LESSONS LEARNED REPORT

HTA Reference: 16/157/02

Title: The Clinical Effectiveness and Cost Effectiveness of Clozapine for Inpatients with Borderline Personality Disorder: A Randomised Controlled Trial.

SHORT Title: The CALMED study
(Clozapine: Assessing Long-term Medication in people with Emotionally unstable personality Disorder)

Sponsor: Imperial College London

Call: Clozapine in the treatment of borderline personality disorder

Trial Registration EudraCT number: 2016-004670-18 [15 Nov 2016]

ISRCTN: ISRCTN44644781 [18 Nov 2016]

IRAS Number: 217828

Chief Investigator: Professor Mike Crawford

Design: Practitioner and participant-blinded, placebo controlled, randomised, superiority trial with an internal pilot phase.

Primary Objective: To determine the clinical effectiveness and cost-effectiveness of adding up to 400mg of clozapine per day to usual treatment received by inpatients with borderline personality disorder.

Number of participants: 222

Proposed start date: 1st November 2018: 30/09/2021

Proposed end date: 30th September 2021

Study Duration: 36 months

Contract end date : 30 September 2021

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EXECUTIVE SUMMARY

No medications are currently licensed for the treatment of borderline personality disorder. Clozapine is an antipsychotic medication, which has started to be prescribed off-label in an effort to improve the mental health of people with borderline personality disorder, especially on forensic wards. Because of the serious side effects associated with this medication, including potentially life-threatening agranulocytosis, all people prescribed clozapine must have regular haematological monitoring. Data from case series of inpatients with borderline personality disorder who have been prescribed clozapine suggest possible patient benefit. The CALMED trial was funded through a commissioned call issued by the NIHR Health Technology Assessment to investigate the clinical effectiveness and cost effectiveness of clozapine for inpatients with borderline personality disorder. The study was conducted by a team of academics and clinicians from Imperial College London, Central & North West London NHS Foundation Trust, Elysium Healthcare, Nottinghamshire Healthcare NHS Foundation Trust, Lancashire and South Cumbria NHS Foundation Trust, Mersey Care NHS Foundation Trust, Nottinghamshire Health NHS Trust, St Andrew's Healthcare, University of Bristol and West London NHS Health Trust, in collaboration with the King's Health Economics, Kings College London and the North Wales Organisation for Randomised Trials in Health, Bangor University.

Delays in setting up contracts meant that patient recruitment started eight months later than originally planned. During the first six months, we recruited 25 participants (46% of the target during this period). Recruitment slowed with the onset of the COVID-19 pandemic and stopped in March 2020. Four study sites reopened in autumn 2020. By January 2021, we had recruited 29 participants. While the rate of follow-up in the trial was greater than we had anticipated (83% at 6 months), the level of adherence to trial medication was low with 45% of participants having discontinued trial medication at three months. It became clear that it would not be possible to complete the study in a timely manner and it was agreed by the sponsor, the Trial Steering Committee, the funder, and research team that the study should close.

Lessons learned during the CALMED study include;

1. While there is clinical equipoise regarding the use of clozapine for inpatients with borderline personality disorder, most clinicians working in forensic mental health services believe that the benefits outweigh the costs and most clinicians working in general adult mental health services believe that the costs outweigh the benefits.

2. People with borderline personality disorder who are admitted to inpatient mental health units are usually highly distressed. This may make it difficult for potential participants to make an informed choice about whether to take part in a clinical trial, especially one involving a medication such as clozapine, which has a high side-effect burden.
3. The pressures placed on general adult inpatient mental health teams to discharge patients as soon as possible mean that there is often insufficient time for the initial dosage titration to be completed before they are discharged from hospital.
4. The side-effect profile of clozapine, which includes sedation in the early stages of treatment, means that in placebo-controlled trials, patients and clinicians may be able to accurately guess which arm of the trial a participant has been randomised to.
5. The demands made on clinicians to allow them to prescribe the study medication, such as completing Good Clinical Practice, are a disincentive to their involvement in clinical trials.

BACKGROUND

Borderline personality disorder (BPD) is a common mental disorder characterized by instability in emotions, identity and relationships. People with BPD are at increased risk of impulsive behaviour including suicidal behaviour. Concerns about risk to self or others may lead to periods of inpatient treatment.

No medication is currently licensed for the treatment of BPD. Despite this people with BPD are often prescribed large amounts of psychotropic medication.(1) Clozapine, an atypical antipsychotic medication, can be effective where schizophrenia has failed to respond to standard antipsychotic treatment.(2) There is also evidence that clozapine may reduce the incidence of aggression and impulsive behaviour among people with schizophrenia.(3) Recently some clinicians have started using clozapine in an effort to reduce the incidence of self-harm and impulsive behaviour among people with BPD.(1) Open-label studies of such patients have reported that clozapine leads to improved mental health, reduced aggression and self-harming behaviour, and lower costs of care.(4) While it is possible that clozapine improves the mental health of people with BPD, it also has serious side effects. Most patients gain weight and a minority develop type II diabetes.(5) Clozapine is also associated with an increased incidence of neutropenia, potentially fatal agranulocytosis, pneumonia, myocarditis and paralytic ileus.(6-8) The CALMED study was funded by NIHR Health Technology Assessment programme to determine the risks and benefits of treating people with BPD with clozapine.

STUDY DESIGN

The CALMED (Clozapine Assessing Long-term Medication in Emotionally unstable personality Disorder) trial was a two-arm, double-blind, placebo-controlled randomised trial with an integrated pilot phase. The trial was designed to investigate whether, among people receiving inpatient treatment for borderline personality disorder, the addition of clozapine to their usual care was a clinically effective and cost-effective strategy for improving their mental health. We aimed to recruit participants from general adult mental health wards, psychiatric intensive care units and secure/forensic mental health inpatient units delivered by seven NHS and independent sector providers; Central and North West London NHS Trust, Elysium Healthcare, Lancashire and South Cumbria NHS Foundation Trust, Mersey Care NHS Foundation Trust, Nottinghamshire Healthcare NHS Foundation Trust, St Andrew's Healthcare and West London Mental Health NHS Trust. These sites were selected because they included all three of England's high secure hospitals. We included private sector providers in our recruitment strategy because the use of clozapine for BPD was pioneered in this sector and because much of the secure inpatient care for NHS patients with borderline personality disorder is now provided by the independent sector.

To take part in the study, potential participants had to be aged 18 years or over, had to meet Diagnostic and Statistical Manual-IV diagnostic criteria for borderline personality disorder using the Structured Clinical Interview for Axis II Personality Disorders (9) and not have made an adequate clinical response despite taking antipsychotic medication other than clozapine for at least three months. We excluded those patients who had a clinical diagnosis of schizophrenia, or bipolar I disorder, as well as those already prescribed clozapine, who were pregnant, had other contraindications to clozapine, were unable to speak sufficient English to complete the baseline assessment, or were unwilling or unable to provide written informed consent to take part in the study. If any potential participant was due to be discharged from the unit within two weeks of the planned recruitment date, recruitment was restricted to those for whom necessary monitoring of physical health as an outpatient had been agreed.

Study participants were prescribed trial medication: either clozapine, titrated to a dose of 300mg daily over a 21-day period or capsules that were identical in appearance that contained a placebo. A dose of up to 400mg of clozapine daily could be prescribed by the clinical team, depending on clinical response, patient preference and side effects. The dose could be maintained at or reduced to a lower dose at any time.

All study participants were enrolled with the Clozaril Patient Monitoring Service and had the mandatory haematological monitoring, with venepuncture weekly for the first eighteen weeks of treatment followed by fortnightly venepuncture for the duration of the study.

Study participants were followed up three and six months after randomisation. The primary outcome measure was the Zanarini rating scale for Borderline Personality Disorder (ZAN-BPD).(10) Secondary outcomes included measures of general mental health, incidents of self-harming behaviour, aggression, health-related quality of life, side effects of medication, adverse events and service use. Each participant was offered a £10 honorarium for completing the baseline interview, £20 for completing the three-month follow-up interview, and £30 for completing the six-month follow-up interview.

The sample size calculation for the study was 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 using the ZAN-BPD. Data from 166 participants (approximately 83 receiving clozapine and 83 receiving placebo) would have been needed to have 90% power to detect a four-point clinically important difference in ZAN-BPD (standard deviation 7.89) score at six months, using a 0.05 level of statistical significance. To take account of 25% loss to follow-up we planned to recruit 222 subjects.

Study progress and safety were regularly overseen by a Trial Steering Committee and an Independent Data Monitoring and Ethics Committee.

STUDY PROGRESS

During the development of plans for the study, we worked with a wide range of users and providers of mental health services to try to develop a design that was acceptable to both clinicians and potential participants. Plans for the study were presented at the annual conference of the British and Irish Group for the Study of Personality Disorder. Additional feedback was obtained from a survey of 376 members of the Royal College of Psychiatrists' Faculty of Forensic Psychiatry. We used this feedback to refine the inclusion and exclusion criteria for the study. We also obtained feedback from service users who attended meetings of the Patient Council at Rampton High Secure Hospital in Nottingham, the 'Recovery and Outcomes group' at River House Medium Secure Unit, Bethlem Royal Hospital, and a focus group on Seacole Ward, a specialist secure unit for women with personality disorder at St Andrews Healthcare, Northampton. We used feedback from these patients to refine study procedures and outcome measures.

Patient recruitment

Recruitment to the study was due to start in January 2019 but did not begin until September 2019 due to administrative delays in setting up sub-contracts. Over the six-month pilot phase of the study, recruitment started at six of the seven planned sites and we recruited 25 participants (46% of the target during this period). By the end of 2019 we were recruiting five participants a month (54% of the target). Following meetings of the Data Monitoring and Ethics Committee and Trial Steering Committee, agreement was researched to extend the pilot phase of the study by six months.

Recruitment on general adult wards was very limited, mainly because clinicians were not used to prescribing clozapine for people with borderline personality disorder. They were concerned about the side effects of clozapine and worried that patients would not adhere to the physical health checks and blood monitoring that patients require. Patients newly admitted to general adult mental health wards who might have been eligible to take part in the study were often highly distressed. Clinical teams reported finding it difficult to raise the study or seek consent from patients who were agitated and often suicidal. Furthermore, teams were under considerable pressure to avoid patients spending longer than necessary in hospital. The need to conduct a rigorous check of physical health prior to initiating clozapine, together with the need to register the potential participant with the monitoring service and monitor their physical health in the days after they started on clozapine were barriers to ensuring timely discharge from hospital and therefore a barrier to recruitment.

In independent sector low and medium secure wards, clozapine was already regularly used for the treatment of people with borderline personality disorder. Patients admitted to these units were aware that others who had been prescribed clozapine had often found it helpful. Some potential participants expressed the concern that recruitment into the trial would slow their recovery and requested they be prescribed clozapine rather than take part in the trial. Most potential participants were already prescribed various combinations of psychotropic medication. While many had experienced little benefit from them, they found it difficult to believe that a placebo could help them.

Patients admitted to the NHS medium and high secure units tended to be characterised by a history of significant self-harm and/or harm to others, long periods of inpatient care, and variable levels of adherence to medication and other treatments. While clinicians working on these units accepted that the evidence base for the clozapine for people with borderline personality disorder was

inadequate, for many patients they judged that the potential for benefit was sufficient to warrant promptly starting clozapine treatment rather than risk a delay in such treatment with participation in the trial.

Requirements for prescribing clinicians to complete Good Clinical Practice training was a disincentive to supporting the study.

Trial medication

Among the participants, some stopped taking the trial medication before their first follow-up assessment. Two participants did not receive a single dose of trial medication: the first withdrew consent after they were randomised and asked to be prescribed clozapine while the second received an unexpected offer of supported accommodation in the community and was rapidly discharged from hospital prior to taking their first dose of trial medication.

Aware of the potential side effects of clozapine, other participants who started trial medication and experienced no side effects, judged that they were being given a placebo and declined to continue taking part in the trial. There were also instances when patients who had started to take trial medication were discharged from hospital before arrangements for monitoring physical health in the community were agreed, and trial medication had to be stopped.

Online concerns about the study

In October 2019, members of the study team were made aware of concerns raised about the ethics and design of the CALMED trial on social media. These concerns culminated in formal letters being sent to representatives of the sponsor, the funder, the Health Research Authority and the Medicines and Healthcare products Regulatory Agency on 09/01/2020. The letter was signed on behalf of two groups called 'Recovery in the Bin', 'We Care About MH' and ten other users and providers of mental health services. The letter raised concerns about a number of issues: study inclusion and exclusion criteria, the contents of the patient information sheet, and the care that study participants were being given.

These concerns were reviewed by the Trial Management Committee, the Data Monitoring and Ethics Committee and the Trial Steering Committee. The MHRA also undertook an exceptional review of the trial documents. Following these reviews, we applied for and received permission from the Research Ethics Committee to amend the study protocol, as follows:

1) Adding the new inclusion criterion that people would only be eligible to take part in the study if they had 'severe personality disorder', defined as (a) having been an inpatient on a mental health ward for more than 28 days in the last 12 months OR (b) having had two or more admissions to hospital/periods of care provided by Home Treatment over the last 12 months, AND (c) 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.
2) Adding information on how procedures in the trial differ from current NHS and NICE guidance.
3) Including additional information on safety monitoring, adverse event recording and pregnancy.
4) Adding measures of blood lipids at baseline, and 3- and 6- month follow-up assessments.
A retrospective examination of the records of all those patients who had been recruited prior to these changes in the eligibility criteria found that they all met the new criteria.

Covid-19 pandemic

The rate of recruitment slowed with the onset of the COVID-19 pandemic in early 2020. We were instructed by NHS Research and Development departments to suspend recruitment on 16th March 2020. Four of the study sites reopened in autumn 2020, but by January 2021 only four further patients had been recruited. While recruitment was technically possible at the sites that had reopened, researchers were not allowed to visit wards and clinicians were tasked with the additional responsibility of obtaining written informed consent from potential patients. Clinicians faced additional challenges associated with screening and treating patients with COVID-19 on wards from which patients were to be recruited. Researchers attempted to maintain regular contact with clinical staff through phone contact and online meetings, but the lack of their physical presence on the ward made it difficult to keep the trial in the minds of clinicians and potential participants. The pandemic affected recruitment in other ways. The number of admissions to hospital fell as staff attempted to avoid the possibility of spreading the virus among inpatients and the number of new admissions to low and medium secure wards provided by the independent sector also fell. Clinicians also raised concerns about prescribing clozapine during the pandemic due to the possibility of greater transmission of COVID-19 related to the mandatory blood monitoring and because of the reported association between clozapine, reductions in immunoglobulin levels and pneumonia.(11-14)

The failure to recruit new participants following the start of the pandemic led to a review of the viability of the trial on 11th February 2021. It became clear that it would not be possible to complete the study in a timely manner and an agreement was reached between the study team, the Trial Steering Committee and the funder to close the study.

Study recruitment, allocation and adherence

Participant flow through the study is presented in Figure 1. Most potential participants who were excluded following a review of their clinical records had a diagnosis of psychosis. Among 135 potentially eligible participants, clinicians judged that 57 (42.2%) were unsuitable for the study. Of 54 potential participants who were approached for consent, 14 (25.9%) declined to take part in the study, others were to be discharged from hospital before physical health checks could be completed or were prevented from taking part due to COVID restrictions. Of 35 potential participants who met with a researcher and were further assessed for eligibility, four were ineligible (one was due to be discharged from hospital, one had a previous adverse reaction to clozapine, and one could not participate due to COVID). The remaining 29 were randomised, 15 to clozapine and 14 to placebo. Three participants did not receive any trial medication; one was discharged from hospital soon after randomisation and two withdrew their consent. Twenty-four (82.8%) participants were followed up at six months (93.3%, n = 14 of those in the clozapine arm of the trial and 71.4%, n = 10 of those in the placebo arm of the trial). At six-month follow-up 11 (78.6%) of 14 of those randomised to clozapine and 6 (42.9%) of 10 randomised to placebo were still taking trial medication.

PROJECT ACHIEVEMENTS

i) Collaboration with industry

At the start of the planning stage of the project it became clear that all study participants would need to have careful monitoring of their physical health. A major challenge was ensuring that a robust system was in place to deliver blood monitoring that would prevent participants receiving trial medication if they had early signs of neutropenia. We approached the main providers of clozapine monitoring services in the UK to seek their help. A number of logistical hurdles had to be overcome. A system was required that enabled the clinical trials team to access data on warning signs of neutropenia. We also needed to ensure that, if a participant in the placebo arm of the trial had a reduction in white blood cell count, they would not erroneously be entered onto databases that record people who have had an adverse reaction to clozapine. We are grateful for the support that Viatris and the Clozaril Patient Monitoring Service provided in setting up these systems. We consider this a good example of a successful collaboration between an NIHR funded study team and industry.

ii) Involvement of providers of independent sector services

Independent sector organisations make an important contribution to providing care for NHS patients in the UK. While such organisations have a history of supporting research studies, most have very

limited experience of supporting large scale trials and the CALMED study is the first NIHR-funded medication trial to have recruited patients in these services. We are grateful for the support that St Andrew's Healthcare and Elysium Healthcare provided. These collaborations were very successful, with both of these independent sector providers recruiting to target. In contrast, only one of the five NHS sites achieved the anticipated rate of participant recruitment. This highlights the value of the involvement of these independent sector organisations in future research studies.

iii) Remote assessments

The onset of the COVID-19 pandemic prevented researchers from visiting study participants to conduct face-to-face assessments. In order to minimise the amount of missing data, we obtained approvals to complete follow-up assessments remotely. We reviewed our outcome measures and judged that all but one (the Simpson-Angus Extrapyramidal Side Effect Scale), could be completed remotely. Most participants consented to be interviewed by pairs of researchers, which allowed us to explore interrater reliability of these assessments. Interrater reliability for the remote assessments proved to be as high as that achieved with the previous face-to-face interviews. While the pandemic curtailed recruitment of new study participants in the trial, we were able to successfully follow-up people who had already been recruited through conducting remote assessments.

DISCUSSION

The CALMED trial set out to discover whether clozapine improves the mental health of people with borderline personality disorder. In accordance with the requirements of the commissioned call HTA 16/157, we designed a two-armed placebo-controlled trial in which the effects of adding clozapine to usual care were compared with those of a placebo plus usual care over a six-month period. We set out to recruit patients who were receiving inpatient treatment on general adult wards or specialist low, medium and high secure units. Recruitment proved challenging on general adult wards and only one participant was recruited from a high secure service. However, by the end of 2019 the rate of recruitment was running at just over 50% of the target. In March 2020, recruitment had to stop because of the COVID-19 pandemic. Even though some service providers allowed recruitment to restart in Autumn 2020, continuing outbreaks of COVID-19 on wards and a slowdown in the rate of admissions to specialist forensic units restricted the opportunities for recruiting eligible patients. Researchers were not able to visit potential participants and contacts with frontline clinical staff were conducted remotely. Having reviewed the rate of recruitment and the low level of adherence to trial medication, a meeting of the funder, the study team and the chair of the Trials

Steering Committee concluded that it would not be possible to complete the study without considerable additional time and funding and recruitment was stopped in February 2021.

LESSONS LEARNED

1) Collective versus individual acceptance of equipoise

When developing plans for this study we received strong support from prescribers working with inpatients with borderline personality disorder. There was widespread agreement that the findings from open-label studies of clozapine suggested potential benefits for patients although also recognition that the potential side effects of clozapine and the absence of data from high quality-controlled trials meant that off-label prescribing of this medication was controversial. This feedback gave us confidence that the CALMED trial would be able to recruit to target. However, as the study progressed it became increasingly apparent that, while recognising the need for the research, many individual clinicians had strong views about what was in the best interests of the patients that they treated. Having seen improvements in mental health among inpatients they had previously treated with clozapine, many prescribers working in forensic settings took the view that it was preferable for the individuals they were treating to be given clozapine, rather than take part in a placebo-controlled trial. Prescribers working on general adult wards understood the rationale for the CALMED trial but were concerned about the side effects and adherence to the required physical health monitoring and were often reluctant to talk to patients about the possibility of their taking part in the trial. While there was collective recognition of clinical equipoise among prescribers, what was true for the group proved not to be true for many individual members of the group.

2) Recruiting people with borderline personality disorder to a trial of clozapine during an acute admission to a general adult ward may not be feasible

Some people admitted to acute adult wards with borderline personality disorder experience very high levels of emotional distress and substantially reduced quality of life. While clozapine has mainly been used to treat people with borderline personality disorder who are admitted to specialist secure wards, data from a national audit in 2012 revealed that it was being used to treat people some people admitted to general adult wards. However, in this study we found that most people with severe borderline personality disorder who were admitted to general adult units did not stay on the ward long enough for them to make an informed choice about whether to take part in the trial or to be safely titrated onto clozapine and have the arrangements made for the necessary post-discharge monitoring.

3) Measuring adherence in the pilot phase of clinical trials

The CALMED trial illustrates the importance of internal pilots in large-scale clinical trials. By setting pre-defined progression criteria for the full-scale trial, the research team, oversight committees and the funder were able to gauge study progress. Progression criteria for the CALMED trial were based on the rate of recruitment, the rate of follow-up and the proportion of participants who started study medication within four weeks of randomisation (with a target set of 75%). In the first six months of the trial, 21 (91%) of 23 participants started trial medication within four weeks of randomisation. However, subsequent data analysis revealed that only, 16 (69.5%) of participants were still taking trial medication at three months. In retrospect, setting a progression criterion based on adherence with trial medication at three months (the time of the first follow-up assessment), would have provided a better way to judge the viability of the trial rather than the proportion who started trial medication.

4) The need for physical presence of researchers when recruiting inpatients to clinical trials

The COVID-19 pandemic had a dramatic effect on the progress of the CALMED trial. While we were able to successfully follow-up remotely those participants who were recruited prior to the start of the pandemic, the recruitment of new study participants after the start of the pandemic was negligible. Many factors contributed to this poor recruitment following the start of the pandemic, but Principal Investigators at all sites reported that the absence of a researcher on the ward made it difficult for referrers to keep the study in mind and that opportunities to discuss the study with eligible patients were lost. Videoconferencing and other technologies have extended the methods that can be used to follow-up study participants, but trials conducted in busy clinical settings, such as inpatient mental health units, probably require the physical presence of researchers to succeed.

5) Use of placebos in controlled trials of clozapine

The commissioning brief for this trial stated that clozapine should be compared to a placebo. This requirement made sense given that there are no licensed medications for the treatment of borderline personality disorder to be used as a comparator. However, in clinical practice it is extremely unusual for inpatients with borderline personality disorder to be prescribed no psychotropic medication, with most being prescribed antipsychotic and antidepressant medications.(1) The high side-effect burden of clozapine means that it is likely many patients who take this medication are aware that they are taking it. This is especially the case on inpatient units where other patients are prescribed clozapine and talk to each other about their treatment. This led some participants in the CALMED trial to become anxious that they were taking placebo when they

did not experience side effects in the days after they started taking trial medication. Use of an alternative antipsychotic medication such as olanzapine, which shares some of the same side effects as clozapine, may have avoided this problem. Off-label olanzapine is widely prescribed to inpatients with borderline personality disorder, however the ethical basis for such a trial could be questioned given that current NICE guidelines advise against the long-term use of antipsychotic medication for people with borderline personality disorder.(15)

6) Regulatory requirements for prescribing medication in clinical trials.

Time constraints are a recognised barrier to recruitment in clinical trials.(16) We attempted to minimise the burden on clinicians by handing over some parts of the consent and screening process to research staff, but regulatory requirements meant that a medically qualified doctor needed to confirm eligibility and complete the trial-specific paperwork for prescribing the trial medication. Even those clinicians who were only delegated this limited trial role were required to complete GCP training and provide a CV, as mandated by the Sponsor. The use of a more focussed approach to demonstrating qualification by "education, training and experience" for clinicians undertaking such a role may improve engagement. The MHRA and HRA have issued a joint statement endorsing a proportionate approach to GCP training (17) but this puts the onus on the Sponsor to establish what is acceptable. By contrast, the standard approach leaves no ambiguity about whether ethical and regulatory requirements have been met and so any attempt to take a proportionate approach may not be supported, as was the case for our trial. We suggest that GMC number is sufficient to demonstrate qualification instead of a CV. A short guideline describing aspects of GCP that are relevant to the role, outlining the trial and specific procedures for prescribing trial medication could be countersigned by the delegate in lieu of GCP training.

7) Wider engagement with people with lived experience of inpatient treatment for people with borderline personality disorder

During the preparation stage of this study, we consulted widely with people with lived experience of receiving inpatient treatment for borderline personality disorder. Current and former inpatients told us about their experience of being given large amounts of medication and not always being told what they were taking or why. These people told us that physical health was important and supported our plan to collect detailed information on the physical health of all participants including those in the placebo arm of the trial. They also requested that detailed information be collected about the side effects of clozapine, which we included in our study measures. However, they did not raise any concerns about ensuring that only patients with severe borderline personality disorder

were recruited or the problems of recruiting potential participants from general adult wards, which were raised online by people with lived experience after the study had started. In retrospect, wider consultation with a broader range of people with lived experience of receiving inpatient treatment for people with borderline personality disorder may have helped identify these issues and improve the protocol prior to the start of the trial.

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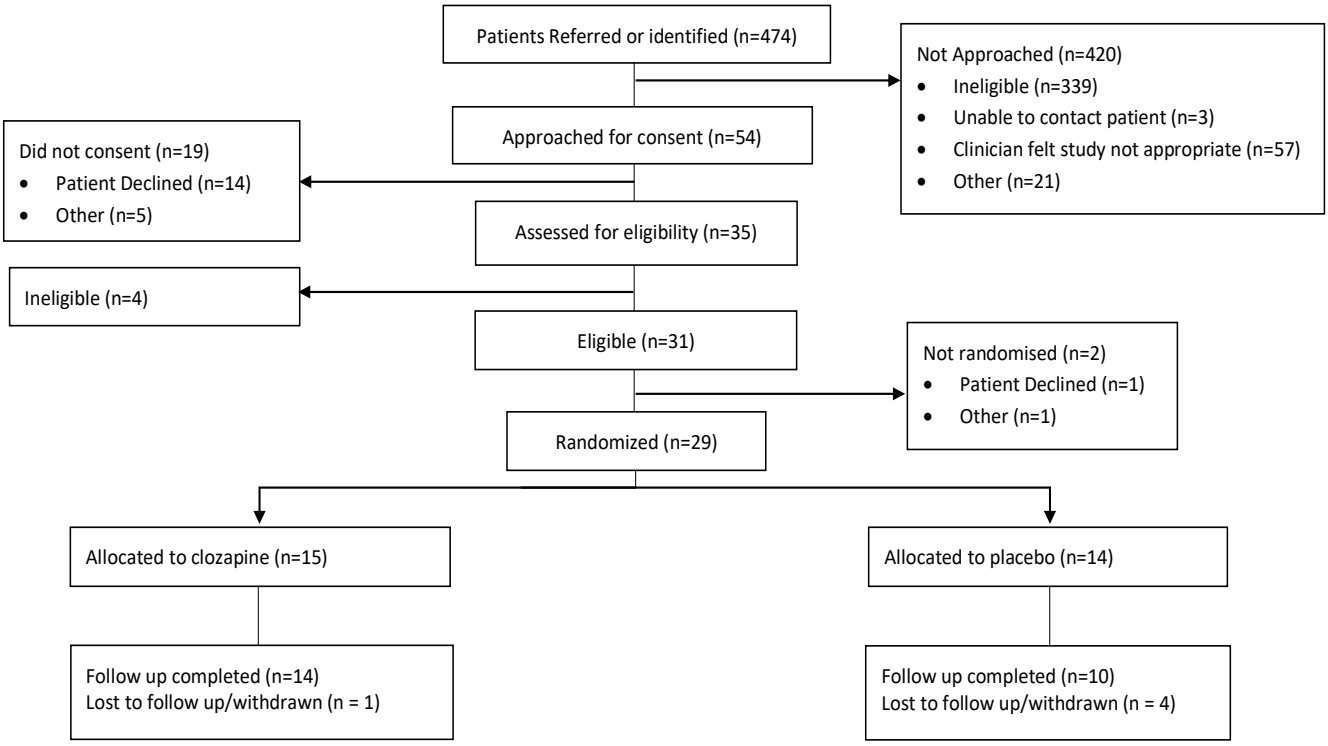

Figure 1: Participant Flow Diagram