - Dulwich Research Ethics Committee
Health Research Authority
Skipton House
80 London Road
London, SE1 6LH

Any subsequent protocol amendments will be submitted to the REC and Regulatory Authorities for approval, and we will comply with regulations including Pharmacovigilance reporting and providing the REC & MHRA with progress reports, and a copy of the Final Study Report.

The Chief Investigator 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 inform the MHRA of the results on behalf of the Sponsor.

The CONSULT SWAT has received separate ethical approval (Leeds West ref. REC 22/YH/0121), including approved documents for participants. The SWAT has been registered on MRC SWAT/SWAR repository (https://nicola.qub.ac.uk/sites/TheNorthernIrelandNetworkforTrialsMethodologyResearch/SWATSWARInformation/Repositories/SWATStore/ CONSULT registration #159).

16. Quality Assurance

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

17. Data Handling

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

- Participant data will be pseudo-anonymised.
- All pseudo-anonymised data will be stored on a password protected computer.

- All trial data will be stored in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006 and the Data Protection Act and archived in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006 as defined in the Kings Health Partners Clinical Trials Office Archiving SOP.
- Source documents will include medical records for adverse events, prescription, eligibility, blood results, height and weight. The eCRF will be used as source for all primary and secondary outcome questionnaires.
- Investigator(s) and the institution(s) will permit trial-related monitoring, audits, REC review, and regulatory inspections (where appropriate) by providing direct access to source data and other documents (i.e. patients' case sheets, blood test reports, etc).

18. Data Management

A web based electronic data capture (EDC) system will be designed, using the InferMed Macro 4 system. The EDC will be created in collaboration with the trial analyst/s and the CI and maintained by the King's Clinical Trials Unit for the duration of the project. It will be hosted on a dedicated server within KCL. The system is compliant with FDA 21 CFR part 11 and Good Clinical Practice (GCP). It is an appropriate system to use for medicinal trials falling under the Medicines for Human Use (Clinical Trials) Regulations 2004 and its subsequent amendments and has also been used for other complex intervention trials. The web-based system can be accessed 24 hours a day.

The CI or delegate will request usernames and passwords from the KCTU. Database access will be strictly restricted through user-specific passwords to the authorised research team members. It is a legal requirement that passwords to the EDC are not shared, and that only those authorised to access the system are allowed to do so. If new staff members join the study, a user-specific username and password must be requested via the CI or delegate (e.g Trial Manager) from the KCTU team and a request for access to be revoked must be requested when staff members leave the project. Study site staff experiencing issues with system access or functionality should contact the CI or delegate (e.g Trial Manager) in the first instance.

Participant initials and date of birth will be entered on the EDC. NHS number, email addresses, participant names and addresses and full postcodes will not be entered into the EDC. No data will be entered onto the EDC system unless a participant has signed a consent form to participate in the trial. Source data will be entered by recruiting site staff and the central rater, directly onto the EDC via 4G enabled laptop. A full audit trail of data entry and any subsequent changes to entered data will be

automatically date and time stamped, alongside information about the user making the entry/changes within the system.

The CI team will undertake appropriate reviews of the entered data, in consultation with the project analyst, for the purpose of data cleaning and will request amendments as required. No data will be amended independently of the study site responsible for entering the data.

The DMC, which is independent of the study team, may request data for safety and study monitoring when necessary.

After the last observation of the last patient, the site PI will review all the data for each participant and to verify that all the data are complete and correct. At this point, all data can be formally locked for analysis.

Upon request, KCTU will provide a copy of the final exported dataset to the CI in .csv format and the CI will onward distribute as appropriate.

19. 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.

20. Insurance / Indemnity

(Co-)Sponsor(s) insurance and indemnity schemes apply.

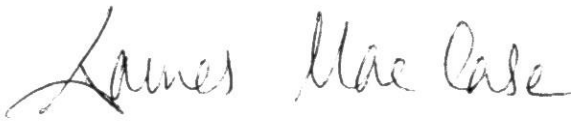
21. Financial Aspects

Funding to conduct the trial is provided by NIHR Health Technology Assessment Programme (Call 19/41 Clozapine for children and young people with treatment resistant schizophrenia.

22. 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 Standard Operating Procedure (SOP).

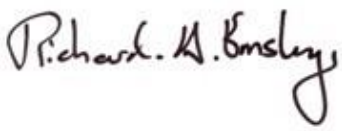
23. Signatures



27/08/2024

Chief Investigator **Date**

Professor James MacCabe



27/08/2024

Chief Statistician **Date**

Professor Richard Emsley

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