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Investigating the use of clozapine in young people with psychosis

Submission date 10/08/2022	**Recruitment status** Recruiting	[X] Prospectively registered [X] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [X] Record updated in last year
Registration date 16/11/2022	**Overall study status** Ongoing	
Last Edited 24/04/2025	**Condition category** Mental and Behavioural Disorders	

Plain English Summary

Background and study aims

Schizophrenia is a condition that causes symptoms like delusions, hallucinations, reduced motivation and muddled thinking. Schizophrenia usually starts in the twenties but can begin earlier, when it is often more severe. The main treatment is antipsychotic medication; if untreated, symptoms typically continue for many years. One antipsychotic, clozapine, works better than any other and has the best chance of working if started early on in treatment. On the other hand, clozapine has more side effects than some other antipsychotics, so doctors only use it when other drugs haven't helped. For this reason, almost all research on clozapine was done with adults who had already taken other antipsychotics. Research in children and young people with schizophrenia shows that antipsychotics do help them, but there is little research focussed on clozapine. Three studies suggest that clozapine works better than other antipsychotics in children and young people, but the studies were too small to be conclusive and doctors still don’t use it often, leading to enduring symptoms. Therefore we will study clozapine as a treatment for schizophrenia in young people, recruiting only people <25 years old and trying to recruit as many as possible aged <18 years.

Who can participate?

People <25 years old and trying to recruit as many as possible aged <18. We will include 260 people, recruited across various hospital clinics and services within the UK, who are still symptomatic after treatment with at least two antipsychotics.

What does the study involve?

A computer will decide randomly whether each person will take clozapine or any other antipsychotic for 12 weeks. Researchers will assess their symptoms several times without knowing which drug they are taking to avoid biases. At the end of the study, towards the end of 2026, we will see if clozapine reduced people’s symptoms more than other antipsychotics, their side effects, how well they feel, how much their treatment costs and how often they need hospital treatment. After the study is over, we will contact them again to see how they are doing in the longer term.

Some participants in the clinical trial will additionally be asked to complete a magnetic resonance imaging (MRI) brain scan and provide a blood sample, once at the beginning and once

at the end of the twelve-week period. The MRI scans will be used to measure glutamate and related aspects of brain structure and function. The blood samples will be used to measure proteins in the blood involved in inflammation, such as cytokines. At the end of the study, we will see if the biological measures in the brain and blood change more during treatment with clozapine compared to other antipsychotics, and how they relate to the amount that symptoms improve.

What are the possible benefits and risks of participating?
Benefits:
Not provided at time of registration
Risks:
People with schizophrenia are routinely treated with antipsychotic medication as part of their usual care, and the participants will also be treated with antipsychotic - it is only the choice of antipsychotic that will be determined by the trial. The potential risks and burdens for research participants will thus be the same as standard care. To minimise side effects, clinicians will have complete freedom to adjust the dose to achieve the best balance between therapeutic and adverse effects. Treatment to combat side effects can also be given to participants in the same way as with usual care. Advice to prevent common side effects such as weight gain and sedation will be given at the beginning of the trial. Participants might not respond to treatment. Nonetheless, after the first 12 weeks of trial, treatment can be changed while remaining in the study for longer-term outcome.

Where is the study run from?
King’s College London (UK)

When is the study starting and how long is it expected to run for?
August 2022 to February 2027

Who is funding the study?
National Institute for Health and Care Research (NIHR) (UK).

Who is the main contact?
Dr James MacCabe, james.maccabe@kcl.ac.uk
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Prof. Alice Egerton (embedded mechanistic study), Alice.Egerton@kcl.ac.uk

Study website
https://ctu.co.uk/CLEAR/

Contact information

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Scientific

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Additional identifiers

EudraCT/CTIS number
2021-006248-28

IRAS number
1004947

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
IRAS 1004947, CPMS 53859

Study information

Scientific Title
CLEAR: (CLozapine in EARly psychosis) A Multi-Centre, Randomised Controlled trial of Clozapine for Young People with Treatment Resistant Psychosis in Real World Settings

Acronym
CLEAR

Study hypothesis
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.

Added 01/02/2023:
In addition, in an embedded mechanistic study we will test the hypothesis that, compared to other antipsychotics, treatment with clozapine is associated with a greater reduction in proinflammatory cytokines, brain glutamate and regional cerebral blood flow, and an increase in anti-inflammatory cytokines and glutathione.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 12/12/2022, London - Dulwich Research Ethics Committee (Health Research Authority, Skipton House, 80 London Road, London, SE1 6LH, UK; +44 (0)2071048089; dulwich.rec@hra.nhs.uk), ref: 22/LO/0605

Study design
Interventional randomized controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet

Condition
Treatment-resistant psychosis

Interventions
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.

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.

Participants in both arms will be followed up at week 2, week 6 and week 12. Following this it will be a clinical decision as to whether the participant continues on the same medication, or switches to a different one and they will be followed-up for 12 months through clinical notes and, whenever possible, videolink assessments (week 24 and 52).
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.

(added 01/02/2023)
Additionally, in an embedded mechanistic study, brain Magnetic Resonance Imaging (MRI) scans and blood samples will be acquired at baseline and 12 weeks in a subset of participants. The MRI session will include acquisition of structural images, proton magnetic resonance spectroscopy (1H-MRS) to measure levels of glutamate, GSH and other brain metabolites and arterial spin labelling to measure regional cerebral blood flow. The blood samples will be used to measure levels of pro- and anti-inflammatory cytokines and GSH.

Intervention Type
Drug

Phase
Phase IV

Drug/device/biological/vaccine name(s)
Clozapine

Primary outcome measure
Change in total PANSS score from baseline to 12 weeks.

Secondary outcome measures
Assessment will take place at weeks 6, 12, 24 and 52:
1. Change in overall clinical impression (CGI)
2. Clinician rated level of adherence (CRS)
3. Side effects (GASS-C)
4. Quality of life (EQ-5D-Y)
5. Subjective experience (DAI-10)
6. Psychotropic treatment, service use and readmission rate, (EI-AD-SUS)
7. Change in PANSS sub-scale (positive, negative and general), and weight gain.

(added 01/02/2023)
In the embedded mechanistic study, outcomes will include, from baseline to 12 weeks:

1. Change in brain glutamate, measured using proton magnetic resonance spectroscopy (1H-MRS)
2. Change in brain glutathione, measured using 1H-MRS
3. Change in regional cerebral blood flow, measured using arterial spin labelling
4. Change in peripheral levels of glutathione and cytokines.

Overall study start date
02/08/2022

Overall study end date
28/02/2027

Eligibility

Participant inclusion criteria
Current inclusion criteria as of 24/04/2025:

1. Age ≥12 and <25 years at randomisation
2. Meets criteria for schizophrenia or related disorder, in the range ICD-10v2016 F20.x, F22.x-F29.x
3. Meets NICE criteria for treatment resistance, defined as:
3.1. 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)
3.2. At least 1 of these trials must be with a second-generation drug
4. Positive and Negative Syndrome Scale (PANSS) total ≥70, at least 2 items >4
5. Clinician Rating Scale [24] (CRS) >3
6. English or Welsh language sufficient to participate
7. Capacity to give informed consent OR has a legal representative able to give consent to the trial

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Previous inclusion criteria as of 13/03/2024:

1. Age ≥12 and <25 years at randomisation
2. Meets criteria for schizophrenia or related disorder, in the range ICD-10v2016 F20.x, F22.x-F29.x
3. Meets NICE criteria for treatment resistance, defined as:
3.1. Previous trials of at least two different antipsychotic drugs with adequate adherence (estimated <20% missed doses) – both treatment trials to exceed 6 weeks at therapeutic dose (≥600 mg chlorpromazine equivalent).
3.2. At least 1 of these trials must be with a second-generation drug.
3.3. Failure to respond to NICE-recommended psychological treatment OR failure to engage in same.
4. Positive and Negative Syndrome Scale (PANSS) total ≥70, at least 2 items >4
5. Clinician Rating Scale [24] (CRS) >3.
6. English or Welsh language sufficient to participate.
7. Capacity to give informed consent OR has a legal representative able to give consent to the trial.

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Previous inclusion criteria:

1. Age ≥12 and <25 years at randomisation
2. Meets criteria for schizophrenia or related disorder, in the range ICD-10v2016 F20.x, F22.x-F29.x
3. Meets NICE criteria for treatment resistance, defined as:
3.1. Previous trials of at least two different antipsychotic drugs with adequate adherence (estimated <20% missed doses) – both treatment trials to exceed 6 weeks at therapeutic dose (≥600 mg chlorpromazine equivalent).
3.2. At least 1 of these trials must be with a second-generation drug
3.3. Failure to respond to NICE-recommended psychological treatment OR failure to engage in same
4. Positive and Negative Syndrome Scale (PANSS) total ≥70, at least 2 items >4
5. Compliance Rating Scale [23] (CRS) >3
6. English or Welsh language sufficient to participate
7. Capacity to give informed consent OR has a consultee (normally a family member) able to give consent to the trial.

Participant type(s)
Patient

Age group
Mixed

Lower age limit
12 Years

Upper age limit
25 Years

Sex
Both

Target number of participants
260

Participant exclusion criteria
Current exclusion criteria as of 13/03/2024:
1. Psychosis predominantly caused by substance misuse.
2. Pregnancy.
3. Breastfeeding.
4 Women of child-bearing potential (WOCBP*) not using at least acceptable methods of contraception** during the trial
5. Contra-indications to clozapine as listed in SmPC as follows:
5.1. Hypersensitivity to the active substance or to any of the excipients, listed in section 6.1.
5.2. Patients unable to undergo regular blood tests.
5.3. History of toxic or idiosyncratic granulocytopenia/agranulocytosis (with the exception of granulocytopenia/agranulocytosis from previous chemotherapy).
5.4. History of clozapine-induced agranulocytosis.

5.5. Impaired bone marrow function.
5.6. Uncontrolled epilepsy.
5.7. Alcoholic and other toxic psychoses, drug intoxication, comatose conditions.
5.8. Circulatory collapse and/or CNS depression of any cause.
5.9. Severe renal or cardiac disorders (e.g. myocarditis).
5.10. Active liver disease associated with nausea, anorexia or jaundice; progressive liver disease, hepatic failure.
5.11. Paralytic ileus.
5.12. 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.
6. Previous adequate trial of clozapine.
7. CNS disorders (ICD-10 G00-26; G40-41, G45-46; G80-94, G97).
8. Concurrent medications with documented interactions with antipsychotics.
9. Participation in a clinical trial involving any investigational medical product (licensed or unlicensed) within the last 3 months.
10. Positive test for COVID-19 within the past 10 days.
11. 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 minimum requirement. 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:
1. Combined (estrogen and progestogen containing) hormonal
2. Contraception associated with inhibition of ovulation 1:
2.1. Oral
2.2. Intravaginal
2.3. Transdermal
3. Progestogen-only hormonal contraception associated with inhibition of ovulation 1:
3.1. Oral
3.2. Injectable
3.3. Implantable
4. Intrauterine device (IUD)
5. Intrauterine hormone-releasing system (IUS)
6. Bilateral tubal occlusion
7. Vasectomised partner
8. Sexual abstinence (if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments).

Previous exclusion criteria:
1. Psychosis predominantly caused by substance misuse
2. Pregnancy
3. Breastfeeding
4. Contra-indications to clozapine as listed in BNF SmPC as follows:
4.1. Hypersensitivity to the active substance or to any of the excipients
4.2. Patients unable to undergo regular blood tests.
4.3. History of toxic or idiosyncratic granulocytopenia/agranulocytosis (with the exception of granulocytopenia/agranulocytosis from previous chemotherapy).
4.4. History of clozapine-induced agranulocytosis.
4.5. Impaired bone marrow function.
4.6. Uncontrolled epilepsy.
4.7. Alcoholic and other toxic psychoses, drug intoxication, comatose conditions.
4.8. Circulatory collapse and/or CNS depression of any cause.
4.9. Severe renal or cardiac disorders (e.g. myocarditis).
4.10. Active liver disease associated with nausea, anorexia or jaundice; progressive liver disease, hepatic failure.
4.11. Paralytic ileus.
4.12. 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.
5. Previous adequate trial of clozapine
6. CNS disorders (ICD-10 G00-26; G40-41, G45-46; G80-94, G97).
7. Concurrent medications with documented interactions with antipsychotics
8. Participation in a medicinal trial involving an unlicensed, investigational medical product within the last 3 months
9. Positive test for COVID-19 within the past 10 days.

Recruitment start date
24/11/2023

Recruitment end date
31/08/2026

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Bethlem Royal Hospital
Monks Orchard Road
Beckenham
United Kingdom
BR3 3BX

Study participating centre
Maudsley Hospital
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SE5 8AZ

Study participating centre
Wonford House
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EX2 5AF

Study participating centre
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OX3 7JX

Study participating centre
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Study participating centre
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Sponsor information

Organisation
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Sponsor type
University/education

Website
http://www.kcl.ac.uk/index.aspx

ROR
https://ror.org/0220mzb33

Organisation
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Sponsor type
Hospital/treatment centre

Website
http://www.slam.nhs.uk/

ROR
https://ror.org/015803449

Funder(s)

Funder type
Government

Funder Name
National Institute for Health and Care Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Peer reviewed scientific journals
Conference presentation
Submission to regulatory authorities
Other
All anonymised study data will be stored on a MACRO database. This will enable the sharing of data and future analysis.
Participants are asked on the consent form that they understand information collected will be used to support other research in the future, and may be shared anonymously with other researchers in accordance with the terms of the NIHR funding for the study.

Intention to publish date
28/02/2028

Individual participant data (IPD) sharing plan
The current data sharing plans for this study are unknown and will be available at a later date

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	version 4.0	14/02/2024	15/02/2024	Yes	No

Protocol file	version 6.0	01/08/2023	13/03/2024	No	No
Protocol file		27/08/2024	24/04/2025	No	No