



Trial Aims and Design

RCPsych Forensic Faculty Conference 2019

Dr Katina Anagnostakis

Consultant Forensic Psychiatrist

St Andrew's Healthcare

kanagnostakis@standrew.co.uk



ResearchCentre
Part of St Andrew's Healthcare



Clozapine: Assessing Long-term Medication in Emotionally unstable personality Disorder

A placebo controlled, double-blind randomised controlled trial exploring the clinical effectiveness and cost effectiveness of clozapine for inpatients with borderline personality disorder



The mental health of inpatients with BPD who are prescribed clozapine appears to improve and people may need less intensive care.

Clozapine is expensive and has serious, potentially life-threatening side effects which require regular blood monitoring.

Observational studies provide a poor guide to treatment effect due to additional attention that patients receive.

A new study is needed to test whether the potential benefits of clozapine are outweighed by the costs and challenges.



CALMED Trial overview



Title	CALMED: The clinical and cost effectiveness of clozapine for inpatients with borderline personality disorder
Funder	National Institute of Health Research (NIHR)
Lead organisation	Imperial College London
Project/trial type	Multi-centre, parallel design, randomised, placebo controlled double-blind trial
Objectives	<ul style="list-style-type: none">• To provide the first high quality evidence of clozapine in BPD to inform clinical practice• To influence prescribing guidelines nationally and internationally• To inform design of mechanistic evaluation
Organisations & Research sites (Approx. 38 individual sites)	Central and North West London NHS Foundation Trust St Andrew's Healthcare Lancashire Care NHS Foundation Trust Merseycare NHS Foundation Trust Elysium Healthcare Nottinghamshire Healthcare NHS Foundation Trust West London Mental Health NHS Trust Imperial College London, King's College London, University of Nottingham, Bristol University, NORTH (North Wales Clinical Trials Unit)
Project duration	Total project duration: 36 months (3 years) / Participant duration: 6 months



- **Design:** A two-arm, parallel group, double-blind, placebo-controlled randomised trial with an integrated pilot study.

- **Setting:** General adult mental health wards, PICU, low, medium and high secure units : *West London NHS Mental Health Trust (Broadmoor); Nottinghamshire Healthcare NHS Foundation Trust (Rampton); Avon and Wiltshire NHS Foundation Trust; Central and North West London NHS Trust; Elysium Healthcare; St Andrew's Healthcare*



- **Target population:**

Inpatients aged 18 years or over; meet diagnostic criteria for BPD; failed to make an adequate clinical response to other antipsychotic medication .

- **Interventions:**

Capsules containing clozapine titrated up to 300mg (400mg allowed)
over a two to three week period

OR

Capsules containing inert placebo

Eligibility: inclusion criteria

- a) Aged 18 years or over
- b) Currently an inpatient on a mental health unit
- c) Meeting DSM-IV diagnostic criteria for borderline personality disorder
- d) Failure to make an adequate clinical response to taking antipsychotic medication other than clozapine for at least three months
- e) Have a satisfactory pre-treatment full blood count
- f) Have had their weight and blood glucose recoded in their clinical records



Eligibility: exclusion criteria

- a) Under 18 years of age
- b) With a current clinical diagnosis of schizophrenia or bipolar I disorder, primary diagnosis of brain injury/dementia/HD/ASD
- c) Prescribed clozapine within the previous two weeks
- d) Who are pregnant or trying to conceive, breastfeeding, or a woman of childbearing potential not using a highly effective birth control
- e) With contraindications to clozapine (full details in protocol)
- f) Due to be discharged from the unit within the following two weeks
- g) Unable to speak sufficient English to complete the baseline assessment
- h) Unwilling or unable to provide written informed consent to take part
- i) Unable to undertake regular blood tests



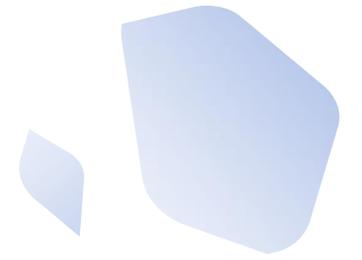


- **Primary outcome:**

Total score on the Zanarini rating scale for Borderline Personality Disorder (ZANBPD) over six months.

- **Secondary outcomes:**

Three and six months, mental health (BPRS), violence to self or others (M-OAS), deliberate self-harm, health-related quality of life (EQ-5D-5L), side effects of treatment, adherence and adverse reactions. Resource use and costs.



- **Sample size:** 166 participants (83 prescribed clozapine and 83 prescribed placebo) to have 90% power to detect a four point difference in ZAN-BPD score at six months (0.05 level of statistical significance). To take account of 25% loss to follow-up we will recruit 222 subjects.

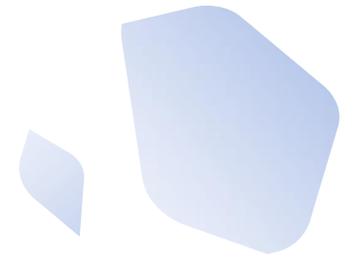


- **Timetable:** 36 months in total. Start of recruitment Spring 2019. Pilot phase for six months, followed by further 18 months recruitment. Follow up until 30.06.21. Final report submitted end of 2021.

Item	Detail	When
Duration	Project: 36 months Trial for participants: 6 months	Spring 19 – Jan 22
Ethics	Application to HREC & MHRA	Oct – Nov 18
Researchers	Research Associates appointed at lead sites	Apr 19
Pilot study	<ul style="list-style-type: none"> Participant recruitment at 3 centres, over 6-months Pilot data presented to Trial Steering Committee against a priori stop/go criteria to determine study progress to Phase 2 	Apr – Oct 19
Main trial	Full trial across all sites (18 months) [Recruitment starts: target 222 participants]	Jun 20 – Aug 21 [Feb 20]
Progression assessment (at 6 months)	<ol style="list-style-type: none"> Participants randomised in first 6 months – target of 55: 75% to start medication within 4 weeks of randomisation 3-month follow-up data will have been collected from >70% of those randomised in first 3 months 	Dec 20
Final report	Final study report submitted to funder	30 May 22

- 1 North West (Ashworth)
Lancashire, Merseyside
?Manchester
- 2 East Midlands (Rampton)
Nottinghamshire,
?Derbyshire
- 3 Northamptonshire (St
Andrew's)
- 4 West London (Broadmoor)
CNWL, WLMHT





- **Second line treatment:** *restricted to those who have not made an adequate clinical response to antipsychotic medication other than clozapine for at least three months.*
- **Excluding people with psychosis:** *a clinical diagnosis of schizophrenia, or bipolar I disorder*
- **Blood monitoring:** *weekly for 18 weeks then fortnightly for all study participants (supported by people with lived experience)*
- **Rescue medication:** *may be prescribed other psychotropic medication (including rescue medication for rapid tranquilisation). Recommend cautious short-term use of benzodiazepines and promethazine in keeping with NICE guidelines*
- **Establishing economic impact:** *May take more than 6 months. Use data from 6, 12 and 18m for economic modelling*





- **Acceptability for patients** - cooperation whilst IP, placebo, blood tests
- **Acceptability for staff in forensic units** - inert placebo, equipoise
- **Acceptability for staff in general adult wards** - length of IP stay, adherence, monitoring in the community
- **Monitoring service:** complicated by use of placebo
- **Increasing use of clozapine in forensic inpatient services**
- **Slow turnover of patients admitted to secure hospitals** – will only succeed if recruitment across PICU, general and forensic wards



Recruitment – from LSUs and PICUs in Central and North West London NHS Foundation Trust, Elysium Healthcare, Lancashire Care NHS Foundation Trust, Merseycare NHS Foundation Trust, Nottinghamshire Healthcare NHS Foundation Trust, St Andrew’s Healthcare, West London Mental Health NHS Trust

Forensic psychiatrists: a way to reduce distress and extreme self harm among inpatients

General psychiatrists: A potentially dangerous drug unsuitable for people who do not respond to medication, have poor compliance, and high levels of suicidal behavior

Teams working on LSU and PICUs: equipoise

