Imperial College London

CALMED

Clinical Trial Protocol

Full title of trial	The clinical effectiveness and cost effectiveness of clozapine for inpatients with borderline personality disorder: randomised controlled trial.
Short title	CALMED
Version and date of protocol	9 (08th December 2020)
Sponsor Name	Imperial College London
Funder (s)	National Institute of for Health Research Health Technology Assessment Programme (HTA)
EudraCT no	2018-002471-18
Active IMP(s)	Clozapine
Comparator/Placebo IMP(s)	Placebo
Phase of trial	Phase IV
Sites(s)	Multi-Site

This study/project is funded by the National Institute for Health Research (NIHR) Health Technology Assessment Programme (16/157/02/HTA). The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

Summary of protocol changes

Version	Date	Summary of changes made
1.0	16 Oct 2018	n/a
2.0	20 Nov 2018	Section 5: all sites included in pilot phase rather than 3 Sections 9.1, 10.7, 10.8: trial medication information updated Section 9.3: Removal of BARS scale from baseline assessment Numbering of tables and sections corrected
3.0	08 Jan 2019	Section 8.8: additional information on medication stopping rules Section 10.7: "QP release" changed to "QP certification" Numbering of tables and sections corrected
4.0	01 May 2019	Section 18: Change to the participant payments Section 16.2: wording on recruitment sites deleted Sections 10.1, 11.1: Capsule size changed from 00 to 0 Addition of Principal Investigator Protocol Signature Page Addition of summary of protocol changes table Change of Sponsor representative contact details Change of Trial Manager email address
5.0	09 July 2019	Clarification of eligibility criterion "Due to be discharged from the unit within the following two weeks" to apply when it is not possible to continue the necessary monitoring of physical health as an outpatient Removal of duplicated of information in section 8.5.1 Addition of the standard deviation for the sample size calculation added to section 15.2
6.0	10 Dec 2019	Addition of an eligibility criterion to include only those with severe personality disorder and how that is defined Addition of the assessment SAS-PD at six-month follow-up Update to the table showing summary of known risks of clozapine to reflect most currently approved RSI in sIMPD v2
7.0	11 Feb 2020	Addition of information on how the trial differs from current NHS and NICE guidance and why this is a safe approach Addition of detail on safety monitoring, adverse event recording and pregnancy Addition of a measure of lipids as a trial procedure at baseline, 3- and 6- months
8.0	26 Mar 2020	Addition of information to section 8.6 to state that telephone or video call interview will be used where it is not possible to complete the 3-month and 6-month interviews face-to-face.
9.0	08 Dec 2020	Addition of Cygnet Healthcare as a site. Addition of a sentence to section 15.3 about the statistical analysis plan

1. Signature Page and Compliance Statement

The Chief Investigator and Sponsor have discussed this protocol.
The trial will be conducted in compliance with the approved protocol, EU GCP and UK Regulations for CTIMPs (SI 2004/1031; as amended), the General Data Protection Regulation (2018), the Sponsor SOPs, and other regulatory requirements as amended.

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Signature: M. Crawford **Date:** 8th Dec 2020	**Signature:** Keith Boland Digitally signed by Keith Boland Date: 2021.01.18 10:55:15 Z **Date:**

Statistician Approval Signatures

Principal Statistician

	Signature:	**Date:**
Zoë Hoare	ZHoare	**08/12/2020**

Trial Statistician

	Signature:	**Date:**
Rachel Evans		**08/12/2020**

Principal Investigator Signature Page

Declaration of Principal Investigator

I confirm that I have read the above-mentioned protocol and agree on its content. I agree to conduct the described trial in compliance with all stipulations of the protocol and in accordance with relevant regulations and ICH-GCP.

I am aware of the changes made since the previous version of this trial Protocol and have considered the impact of these on the conduct of the trial.

Principal Investigator Name: _____

Principal Investigator Signature: _____

Trial Site: _____

Date: _____

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List of Abbreviations

AE	Adverse Event
ANNSERS	Antipsychotic Non-Neurological Side Effect Rating Scale
APR	Annual Progress Report
AR	Adverse Reaction
BPRS	Brief Psychiatric Rating Scale
CI	Chief Investigator
CRF	Case Report Form
CTIMP	Clinical Trial of Investigational Medicinal Product
DIBD	Developmental International Birth Date
DMC	Data Monitoring Committee
DSM	Diagnostic and Statistical Manual
DSUR	Development Safety Update Report
EU	European Union
EudraCT	European Clinical Trials Database
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GP	General Practitioner
IDMEC	Independent Data Monitoring and Ethics Committee
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
ITT	Intention to treat
Main REC	Main Research Ethics Committee
MHRA	Medicines and Healthcare Products Regulatory Agency
mITT	Modified Intention-To-Treat analysis
NHS	National Health Service
MOAS	Modified Overt Aggression Scale
PI	Principal Investigator
PIS	Participant Information Sheet
PSS	Personal Social Services
QUALY	Quality of life - Adjusted years
QP	Qualified Person for release of trial drug
R&D	Research and Development
RCT	Randomised Control Trial
REC	Research Ethics Committee
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SAE	Serious Adverse Event
SCID	Structured Clinical Interview for DSM
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TSC	Trial Steering Committee
UAR	Unexpected Adverse Reaction
ZAN-BPD	Zanarini rating scale for Borderline Personality Disorder

1 Trial personnel

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2 Trial synopsis

Full trial title	The Clinical Effectiveness and Cost Effectiveness of Clozapine for inpatients with Borderline Personality Disorder: Randomised controlled trial.
Short trial title	CALMED
Type of trial	A multi-centre, parallel design, randomised, placebo controlled (1:1 ratio) double-blind trial of clozapine for adult inpatients with borderline personality disorder (BPD).
Trial medication	Clozapine and matching placebo
Trial phase	Phase IV
Primary Objective	Assess outcome at six months using total score on the Zanarini rating scale for Borderline Personality Disorder (ZAN-BPD).
Design & methodology	222 inpatients with BPD will be recruited from seven centres in England over a 24-month period. All participants will be followed-up at three and six months using a battery of assessment scales to measure mental health (Zanarini rating scale for Borderline Personality Disorder - ZAN-BPD, and the Brief Psychiatric rating Scale - BPRS), incidence of violence to self or others (MOAS), acts of deliberate self-harm, health-related quality of life (EQ-5D-3L), side effects of treatment, adherence and adverse reactions. Resource use and costs (from an NHS/PSS perspective) will be assessed using a modified version of the Adult Service Use Schedule and with nationally available unit costs. We will continue to collect economic data from clinical records on use and type of inpatient treatment, use of community services and quantity and type of medication that participants take throughout the study. We will use a flexible dosing regimen of clozapine. Dosing will start with 12.5 mg once daily and be titrated to 300mg over a 15-day period. Study participants may be prescribed a dose of up to 400mg of clozapine daily, depending on clinical response, patient preference and side effects. The dose may be maintained at or reduced to a lower dose at any time. Equivalent numbers of placebo capsules will be administered to participants in the control arm of the trial. All those taking part in the study will continue to receive all other treatments as usual.
Definition of end of trial	The trial will end at last participant, last visit.
Estimated total duration of trial	Trial duration is 30 months, total project is 36 months.
Trial duration (for participant)	Six months
Total number of participants planned	222
Trial population	Adults inpatients with borderline personality disorder

Eligibility criteria	**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 g) Has severe personality disorder
	Exclusion criteria: a) Current clinical diagnosis of schizophrenia or bipolar I disorder b) Prescribed clozapine within the previous two weeks c) Is pregnant or trying to conceive, breastfeeding, or a woman of childbearing potential not using a highly effective birth control. d) Contraindications to clozapine (see section 6.2 for list) e) Due to be discharged from the unit within the following two weeks and it is not possible to continue the necessary monitoring of physical health as an outpatient f) Unable to speak sufficient English to complete the baseline assessment g) Unwilling or unable to provide written informed consent to take part in the study h) unable to undertake regular blood tests
Research Sites	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
	Cygnet Healthcare
Statistical methodology and analysis	The main analysis for the primary outcome will be a modified ITT analysis, in which all randomised participants will be included who have taken at least one dose of trial medication. We will analyse data using a general linear model fitted at six months and adjusted for baseline score, allocation group and stratification variables: centre, gender and type of ward. Any additional covariates added to the model will be assessed for their appropriateness and defined a priori in the SAP. All treatment effect estimates will be presented with 95% confidence intervals. Exploratory analysis of the potential modification of the treatment effect will also be undertaken for pre-planned variables of gender and baseline score on the BPRS. The economic evaluation will take an NHS/PSS perspective, as required by NICE, which is relevant in this patient group. Data on the use of health and social services will be collected using a modified version of the Adult Service Use Schedule (AD-SUS). The primary cost-effectiveness analysis will consider costs alongside QALYs. A secondary cost-effectiveness analysis will be completed using the ZAN-BPD outcome measure.

3 Introduction

Borderline personality disorder (BPD) is a common mental disorder characterized by severe instability in emotions, identity, relationships, and impulsive behaviour. The condition occurs globally, with a lifetime community prevalence of up to 6%.[1] Functional impairment is an enduring feature of the disorder and people with BPD are at significantly increased risk of suicide, which affects up to 10% of individuals. [2] People with severe BPD may have very high levels of contact with mental health services and emergency medical services. [3] It is estimated that between a fifth and a quarter of inpatients in mental health units have borderline personality disorder. [4, 5] Levels of nursing care that are available on general mental health inpatient units may not be enough to ensure the safety of some patients with borderline personality disorder. This can lead to patients with BPD being transferred to specialist treatment units such as Psychiatric Intensive Care Units and secure wards. It is estimated that over 40% of women treated on Psychiatric Intensive Care Units, [6] and over 60% of women treated on medium secure units have Borderline Personality Disorder. [7] Even within these specialist treatment units people with borderline personality disorder often require additional levels of nursing care to limit the incidence and impact of self-harming and aggressive behaviour. [8]

3.1 Treatments of borderline personality disorder

At present treatment options for people with borderline personality disorder are limited. No medication is currently licensed for the treatment of borderline personality disorder, and NICE guidelines state that long-term medication should not be used. [9] Despite this people with BPD are often prescribed large amounts of psychotropic medication. [10] Antidepressants are widely used despite evidence that they do not improve the mental health or social functioning of people with BPD. [11] Mood stabilisers are also widely prescribed but do not appear to improve the mental health or social functioning of people with BPD. [12] The results of randomised trials of antipsychotic medications are equivocal. While some small-scale studies have reported short-term reductions in symptoms of anger and hostility, [11] the largest trial conducted found no difference in symptoms of BPD at three months. [13] Despite this most people with BPD who are in contact with mental health services are prescribed psychotropic drugs, often in combination and sometimes at high doses. [14]

While psychological treatments such as Dialectical Behaviour Therapy and Mentalisation Based Therapy have been shown to improve the mental health of people with borderline personality disorder, [15] such treatments require a high degree of commitment and many people with BPD are unable or unwilling to engage in them. Indeed, those individuals with the most severe problems and the greatest need for treatment are less likely to engage successfully in psychological treatments than those with milder forms of the disorder. [16] This is particularly important for inpatients with BPD. While uptake of psychosocial interventions offered to women in medium secure units is associated with reduced length of time on the ward, engagement in these interventions is lower among people with higher levels of borderline traits. [17]

3.2 The role of clozapine

Clozapine is an atypical antipsychotic drug that is used to treat people with schizophrenia who have not responded to other antipsychotic drugs. [18] Like most antipsychotic drugs, clozapine is a

dopamine antagonist. In addition to this clozapine also binds to serotonin receptors and is a partial antagonist at the 5-HT_{2A} site. [19] There is evidence that, as well as reducing psychotic symptoms experienced by people with schizophrenia, clozapine also reduces the incidence of aggression and impulsive behaviour among people with schizophrenia. [20] Clozapine also appears to reduce the incidence of suicidal behaviour more than other antipsychotic drugs, [21] and is now license in the USA for reducing suicidal risk among people with psychosis. [22]

Recently some clinicians have started using clozapine in an effort to reduce the incidence of self-harm and violent behaviour among people with severe BPD. [14] Seven open-label studies have reported that clozapine leads to improved mental health, [20, 23, 24] reductions in aggressive and self-harming behaviour, and lower costs of care. [20] Results of one such study, conducted among 22 women with BPD on a secure inpatient unit, reported that, within six months of starting clozapine, the mental health of the sample improved by 32%, aggressive behaviour fell by 71% and self-harming behaviour were reduced by over 80%. [20] Furthermore, a qualitative study of 20 inpatients with BPD who were treated with clozapine found that responses to taking the drug were very positive with many reporting substantial improvements in their mental health and well-being. [25]

While it is possible that clozapine improves mental health and reduces aggressive and self-harming behaviour of people with BPD, it also has serious side effects. Most patients gain weight and a minority develop type II diabetes. [26] Clozapine is also associated with an increased incidence of neutropenia and potentially fatal agranulocytosis, also pneumonia and severe constipation. [27] Despite these side effects clozapine is licensed in the UK for the treatment of people with schizophrenia who are unresponsive to, or intolerant of, conventional antipsychotic drugs. This is because, for people with treatment resistant schizophrenia, the benefits of taking clozapine outweigh the risks. At present the true risks and benefits of treating people with BPD with clozapine are unknown.

3.3 Why this research is needed now

High levels of contact with health services, and specifically with specialist secure inpatient services, mean that the costs associated with treating people with severe borderline personality disorder are high. For example the cost of care on a secure inpatient ward in England is as much as £250,000 per annum, [28] with length of stay typically measured in years. [29] In 2007 it was estimated that the total cost of providing NHS services to people with personality disorder was £7,000,000 a year. [30] When wider costs associated with use of criminal justice and social services are taken into account the costs of the illness are far higher at over £7,000,000,000 per year. [30]

In England efforts to improve the effectiveness and reduce the cost of inpatient mental health care is a national policy priority. [31] Often one of the main barriers to discharging people with BPD from inpatient units is the ongoing risk that they pose both to themselves and to others as a result of the disorder. [32, 33]

In 2010 a Cochrane systematic review of pharmacotherapy in BPD noted the potential of clozapine as a treatment for people with borderline personality disorder and highlighted the absence of randomised trials examining the effects of this drug. [11] In preparation for this application we updated this review and found no new trials of clozapine for people with

borderline personality disorder. [34] A searcher of the ISRCTN registry and Clinicaltrials.gov conducted in June 2017 revealed no evidence of relevant ongoing trials.

To summarise, inpatients with severe borderline personality disorder experience high levels of emotional distress which may be accompanied by high levels of self-harming and aggressive behaviour. Open label studies of treating inpatients with clozapine show major improvements in mental health and reductions in self-harming behaviour. However, to date there are no published or on-going clinical trials of clozapine for people with borderline personality disorder. While clozapine has the potential to generate considerable savings for the NHS, the true risks and benefits of treating people with clozapine are unknown. The CALMED trial is a fully powered two-arm, double-blind, placebo-controlled randomised trial which is designed to establish the clinical effectiveness and cost effectiveness of clozapine for inpatients with severe borderline personality disorder.

4 Aims and objectives

The aim of the study is to investigate whether, among people receiving inpatient treatment for severe borderline personality disorder, the addition of clozapine to their usual care is a clinically effective and cost-effective strategy for improving their mental health. Although clozapine is not currently licensed for the treatment of people with borderline personality disorder and is not recommended by NICE, patients and clinicians who have tried this approach believe it is helpful. Results of open label studies indicate that clozapine can improve the mental health of people with borderline personality disorder and that negative effects can be minimised through carefully monitoring physical health.

The main research question is: for people receiving inpatient treatment for severe borderline personality disorder who have not made an adequate clinical response despite receiving usual care (including at least three months taking another antipsychotic drug), does the addition of clozapine to their usual care lead to improved mental health six months later, compared to adding an inert placebo to their usual care?

The secondary research questions are:
i) For people receiving inpatient treatment for borderline personality disorder who have not made an adequate clinical response to usual care, does the addition of clozapine lead to greater improvements in health-related quality of life, greater reductions in aggression, suicidal behaviour, and use of services compared to adding a placebo?

ii) For people receiving inpatient treatment for borderline personality disorder who have not made an adequate clinical response to usual care, does the addition of clozapine provide a cost-effective treatment compared to the addition of a placebo?

5 Trial design

A two-arm, parallel-group, placebo-controlled trial with an internal pilot and an integrated economic evaluation. The study is funded by the National Institute of Health Research (NIHR) Health Technology Assessment programme. Study groups are standard care plus clozapine, titrated up to a maximum dose of 400mg daily, versus standard care plus an inert placebo.

Standard care will include access to psychological interventions, occupational activities and nursing care that are provided to inpatients with BPD.

The trial will involve two linked phases:
Phase 1 - An internal pilot in which participants will be recruited from all centres over a six-month period. Data from the internal pilot will be presented to the Trial Steering Committee (TSC) indexed against a priori stop/go criteria, that will be used to determine if the study progresses to phase 2.
Phase 2 - Full trial across all sites over a further 18-month period.

Progression criteria will be assessed at six months according to the following three parameters:

- Number of participants randomised in the first six months. Our target is 55. If above 42 (75% of the target) recruitment would continue. If between 35 and 41 we would discuss continuation with the independent committees and funder. If below 32 (less than 60% of the target) we would stop. Mitigating circumstances for under-recruitment such as a delay in opening one or more of the pilot sites will be discussed with the TSC and may result in an adjustment to the participant target or pilot period.
- At least 75% of the participants recruited to the active arm of the trial in the first three months of the pilot phase of the trial will have started study medication within four weeks of randomisation.
- Three-month follow-up data will have been collected from >70% of those randomised during the first three months of the pilot study.

6 Selection of participants

6.1 Inclusion criteria

To take part in the study potential participants must:

- be aged 18 years or over
- be receiving inpatient treatment
- meet DSM-IV diagnostic criteria for borderline personality disorder using the Structured Clinical Interview for Axis II Personality Disorders (SCID II) (44)
- have not made an adequate clinical response despite ever taking antipsychotic medication other than clozapine for at least three months
- Have a satisfactory pre-treatment full blood count (white blood cell count >=3.5 and absolute neutrophil count >=2.0)
- Have had their weight and blood glucose recoded in their clinical records
- Have demonstrated severe personality disorder by evidence of at least one of the following criteria:
  a) Has been an inpatient on a mental health ward for more than 28 days in the last 12 months; OR
  b) Has had two or more admissions to hospital/periods of care provided by Home Treatment over the last 12 months, AND a lifetime history of two or more incidents of harm to self or others which resulted in permanent damage/ disability, or would have done so had services not intervened

6.2 Exclusion criteria

We will exclude those who:

- have a current coexisting clinical diagnosis of schizophrenia, or bipolar I disorder
- prescribed clozapine within the last two weeks
- are known to be pregnant, trying to conceive, breastfeeding, or a woman of childbearing potential and is not using a highly effective birth control. (see box 1 below for guidance)
- are due to be discharged from the unit within the following two weeks and it is not possible to continue the necessary monitoring of physical health as an outpatient
- are unable to speak sufficient English to complete the baseline assessment
- are unwilling or unable to provide written informed consent to take part in the study
- are unable to undergo regular blood tests
- have a contraindication to clozapine or other listed condition, namely:
    - a known history of primary bone marrow disorders or impaired bone marrow function
    - severe renal or cardiac disorders (e.g. myocarditis), or a known history of cardiac illness or abnormal cardiac findings on physical examination
    - have hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption
    - have hypersensitivity to
        - Magnesium stearate
        - Silica, colloidal anhydrous
        - Povidone K30
        - Talc
        - Maize starch
        - Lactose monohydrate
    - have a known history of toxic or idiosyncratic granulocytopenia/agranulocytosis (with the exception of granulocytopenia/agranulocytosis from previous chemotherapy)
    - have a history of clozapine-induced agranulocytosis
    - have uncontrolled epilepsy
    - have alcoholic and other toxic psychoses, drug intoxication, comatose conditions
    - Have circulatory collapse and/or CNS depression of any cause
    - Have active liver disease associated with nausea, anorexia or jaundice; progressive liver disease, hepatic failure
    - Have paralytic ileus

Where any of the eligibility criteria cannot be confirmed, the individual will not be entered into the trial until there is clinical evidence that satisfies the medically qualified doctor confirming eligibility e.g. an ECG for an individual that is judged to be at increased risk of cardiac disorder. The doctor confirming eligibility will judge which tests are necessary in these circumstances, acting as they would for any other patient being considered for treatment with clozapine. Where the individual cannot be certain that they are not pregnant, we will wait for the clinical team to arrange a pregnancy test to establish pregnancy status before proceeding.

We will not exclude people who are currently receiving treatment on a compulsory basis under the Mental Health Act. While many people who are receiving inpatient treatment for borderline personality disorder are detained in hospital, this is generally because of concerns about the risk they pose to their health, their safety or for protection of others. Only a small proportion of inpatients with BPD lack capacity to make choices about the medication they receive, [35] and those unable to make an informed choice about taking part in the study would be excluded from taking part in the trial.

Additional Guidance 1: Birth Control Methods

A woman is considered of childbearing potential if she is 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.

Methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods. Such methods include:

- combined (oestrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal)
- progesterone-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable)
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomised partner
- sexual abstinence from heterosexual sexual intercourse

7 Recruitment

We will recruit study participants from general adult mental health wards, psychiatric intensive care units and secure/forensic mental health inpatient units in England. We will recruit participants from all those using inpatient services delivered by seven NHS and independent sector providers; Central and North West London NHS Foundation Trust, Elysium Healthcare, Lancashire Care NHS Foundation Trust, Mersey Care NHS Foundation Trust, Nottinghamshire Healthcare NHS Foundation Trust, St Andrew's Healthcare, West London Mental Health NHS Trust. These sites include all three high secure hospitals in England (Ashworth Hospital, Broadmoor Hospital and Rampton Hospital). The inclusion of independent sector providers in our recruitment strategy is key as much of the secure inpatient care for NHS patients with borderline personality disorder is now provided by the independent sector.

At each study centre information about the trial will be widely publicised among clinicians working on inpatient units including high secure, medium secure and low secure wards, Psychiatric Intensive Care Units (PICU), and general adult inpatient units. We will make it clear to potential referrers that we are only aiming to recruit people who have severe borderline personality disorder (as indicated by high levels of use of services).

Members of the research team will work with Clinical Studies Officers from the Clinical Research Network to present plans for the study at local academic and clinical meetings and continue to

visit inpatient staff on a regular basis to remind them about the study. Potential participants will be approached initially by a staff member and asked to provide verbal agreement to be contacted by a member of the study team. If they agree the researcher will meet the potential participant to explain the rationale for the study and give them a copy of the Patient Information Sheet.

8 Trial procedures and schedule of assessments

8.1 Informed consent procedure

In all instances potential participants will have at least 24 hours before deciding whether they wish to take part in the study. Before any trial specific procedures are performed, the participant will need to sign and date an Informed Consent Form. We will ask staff to only refer people into the study who they believe have capacity to provide informed consent to take part. Researchers will assess capacity to give informed consent in accordance with the requirements of Research Ethics Committee guidance and Good Clinical Practice. (50) For those willing and able to provide consent, eligibility to participate in the study will be assessed and baseline clinical and demographic data will be collected. Those who are ineligible will be thanked for their time and informed of the reason(s) for this. Researchers will ask patients who meet inclusion criteria but decline to participate their reasons for refusal and this information will be recorded.

If new safety information results in significant changes in the risk/benefit assessment, the Consent Form will be reviewed and updated if necessary and subjects will be re-consented as appropriate.

Additionally, potential participants will be asked whether a family member or friend can be contacted solely for the purpose of helping the research team to get in contact with the participant, if the research team are not able to get in contact with the participant directly. A separate written informed consent will be required for this. The patient will not be excluded from the study if he/she does not give consent for the research team to contact family members or friends.

8.2 Screening

A pre-randomisation assessment of eligibility will be undertaken following consent by a check of the medical records for the patient, for information about current and previous medication, including use of inpatient and outpatient mental health services, previous use of clozapine and other antipsychotic medications, contraindications to clozapine. The information obtained from the patient's medical records will be documented on a Referral and Screening Form. This form will be endorsed by a medically qualified doctor who has clinical responsibility for the patient's care. The clinician will also be asked to ensure that a history and physical examination for the patient that includes recording his/her weight, blood glucose and lipids in the last month, together with any other physical health tests they judge necessary before prescribing trial medication.

Finally, the clinician will also be asked whether there are any plans for the potential participant to be discharged from the unit within the following two weeks and if so, if adequate support is in place to continue the necessary monitoring of physical health as an outpatient, and this also documented on the Referral and Screening Form. Where no reason for ineligibility has been

identified during completion of the Referral and Screening Form, a discussion with the patient will then take place to complete the eligibility check. This will establish, whether the patient:
i. May be pregnant or trying to conceive, breastfeeding, or a woman of childbearing potential not using a highly effective birth control.
ii. Meets criteria for borderline personality disorder according to DSM-IV criteria using the Structured Clinical Interview for Axis II Personality Disorders (SCID-II). [36] [37]
iii. The extent of psychotic symptoms that the participant experiences. [38]
iv. The extent of personality-related problems using the International Personality Disorder Examination (IPDE) self-complete screening questionnaire. [39]
v. Has taken clozapine in the past and is aware of having experienced any adverse events

The assessment will be recorded in the Screening CRF, which will also include a collection of demographic data on age, gender and ethnicity. As soon as any eligibility criteria are found to not be met, no further assessments will be carried out. Those who are ineligible will be thanked for their time and informed of the reason(s) for this.
If all eligibility criteria are met, the patient will be randomised into the trial. Once eligibility is confirmed, the researcher will use the randomisation system to obtain a randomisation code for the participant. Following randomisation, the participant's GP will be informed of their enrolment into the trial via letter.

8.3 Baseline assessments

If the participant fulfils the eligibility criteria, completion of the Baseline Assessment CRF may commence immediately. The baseline CRF will include the following assessments:
i. The Zanarini rating scale for Borderline Personality Disorder (ZAN-BPD). [40] The ZAN-BPD is the most widely used outcome in trials of BPD. It provides a reliable and valid assessment of core features of the condition and is sensitive to change. [41, 42] Feedback from our preparatory survey was that ZAN-BPD is acceptable to inpatients with borderline personality disorder and addresses the key emotional and behavioural problems that inpatients with this condition experience.
ii. The Standardised Assessment of Severity of Personality Disorder (SAS-PD)– a nine item self-report measure provides a reliable indicator of the severity of a person's personality problems. [43] By using this measure we will be able to describe the study population in terms of proposed ICD-11 system for the classification of personality disorder.[44]
iii. The Brief Psychiatric Rating Scale (BPRS) - a 24-item researcher-rated structured assessment which provides a comprehensive assessment of mental health. [45] The BPRS was used in previous open-label studies of clozapine for people with borderline personality disorder, [20, 24] By including the scale in this trial we will be able to compare the results with those of previous open-label studies.
iv. The Acts of Deliberate Self-Harm Inventory - a structured interview which collects detailed information about the number and severity of episodes of self-harm. [46] The inventory has been used successfully in other trials of treatments for people with borderline personality disorder. [47]
v. The Modified Overt-Aggression Scale- (MOAS), [48] which provides a reliable measure of the frequency and severity of aggressive behaviour among people with mental disorders. [49]
vi. The European Quality of Life-5 Dimensions, [50] which provides a brief and reliable measure of health-rated quality of life and is responsive to change in people with borderline personality disorder. [51]

vii. The Antipsychotic Non-Neurological Side Effects Scale (ANNSERS) which covers a range of aversive subjective experiences as well the cardiovascular, gastrointestinal, and central nervous system side effects of antipsychotic medication, [52]
viii. The Extrapyramidal Side Effects Scale, which assesses motor and extrapyramidal side effects of antipsychotic drugs. [53, 54]
ix. The Adult Service Use Schedule, [55] which will enable us to collect detailed data on use of all hospital and community services including medication. [56]

Post-consent and prior to randomisation a potential participant must have a satisfactory pre-treatment full blood count (white blood cell count >=3.5 and absolute neutrophil count >=2.0). These results are required in order to register an individual with the Clozaril Patient Monitoring Service (CPMS). Registration with CPMS must be completed before any trial medication will be dispensed.

8.4 Randomisation procedures

Researchers at each site will enter the results of the baseline assessment on a web-based Case Report Form. Remote web-based randomisation will be undertaken through a fully automated service operated by the NWORTH, University of Bangor. Randomisation will be via a secure online system using a sequentially randomised dynamic adaptive algorithm stratified by centre (for a list of centres please see section 3, Trial Synopsis, Research Sites), ward type (general adult, low secure, medium secure and high secure) and gender (male or female). Within the algorithm, the likelihood of the participant being allocated to each treatment group is recalculated based on the participants already recruited and allocated. [59] This recalculation is done at the overall allocation level, within stratification variables and within stratum level (the relevant combination of stratification levels). By undertaking this re-calculation, the algorithm ensures that balance is maintained within acceptable limits of the assigned allocation ratio while maintaining unpredictability.

Randomisation will create a unique randomisation code for the participant. A trial prescription form will then be completed by the local investigator. This will be sent to the pharmacy that will dispense the trial medication to the ward where the participant is being treated.

8.5 Treatment procedures and monitoring

The use of clozapine in psychiatric services is well established. National guidelines and the Summary of Product Characteristics for Clozaril specify the mandatory and recommended physical health monitoring for individuals prescribed clozapine, based on data from large scale clinical trials and extensive post-marketing reporting. This monitoring aims to identify adverse events that are associated with clozapine and may result in serious outcomes if not treated promptly.

In addition, each research site will have a comprehensive monitoring strategy for patients that are prescribed clozapine in usual clinic practice, which incorporates these physical health monitoring requirements. Local procedures take into account the structure and organisation of the research site in delivering best practice. Study sites will therefore follow their own local policies on physical health monitoring of patients that are prescribed clozapine for all study

participants. Data will be collected on the minimum measures that are required to ensure that the recommendations of the Summary of Product Characteristics for Clozaril and the Maudsley Prescribing Guidelines in Psychiatry are followed, as detailed below. This is not an exhaustive list of the physical health monitoring that will take place at each site.

The services in place to carry out the physical health monitoring will be established prior to enrolment of each patient into the trial. Where participants are inpatients, the monitoring activities will usually be managed on the ward whereas outpatients may be monitored by services such as clozapine clinics or home treatment teams. Where the patient is transferred or discharged to a setting that cannot support the monitoring requirements of the trial, trial medication will be discontinued.

All study participants will be monitored in the same way regardless of the treatment arm they are in. There are three components to assessing and monitoring the health of people prescribed clozapine: full blood counts, monitoring of short term adverse events and long-term side effects of the drug physical health monitoring during initiation of treatment and continuing during trial treatment. A member of the research team will extract information about each of these measures for the participant's clinical record and enter them into the CRF.

8.5.1 Full blood counts

All participants will have a full blood count assessed no more than 10 days prior to taking the first dose of trial medication. Participants who do not have a normal white cell count (>3500/mm^3) and a normal absolute neutrophil count (> 2000/mm^3) will not be eligible to take part in the trial. If eligible, and once the first dose of trial medication has been administered, each study participant will have repeat full blood counts weekly for first 18 weeks and fortnightly thereafter which will be assessed through the Clozaril Patient Monitoring Service. Future supply of trial medication will not be permitted unless the result of the blood test is 'green'. If the result is returned as 'amber' this indicates that there has been a reduction in the participant's white blood cell count or their absolute neutrophil count. While the participant can continue to take trial medication twice weekly blood tests need to be initiated until a 'green' result is achieved. 'Red' test results are ones where white blood cell count, or the absolute neutrophil count are unsafe and require clozapine to be stopped, daily blood tests to be initiated and clinicians to monitor for signs of infection. Daily blood tests should continue until the white cell count is in the normal range. No participant that has a red test result will be restarted on clozapine during the course of the trial.

Once a 'green' result has been confirmed via CPMS for the participant, the site pharmacy will send the first supply of trial medication to the participant's ward to ensure that all are within acceptable parameters.

Once the maintenance dose is reached, trial medication will be given by ward staff in the same way as other prescribed medication would be in this setting and it written up on the participant's drug chart. For outpatients the medication may be handed to a patient by the hospital pharmacy, by research or clinical staff, for example at a clozapine clinic.

8.5.2 Physical health monitoring during initiation of treatment

All study participants will have their blood pressure (lying and standing), temperature and pulse measured in accordance with local protocols. This will include an assessment prior to the first dose of trial medication, at least daily for the first three days after first dose is administered and weekly for the first three weeks after first dose is administered.

8.5.3 Continuing monitoring of physical health

Prior to the administration of the first dose of study medication participants will have baseline measures of their weight, blood glucose, and lipids. These tests will not be repeated if they were conducted less than one month prior to the baseline assessment. All participants will also have these assessments repeated within three months of taking their first dose of trial medication and after six months.

In accordance with the SmPC, appropriate additional monitoring will be advised for participants as follows, and consideration of whether this can be undertaken will be given prior to entering patients that requires these assessments:

- Monitoring of standing and supine blood pressure is necessary during the first weeks of treatment in patients with Parkinson's disease.
- Patients with a history of epilepsy should be closely observed during Clozaril therapy since dose-related convulsions have been reported.
- Clozapine should be used with caution in patients with risk factors for stroke.
- Patients with stable pre-existing liver disorders may receive Clozaril, but need regular liver function tests.
- Particular care is necessary in patients who are receiving concomitant medications known to cause constipation (especially those with anticholinergic properties such as some antipsychotics, antidepressants and antiparkinsonian treatments), have a history of colonic disease or a history of lower abdominal surgery as these may exacerbate the situation.
- Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g. obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment.

8.6 Subsequent assessments

We will follow up all study participants three and six months after randomisation. All follow-up assessments will be carried out through face-to-face interviews by researchers who are masked to the participant's allocation status. In circumstances where face-to-face interview are not possible e.g. social distancing due to novel coronavirus, telephone or video call interviews will be used.

i. Zanarini rating scale for Borderline Personality Disorder (ZAN-BPD). [40]
ii. Brief Psychiatric Rating Scale (BPRS). [45]
iii. Acts of Deliberate Self-Harm Inventory. [46]

iv. Modified Overt-Aggression Scale. [48]
v. EuroQoL EQ-5D 3 level (EQ-5D-3L). [50]
vi. Antipsychotic Non-Neurological Side Effects Scale (ANNSERS) [52]
vii. The Extrapyramidal Side Effects Scale. [53]
viii. Adult Service Use Schedule. [5]
ix. Brief Adherence Rating Scale (BARS), which provides a reliable indicator of medication adherence. [57]
x. The Standardised Assessment of Severity of Personality Disorder (SAS-PD[43] (6 months only)
In addition to this, data on the participant's weight and blood glucose will be extracted from clinical records at both three and six months. We will also ask both the participant and researcher to guess the participant's trial arm allocation at six months.

As the full extent of savings associated with any improvement in mental health may take longer to generate we will obtain written informed consent from participants to examine routine data on service utilisation and the option of further contact from a member of the research team. We will continue to collect economic data from clinical records on use and type of inpatient treatment, use of community services and quantity and type of medication that participants take throughout the study. Data will be collected every six months so that, for those recruited in the first six of the trial, we will have economic data for a full 18-month period after randomisation. These data will be used to build the economic model (see section 5.11.1). Evidence from open-label studies of clozapine for people with BPD has shown that improvements in mental health and reductions in impulsive and aggressive behaviour are seen within the first three months of treatment. [20, 23, 24, 60] Changes in costs of care may also be seen during this period due to reduced need for enhanced nursing support and escort. These results are in keeping with trials of clozapine in the treatment of psychosis which show that the greatest impact occurs early in treatment. [61]

The timing and sequence of assessments are summarised in table 1 below.
With the exception of procedures for monitoring the physical health of participants prior to and during initiation of trial treatment and the ongoing full blood count assessments in collaboration with the Clozaril Patient Monitoring Service, assessments that occur +/- 21 days from the due date will not be considered protocol deviations.

Table 1: Study Assessment Schedule.

Assessments	**Screening**	**Baseline**	**3- month follow-up**	**6-month follow-up**	**12 and 18-month**
Structured Clinical Interview for Axis II Personality Disorders (SCID-II)	X	-	-	-	-
Psychosis Screening Questionnaire	X	-	-	-	-
International Personality Disorder Examination (IPDE)	X	-	-	-	-
Standardised Assessment of Severity of Personality Disorder (SASPD)	-	X	-	X	-
Zanarini rating scale for Borderline Personality Disorder (ZAN-BPD)	-	X	X	X	-
Brief Psychiatric Rating Scale (BPRS)	-	X	X	X	-
Acts of Deliberate Self Harm Inventory	-	X	X	X	-
Modified Overt-Aggression Scale (MOAS)	-	X	X	X	-
EuroQoL EQ-5D 3 level	-	X	X	X	-
The Antipsychotic Non-Neurological Side Effects Scale (ANNSERS)	-	X	X	X	-
The Extrapyramidal Side Effects Scale	-	X	X	X	
Brief Adherence Rating Scale (BARS)	-		X	X	-
Adult Service Use Schedule (ADSUS) Use of inpatient and community mental health services	-	X	X	X	X
Trial Arm allocation guess				X	

Table 2: Physical Health Measures Schedule

Timepoint	**WBC/ANC x10^9 /L**	**Blood Glucose**	**Blood lipids**	**Body weight**	**Blood Pressure – lying [mmHg]**	**Blood Pressure – standing [mmHg]**	**Temp [° C]**	**Pulse [BPM]**
Screening	X (<=10 days of 1st dose)	X (<=1 month of 1st dose)	X (<=1 month of 1st dose)	X (<=1 month of 1st dose)				
Immediately prior to 1st dose					X	X	X	X
Day 1 - after 1st dose					X	X	X	X
Day 2					X	X	X	X
Day 3					X	X	X	X
Week 2	X				X	X	X	X
Week 3	X				X	X	X	X
Week 4	X							
Week 5	X							
Week 6	X							
Week 7	X							
Week 8	X							
Week 9	X							
Week 10	X							
Week 11	X							
Week 12	X							
Week 13	X	X	X	X				
Week 14	X							
Week 15	X							
Week 16	X							
Week 17	X							
Week 18	X							
Week 20	X							
Week 22	X							
Week 24	X							
Week 26	X	X	X	X				
	Below is required only for discontinuation of unblinded clozapine or until switched to non-trial prescription of clozapine							
Week 28	X							
Week 30	X							

Participants will be asked if they would consent to longer-term follow-up. After the study has ended we would like to follow up participants for up to five years which would involve tracking patient records to gather information on service utilisation, check contact details are current and may involve contacting people for further face-to-face follow up assessments. Consent for long term follow-up would be optional. Whether the additional work is carried out is dependent on sourcing additional funding for longer term follow up, and separate research ethics committee approval would be sought prior to the work being carried out.

8.7 Emergency unblinding

Premature disclosure of allocation runs the risk of introducing bias and invalidating the trial results. Masking of treatment allocation will therefore be maintained during an individual's participation in the trial unless the following occur:

- A serious adverse event arises that clinically requires disclosure.
- Another clinical reason to need to know the allocation such as to start the participant on medication which has a risk of interaction.
- A confirmed red result from CPMS. If participant is in the active arm, s/he will be registered on the Central Non-Rechallenge Database (CNRD).

Brief details on the study, the participant's randomisation code and the telephone number for 24-hour emergency unblinding will be added to the participant's medical records on study entry, will be on the trial medication bottle, and, for patients discharged from hospital during the follow-up period, given on a card that the participant will be asked to carry. The service will be provided by the Emergency Scientific and Medical Services Global, Medical Toxicology Information Service Ltd.
All unblinding requests will be notified to the Chief Investigator, trial coordinating office and sponsor. These will be recorded and reviewed, and the PI of the site where the participant was unblinded contacted and advised to complete any paperwork that is appropriate such as a Serious Adverse Event Form.

Subject always to clinical need, where possible, members of the research team will remain blinded. All adverse events will be reported according to Sponsor Safety Reporting SOPs.

8.8 Discontinuation/withdrawal of participants and 'stopping rules'

8.8.1 Individual stopping criteria

In accordance with the current revision of the Declaration of Helsinki (amended October 2000, with additional footnotes added 2002 and 2004), a participant has the right to stop trial treatment and to withdraw from the trial at any time and for any reason, without prejudice to his or her future medical care by the physician or at the institution, and is not obliged to give his or her reasons for doing so.
A participant will also stop trial medication if any of the following occur:

- CPMS blood monitoring shows that participant's white blood cell count or absolute neutrophil count is unsafe (red result)

- An SAE that necessitates unblinding. It will be left to the Principal Investigator's clinical judgement whether or not any other adverse event is of sufficient severity to require discontinuation of trial treatment.
- Intention to initiate medication that has a known interaction with clozapine
- Pregnancy

Provided they have not withdrawn their consent, the participant would continue to be followed up to enable an intention-to-treat analysis.

8.8.2 Overall trial stopping rules

The Data Monitoring and Ethics Committee (DMEC) will have access to adverse event data by blinded treatment arm. The trial may be stopped by the sponsor or the funder on the advice of the Trial Steering Committee or DMEC if they have concerns about any potential harms to study. The DMEC may request that the treatment arms are unblinded if there is an excess of adverse events in one arm. Recommended practice [62] is to stop the trial if there is an increase in serious adverse events among those in the active arm of the trial at a 10% level of statistical significance (i.e. an α of 0.1).

8.9 Definition of end of trial

The end of trial is defined as last participant, last visit.

9 Drugs to be used in the trial

9.1 Treatment of participants

The following drugs will be used in this trial:

Clozapine 12.5mg, 25mg and 100mg doses will be enclosed in Capsugel size 0 gelatine capsules of varying colours, with a microcrystalline cellulose backfill. 12.5 mg dose will be enclosed in white opaque, 25 mg dose in dark green and the 100 mg dose in scarlet capsules. The placebo capsules will have an identical appearance to the IMP such that allocation concealment and blinding of the trial is maintained.
Capsules will be packed into HDPE bottles and labelled with the approved label. These will be supplied to sites pharmacies in small sized bulk packs containing 20 (12.5mg) or 100 (25mg and 100mg) capsules.

Bottles of clozapine and placebo will be labelled by blinded trial arm (e.g. A or B) and site pharmacies will then dispense the capsules into smaller bottles according to the trial prescription for a participant, with trial arm not shown on the label.
The IMP and the placebo will be manufactured by St Mary's Pharmaceuticals Unit (Cardiff and Vale University Health Board).

9.2 Concomitant medication

It would be unethical to restrict the therapeutic options of the clinical team; therefore, no restrictions will be imposed on the use of other treatments, except that those who remain in the trial will not be prescribed clozapine (aside from trial medication). National guidelines recommend that people should not be prescribed more than one antipsychotic medication simultaneously. [63] While study participants may be prescribed other psychotropic medication during the trial (including medication for rapid tranquilisation), we will recommend the cautious short-term use of benzodiazepines and promethazine for those who are judged to need additional medication in keeping with NICE guidelines on the treatment of people with BPD. When any other medication is prescribed for a participant, or there is a change in smoking status or a significant change in caffeine consumption, all patients should be managed as if they were prescribed clozapine, whether the clinical team believe this to be the case or not.

We will record the use of all other medication, documenting details of dosage, and ensure the follow-up of all randomised participants, irrespective of the medication they subsequently receive.

10 Investigational Medicinal Product

According to the definition of the EU clinical trial directive 2001/20/EC, an investigational medicinal product is a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorisation, but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form.

10.1 Name, description and source of investigational medicinal product(s)

Clozapine is an 'atypical' antipsychotic drug. As well as being a dopamine antagonist, it binds to serotonin receptors and is a partial antagonist at the 5-HT_{2A} site. [19] In this trial clozapine will be over encapsulated in caps size 0

Placebo (matching caps size 0)

10.2 Summary of findings from non-clinical studies

May be found in the summary of product characteristics.

10.3 Summary of findings from clinical studies

Maybe found in the summary of product characteristics.

10.4 Summary of known and potential risks and benefits

The SmPC details the known and potential risks and benefits of clozapine. The known side effects are detailed below by System Organ Class and Frequency (very common is ≥1/10, common is

≥1/100 to <1/10, uncommon is (≥1/1000 to <1/100, rare is ≥1/10,000 to <1/1000 and very rare is <1/10,000).

Very Common	Common	Uncommon	Rare	Very Rare	Unknown
Blood and lymphatic system disorders					
	Leukopenia, decreased WBC, neutropenia, eosinophilia, leukocytosis	Agranulocytosis	Anaemia	Thrombocytopenia, thrombocythaemia	
Gastrointestinal disorders					
Constipation, hypersalivation	Nausea, vomiting, anorexia, dry mouth		Dysphagia	Intestinal obstruction/ paralytic ileus/faecal impaction, parotid gland enlargement	Megacolon sometimes fatal*, intestinal infarction/ ischaemia sometimes fatal*, diarrhoea*, abdominal discomfort/ heartburn/ dyspepsia*, colitis*
Hepatobiliary disorders					
Elevated liver enzymes			Pancreatitis, hepatitis, cholestatic jaundice	Fulminant hepatic necrosis	Hepatic steatosis*, hepatic necrosis*, hepatotoxicity*, hepatic fibrosis*, hepatic cirrhosis*, liver disorders including those hepatic events leading to life-threatening consequences such as liver injury (hepatic, cholestatic and mixed), liver failure which may be fatal and liver transplant*.

Very Common	Common	Uncommon	Rare	Very Rare	Unknown
Metabolism and nutrition disorders					
	Weight gain		Diabetes mellitus, impaired glucose tolerance	Hyperosmolar coma, ketoacidosis, severe hyperglycaemia, hyper-cholesterolemia, hyper-triglyceridemia	
Psychiatric disorders					
	Dysarthria	Dysphemia	Agitation, restlessness		
Eye disorders					
	Blurred vision				
Vascular disorders					
	Syncope, postural hypotension, hypertension		Thrombo-embolism		Hypotension*, Venous thromboembolism
Renal and urinary disorders					
	Urinary retention, urinary incontinence			Interstitial nephritis	Renal failure*, Nocturnal enuresis*
Respiratory, thoracic and mediastinal disorders					
			Aspiration of ingested food, pneumonia and lower respiratory tract infection which may be fatal, sleep apnoea syndrome	Respiratory depression/arrest	Pleural effusion *, Nasal congestion*

Very Common	Common	Uncommon	Rare	Very Rare	Unknown
Nervous system disorders					
Drowsiness/ sedation, dizziness	Seizures/ convulsions/ myoclonic jerks, extrapyramidal symptoms, akathisia, tremor, rigidity, headache	Neuroleptic malignant syndrome	Confusion, delirium	Tardive dyskinesia, obsessive compulsive symptoms	Cholinergic syndrome (after abrupt withdrawal)*, EEG changes*, pleurothotonus*, restless leg syndrome*
Skin and subcutaneous tissue disorders					
				Skin reactions	Pigmentation disorder*
Cardiac disorders					
Tachycardia	ECG changes		Circulatory collapse, arrhythmias, myocarditis, pericarditis/ pericardial effusion	Cardiomyopathy, cardiac arrest	Myocardial infarction which may be fatal*, chest pain/angina pectoris*, atrial fibrillation*, palpitations*, mitral valve incompetence associated with clozapine related cardiomyopathy*
Reproductive system and breast disorders					
				Priapism	Retrograde ejaculation*
Vascular disorders					
	Syncope, postural hypotension, hypertension		Thromboembolism		Hypotension*, Venous thromboembolism
General disorders and administration site conditions					
	Benign hyperthermia, disturbances in sweating/ temperature regulation, fever, fatigue			Sudden unexplained death	Polyserositis*
Investigations					
			Increased CPK		

Very Common	Common	Uncommon	Rare	Very Rare	Unknown
Injury, poisoning and procedural complications					
					Falls (associated with clozapine-induced seizures, somnolence, postural hypotension, motor and sensory instability)*

* Adverse drug reactions derived from post-marketing experience via spontaneous case reports and literature cases.

Prescribing clinicians will be asked to monitor for signs of constipation in the weeks following initiation of trial medication. Particular care will be taken in participants who are receiving other drugs that can cause constipation (analgesics, tricyclic antidepressants, calcium channel blockers and antihypertensives). Any constipation that emerges will be actively treated using diary measures, exercise and, if no response, use of laxatives in accordance with local protocols.

10.5 Route of administration, dosage, regime and treatment period

Initial titration will be undertaken whilst the participant is an inpatient as the titration schedule is based on Maudsley Prescribing Guidelines for inpatients (see table below). [64]

R*ecommended Titration Regime*

Day	Morning dose	Evening dose	Blood test
1	-	12.5mg	
2	12.5mg	12.5mg	
3	12.5mg	25mg	
4	25mg	25mg	
5	25mg	50mg	
6	25mg	50mg	
7	50mg	50mg	Full blood count
8	50mg	75mg	
9	75mg	75mg	
10	75mg	100mg	
11	100mg	100mg	
12	100mg	125mg	
13	100mg	150mg	
14	100mg	175mg	Full blood count
15	100mg	200mg	
16	100mg	200mg	
17	100mg	200mg	
18	100mg	250mg	
19	100mg	250mg	
20	100mg	250mg	
21	100mg	300mg	Full blood count

For participants who prefer to take their medication as a single daily dose, clinicians will be permitted to administer the total daily dose in the evening.

In the event that a participant is discharged from hospital care before the first 14 days of trial medication is completed, he/she may still remain in the trial. Prescribers should consider revising the remaining titration schedule to increase the dose more slowly in line with the Maudsley guidelines for initiating clozapine for patients in the community

Once a 'green' result has been confirmed via CPMS for the participant, the site pharmacy will send the first supply of trial medication to the participant's ward.

Re-supply of trial medication for the participant will be either to their ward or to the participant themselves where he/she is an outpatient. This will be permitted at the frequency indicated by the

CPMS monitoring results. This will usually be for seven days during the first 18 weeks and for 14 days thereafter.

10.6 Blood sample timing

The date of the last blood sample informs when the next one is due and is irrespective of the date the participant commences trial medication or the date that the last supply of trial medication was given to the participant. Therefore, if trial medication is supplied to a participant on a day other than the day of the blood test, fewer days' supply of trial medication are permitted before the next blood test must be obtained.

For weekly monitored participants the maximum cover from the date of the last sample is 10 days and for fortnightly monitored participants it is 21 days. Thus, blood samples must be timed to allow the appropriate amount of trial medication to be supplied and leave sufficient time for the next blood test before further supply is prohibited because the window of cover is exceeded.

Accordingly, although trial medication will usually be supplied for seven days during the weekly monitoring period and 14 days during the fortnightly monitoring period, this may be less if the window of cover is shorter because of the date of the last blood test.

Conversely, once titration is completed, where there will be or has been a delay in obtaining a full blood count for CPMS analysis, additional trial medication may be supplied, up to the maximum window of cover. Thus, up to 10 days' supply is allowed up to week 18 and up to 21 days' supply thereafter may be provided in exceptional circumstances, unless more frequent monitoring has been indicated (e.g. by an 'amber' result).

A member of the research team and/or site PI will facilitate the communication between pharmacy and clinical team (including the prescriber and other members of the participant's clinical care team) to ensure that a constant supply of trial medication is maintained for each participant. However, the procedure is similar to usual clozapine prescribing so each trust will already have a system in place for communicating the monitoring results and supply requirements of a patient.

Any alteration to the initiation regime or intended maintenance dose will be communicated to the site pharmacy on a new trial Prescription Form and CALMED Trial Medication Titration Chart. In keeping with prescribing guidelines for clozapine, any participant who misses more than 48 hours of trial medication for any reason will need to re-start titration. Re-titration of trial medication for those that have been discharged to the community does not require readmission to hospital. Necessary discontinuation of trial treatment will also be communicated to the site pharmacy by sending a copy of the Discontinuation of Trial Treatment Form.

The participant will be required to take the trial medication for a minimum of 183 consecutive days. Those allocated to clozapine may be prescribed an additional 14 days either (a) at reducing dose to allow trial medication to be safely discontinued or (b) at the current maintenance dose to allow a switch to non-trial clozapine. Therefore the total days of treatment may be up to 197 days.

10.7 Preparation and labelling of Investigational Medicinal Product

St Mary's Pharmaceutical Unit will be responsible for the procurement of trial medications, subsequent manufacture and packaging into a double-blind format, QP certification and distribution to recruiting sites. They will be produced in accordance with GMP and using local Trust Policies and Standard Operating Procudures. St Mary's Pharmaceutical Unit will manfuacture and carry out all the necessary quality assurance activities.

10.8 Drug accountability

Once randomisation has taken place, a CALMED trial prescription form containing the patient's details (including the participant randomisation code) will be signed by the site Principal Investigator or other psychiatrist to whom the task is delegated, and sent to the study site pharmacy, along with a Trial Medication Titration Chart that documents whether the standardised titration schedule should be followed or detailing the alternative schedule, and the target dose. This prescription will allow for the local site pharmacy to give the first and subsequent supplies of trial medication to the participant providing full blood count results indicate that initiating/continuing treatment with clozapine is appropriate (see below) and unless a Discontinuation of Trial Treatment Form is received.

Each pharmacy will have a master list containing randomisation codes and blinded treatment arm allocations. Following receipt of a trial prescription form and Trial Medication Titration Chart, and once the initial 'green' result is confirmed for a participant, a seven-day supply will be prepared for the participant and sent to his/her ward. Subsequent resupply will also be provided by the site pharmacy dependent on acceptable CPMS monitoring results and for the number of days permitted based on monitoring results and trial week.

The original prescription form and trial medication titration chart will be stored in a Pharmacy Site File specific to the study and a copy attached to the supply of trial medication for the participant.

Each time the participant requires a supply of trial medication, the site pharmacy will use capsules from the bottles of IMP of each dose that they have in stock for the appropriate trial arm to provide up to three bottles (one for each dose required) of trial medication for a participant. The number of capsules will be determined by the dose required for the number of days that supply covers. Each participant supply bottle will have a label added that is prepopulated with all the required label information, to which the randomisation code, date of dispensing, and number of capsules will be added. The prepopulated labels will have been supplied to the site pharmacy along with a duplicate of the label that is also completed by the pharmacy (randomisation code etc added here too) at the time of dispensing and acts as a record of what was dispensed. As there will be multiple dispensing from each bottle of study medication, multiple labels will be used to take account of changes in dose of medication given. On each occasion the pharmacy will attach the new label to the empty bottle they dispense into and attached a copy of the label to the study documentation.

10.9 Dose modifications

The prescribing clinician will be able to alter the dose of trial medication throughout the trial according to clinical response, side effects and participant preference.

10.10 Trial medication storage and temperature monitoring

IMP must be stored in a secure area, free of environmental extremes. Temperature will be monitored in the clinical trials area of all site pharmacies. Once the trial medication is dispensed and leaves pharmacy, however, the temperature will not be monitored for trial purposes. This applies whether the trial medication is passed to a ward on which the participant is an inpatient or passed to a participant or delegated individual involved in the trial who is delivering the study medication to the participant.

Participants will be asked to return the study medication bottles including any study medication that they have not taken at the time of receiving their follow-on supply in order to prevent any excessive

stock-piling of trial medication by the participant. Where the participant is collecting the follow-on study medication themselves, the person dispensing in pharmacy will ask for the returns. In cases where the participant does not visit the pharmacy or see the researcher between assessments, the empty bottles will be requested by the researcher when meeting with the participant to carry out the assessments at 12-weeks, 24-weeks, and 52-weeks. These will therefore be returned to the pharmacy by the researcher

10.11 Assessment of Participant Adherence

Non-adherence to the protocol or trial procedures will be documented by the investigator in the participant CRF.

Additional data on adherence will be obtained from interviewing participants at three and six months to complete the Brief Adherence Rating Scale. [57, 58]

10.12 Post-trial IMP arrangements

Six months after a participant was randomised, regardless of whether they withdrew from the study early or completed the participation period in full, a letter will be sent to the referring prescriber informing them of the participant's allocation status. Where a participant has completed the treatment period in full, this will allow the prescriber time to make arrangements for the participant to continue on clozapine if appropriate and desired. Upon completion of their six-month assessment, the participant will be advised to contact their prescriber to discuss their trial arm allocation and their future treatment. The decision whether to continue with clozapine or not will be made by the prescriber in consultation with the treatment team and taking into account patient preferences.

For those participants that are found to have been randomised to clozapine but intending to discontinue the medication the dose will be gradually reduced over a 2-week period as part of the trial. Follow-up blood samples will be taken for four weeks after stopping clozapine (i.e. four further tests for those on weekly monitoring and two more tests for those being monitored every fortnight).

For those continuing with clozapine, regular blood tests will be taken as part of the trial, up until the date the participant is switched from trial medication to medication prescribed by the clinical team. The date of the switch from IMP to clozapine will mark the end of trial procedures for these participants. Arrangements will be made for monitoring such patients after the date of the switch in accordance will local procedures and policies.

An individual from the trial coordination office that had no other role on the trial will be unblinded for the purpose of informing the referring clinician of the trial arm allocation of participants as part of routine unblinding.

11 Recording and Reporting Adverse Events and Reactions

At the baseline, three- and six-month follow-up assessments, questionnaires on side effects associated with antipsychotic medication are used to elicit information about adverse events that

have started or worsened since initiation of trial treatment. Where these are reported, they will also be recorded as adverse event(s).

All participants will have frequent, regular contact with clinical staff because they are either receiving in-patient care or are under the care of a clinical team. At minimum, contact will be required for blood tests and collecting trial medication. Clinical staff at each research sites will follow usual local procedures for ensuring continuing physical health of an individual that is prescribed clozapine. For example, enquiring about new health issues, checking for abdominal pain and/or constipation, changes in smoking status, and ensuring that the medication is being taken as prescribed. Any issues identified will be managed as part of clinical practice and the details noted on medical records. In some circumstances the information will be shared directly with the research team (e.g. where a change in dose is required). In addition, research staff regularly review the medical records of participants to ensure that all adverse events are recorded and any necessary actions are completed.

ICH GCP requires that both investigators and sponsors follow specific procedures when notifying and reporting adverse events/reactions in clinical trials. The procedures are described in this section of the protocol.

11.1 Definitions

The definitions of the EU Directive 2001/20/EC Article 2 based on ICH GCP apply in this trial protocol as shown in the table below:

Table 4: Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical trial subject 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 to an investigational medicinal product related to any dose administered.
Unexpected Adverse Reaction (UAR)	An adverse reaction, the nature or severity of which is not consistent with the information about the medicinal product in question set out in the Investigator Brochure for that product.
Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR)	Respectively any adverse event, adverse reaction or unexpected adverse reaction that: • results in death • is life-threatening* • requires hospitalisation or prolongation of existing hospitalisation** • results in persistent or significant disability or incapacity • consists of a congenital anomaly or birth defect

**The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.*

***Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition (including elective procedures that have not worsened) do not constitute an SAE.*

In the context of the CALMED trial, in which all participants will be in hospital at the time when they are recruited, Serious Adverse Events and Reactions will be those that result in transfer to a medical ward, readmission to hospital of those who are discharged during the study or incidents that increase the length of stay on an inpatient unit.

Medical judgement will be exercised in deciding whether an AE/AR is serious in other situations. Important AE/ARs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, will also be considered serious.

11.2 Recording adverse events

Each adverse event will be assessed for the following criteria:

(a) Seriousness

When an AE/AR occurs, the investigator responsible for the care of the patient will first assess whether the event is serious using the definition given in Table 1 in section 11.1

(b) Causality

The Investigator will assess the causality of all serious events/reactions in relation to the trial medication using the definitions in Table 5 below. If the causality assessment is unrelated or unlikely to be related the event is classified as an adverse event. If the causality is assessed as either possible, probable or definitely related then the event is classified as an adverse reaction.

Table 5: Definitions of causality

Relationship	Description	Event Type
Unrelated	There is no evidence of any causal relationship	SAE
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).	SAE
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).	SAR
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.	SAR
Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	SAR

(c) Expectedness

If the event is a SAR the Investigator will assess the expectedness of the event (refer to Table 6). The definition of an unexpected adverse reaction (UAR) is given in Table 4: Definitions in section 11.1 and is based on the summary of known and potential risks listed in section 10.4. If a SAR is assessed as being unexpected it becomes a SUSAR (refer to section 11.5).

Table 6 : Expectedness

Category	Definition
Expected	An adverse event that is classed in nature as serious and which is consistent with the information about the IMP listed in section 4.8 of the Summary of Product Characteristics (this is appended to the CALMED IMPD)
Unexpected	An adverse event that is classed in nature as serious and which is not consistent with the information about the IMP listed in section 4.8 of the Summary of Product Characteristics (this is appended to the CALMED IMPD)

11.3 Procedures for recording and reporting adverse events

All AEs/ARs (whether expected or not) occurring from the time a participant signs the consent form until completion of the last trial-related procedure will be recorded on an Adverse Event Record Sheet.
If the AE is assessed as serious, the PI must report the event to the CI and trial coordinating office within 24 hours of being made aware of the event. All SAEs will be reported onward to the Sponsor as soon as received.
The SAE form will be completed and submitted by the clinician who is responsible for the patient's care. The patient will be identified by trial randomisation code, date of birth and initials only.
In the absence of the responsible clinician, the SAE form will be completed and signed by a member of the site trial team. The responsible investigator will subsequently check the SAE form, make changes as appropriate, sign and then re-submit the form as soon as possible. The initial report will be followed by detailed follow-up and resolution reports as appropriate.
All AEs will be followed-up until resolved, stabilised or the event returns to baseline, if a baseline value is available.
All adverse events occurring up to 30 days after the last time that the participant took trial medication will be recorded.

11.4 Chief Investigator and sponsor responsibilities

On behalf of the Sponsor, the trial coordinating office will review all event reports received with the Chief Investigator. The causality assessment given by the local investigator at site cannot be overruled and in the case of disagreement, both opinions will be provided in any subsequent reports.
The trial coordinating office will report SUSARs and other SARs on behalf of the Sponsor to the regulatory authority (MHRA) and the research ethics committees within required timelines.
The Chief Investigator will keep all investigators informed of any safety issues that arise during the course of the trial.

11.5 Reporting SUSARs

The trial coordinating office will notify the main REC and MHRA of all SUSARs. SUSARs that are fatal or life-threatening will be notified to the MHRA and REC within 7 days of the sponsor having been

made aware. Other SUSARs will be notified to the REC and MHRA within 15 days of the sponsor having been notified.
In the event of a SUSAR, unblinding will occur the CI and trial coordinating office will discuss any adverse event with the Principal Investigator for the site at which the participant was unblinded and generate a plan to ensure that onward reporting occurs within the required timeframe.

11.6 Pregnancy

Should a participant become pregnant, the pregnancy and resulting child will be followed up for a period of no less than 18 months to verify whether a congenital anomaly or birth defect is present. This process will be documented on a Pregnancy Reporting Form to the trial coordinating office and the pregnancy report to the MHRA and Research Ethics Committee by the Chief Investigator. For pregnancy outcome, the local research team or trial coordinating office will monitor the outcome, as appropriate. A participant who is pregnant must have the trial medication discontinued although need not withdraw from the study.

11.7 Overdose

A report of an overdose of the trial medication by the participant or an individual who has a responsibility for the participant or their medication is a protocol deviation and will be recorded as such. Where the overdose results in any untoward medical occurrence, this will also be recorded as an adverse event. An intentional overdose will be treated as an adverse event in itself.

11.8 Urgent Safety Measures

Regulation 30 of the Medicines for Human Use (Clinical Trials) Regulations 2004 [Statutory Instrument 2004/1031], as amended by Statutory Instrument 2006/1928 states “the Sponsor and the Investigator may take appropriate urgent safety measures in order to protect the subjects of a clinical trial against any immediate hazard to their health or safety. If measures are taken, the Sponsor shall immediately and in any event no later than three days from the date the measures are taken, give written notice to the MHRA and the relevant REC of the measures taken and the circumstances giving rise to those measures.”

12 Protocol Deviations, Non-compliance and Serious Breaches

12.1 Protocol Deviations

Protocol deviations will be recorded on a Protocol Deviation Record Sheet and retained at site in the ISF. The Chief Investigator and study oversight groups will continually monitor protocol deviations to establish whether an amendment to the protocol or further training is required to prevent escalation into more serious violations or breaches.

12.2 Serious Breaches

Regulation 29A of the Medicines for Human Use (Clinical Trials) Regulations 2004 [Statutory Instrument 2004/1031], as amended by Statutory Instrument 2006/1928, contains a requirement for the notification of “serious breaches” of GCP or the trial protocol.
A “serious breach” is a breach which is likely to affect to a significant degree the safety or physical or mental integrity of the subjects of the trial; or the scientific value of the trial.

A protocol violation or non-compliance to the protocol, study or sponsor procedures that has not been approved by the sponsor/REC/MHRA prior to implementation may constitute a serious breach.

Protocol violations and non-compliances must be reported to the sponsor by the Principal Investigator within 24 hours of the Principal Investigator becoming aware of the event by submitting the Non-Compliance Report Form. The sponsor and Chief Investigator will ensure that appropriate action and investigation takes place in a timely manner.

The Sponsor will notify the licensing authority of any serious breach of:
1. The conditions and principles of GCP in connection with that trial; or
2. The protocol relating to that trial, as amended from time to time in accordance with regulations 22 to 25

The sponsor will notify the MHRA and REC in writing within 7 calendar days of becoming aware of the breach according to the Sponsor Serious Breaches SOP.

13 Reporting Requirements

13.1 Development Safety Update Reports

On behalf of the Sponsor, the trial coordinating office will provide the main REC and the MHRA with a Development Safety Update Reports (DSUR) which will be written in conjunction with the Chief Investigator and the Sponsor. The report will be submitted within 60 days of the anniversary of the Developmental International Birth Date (DIBD) of the trial each year until the trial is declared ended.

13.2 Annual progress reports

An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended. The Chief Investigator will prepare the APR.

14 Data management and quality assurance

14.1 Confidentiality

All data will be handled in accordance with General Data Protection Regulation (2018).
The Case Report Forms (CRFs) will not bear the subject's name or other personal identifiable data.

14.2 Data collection tools and source document identification

It will be the responsibility of the investigator as delegated to ensure the accuracy of all data entered in the CRFs. The delegation log will identify all those personnel with responsibilities for data collection and handling, including those who have access to the trial database.

14.3 Data handling and analysis

Data will be collected using paper CRFs and then transcribed onto a web-based Case Report Form that will not include the patient's name or other information that could identify them. All data will

be stored on a secure dedicated web server. Access will be restricted by user identifiers and passwords (encrypted using a one-way encryption method). All electronic databases will use a patient identification number rather than the patient's name. Hard copies of data sheets linking the patient identification number to the person's contact details will be kept securely in a locked filing cabinet in a locked office and will only be accessible to a small number of people who are involved in the study.

Data monitoring will be carried out according to the trial-specific monitoring plan. This details the quality control checks to be carried out during site visits and when checking the database. All serious adverse event and primary outcome data will be checked and a random sample of the secondary outcome data. The database will be stored on a network drive at University of Bangor, which is backed-up daily.

At the end of the trial, data monitoring will be completed and the database “locked” so that no further data entry is possible. At this point the data will be given to the trial statistician along with the randomisation list stating whether participants were allocated to Arm A or B. The data will be analysed without knowledge of which arm relates to the active trial medication.

15 Statistical considerations

The aim of this research is to examine the clinical and costs effectiveness of adding clozapine to inpatient treatment as usual for people with borderline personality disorder who are receiving treatment in hospital. All primary analysis will be using modified ITT analysis (mITT), in which all randomised participants will be included who have taken at least one dose of trial medication.

15.1 Outcomes

Primary outcomes

The primary outcome is total score on the Zanarini rating scale for Borderline Personality Disorder (ZAN-BPD) at six months (primary end point) to assess this. [40] The ZAN-BPD is the most widely used outcome in trials of BPD. It provides a reliable and valid assessment of core features of the condition and is sensitive to change. [41, 42] Feedback from our preparatory survey was that ZAN-BPD is acceptable to inpatients with borderline personality disorder and addresses the key emotional and behavioural problems that inpatients with this condition experience.

Secondary outcomes

i. Total score on the Zanarini rating scale for Borderline Personality Disorder at three months.
ii. General mental health using the Brief Psychiatric Rating Scale (BPRS) at three and six months.
iii. Incidence and severity of suicidal behaviour using the Acts of Deliberate Self-Harm Inventory.
iv. Level of aggressive behaviour using the Modified Overt Aggression Scale
v. Health related quality of life using the EQ-5D-5L.
vi. Side effects of medication using the Antipsychotic Non-Neurological Side Effects Scale (ANNSERS) and motor and extrapyramidal side effects using the Extrapyramidal Side Effects Scale.
vii. Incidence of withdrawal of trial medication due to adverse effects.
viii. Medication adherence at three and six months using the Brief Adherence Rating Scale.

ix. Resource use collected using a modified version of the Adult Service Use Schedule and by examining clinical records at six, 12 and 18 months, This will include detailed information about length of inpatient treatment and type of ward (high, medium, low secure, Psychiatric Intensive Care, general adult etc.), contacts with community mental health services and emergency medical services, and the type and dose of psychotropic medication that people are prescribed.

15.2 Sample size and recruitment

Sample size calculation

The sample size calculation for the study is based on the primary hypothesis that, for inpatients with borderline personality disorder, the addition of clozapine to usual treatment reduces symptoms of the disorder measured at six months (standard deviation 7.89) using the Zanarini Rating scale for Borderline Personality Disorder (ZAN-BPD). 166 participants (83 receiving clozapine and 83 receiving placebo) will need to be randomised to have 90% power to detect a four point clinically important difference in ZAN-BPD score at six months, using a 0.05 level of statistical significance. To take account of 25% loss to follow-up we plan to recruit 222 subjects. We will seek to further increase the sample size to ensure that we have data on 166 participants who took at least one dose of trial medication.

Planned recruitment rate

This will mean 9.3 participants per month being recruited throughout the 24-month recruitment period.

15.3 Statistical analysis plan

A fully documented Statistical Analysis Plan (SAP) will be written and agreed by the co-applicants and the DMEC before data collection has been completed. If any deviations from the planned statistical analysis are required these will be fully documented and justified in the final analysis report.

The main analysis for the primary outcome will be a general linear model fitted at six months and adjusted for baseline score, allocation group and stratification variables: gender and type of ward. Any additional covariates added to the model will be assessed for their appropriateness and defined a priori in the SAP. Data will be analysed using a modified intention-to treat principle in which, for the main analysis, data from all randomised participants who took at least one dose of trial medication are analysed. Secondary outcomes will be assessed with an equivalent analysis model. Patterns of missing data will be assessed, and the sensitivity of treatment effect estimates to the missing data will be tested using multiple imputation strategies. All treatment effect estimates will be presented with 95% confidence intervals.

Exploratory analysis of the potential modification of the treatment effect will also be undertaken for pre-planned variables of gender and baseline score on the BPRS. Initially an interaction term between each variable and allocated group will be added to the model. Further modelling will then be undertaken if appropriate.

We will investigate the effect of treatment adherence using complier average causal effect (CACE) estimation methods. Intention To Treat analysis does not represent treatment effect under non-compliance of treatment, we will therefore use CACE analysis to explore whether treatment effect is directly affected by the level of compliance. The level of compliance will examined using both a dichotomous and a continuous measures a) Dichotomous: whether the participant took medication at a dose of 100mg or more without interruption during the six months prior to the final follow-up

interview; b) Continuous - percentage of medication the participant took in the month prior to competing the six month follow up assessment using data from the Brief Adherence Rating Scale.

With regards to the analysis of economic data - a fully documented Health Economics Analysis Plan (HEAP) will be written and agreed by the co-applicants and approved by DMEC Prior to the completion of data collection. The economic evaluation will take an NHS/PSS perspective, as required by NICE, which is relevant in this patient group. [65] Data on the use of health and social services will be collected using a modified version of the Adult Service Use Schedule (AD-SUS). During the set-up phase of the trial the questionnaire will be modified based on a literature review and in collaboration with clinical and service user members of the research team. Detailed information on the prescription of study medication and other psychotropic drugs will be extracted from trial records. For each service use item, a relevant and suitable unit cost will be identified.
Differences in service use over follow-up will be explored descriptively. While statistical differences in total costs by randomised group will be calculated using standard t-tests [66], the focus of the analysis will be on the impact of costs and outcomes together. The primary cost-effectiveness analysis will consider costs alongside QALYs and will thus report on the incremental cost per QALY, in keeping with the requirements of analyses for use in NICE guidance. [65] A secondary cost-effectiveness analysis will be completed using the ZAN-BPD outcome measure, which may be of interest to more local and specific mental health decision makers. The statistical uncertainty around the estimates of cost-effectiveness will be explored using net benefit calculations and through the construction of cost-effectiveness acceptability curves. [67] Sensitivity analyses will be completed to test the assumptions used in the economic evaluation.

We will begin to build an economic model during the pilot phase of the trial, which we will use to examine what the long-term impact of clozapine could be. The potential to reduce the length of costly inpatient admissions has been identified as an advantage of prescribing clozapine to inpatients with BPD, so we will collect detailed information about length of inpatient treatment and type of ward (high, medium, low secure, Psychiatric Intensive Care, general adult etc.) that each participant receives. We will also collect data on contact with community mental health services and emergency medical services for those who are discharged from hospital during the follow-up period of the trial and information about the type and dose of psychotropic medication that people are prescribed. By using routine clinical data, we will minimise the amount of missing data, such that we will have near complete data on costs for all participants at 6 months, data at six and 12 months for those recruited in the first year and data at six, 12 and 18 months for those recruited within the first 6 months of the trial.

Modelling the results of the trial over a longer period will help to establish what, if any, longer term savings are associated with treating inpatients with BPD with clozapine in addition to their treatment as usual. The structure of the model will be determined during the study, but it will make full use of data collected at six, 12 and 18 months as well as information from previous studies and the literature.

15.4 Randomisation methods

Researchers at each site will enter the results of the baseline assessment on a web-based Case Report Form. Remote web-based randomisation will be undertaken through a fully automated service operated by the NWORTH, University of Bangor. Randomisation will be via a secure online

system using a sequentially randomised dynamic adaptive algorithm stratified by centre, ward type and gender. [59] Within the algorithm, the likelihood of the participant being allocated to each treatment group is recalculated based on the participants already recruited and allocated. This recalculation is done at the overall allocation level, within stratification variables and within stratum level (the relevant combination of stratification levels). By undertaking this re-calculation the algorithm ensures that balance is maintained within acceptable limits of the assigned allocation ratio while maintaining unpredictability.
Randomisation will create a unique randomisation code for the participant. A trial prescription form will then be completed by the local investigator. This will be sent to the pharmacy that will dispense the trial medication to the ward where the participant is being treated.

15.5 Interim analysis

There are no planned interim analyses except for any requested by the Data Management and Ethics Committee.

16 Trial oversight committees

A Trial Steering Committee and an Independent Data Monitoring and Ethics Committee will be in place prior to the start of the study. Each group will have an independent Chair and a majority of other independent members.

These committees will provide overall supervision of the trial and ensure that it is being conducted in accordance with protocol and current legislation. It will also review trial data in order to identify patterns in the data that may suggest the need to halt the trial. The IDMEC will also monitor (1) recruitment of study participants, (2) ethical issues of consent, (3) quality of data (including missing data), (4) the incidence of adverse events, and (5) any other factors that might compromise the progress and satisfactory completion of the trial.

A Trial Management Group will also be set-up prior to the start of the study and will include those individuals responsible for the day-to-day management of the trial, such as the Chief Investigator, representative Principal Investigator(s) and trial management staff. In addition, a research assistant and individual(s) who is able to contribute a patient and/or wider public perspective. The role of the group will be to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself. The group should consider and act on the recommendations of the TSC, IDMEC, the MHRA, and REC. The terms of reference for these committees are provided in a study SOP on trial oversight committees.

17 Access to Source Data/Documents

The investigator(s)/ institution(s) will permit trial-related monitoring, audits, REC review, and regulatory inspection(s), providing direct access to source data/documents. Trial participants are informed of this during the informed consent discussion. Participants will consent to provide access to their medical records.

18 Ethics and regulatory requirements

The sponsor will ensure that the trial Protocol, study Information Sheets, Consent Forms, GP letter and submitted supporting documents have been approved by the MHRA and a main REC, prior to any patient recruitment. The protocol and all agreed substantial protocol amendments, will be documented and submitted for ethical and regulatory approval prior to implementation according to Sponsor SOPs.

Before the site can enrol patients into the trial, the Trust Research & Development (R&D) for the site must grant written permission. It is the responsibility of the Principal Investigator at each site to ensure that all subsequent amendments gain the necessary approval. This does not affect the individual clinician's responsibility to take immediate action if thought necessary to protect the health and interest of individual patients (see section 0 for reporting urgent safety measures).
Within 90 days after the end of the trial, the CI/Sponsor will ensure that the main REC and the MHRA are notified that the trial has finished. If the trial is terminated prematurely, those reports will be made within 15 days after the end of the trial.

Study participants will be asked to give up their time to take part in study interviews and to complete study questionnaires. The baseline assessment takes 110 minutes and the follow-up interview at six months will take 90 minutes to complete. All participants will be offered a £10 voucher, credit note or equivalent at the baseline assessment, £20 at three months and £30 following completion of the six-month follow-up interview.

The CI will supply the Sponsor with a summary report of the clinical trial, which will then be submitted to the MHRA and main REC within 1 year after the end of the trial.

19 Monitoring requirements for the trial

A trial-specific monitoring plan will be established based on the trial risk assessment. The trial will be monitored according to the agreed plan.

20 Finance

This study is funded by the Health Technology Assessment programme of the National Institute for Health Research.

21 Indemnity

Indemnity and/or compensation for harm arising specifically from an accidental injury, and occurring as a consequence of the research participant's participation in the trial for which the University is the research sponsor will be covered by Imperial College London. Indemnity and/or compensation for negligent harm arising specifically from an accidental injury for which the University is legally liable as the research sponsor will be covered by Imperial College London. The NHS will owe a duty of care to those undergoing clinical treatment, with Trust Indemnity available through the NHS Litigation Authority Scheme.

22 Archiving

Archiving will be authorised by the Sponsor following submission of the end of clinical trial summary report. The Trial Master File (TMF) will be prepared for archive by the Chief Investigator and archived by the Sponsor according to Sponsor's archiving procedures
Investigators are responsible (as delegated through the model clinical trial agreement) for GCP compliant archiving of essential trial documents and the trial database at their site according to their local trust archiving policy

All essential documents will be archived for a minimum of 10 years after completion of trial.
Destruction of essential documents will require authorisation from the Sponsor.

23 Publication policy

We will use a broad range of methods to communicate the results of this research to all stakeholders including both those who provide and use mental health services for people with BPD. This will include written reports, presentations at conferences, social media, a webinar, and communications with NICE, service user groups and professional bodies. We will publish our findings in the Health Technology Assessment Journal and in widely read high-quality peer-reviewed open access journals. We will present the results of the study at the leading conferences for personality disorder and those for mental health nurses and pharmacists: the Annual Conference of the British and Irish Group for the Study of Personality Disorder, the Annual Congress of the Royal College of Psychiatrists, the Forensic Faculty of the Royal College of Psychiatrists, the Summer Meeting of the Royal College of Nursing, and the annual meeting of the College of Mental Health Pharmacy.

The results of the trial will also be posted on EudraCT and made available to the public via the EU Clinical Trials Register.

24 Statement of compliance

The trial will be conducted in compliance with the approved protocol, the UK Regulations,
EU GCP and the applicable regulatory requirement(s).

25 References

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