BMJ Open

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| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2017-021000 |
| Article Type: | Protocol |
| Date Submitted by the Author: | 10-Dec-2017 |
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| Keywords: | clozapine, Schizophrenia & psychotic disorders < PSYCHIATRY, obesity, DIABETES & ENDOCRINOLOGY, metabolic syndrome |
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# CoMET: A Protocol for a Randomised Controlled Trial of Co-commencement of METformin as an adjunctive treatment to attenuate weight gain and metabolic syndrome in patients with schizophrenia newly commenced on clozapine

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Keywords: Clozapine, Schizophrenia, Obesity, Diabetes, Metabolic Syndrome

Word Count: 4382

Abstract (198)

Introduction:

Clozapine, while effective in treatment refractory schizophrenia, is associated with significant weight gain, heart disease, and increased risk of type 2 diabetes mellitus (T2DM). Although there is evidence for weight loss with metformin for obese people who are already taking clozapine, there have been no published trials that have investigated the effect of metformin in attenuating weight gain at the time of clozapine initiation.

Methods and Analysis:

A 24-week double-blind placebo-controlled trial of concomitant prescription of metformin at clozapine commencement. Eighty-six people being commenced on clozapine will be randomised to placebo or metformin (variable dose, up to 2gm per day). The primary outcome is comparative endpoint weight, adjusted for baseline, between the placebo and metformin groups. Secondary outcomes are comparative rates of conversion to T2DM, alteration of metabolic syndrome parameters, proportion gaining >5% body weight, and changes in diet and appetite. We will additionally examine biomarkers associated with change in weight among trial participants.

Ethics and dissemination:

Ethics approval was granted by the Metro South Human Research Ethics Committee HREC/17/QPAH/538 - SSA/17/QPAH/565. We plan to submit a manuscript of the results to a peer reviewed journal, and present results at conferences, consumer forums and hospital grand rounds.

Registration: Australian and New Zealand Clinical Trials Registry (ACTRN12617001547336)

Keywords: Clozapine, Schizophrenia, Obesity, Diabetes, Metabolic Syndrome

Protocol Version 1.0

## Strengths and Limitations or this Study

### Strengths

- This is the first randomised controlled trial investigating metformin for amelioration of clozapine associated weight gain at the time of clozapine initiation.
- If effective, co-commencement of metformin at the time of clozapine initiation could reduce the cardiovascular and metabolic disease burden of clozapine.

### Limitations

- People with treatment refractory schizophrenia being commenced on clozapine will be a challenging group from which to recruit
- Dropouts from the trial may occur when people commenced on clozapine cease clozapine

## Introduction

Schizophrenia is associated with substantial disability and excess morbidity/mortality; life expectancy is curtailed by over 16 years [1] with over a third of excess deaths attributable to cardiovascular disease and type 2 diabetes mellitus (T2DM)[1]. Increased risk of cardio-metabolic disease in this population is multi-factorial with possible contributing components including genetic predisposition to developing T2DM[2], reduced physical activity[3], suboptimal nutrition[4], and glucose dysregulation associated with antipsychotic medications[5].

Although other antipsychotic medications are effective treatments for schizophrenia[6], approximately 20-33% of patients remain treatment refractory[7]. Treatment refractory schizophrenia is defined as non-response with ongoing psychotic symptoms and functional deficits despite adequate trials of at least two different antipsychotic medications [8]. For people with treatment refractory schizophrenia, clozapine is the most effective medication for reducing the positive symptoms of schizophrenia[9], and the rate of psychiatric hospitalisations[10]. Compared to other antipsychotic medications, clozapine is associated with the highest rates of weight gain, T2DM and metabolic syndrome [5]. A representative survey of people with schizophrenia in Australia found that, compared to people on other antipsychotic medications, people on clozapine were almost twice as likely to develop T2DM, and more than twice as likely to develop metabolic syndrome [11]. In an American study of clozapine users with a 10 year follow up, 43% of participants developed T2DM. The mean weight gain was 13.5kg, of which 4.5kg occurred in the first 10 weeks of commencing clozapine [12].

Weight gain is a significant concern for patients. It is associated with poorer quality of life outcomes[13], creates barriers to social engagement[14] and is the most distressing side effect reported to callers of mental health helplines[15]. Weight gain also reinforces patients' negative views of themselves and may compromise adherence with treatment[15]. Furthermore, there is an established body of evidence that being overweight or obese increases the risk of all-cause mortality with higher weight associated with higher mortality risk[16 17].

Although there is some evidence for the efficacy of lifestyle modification interventions for people with schizophrenia[3], poor rates of uptake of lifestyle modification remain a barrier to their effectiveness[3]. Cognitive deficits associated with schizophrenia can contribute to difficulties with meal planning and accessing physical activity programs[18]. Consequently,

interest is increasing in effectiveness and acceptability of other interventions such as oral medication.

Among people taking clozapine who are obese, there is increasing evidence that metformin can lead to modest weight loss[19]. Metformin, a biguanide anti-hyperglycaemic commonly used in the management of T2DM[20], reduces fasting glucose and triglyceride (TG) and high-density lipoprotein (HDL) cholesterol[21]. Anti-hyperglycaemic properties are attributed primarily to suppression of hepatic gluconeogenesis and increased peripheral insulin sensitivity[20]. In people without T2DM who are not on antipsychotic medications, metformin can lead to mild weight loss[22]. Further, when initiated in overweight patients with newly diagnosed T2DM, metformin can reduce the long term risk of any T2DM endpoint and all-cause mortality [23]. Metformin also has a much lower rate of hypoglycaemia compared to other antidiabetic drugs such as sulphonamides[24].

There is also evidence that metformin increases the production of Glucagon-like Peptide (GLP-1), an intestinal epithelium produced peptide following food consumption[25]. In turn, GLP-1 stimulates insulin secretion while inhibiting glucagon secretion, and also appears to regulate appetite by inducing satiety[26]. Metformin's role in GLP-1 regulation is of particular relevance for people on clozapine as clozapine disrupts the GLP-1 pathway in the intestinal epithelium, thereby reducing GLP-1 levels [27]. As such, it is possible that metformin may have particular benefits with respect to weight gain associated with clozapine (versus other anti-psychotics).

A recent meta-analysis by our group demonstrated that addition of metformin contributed to weight loss of more than 3kg among people already taking clozapine who are obese[19], with significant improvements in BMI, and on three out of the five components of the metabolic syndrome: waist circumference, fasting glucose and triglycerides.

There is, however, an absence of robust evidence for treatments to mitigate or avoid weight gain among people being commenced on clozapine. Two studies explored the role of metformin to attenuate weight gain on people commenced on olanzapine, an antipsychotic similar to, clozapine, but with a lower propensity for weight gain. One study showed amelioration of weight gain[28] while the other reported equivocal results[29]. To date no RCTs have examined the effect of concomitant prescription of metformin with clozapine to attenuate weight gain.

Identifying potential biomarkers that predict poor metabolic outcomes can aid in developing personalised medicine, with an aim of using genetic testing to identify those at highest risk of weight gain associated with clozapine, and those who may benefit most from adjunctive metformin. A review by our group identified genetic associations between clozapine, and BMI and metabolic syndrome, in genes including LEP, HTR2C and rs381328 [30]. Another meta-analysis of people with T2DM identified that rs11212617 was associated with better glycaemic response to metformin[31].

The primary aim of this study is to investigate the effectiveness of metformin in attenuating weight gain in people with schizophrenia newly commenced on clozapine. We hypothesise that people who are co-commenced on metformin will have significantly lower endpoint weight, adjusted for baseline, compared to those started on placebo. We also aim to investigate secondary outcomes including comparative rate of conversion to T2DM, proportion with >5% gain in body weight, derangement of metabolic syndrome components, change in diet and appetite, and association with genetic biomarkers of change in weight among trial participants.

## Methods and Analysis

### Study Design/Setting

The CoMET study is a 24-week parallel, double-blind, placebo-controlled, randomised controlled trial (RCT) testing the efficacy of adjunctive metformin to attenuate weight gain in clozapine naïve people with schizophrenia or schizoaffective disorder who are newly commenced on clozapine. We aim to recruit 86 participants with diagnoses of schizophrenia or schizoaffective disorder within two weeks of being commenced on clozapine.

Participants will be randomised to receive treatment as usual including clozapine plus either metformin or placebo. The dose of metformin will be titrated over a three-week period up to 2gm daily, as tolerated. Placebo dosing will be increased accordingly.

The study will be conducted across four Hospital and Health Service (HHS) Districts in South East Queensland: Metro North HHS, Metro South HHS, West Moreton HHS and Gold Coast HHS. Participants will be recruited with support of treating clinicians from inpatient units, clozapine clinics, community care units and community clinics.

### Study Population

The CoMET study will recruit 86 participants with schizophrenia or schizoaffective disorder who have commenced treatment with clozapine in the last two weeks. Participants will have a BMI between 18kg/$m^2$ and 40 kg/$m^2$. Participants will be excluded from the study if they have pre-existing diagnosis of T2DM, or are already taking metformin or any other weight lowering medications. The full inclusion and exclusion criteria are detailed in Appendix 1.

### Patient Screening and Enrolment

Clozapine is a highly monitored drug in Australia. Individuals must undergo a medical screening process prior to clozapine commencement, and once commenced on clozapine, they need to attend structured weekly medical appointments, with weekly biometric measurements and blood tests for the first 18 weeks of clozapine treatment. Thereafter patients are reviewed four-weekly as per existing clozapine protocol. For people newly commenced on clozapine in Australia, pre-registration with a clozapine manufacturer patient monitoring system is required.

This pre-registration requires the involvement of the hospital service clozapine coordinator and/or mental health pharmacist. Hence, the participating hospital service clozapine coordinator and pharmacists will be aware of all people being commenced on clozapine. The study team will liaise with the clozapine coordinators and mental health pharmacists to identify potential study participants. Potential participants who agree to being approached by the research team will be provided with written and verbal information about the study and invited to consider participation.

The study screening process will begin by assessing the capacity of all potential participants. Once potential participants are deemed to have capacity they will be thoroughly informed about the trial's components and requirements. If they wish to proceed, informed consent will be obtained and witnessed.

Previous research by members of our group found that in Queensland, approximately 8 people are newly commenced on clozapine per year per 100,000 catchment population[32]. The participating HHS cover a population of at least 2.5 million people, with an estimated 200 patients commenced on clozapine annually. With a conservatively estimated 30% study participation rate, 60 people could be commenced in the study annually.

Figure 1 documents the flow of participants from screening to follow-up.

**Allocation Concealment, Randomisation and Masking**

Participants will be randomised once written consent has been obtained and the study screening assessments have determined that the participant is eligible. Participants will be randomised to metformin (active treatment) or placebo in a 1:1 ratio using blocks of 4 via a computer-generated randomisation table. The treating team, participants and the research team will all be blinded to allocation of intervention. Randomisation will not be stratified by site. The randomisation list will be generated by an independent statistician not directly involved in the delivery of intervention or outcome assessment. The randomisation list will be provided to an independent pharmacy team at the Princess Alexandra Hospital. This pharmacy team will be the only service with the ability to unblind patients. Participants will be provided with a 24-hour contact number in case there is an emergent situation where it is crucial that medical staff know whether they are receiving metformin or placebo.

Allocation concealment will be maintained by using placebo tablets that are identical in packaging, appearance, colour and taste to the metformin tablets and by increasing the number of placebo tablets to match the titration of metformin. All other study assessments and procedures will be identical between the two groups.

**Treatment Protocol**

*Metformin Group*

Those in the metformin group will be provided with an extended release (XR) formulation of metformin with their evening meal for 24 weeks. Metformin XR 500mg tablets will be used. To reduce potential side effects metformin will be titrated as tolerated over a 3-week period with 500mg XR daily given the first week, 1000mg XR daily the second week and 2000mg XR daily for the remainder of the study. The titration regime will be discussed weekly with the co-ordinating principal investigator or delegate and the study endocrinologist or delegate. If 2000mg XR daily is not tolerated than participants will be given the maximum tolerated dose.

Participants will also receive treatment as usual. In keeping with Queensland Health standards of care for psychosis this may include individualised combinations of psychopharmacology, behavioural interventions, dietary advice, physical activity programs, rehabilitation and associated clinical services. Participant's engagement in dietary and physical activity programs will be recorded in the case files.

*Placebo Group*

Those in the placebo group will be provided with a daily dose of placebo with their evening meal for 24 weeks. The placebo tablets are identical to the metformin XR tablets. The dose will also be titrated as tolerated over 3 weeks with one tablet being given in the first week, then two tablets from week two and then four tablets from week three. If four tablets are not tolerated then participants will be given the maximum tolerated dose. Those in the placebo group will also receive treatment as usual.

Adherence will be monitored through return of unused tablets and tablet counts at each visit.

**Dose Justification**

In a recent meta-analysis, the mean metformin dose used in RCTs comparing metformin to placebo in people without T2DM who were prescribed clozapine ranged from 250mg to 1500mg[19]. Clinical recommendations for the use of metformin in T2DM suggest starting at 500mg and titrating up to 2000mg based on serial blood glucose measurements [33 34]. A study by Chiu et al [35] compared metformin doses of 500mg and 1000mg among people already obese on clozapine. They found a statistically significant reduction in body weight after 12 weeks in the 1000mg group but not the 500mg group. This suggests that a dose of at least 1000mg is required for consistent weight reduction in patients on clozapine. We have elected to use the maximum dose tolerated within the recommended dosing range of metformin XR (500-2000mg) to explore the maximum possible effect with metformin.

**Outcomes**

*Primary*

The primary outcome will be weight in kilograms (kg) at 24 weeks, adjusted for baseline weight.

*Secondary*

Secondary outcome measures are:

- Rate of conversion to T2DM (fasting 2 hour glucose tolerance test and HbA1c)
- Metabolic syndrome components[36] (waist circumference , fasting glucose, HDL, total cholesterol, triglycerides, and blood pressure ).
- Homeostatic model assessment (HOMA) of insulin resistance and secretion based on fasting glucose and insulin
- Diet and appetite (Food Craving Inventory)
- Physical activity (International Physical Activity Questionnaire (IPAQ) and Simple Physical Activity Questionnaire (SIMPAQ))
- Proportion with weight gain of 5% or more at endpoint versus baseline
- Dropout rates
- Quality of Life (Assessment of Quality of Life (AQoL))

A range of symptom, cognitive and plasma drug measures will also be examined to explore whether any group differences in endpoint weight can be attributed to differences in the following clinical assessments:

- Psychotic symptoms (Positive and Negative Syndrome Scale (PANSS))
- Psychosocial Function (Global Assessment of Functioning (GAF))
- Cognitive function (Brief Cognitive Assessment Tool for Schizophrenia (B-CATS), Test of Premorbid Functioning (TOPF) and California Verbal Learning Test (CVLT-II)
- Clozapine/Norclozapine levels and ratio

*Tertiary*

Collect DNA for future study into genetic biomarkers associated with weight gain with clozapine and/or response to metformin.

**Trial visits, Assessments and Outcome Measures**

Study visits and assessments, identical in both groups, will be conducted as per Table 1. Study visits will be weekly for the first four weeks and then every four weeks for the remainder of the study. The investigational product will be dispensed at every study visit. Physical measurements and adverse drug reaction monitoring will be conducted by the research team at every study visit. A range of validated clinical assessments (Table 1), will be conducted at weeks 4, 8, 12, 16, 20 and 24. Participants will have three blood tests during the study, at baseline and weeks 12 and 24. Every effort will be made to ensure that these blood tests coincide with mandatory blood tests for clozapine monitoring.

People with pre-existing T2DM, chronic kidney disease, and pregnancy will be excluded (Appendix 1 Inclusion and Exclusion Criteria). Pre-clozapine investigations will be ordered by the treating team, as part of the mandatory workup for clozapine, including fasting serum glucose, estimated glomerular filtrate rate (eGFR) and Beta Human Chorionic Gonadotropin (Beta HCG). This data will be used for the screening of participants. Vitamin B12 serum levels will be monitored at baseline, week 12 and week 24 as a rare side effect of metformin includes vitamin B12 deficiency.

Blood will also be collected at baseline for future DNA analysis. Participation in this part of the study is optional and separate consent will be sought.

In addition to the scheduled study visits, participants will be contacted regularly by the research trial team during the trial in an effort to improve adherence to the investigational product and increase retention rate.

All anthropometric measurements will be collected by the research trial team while participants wear light clothing, after the participants have emptied their bladder and removed their shoes. Height will be recorded at the screening assessment. At each visit, weight will be recorded to the nearest 0.1 kg using calibrated scales. Waist circumference will be measured in the horizontal plane to the nearest 0.5 cm using a non-stretchable measuring tape placed around the abdomen at a level halfway between the top of the iliac crest and the bottom of the ribs [37]. Hip circumference will be measured at the maximum circumference of the buttocks [37]. The Hip/Waist ratio is the ratio of hip circumference and waist circumference.

Pulse and blood pressure will be recorded after sitting for 5 minutes [38]. Blood pressure will also be recorded in the standing position after the participant has been standing for 2 minutes.

PANSS

The PANSS (Positive and Negative Syndrome Scale), a validated 30 item investigator rated measure, will be used to measure positive and negative symptoms of schizophrenia [39].

GAF

The Global Assessment of Functioning scale (GAF) is a validated investigator rated scale incorporating symptom severity, psychological, social, and occupational functioning on a scale from 0 to 100 [40].

IPAQ and SIMPAQ

The IPAQ (International Physical Activity Questionnaire) is a validated participant recall based measure of physical activity in the past week [41]. The SIMPAQ (Simple Physical Activity Questionnaire) is a participant recall based measure of physical activity in the past week that is specifically designed for people living with mental illness [42].

AQoL

The Assessment of Quality of Life (AQoL) is a validated instrument that measures 5 health dimensions: illness, independent living, social relationships, physical senses and psychological wellbeing, and can be used for economic evaluations [43].

Cognitive Assessments

TOPF

The Test of Premorbid Functioning (TOPF) is a revised version of the Wechsler Test of Adult Reading and is a measure of pre-morbid cognitive and memory functioning [44].

CVLT-II short form

The California Verbal Learning Test 2nd edition short form is a validated test of verbal learning and memory [45].

Brief Cognitive Assessment

The B-CATS (Brief Cognitive Assessment Tool for Schizophrenia) includes the Digit Symbol Substitution Test, Trail Making Test and Verbal Fluency Test. These test, respectively, complex processing speed, visual attention and task switching, and semantic fluency and strategy generation. The B-CATS is validated and has good reliability and consistency and can be delivered in around 10 minutes [46].

Food Craving Inventory

The Food Craving Inventory is a validated measure of food cravings, and is based on participant self-report. It has two scales, one for subjective cravings and the other for consumption of particular foods [47].

Data will be initially recorded on paper case report forms. Data will be checked by two independent members of the research team and thenentered into an electronic data management software program (RedCAP). All confidential data will be securely stored as per Good Clinical Practice guidelines.

**Statistical Methods**

*Sample Size*

We powered our study based on the primary outcome, weight change using the repeated measures ANCOVA approach. Sample size was estimated using data from a meta-analysis of

metformin for clozapine associated obesity conducted by our group [19]. To observe a minimal clinically difference in weight change of 3.12kg, assuming standard deviation (SD) of 9.6 in both groups (overall SD from the meta-analysis), $\alpha = 0.05$, and correlation between baseline and repeated measures of 0.7, we will require 34 participants per group to achieve 80% power. Allowing for an attrition rate of 20% from baseline to follow-up, we will need to recruit 86 participants across the four sites.

*Data analysis*

Analysis will be conducted according to intention-to-treat principle with participants analysed in the group they were originally allocated to regardless of treatment compliance. Baseline characteristics will be summarized using mean and standard deviation for continuous variables, and n (%) for categorical variables. The distribution of continuous variables, if skewed, where appropriate will be transformed using log-transformation. Baseline characteristics between the two groups will be compared using either the t-test (continuous data) or Chi-square test /Fisher's exact test (categorical data). The primary outcome, endpoint weight, will be analysed using a mixed model repeated measure model (MMRM). The MMRM is a superior approach in controlling for type I error and minimize bias as it does not impute or exclude participants with missing data [48]. We will include weight at baseline assessment, intervention group, visit and visit by intervention in the model. We will also test the sensitivity of our results by imputing for missing values in the primary outcome using multiple imputation. Results will be presented as mean difference along with 95% confidence intervals. Secondary outcomes will be analysed in a similar fashion using MMRM for normal outcomes or generalized linear mixed models for non-normal outcomes. Number needed to treat and number needed to harm will be calculated. All analyses will be conducted using SAS 9.4 (ref: SAS Institute Inc, NC).

**Participant Safety**

Metformin has been used extensively for the treatment of T2DM. It is well tolerated, with hypoglycaemic episodes very rare unless combined with other anti-hyperglycaemics [24]. There are no known pharmacokinetic interactions between metformin and clozapine. Previous studies exploring the tolerability of metformin in people with schizophrenia taking various antipsychotics found that the reported side effects were very similar between the metformin and placebo groups [49].

The most common side effect of metformin is gastrointestinal disturbance which includes diarrhoea, flatus, nausea, abdominal discomfort, and reduced appetite [33]. Metformin associated gastrointestinal disturbance normally resolves in the first few weeks and can be reduced by using the XR formulation, taking metformin with the evening meal and titrating the dose slowly [33].

Other possible rarer side effects include taste disturbance, vitamin $B_{12}$ deficiency, lactic acidosis, and hepatobiliary disorders. Serious side effects including vitamin $B_{12}$ deficiency, lactic acidosis and hepatobiliary disorders are rare. Most cases of lactic acidosis have occurred in diabetic patients with significant renal failure and other risk factors [33]. We will monitor for the side effects by testing vitamin $B_{12}$ levels, electrolytes and liver function at baseline, week 12 and week 24.

The use of iodinated contrast materials concomitantly with metformin may be associated with nephropathy. Our participants' kidney function will be protected during the study by withholding metformin or placebo for 48 hours after intravenous contrast is administered[33].

Metformin is relatively safe even when taken in overdose. Despite ingestion of large amounts of metformin (up to 85g) hypoglycaemia has not been observed[33]. Lactic acidosis has been reported as a consequence of overdose in people with pre-existing T2DM[33]. Pre-existing T2DM is an exclusion criteria, and participants who develop T2DM during the study will be withdrawn. Any dose taken above the highest recommended daily dose of 2000mg will be considered an overdose and recorded and reported as a Serious Adverse Event (SAE). To reduce the risk of a serious overdose the investigational product will be dispensed weekly for the first 4 weeks and then every 4 weeks for the remainder of the study.

Participants will be assessed for possible adverse effects (AE's), at every study visit, including use of the Systematic Assessment for Treatment Emergent Events – Systematic Inquiry (SAFTEE-SI) tool [50]. AE can refer to serious and non-serious AE's. For this study, an AE is defined as any unfavourable and unintended sign (including abnormal laboratory findings), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Medical and Surgical Procedures will not be classed as AE's. SAEs, as defined in Appendix 2 will be

reported to the study monitor as soon as possible and to the reviewing ethics committee. Any serious, unexpected adverse events (SUSAR) that are causally related to the investigational product will be reported to the Australian Therapeutic Goods Administration (TGA) and other appropriate regulatory as per the applicable guidelines.

Safety outcomes will also be collected to assess the preliminary safety and tolerability of metformin. These include

- Number of dropouts between intervention and control arm
- Number of adverse drug reactions in the intervention and control arm
- Scores from a structured qualitative interview with participants about their experiences with study drug using the SAFTEE-SI
- Serum bicarbonate and lactate to assess for lactic acidosis
- Vitamin B12 levels to assess for Vitamin B12 deficiency

**Study Completion and Withdrawal**

Participants will be deemed to have completed the trial when they complete 24 weeks of dosing. Participants have the right to remove their consent and withdraw from the study at any time and this will be clearly discussed during the screening process. Participants who cease clozapine during the study period will be withdrawn from the study. In addition, participants may also be withdrawn by the investigator if they meet withdrawal criteria (Appendix 3).

Any participant withdrawn from the study will have their last observation carried forward in an intention to treat analysis.

**Reimbursement**

Participants will receive honorarium in the form of gift cards to the total value of $140, over the course of the study.

**Ethics and Dissemination**

The study will be carried out according to the Declaration of Helsinki, the NHMRC National Statement on the Ethical Conduct in Research involving Humans (2007) and the Notes for

Guidance on Good Clinical Practice as adopted by the Australian Therapeutic Goods Administration (2000) (CPMP/ICH/135/95) and the ICH GCP Guidelines.

Ethics approval was granted by the Metro South Human Research Ethics Committee HREC/17/QPAH/538 - SSA/17/QPAH/565.

This study has Therapeutic Good Administration Clinical Trial Notification (2017-CTN-02935), and has been listed on the Australian and New Zealand Clinical Trials Registry (ACTRN12617001547336).

An independent Data Safety Monitoring Board will monitor safety data during the trial.

This study protocol has been devised in line with the SPIRIT guidelines [51] (see supplemental SPIRIT Checklist).

On study completion, results will be disseminated by peer reviewed publications and conference presentations, regardless of the findings. Manuscripts will be prepared in accordance with the CONSORT 2010 Statement[52]. Our findings will also be summarised in several brochures, including one designed for feedback to participants and hospital sites that participate in the study.

## Discussion

Clozapine is the most effective antipsychotic for treatment refractory schizophrenia but has the worst metabolic profile of all antipsychotics. Although there is evidence that some pharmacological interventions such as exenatide [53] and metformin [19] can reduce weight for people who are already obese taking clozapine, the magnitude of this reduction in weight gain is small. There is a critical need for evidence based therapies to avert the initial clozapine associated weight gain. To date there have been no randomised controlled trials examining the effectiveness of metformin to attenuate weight gain in patients newly commenced on clozapine.

This study will examine whether metformin can attenuate weight gain over a 24-week period when compared to placebo as its primary outcome. It will also examine whether metformin has an effect on the components of the metabolic syndrome, rates of conversion to T2DM, and changes to diet and exercise.

Reducing the metabolic burden of clozapine from commencement has the potential to reduce the risk of developing cardiovascular disease and T2DM. If efficacious and safe, metformin would be a relatively accessible, cost-effective intervention. Because weight gain is a major concern among people on clozapine, attenuation of weight gain can enhance self-image, adherence, and is thus likely to improve health outcomes and the quality of life of people living with schizophrenia. Ultimately, interventions that ameliorate weight gain in those with schizophrenia may also reduce the unacceptable high mortality and morbidity gaps between people living with schizophrenia and the general population.

Funding

The trial is funded in part from a NHMRC ECF APP1111136 awarded to DS, and a Royal Brisbane and Women's Hospital Project Grant awarded to DF, SP, DS and VM. The funding sources had no role in the design, conduct or data analysis of the present study. The University of Queensland is the research sponsor and will be responsible for monitoring and indemnifying the trial. There are no stipulations on publication in place by any party.

Competing interests

AR has received speaker honoraria and travel grants from Astra Zenica, Boehringer Ingelheim, Eli Lilly, MSD, Novo Nordisk and Sanofi and has participated on advisory panels for MSD and Novo Nordisk. None of the other authors have conflicts of interest.

Authors' contributions

DS is the principal investigator of the study and was involved in conception, design, drafting and revising the protocol, grant acquisition and will be responsible for recruitment and trial coordination. All authors, particularly AB, AR and JM, contributed to the study design and planning. NF prepared the first draft of the manuscript with DS, AB and AR reviewing and amending early draft versions. All authors edited and contributed to the final version of the manuscript.

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**Table 1: Schedule of Visits and Assessments**

| VISIT | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|---|---|
| | **Screening** | **Baseline** | | | | | | | | |
| **WEEK** | | 0 | 2 | 3 | 4 | 8 | 12 | 16 | 20 | 24 |
| **Study medication period(24 weeks)** | | | | | | | | | | |
| **SCREENING AND CONSENT** | | | | | | | | | | |
| Assessment of current medication | x | x | x | x | x | x | x | x | x | x |
| Informed consent | x | | | | | | | | | |
| Ongoing capacity | x | x | x | x | x | x | x | x | x | x |
| Inclusion / exclusion criteria | x | | | | | | | | | |
| Beta HCG (females only) | x | | | | | | | | | |
| Drug dispensation (after randomisation) | | x | x | x | x | x | x | x | x | x |
| **SAFETY** | | | | | | | | | | |
| Adverse events | | | x | x | x | x | x | x | x | x |
| SAFTEE-SI | | x | x | x | x | x | x | x | x | x |
| Vitamin B12 | | x | | | | | x | | | x |
| **EFFICACY** | | | | | | | | | | |
| Height | x | x | | | | | | | | |
| Body weight | x | x | x | x | x | x | x | x | x | x |
| Waist circumference & hip/waist ratio | | x | x | x | x | x | x | x | x | x |
| Blood pressure | | x | x | x | x | x | x | x | x | x |
| Fasting glucose, insulin | | x | | | | | x | | | x |
| Fasting Cholesterol, HDL, LDL, Triglycerides | | x | | | | | x | | | x |
| HbA1c | | x | | | | | x | | | x |
| OGTT | | x | | | | | | | | x |
| **OTHER** | | | | | | | | | | |
| Heart Rate | | x | x | x | x | x | x | x | x | x |
| PANSS | | x | | | | | x | | | x |
| GAF | | x | | | | | x | | | x |
| SIMPAQ/IPAQ | | x | | | | | x | | | x |
| AQOL | | x | | | | | x | | | x |
| TOPF | | x | | | | | | | | x |
| CVLT-II short form | | x | | | | | | | | x |
| Symbol Digit | | x | | | | | | | | x |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Modalities Test | | | | | | | | | | |
| Controlled Oral Word Association Test | | x | | | | | | | | x |
| Trail Making Test | | x | | | | | | | | x |
| Food Craving Inventory | | x | | | | | x | | | x |
| **OTHER** | | | | | | | | | | |
| Drug compliance | | | x | x | x | x | x | x | x | x |
| Blood (other) - FBC (including WCC, Neutrophils), ELFT (including Serum bicarbonate and lactate) clozapine/nor clozapine levels | | x | | | | | x | | | x |

HCG – Human chorionic gonadotropin
SAFTEE-SI - Systematic Assessment for Treatment Emergent Events – Systematic Inquiry
HDL – High Density Lipoprotein
LDL – Low Density Lipoprotein
OGTT – Oral Glucose Tolerance Test
PANSS - Positive and Negative Syndrome Scale
GAF – Global Assessment of Functioning
IPAQ - International Physical Activity Questionnaire
SIMPAQ - Simple Physical Activity Questionnaire
AQoL - Assessment of Quality of Life
TOPF - Test of Premorbid Functioning
CVLT-II - The California Verbal Learning Test 2nd edition
FBC – Full Blood Count
ELFT – Electrolytes and Liver Function Tests

Figure Legend

Figure 1: Flow chart of the CoMET Trial

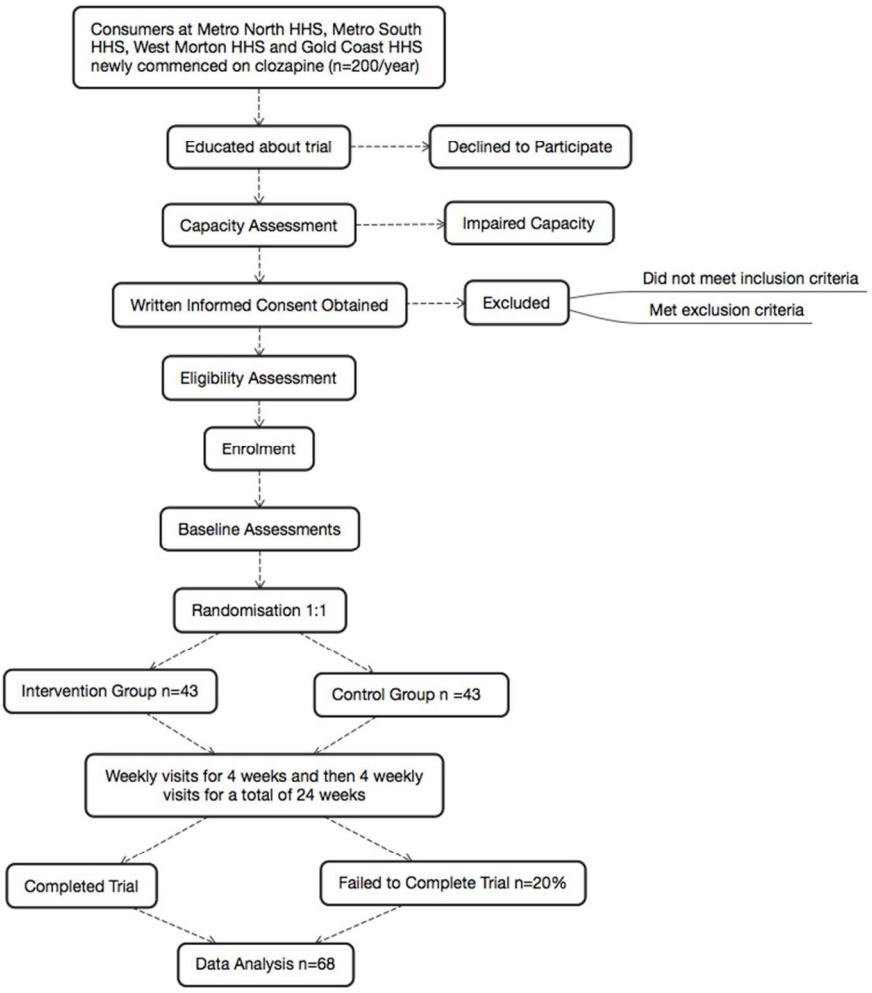


Figure 1

304x340mm (72 x 72 DPI)

Appendix 1 Inclusion/Exclusion Criteria

Inclusion Criteria

Patients will be invited to participate in the study if they meet all of the following criteria:

1. Aged between 18 and 64 years (inclusive)
2. Fulfil the DSM-IV criteria practice for schizophrenia or schizoaffective disorder, based on the Diagnostic Interview for Psychosis (DIP)
3. Have received oral clozapine for a period of no more than 2 weeks
4. Agree to participate, have capacity to consent and are able to follow the study instructions and procedures
5. Fasting Blood Glucose Level ≤6.0 mmols (confirmed within the previous two weeks of commencing clozapine)
6. BMI ≥18 and ≤40

Exclusion Criteria

Patients will be excluded from the study if they meet any one of the following criteria:

1. Known allergies to Metformin or any part of the formulation of the investigational product
2. Obesity induced by other endocrinologic disorder (e.g Cushing Syndrome, untreated Hypothyroidism)
3. Current use of any weight-lowering therapy including: pramlintide, sibutramine, orlistat, zonisamide, topiramate or phenteremine (either by prescription or as part of a clinical trial)
4. Diagnosis of Type 1 or Type 2 Diabetes mellitus or already on metformin
5. Participants treated with corticosteroids or other hormone therapy (except oestrogens or thyroxine) for greater than 10 days
6. Chronic kidney disease (eGFR<60mL/min)
7. Use of Diuretics
8. Use of Warfarin
9. Previous surgical treatment of obesity
10. BMI ≤18 or BMI ≥40
11. Any concomitant disease or condition that according to the investigator's assessment makes the patients unsuitable for trial participation
12. People who are unable to understand or communicate in English
13. For female participants, those currently pregnant, or planning to become pregnant or lactating or no acceptance to the use of effective contraception during the study period
14. Inability to follow the study instructions and procedures

Appendix 2 Additional Outcomes/Objective

Ancillary Measures

- clozapine/norclozapine ratio
- lactate
- serum bicarbonate
- heart rate
- B12

Secondary moderating variables will include the following clinical assessments:

- Positive and Negative Symptom Scale (PANSS) widely used scale for measuring symptom severity of patients with schizophrenia
- Test of Premorbid Functioning which is a measure of pre-injury IQ and memory ability
- Global Assessment of Function (GAF) which is a numeric scale (1 through 100) used by mental health clinicians and physicians to rate subjectively the social, occupational, and psychological functioning of adults
- The "Simple Physical Activity Questionnaire" (SIMPAQ) measures physical activity. It has been designed for use in various populations including clinical samples with high levels of sedentary behaviour.
- International Physical Activity Questionnaires (IPAQ) provides a common instrument that can be used to obtain internationally comparable data on health–related physical activity.
- Australian Quality of Life Scale (AQOL) is a 15 item instrument that measures five broad domains: Psychological well-being, physical senses, social relationships, independent living, and illness.
- CVLT-II short form is a measure of episodic verbal learning memory, which demonstrates sensitivity to a range of clinical conditions
- Controlled Oral Word Association Test (verbal fluency) is a verbal fluency test that measures spontaneous production of words belonging to the same category or beginning with some designated letter
- Trail Making Test is a neuropsychological test of visual attention and task switching. The test can provide information about visual search speed, scanning and speed of processing, mental flexibility as well as executive functioning.
- Symbol Digit Modalities Test taps into non-verbal functions (e.g. attention, flexibility, speed of processing and abstraction) that are much more likely to be affected by disease processes.

Tertiary objectives include the collecting of DNA for future collaborative studies related to metabolic syndrome.

Appendix 3 SAE

Definition of a Serious Adverse Event (SAE)

A serious adverse event is any untoward medical occurrence that, at any dose:

a) results in death

b) is life threatening*

c) requires in-patient **hospitalisation or prolongation of an existing hospitalisation.

Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d) results in disability/incapacity, or

e) is a congenital abnormality / birth defect.

f) Any event deemed by the investigator as being a significant medical event.

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

** The term “hospitalisation” is the definition of a subject admitted to a hospital/inpatient (irrespective of the duration of physical stay), or not admitted to a hospital/not inpatient, but stays at the hospital for treatment or observation for more than 24 hours. Hospitalisations for administrative, trial related and social purposes do not constitute AEs and should therefore neither be reported as AEs or SAEs. Likewise, hospital admissions for surgical procedures planned prior to trial inclusion are not considered AEs or SAEs.

Appendix 4 Withdrawl Criteria

Participant Withdrawal by the Investigator

Participants will be withdrawn from the study by the Investigator, prior to completion of treatment, under the following conditions:

- Non-adherence with study medication for seven or more consecutive days
- Non-adherence with or self-ceased clozapine for 7 or more consecutive days
- Clozapine ceased due to medical reasons with no planned re-challenge within 7 days of ceasing
- Development of a serious adverse event assumed to be associated with the study medication
- Cessation of effective contraception or confirmed pregnancy
- Development of T2DM
- Continual inability to provide informed consent

**Abbreviations**

AE Adverse Event
CRP Case Report Form
eGFR estimated Glomerular Filtration Rate
GCP Good Clinical Practice
HREC Human Research and Ethics Committee
ICH International Council for Harmonisation
PICF Patient Informed Consent Form
RCT Randomised Controlled Trial
SAE Serious Adverse Event
SNP Single Nucleotide Polymorphism
SUSAR Serious and Unexpected Serious Adverse Reaction
T2DM Type 2 Diabetes Mellitus

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | Item No | Description | Addressed on page number |
|---|---|---|---|
| **Administrative information** | | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | 1 |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry | 17 |
| | 2b | All items from the World Health Organization Trial Registration Data Set | |
| Protocol version | 3 | Date and version identifier | 2 |
| Funding | 4 | Sources and types of financial, material, and other support | 18 |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | 19 |
| | 5b | Name and contact information for the trial sponsor | 18 |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | 18 |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | 17 |

| | | | |
|---|---|---|---|
| **Introduction** | | | |
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | ____4-6____ |
| | 6b | Explanation for choice of comparators | ___4-6_____ |
| Objectives | 7 | Specific objectives or hypotheses | ___6_____ |
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) | ____7_____ |
| **Methods: Participants, interventions, and outcomes** | | | |
| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | _____7_____ |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | _7 and Appendix_ |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | ____9_____ |
| | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) | __9_____ |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | ____9_____ |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | _____9_____ |
| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | ____10_____ |
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | _____11_____ |

| | | | |
|---|---|---|---|
| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | 13 |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | 8 |
| **Methods: Assignment of interventions (for controlled trials)** | | | |
| Allocation: | | | |
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | 8 |
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | 8 |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | 8 |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | 8 |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | 8 |
| **Methods: Data collection, management, and analysis** | | | |
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | 11 |
| | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | 12 & 16 |

| | | | |
|---|---|---|---|
| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | 13 |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | 13-14 |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | 14 |
| | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | 14 |
| **Methods: Monitoring** | | | |
| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | 17 |
| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | |
| Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | 15 |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | |
| **Ethics and dissemination** | | | |
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | 17 |
| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | |

| | | | |
|---|---|---|---|
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | ___8_____ |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | _____ |
| Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | ____13____ |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | ___19_____ |
| Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | _____ |
| Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | _____ |
| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | ____17_____ |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers | _____ |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | _____ |
| **Appendices** | | | |
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates | _____ |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | _____ |

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

# CoMET: A Protocol for a Randomised Controlled Trial of Co-commencement of METformin as an adjunctive treatment to attenuate weight gain and metabolic syndrome in patients with schizophrenia newly commenced on clozapine



| | |
|---|---|
| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2017-021000.R1 |
| Article Type: | Protocol |
| Date Submitted by the Author: | 19-Jan-2018 |
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| Primary Subject Heading: | Mental health |
| Secondary Subject Heading: | Diabetes and endocrinology |
| Keywords: | clozapine, Schizophrenia & psychotic disorders < PSYCHIATRY, obesity, DIABETES & ENDOCRINOLOGY, metabolic syndrome |
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# CoMET: A Protocol for a Randomised Controlled Trial of Co-commencement of METformin as an adjunctive treatment to attenuate weight gain and metabolic syndrome in patients with schizophrenia newly commenced on clozapine

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Keywords: Clozapine, Schizophrenia, Obesity, Diabetes, Metabolic Syndrome

Word Count: 4382

Abstract (198)

Introduction:

Clozapine, while effective in treatment refractory schizophrenia, is associated with significant weight gain, heart disease, and increased risk of type 2 diabetes mellitus (T2DM). Although there is evidence for weight loss with metformin for obese people who are already taking clozapine, there have been no published trials that have investigated the effect of metformin in attenuating weight gain at the time of clozapine initiation.

Methods and Analysis:

A 24-week double-blind placebo-controlled trial of concomitant prescription of metformin at clozapine commencement. Eighty-six people being commenced on clozapine will be randomised to placebo or metformin (variable dose, up to 2gm per day). The primary outcome is comparative endpoint body weight, between the placebo and metformin groups. Secondary outcomes are comparative rates of conversion to T2DM, alteration of metabolic syndrome parameters, proportion gaining >5% body weight, and changes in diet and appetite. We will additionally examine biomarkers associated with change in weight among trial participants.

Ethics and dissemination:

Ethics approval was granted by the Metro South Human Research Ethics Committee HREC/17/QPAH/538 - SSA/17/QPAH/565. We plan to submit a manuscript of the results to a peer reviewed journal, and present results at conferences, consumer forums and hospital grand rounds.

Registration: Australian and New Zealand Clinical Trials Registry (ACTRN12617001547336)

Keywords: Clozapine, Schizophrenia, Obesity, Diabetes, Metabolic Syndrome

Protocol Version 1.0

## Strengths and Limitations or this Study

### Strengths

- This is the first randomised controlled trial investigating metformin for amelioration of clozapine associated weight gain at the time of clozapine initiation.
- If effective, co-commencement of metformin at the time of clozapine initiation could reduce the cardiovascular and metabolic disease burden of clozapine.

### Limitations

- People with treatment refractory schizophrenia being commenced on clozapine will be a challenging group from which to recruit
- Dropouts from the trial may occur when people commenced on clozapine cease clozapine

## Introduction

Schizophrenia is associated with substantial disability and excess morbidity/mortality; life expectancy is curtailed by over 16 years [1] with over a third of excess deaths attributable to cardiovascular disease and type 2 diabetes mellitus (T2DM)[1]. Increased risk of cardio-metabolic disease in this population is multi-factorial with possible contributing components including genetic predisposition to developing T2DM[2], reduced physical activity[3], suboptimal nutrition[4], and glucose dysregulation associated with antipsychotic medications[5].

Although other antipsychotic medications are effective treatments for schizophrenia[6], approximately 20-33% of patients remain treatment refractory[7]. Treatment refractory schizophrenia is defined as non-response with ongoing psychotic symptoms and functional deficits despite adequate trials of at least two different antipsychotic medications [8]. For people with treatment refractory schizophrenia, clozapine is the most effective medication for reducing the positive symptoms of schizophrenia[9], and the rate of psychiatric hospitalisations[10]. Compared to other antipsychotic medications, clozapine is associated with the highest rates of weight gain, T2DM and metabolic syndrome [5]. A representative survey of people with schizophrenia in Australia found that, compared to people on other antipsychotic medications, people on clozapine were almost twice as likely to develop T2DM, and more than twice as likely to develop metabolic syndrome [11]. In an American study of clozapine users with a 10 year follow up, 43% of participants developed T2DM. The mean weight gain was 13.5kg, of which 4.5kg occurred in the first 10 weeks of commencing clozapine [12].

Weight gain is a significant concern for patients. It is associated with poorer quality of life outcomes[13], creates barriers to social engagement[14] and is the most distressing side effect reported to callers of mental health helplines[15]. Weight gain also reinforces patients' negative views of themselves and may compromise adherence with treatment[15]. Furthermore, there is an established body of evidence that being overweight or obese increases the risk of all-cause mortality with higher weight associated with higher mortality risk[16 17].

Although there is some evidence for the efficacy of lifestyle modification interventions for people with schizophrenia[3], poor rates of uptake of lifestyle modification remain a barrier to their effectiveness[3]. Cognitive deficits associated with schizophrenia can contribute to difficulties with meal planning and accessing physical activity programs[18]. Consequently,

interest is increasing in effectiveness and acceptability of other interventions such as oral medication.

Among people taking clozapine who are obese, there is increasing evidence that metformin can lead to modest weight loss[19]. Metformin, a biguanide anti-hyperglycaemic commonly used in the management of T2DM[20], reduces fasting glucose and triglyceride (TG) and high-density lipoprotein (HDL) cholesterol[21]. Anti-hyperglycaemic properties are attributed primarily to suppression of hepatic gluconeogenesis and increased peripheral insulin sensitivity[20]. In people without T2DM who are not on antipsychotic medications, metformin can lead to mild weight loss[22]. Further, when initiated in overweight patients with newly diagnosed T2DM, metformin can reduce the long term risk of any T2DM endpoint and all-cause mortality [23]. Metformin also has a much lower rate of hypoglycaemia compared to other antidiabetic drugs such as sulphonamides[24].

There is also evidence that metformin increases the production of Glucagon-like Peptide (GLP-1), an intestinal epithelium produced peptide following food consumption[25]. In turn, GLP-1 stimulates insulin secretion while inhibiting glucagon secretion, and also appears to regulate appetite by inducing satiety[26]. Metformin's role in GLP-1 regulation is of particular relevance for people on clozapine as clozapine disrupts the GLP-1 pathway in the intestinal epithelium, thereby reducing GLP-1 levels [27]. As such, it is possible that metformin may have particular benefits with respect to weight gain associated with clozapine (versus other anti-psychotics).

A recent meta-analysis by our group demonstrated that addition of metformin contributed to weight loss of more than 3kg among people already taking clozapine who are obese[19], with significant improvements in BMI, and on three out of the five components of the metabolic syndrome: waist circumference, fasting glucose and triglycerides.

There is, however, an absence of robust evidence for treatments to mitigate or avoid weight gain among people being commenced on clozapine. Two studies explored the role of metformin to attenuate weight gain on people commenced on olanzapine, an antipsychotic similar to, clozapine, but with a lower propensity for weight gain. One study showed amelioration of weight gain[28] while the other reported equivocal results[29]. To date no RCTs have examined the effect of concomitant prescription of metformin with clozapine to attenuate weight gain.

Identifying potential biomarkers that predict poor metabolic outcomes can aid in developing personalised medicine, with an aim of using genetic testing to identify those at highest risk of weight gain associated with clozapine, and those who may benefit most from adjunctive metformin. A review by our group identified genetic associations between clozapine, and BMI and metabolic syndrome, in genes including LEP, HTR2C and rs381328 [30]. Another meta-analysis of people with T2DM identified that rs11212617 was associated with better glycaemic response to metformin[31].

The primary aim of this study is to investigate the effectiveness of metformin in attenuating weight gain in people with schizophrenia newly commenced on clozapine. We hypothesise that people who are co-commenced on metformin will have significantly lower endpoint weight, compared to those started on placebo. We also aim to investigate secondary outcomes including comparative rate of conversion to T2DM, proportion with >5% gain in body weight, derangement of metabolic syndrome components, change in diet and appetite, and association with genetic biomarkers of change in weight among trial participants.

## Methods and Analysis

### Study Design/Setting

The CoMET study is a 24-week parallel, double-blind, placebo-controlled, randomised controlled trial (RCT) testing the efficacy of adjunctive metformin to attenuate weight gain in clozapine naïve people with schizophrenia or schizoaffective disorder who are newly commenced on clozapine. We aim to recruit 86 participants with diagnoses of schizophrenia or schizoaffective disorder within two weeks of being commenced on clozapine.

Participants will be randomised to receive treatment as usual including clozapine plus either metformin or placebo. The dose of metformin will be titrated over a three-week period up to 2gm daily, as tolerated. Placebo dosing will be increased accordingly.

The study will be conducted across four Hospital and Health Service (HHS) Districts in South East Queensland: Metro North HHS, Metro South HHS, West Moreton HHS and Gold Coast HHS. Participants will be recruited with support of treating clinicians from inpatient units, clozapine clinics, community care units and community clinics.

### Study Population

The CoMET study will recruit 86 participants with schizophrenia or schizoaffective disorder who have commenced treatment with clozapine in the last two weeks. Participants will have a BMI between 18kg/$m^2$ and 40 kg/$m^2$. Participants will be excluded from the study if they have pre-existing diagnosis of T2DM, or are already taking metformin or any other weight lowering medications. The full inclusion and exclusion criteria are detailed in Appendix 1.

### Patient Screening and Enrolment

Clozapine is a highly monitored drug in Australia. Individuals must undergo a medical screening process prior to clozapine commencement, and once commenced on clozapine, they need to attend structured weekly medical appointments, with weekly biometric measurements and blood tests for the first 18 weeks of clozapine treatment. Thereafter patients are reviewed four-weekly as per existing clozapine protocol. For people newly commenced on clozapine in Australia, pre-registration with a clozapine manufacturer patient monitoring system is required.

This pre-registration requires the involvement of the hospital service clozapine coordinator and/or mental health pharmacist. Hence, the participating hospital service clozapine coordinator and pharmacists will be aware of all people being commenced on clozapine. The study team will liaise with the clozapine coordinators and mental health pharmacists to identify potential study participants. Potential participants who agree to being approached by the research team will be provided with written and verbal information about the study and invited to consider participation.

The study screening process will begin by assessing the capacity of all potential participants. Once potential participants are deemed to have capacity they will be thoroughly informed about the trial's components and requirements. If they wish to proceed, informed consent will be obtained and witnessed.

Previous research by members of our group found that in Queensland, approximately 8 people are newly commenced on clozapine per year per 100,000 catchment population[32]. The participating HHS cover a population of at least 2.5 million people, with an estimated 200 patients commenced on clozapine annually. With a conservatively estimated 30% study participation rate, 60 people could be commenced in the study annually.

Figure 1 documents the flow of participants from screening to follow-up.

**Allocation Concealment, Randomisation and Masking**

Participants will be randomised once written consent has been obtained and the study screening assessments have determined that the participant is eligible. Participants will be randomised to metformin (active treatment) or placebo in a 1:1 ratio using blocks of 4 via a computer-generated randomisation table. The treating team, participants and the research team will all be blinded to allocation of intervention. Randomisation will not be stratified by site. The randomisation list will be generated by an independent statistician not directly involved in the delivery of intervention or outcome assessment. The randomisation list will be provided to an independent pharmacy team at the Princess Alexandra Hospital. This pharmacy team will be the only service with the ability to unblind patients. Participants will be provided with a 24-hour contact number in case there is an emergent situation where it is crucial that medical staff know whether they are receiving metformin or placebo.

Allocation concealment will be maintained by using placebo tablets that are identical in packaging, appearance, colour and taste to the metformin tablets and by increasing the number of placebo tablets to match the titration of metformin. All other study assessments and procedures will be identical between the two groups.

**Treatment Protocol**

*Metformin Group*

Those in the metformin group will be provided with an extended release (XR) formulation of metformin with their evening meal for 24 weeks. Metformin XR 500mg tablets will be used. To reduce potential side effects metformin will be titrated as tolerated over a 3-week period with 500mg XR daily given the first week, 1000mg XR daily the second week and 2000mg XR daily for the remainder of the study. The titration regime will be discussed weekly with the co-ordinating principal investigator or delegate and the study endocrinologist or delegate. If 2000mg XR daily is not tolerated than participants will be given the maximum tolerated dose.

Participants will also receive treatment as usual. In keeping with Queensland Health standards of care for psychosis this may include individualised combinations of psychopharmacology, behavioural interventions, dietary advice, physical activity programs, rehabilitation and associated clinical services. Participant's engagement in dietary and physical activity programs will be recorded in the case files.

*Placebo Group*

Those in the placebo group will be provided with a daily dose of placebo with their evening meal for 24 weeks. The placebo tablets are identical to the metformin XR tablets. The dose will also be titrated as tolerated over 3 weeks with one tablet being given in the first week, then two tablets from week two and then four tablets from week three. If four tablets are not tolerated then participants will be given the maximum tolerated dose. Those in the placebo group will also receive treatment as usual.

Adherence will be monitored through return of unused tablets and tablet counts at each visit.

**Dose Justification**

In a recent meta-analysis, the mean metformin dose used in RCTs comparing metformin to placebo in people without T2DM who were prescribed clozapine ranged from 250mg to 1500mg[19]. Clinical recommendations for the use of metformin in T2DM suggest starting at 500mg and titrating up to 2000mg based on serial blood glucose measurements [33 34]. A study by Chiu et al [35] compared metformin doses of 500mg and 1000mg among people already obese on clozapine. They found a statistically significant reduction in body weight after 12 weeks in the 1000mg group but not the 500mg group. This suggests that a dose of at least 1000mg is required for consistent weight reduction in patients on clozapine. We have elected to use the maximum dose tolerated within the recommended dosing range of metformin XR (500-2000mg) to explore the maximum possible effect with metformin.

**Outcomes**

*Primary*

The primary outcome will be endpoint body weight in kilograms (kg) at 24 weeks, between the placebo and metformin groups.

*Secondary*

Secondary outcome measures are:

- Rate of conversion to T2DM (fasting 2 hour glucose tolerance test and HbA1c)
- Metabolic syndrome components[36] (waist circumference , fasting glucose, HDL, total cholesterol, triglycerides, and blood pressure ).
- Homeostatic model assessment (HOMA) of insulin resistance and secretion based on fasting glucose and insulin
- Diet and appetite (Food Craving Inventory)
- Physical activity (International Physical Activity Questionnaire (IPAQ) and Simple Physical Activity Questionnaire (SIMPAQ))
- Proportion with weight gain of 5% or more at endpoint versus baseline
- Dropout rates
- Quality of Life (Assessment of Quality of Life (AQoL))

A range of symptom, cognitive and plasma drug measures will also be examined to explore whether any group differences in endpoint weight can be attributed to differences in the following clinical assessments:

- Psychotic symptoms (Positive and Negative Syndrome Scale (PANSS))
- Psychosocial Function (Global Assessment of Functioning (GAF))
- Cognitive function (Brief Cognitive Assessment Tool for Schizophrenia (B-CATS), Test of Premorbid Functioning (TOPF) and California Verbal Learning Test (CVLT-II)
- Clozapine/Norclozapine levels and ratio

*Tertiary*

Collect DNA for future study into genetic biomarkers associated with weight gain with clozapine and/or response to metformin.

**Trial visits, Assessments and Outcome Measures**

Study visits and assessments, identical in both groups, will be conducted as per Table 1. Study visits will be weekly for the first four weeks and then every four weeks for the remainder of the study. The investigational product will be dispensed at every study visit. Physical measurements and adverse drug reaction monitoring will be conducted by the research team at every study visit. A range of validated clinical assessments (Table 1), will be conducted at weeks 4, 8, 12, 16, 20 and 24. Participants will have three blood tests during the study, at baseline and weeks 12 and 24. Every effort will be made to ensure that these blood tests coincide with mandatory blood tests for clozapine monitoring.

People with pre-existing T2DM, chronic kidney disease, and pregnancy will be excluded (Appendix 1 Inclusion and Exclusion Criteria). Pre-clozapine investigations will be ordered by the treating team, as part of the mandatory workup for clozapine, including fasting serum glucose, estimated glomerular filtrate rate (eGFR) and Beta Human Chorionic Gonadotropin (Beta HCG). This data will be used for the screening of participants. Vitamin B12 serum levels will be monitored at baseline, week 12 and week 24 as a rare side effect of metformin includes vitamin B12 deficiency.

Blood will also be collected at baseline for future DNA analysis. Participation in this part of the study is optional and separate consent will be sought.

All assessments will be conducted by trained members of the research team. In addition to the scheduled study visits, participants will be contacted regularly by the research trial team during the trial in an effort to improve adherence to the investigational product and increase retention rate. We will record use and dose of concomitant psychotropic medications.

All anthropometric measurements will be collected by the research trial team while participants wear light clothing, after the participants have emptied their bladder and removed their shoes. Height will be recorded at the screening assessment. At each visit, weight will be recorded to the nearest 0.1 kg using calibrated scales. Waist circumference will be measured in the horizontal plane to the nearest 0.5 cm using a non-stretchable measuring tape placed around the abdomen at a level halfway between the top of the iliac crest and the bottom of the ribs [37]. Hip circumference will be measured at the maximum circumference of the buttocks [37]. The Hip/Waist ratio is the ratio of hip circumference and waist circumference.

Pulse and blood pressure will be recorded after sitting for 5 minutes [38]. Blood pressure will also be recorded in the standing position after the participant has been standing for 2 minutes.

PANSS

The PANSS (Positive and Negative Syndrome Scale), a validated 30 item investigator rated measure, will be used to measure positive and negative symptoms of schizophrenia [39].

GAF

The Global Assessment of Functioning scale (GAF) is a validated investigator rated scale incorporating symptom severity, psychological, social, and occupational functioning on a scale from 0 to 100 [40].

IPAQ and SIMPAQ

The IPAQ (International Physical Activity Questionnaire) is a validated participant recall based measure of physical activity in the past week [41]. The SIMPAQ (Simple Physical Activity Questionnaire) is a participant recall based measure of physical activity in the past week that is specifically designed for people living with mental illness [42].

AQoL

The Assessment of Quality of Life (AQoL) is a validated instrument that measures 5 health dimensions: illness, independent living, social relationships, physical senses and psychological wellbeing, and can be used for economic evaluations [43].

Cognitive Assessments

TOPF

The Test of Premorbid Functioning (TOPF) is a revised version of the Wechsler Test of Adult Reading and is a measure of pre-morbid cognitive and memory functioning [44].

CVLT-II short form

The California Verbal Learning Test 2nd edition short form is a validated test of verbal learning and memory [45].

Brief Cognitive Assessment

The B-CATS (Brief Cognitive Assessment Tool for Schizophrenia) includes the Digit Symbol Substitution Test, Trail Making Test and Verbal Fluency Test. These test, respectively, complex processing speed, visual attention and task switching, and semantic fluency and strategy generation. The B-CATS is validated and has good reliability and consistency and can be delivered in around 10 minutes [46].

Food Craving Inventory

The Food Craving Inventory is a validated measure of food cravings, and is based on participant self-report. It has two scales, one for subjective cravings and the other for consumption of particular foods [47].

Data will be initially recorded on paper case report forms. Data will be checked by two independent members of the research team and thenentered into an electronic data management software program (RedCAP). All confidential data will be securely stored as per Good Clinical Practice guidelines.

**Statistical Methods**

*Sample Size*

We powered our study based on the primary outcome, body weight at 24 weeks, using the repeated measures ANCOVA approach. Sample size was estimated using data from a meta-

analysis of metformin for clozapine associated obesity conducted by our group [19]. To observe a minimal clinically difference in weight change of 3.12kg, assuming standard deviation (SD) of 9.6 in both groups (overall SD from the meta-analysis), $\alpha = 0.05$, and correlation between baseline and repeated measures of 0.7, we will require 34 participants per group to achieve 80% power. Allowing for an attrition rate of 20% from baseline to follow-up, we will need to recruit 86 participants across the four sites.

*Data analysis*

Analysis will be conducted according to intention-to-treat principle with participants analysed in the group they were originally allocated to regardless of treatment compliance. Baseline characteristics will be summarized using mean and standard deviation for continuous variables, and n (%) for categorical variables. The distribution of continuous variables, if skewed, where appropriate will be transformed using log-transformation. Baseline characteristics between the two groups will be compared using either the t-test (continuous data) or Chi-square test /Fisher's exact test (categorical data). The primary outcome, endpoint weight, will be analysed using a mixed model repeated measure model (MMRM). The MMRM is a superior approach in controlling for type I error and minimize bias as it does not impute or exclude participants with missing data [48]. We will include weight at baseline assessment, intervention group, visit and visit by intervention in the model. We will also test the sensitivity of our results by imputing for missing values in the primary outcome using multiple imputation. We will test for the impact of potential confounders, such as concomitant medications, on the results and adjust for these as appropriate. Results will be presented as mean difference along with 95% confidence intervals. Secondary outcomes will be analysed in a similar fashion using MMRM for normal outcomes or generalized linear mixed models for non-normal outcomes. Number needed to treat and number needed to harm will be calculated. All analyses will be conducted using SAS software, Version 9.4.[49]

**Participant Safety**

Metformin has been used extensively for the treatment of T2DM. It is well tolerated, with hypoglycaemic episodes very rare unless combined with other anti-hyperglycaemics [24]. There are no known pharmacokinetic interactions between metformin and clozapine. Previous studies exploring the tolerability of metformin in people with schizophrenia taking various

antipsychotics found that the reported side effects were very similar between the metformin and placebo groups [50].

The most common side effect of metformin is gastrointestinal disturbance which includes diarrhoea, flatus, nausea, abdominal discomfort, and reduced appetite [33]. Metformin associated gastrointestinal disturbance normally resolves in the first few weeks and can be reduced by using the XR formulation, taking metformin with the evening meal and titrating the dose slowly [33].

Other possible rarer side effects include taste disturbance, vitamin $B_{12}$ deficiency, lactic acidosis, and hepatobiliary disorders. Serious side effects including vitamin $B_{12}$ deficiency, lactic acidosis and hepatobiliary disorders are rare. Most cases of lactic acidosis have occurred in diabetic patients with significant renal failure and other risk factors [33]. We will monitor for the side effects by testing vitamin $B_{12}$ levels, electrolytes and liver function at baseline, week 12 and week 24.

The use of iodinated contrast materials concomitantly with metformin may be associated with nephropathy. Our participants' kidney function will be protected during the study by withholding metformin or placebo for 48 hours after intravenous contrast is administered[33].

Metformin is relatively safe even when taken in overdose. Despite ingestion of large amounts of metformin (up to 85g) hypoglycaemia has not been observed[33]. Lactic acidosis has been reported as a consequence of overdose in people with pre-existing T2DM[33]. Pre-existing T2DM is an exclusion criteria, and participants who develop T2DM during the study will be withdrawn. Any dose taken above the highest recommended daily dose of 2000mg will be considered an overdose and recorded and reported as a Serious Adverse Event (SAE). To reduce the risk of a serious overdose the investigational product will be dispensed weekly for the first 4 weeks and then every 4 weeks for the remainder of the study.

Participants will be assessed for possible adverse effects (AE's), at every study visit, including use of the Systematic Assessment for Treatment Emergent Events – Systematic Inquiry (SAFTEE-SI) tool [51]. AE can refer to serious and non-serious AE's. For this study, an AE is defined as any unfavourable and unintended sign (including abnormal laboratory findings), symptom, or disease (new or exacerbated) temporally associated with the use of a

medicinal product, whether or not considered related to the medicinal product. Medical and Surgical Procedures will not be classed as AE's. SAEs, as defined in Appendix 2 will be reported to the study monitor as soon as possible and to the reviewing ethics committee. Any serious, unexpected adverse events (SUSAR) that are causally related to the investigational product will be reported to the Australian Therapeutic Goods Administration (TGA) and other appropriate regulatory as per the applicable guidelines.

Safety outcomes will also be collected to assess the preliminary safety and tolerability of metformin. These include

- Number of dropouts between intervention and control arm
- Number of adverse drug reactions in the intervention and control arm
- Scores from a structured qualitative interview with participants about their experiences with study drug using the SAFTEE-SI
- Serum bicarbonate and lactate to assess for lactic acidosis
- Vitamin B12 levels to assess for Vitamin B12 deficiency

**Study Completion and Withdrawal**

Participants will be deemed to have completed the trial when they complete 24 weeks of dosing. Participants have the right to remove their consent and withdraw from the study at any time and this will be clearly discussed during the screening process. Participants who cease clozapine during the study period will be withdrawn from the study. In addition, participants may also be withdrawn by the investigator if they meet withdrawal criteria (Appendix 3).

Any participant withdrawn from the study will have their last observation carried forward in an intention to treat analysis.

**Reimbursement**

Participants will receive honorarium in the form of gift cards to the total value of $140, over the course of the study.

**Ethics and Dissemination**

The study will be carried out according to the Declaration of Helsinki, the NHMRC National Statement on the Ethical Conduct in Research involving Humans (2007) and the Notes for Guidance on Good Clinical Practice as adopted by the Australian Therapeutic Goods Administration (2000) (CPMP/ICH/135/95) and the ICH GCP Guidelines.

Ethics approval was granted by the Metro South Human Research Ethics Committee HREC/17/QPAH/538 - SSA/17/QPAH/565.

This study has Therapeutic Good Administration Clinical Trial Notification (2017-CTN-02935), and has been listed on the Australian and New Zealand Clinical Trials Registry (ACTRN12617001547336).

An independent Data Safety Monitoring Board will monitor safety data during the trial.

This study protocol has been devised in line with the SPIRIT guidelines [52] (see supplemental SPIRIT Checklist).

On study completion, results will be disseminated by peer reviewed publications and conference presentations, regardless of the findings. Manuscripts will be prepared in accordance with the CONSORT 2010 Statement[53]. Our findings will also be summarised in several brochures, including one designed for feedback to participants and hospital sites that participate in the study.

## Discussion

Clozapine is the most effective antipsychotic for treatment refractory schizophrenia but has the worst metabolic profile of all antipsychotics. Although there is evidence that some pharmacological interventions such as exenatide [54] and metformin [19] can reduce weight for people who are already obese taking clozapine, the magnitude of this reduction in weight gain is small. There is a critical need for evidence based therapies to avert the initial clozapine associated weight gain. To date there have been no randomised controlled trials examining the effectiveness of metformin to attenuate weight gain in patients newly commenced on clozapine.

This study will examine whether metformin can attenuate weight gain over a 24-week period when compared to placebo as its primary outcome. It will also examine whether metformin has an effect on the components of the metabolic syndrome, rates of conversion to T2DM, and changes to diet and exercise.

There are limitations inherent to randomized, placebo control trials, that apply here. The study population who enrol in this trial may not be generalizable to all people commencing on clozapine, nor can the findings for a trial of people commencing clozapine be translatable to other antipsychotic medications.

Reducing the metabolic burden of clozapine from commencement has the potential to reduce the risk of developing cardiovascular disease and T2DM. If efficacious and safe, metformin would be a relatively accessible, cost-effective intervention. Because weight gain is a major concern among people on clozapine, attenuation of weight gain can enhance self-image, adherence, and is thus likely to improve health outcomes and the quality of life of people living with schizophrenia. Ultimately, interventions that ameliorate weight gain in those with schizophrenia may also reduce the unacceptable high mortality and morbidity gaps between people living with schizophrenia and the general population.

Funding

The trial is funded in part from a NHMRC ECF APP1111136 awarded to DS, and a Royal Brisbane and Women's Hospital Project Grant awarded to DF, SP, DS and VM. The funding

sources had no role in the design, conduct or data analysis of the present study. The University of Queensland is the research sponsor and will be responsible for monitoring and indemnifying the trial. There are no stipulations on publication in place by any party.

Competing interests

AR has received speaker honoraria and travel grants from Astra Zenica, Boehringer Ingelheim, Eli Lilly, MSD, Novo Nordisk and Sanofi and has participated on advisory panels for MSD and Novo Nordisk. None of the other authors have conflicts of interest.

Authors' contributions

Dan Siskind, Anthony Russell, Andrea Baker and John McGrath conceived the study. All authors (Dan Siskind, Nadia Friend, Anthony Russell, John McGrath, Carmen Lim, Sue Patterson, Dylan Flaws, Terry Stedman, Vikas Moudgil, Savio Sardinha, Shuichi Suetani, Steve Kisely, Karl Winckel, Andrea Baker), contributed to the study design and planning. Nadia Friend prepared the first draft of the manuscript with Dan Siskind, Anthony Russell, Andrea Baker and John McGrath reviewing and amending early draft versions. Karl Winckel provided advice on study drug pharmacokinetics and pharmacodynamics. Carmen Lim provided statistical advice. The site PIs (Dan Siskind, Sue Patterson, Dylan Flaws, Terry Stedman, Vikas Moudgil, Savio Sardinha, Shuichi Suetani and Steve Kisely) assisted with guiding the protocol drafting in light of local site issues. All authors (Dan Siskind, Nadia Friend, Anthony Russell, John McGrath, Carmen Lim, Sue Patterson, Dylan Flaws, Terry Stedman, Vikas Moudgil, Savio Sardinha, Shuichi Suetani, Steve Kisely, Karl Winckel, Andrea Baker) edited and contributed to the final version of the manuscript, and all authors gave final approval to the submitted version.

For the clinical trial itself, Dan Siskind is the study chief investigator, Andrea Baker is the trial coordinator, and Dan Siskind, Sue Patterson, Dylan Flaws, Terry Stedman, Vikas Moudgil, Savio Sardinha, Shuichi Suetani and Steve Kisely are site principal investigators and will be actively involved in participant recruitment. Karl Winckel will provide pharmacological support and liaison with the dispensing pharmacy, Anthony Russell will provide endocrinology guidance during the course of the clinical trial. Carmen Lim will develop the statistical analysis plan, with support from Dan Siskind, Steve Kisely and John McGrath.

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**Table 1: Schedule of Visits and Assessments**

| VISIT | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|---|---|
| | **Screening** | **Baseline** | | | | | | | | |
| **WEEK** | | 0 | 2 | 3 | 4 | 8 | 12 | 16 | 20 | 24 |
| **Study medication period(24 weeks)** | | | | | | | | | | |
| **SCREENING AND CONSENT** | | | | | | | | | | |
| Assessment of current medication | x | x | x | x | x | x | x | x | x | x |
| Informed consent | x | | | | | | | | | |
| Ongoing capacity | x | x | x | x | x | x | x | x | x | x |
| Inclusion / exclusion criteria | x | | | | | | | | | |
| Beta HCG (females only) | x | | | | | | | | | |
| Drug dispensation (after randomisation) | | x | x | x | x | x | x | x | x | x |
| **SAFETY** | | | | | | | | | | |
| Adverse events | | | x | x | x | x | x | x | x | x |
| SAFTEE-SI | | x | x | x | x | x | x | x | x | x |
| Vitamin B12 | | x | | | | | x | | | x |
| **EFFICACY** | | | | | | | | | | |
| Height | x | x | | | | | | | | |
| Body weight | x | x | x | x | x | x | x | x | x | x |
| Waist circumference & hip/waist ratio | | x | x | x | x | x | x | x | x | x |
| Blood pressure | | x | x | x | x | x | x | x | x | x |
| Fasting glucose, insulin | | x | | | | | x | | | x |
| Fasting Cholesterol, HDL, LDL, Triglycerides | | x | | | | | x | | | x |
| HbA1c | | x | | | | | x | | | x |
| OGTT | | x | | | | | | | | x |
| **OTHER** | | | | | | | | | | |
| Heart Rate | | x | x | x | x | x | x | x | x | x |
| PANSS | | x | | | | | x | | | x |
| GAF | | x | | | | | x | | | x |
| SIMPAQ/IPAQ | | x | | | | | x | | | x |
| AQOL | | x | | | | | x | | | x |
| TOPF | | x | | | | | | | | x |
| CVLT-II short form | | x | | | | | | | | x |
| Symbol Digit | | x | | | | | | | | x |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Modalities Test | | | | | | | | | | |
| Controlled Oral Word Association Test | | x | | | | | | | | x |
| Trail Making Test | | x | | | | | | | | x |
| Food Craving Inventory | | x | | | | | x | | | x |
| **OTHER** | | | | | | | | | | |
| Drug compliance | | | x | x | x | x | x | x | x | x |
| Blood (other) - FBC (including WCC, Neutrophils), ELFT (including Serum bicarbonate and lactate) clozapine/nor clozapine levels | | x | | | | | x | | | x |

HCG – Human chorionic gonadotropin
SAFTEE-SI - Systematic Assessment for Treatment Emergent Events – Systematic Inquiry
HDL – High Density Lipoprotein
LDL – Low Density Lipoprotein
OGTT – Oral Glucose Tolerance Test
PANSS - Positive and Negative Syndrome Scale
GAF – Global Assessment of Functioning
IPAQ - International Physical Activity Questionnaire
SIMPAQ - Simple Physical Activity Questionnaire
AQoL - Assessment of Quality of Life
TOPF - Test of Premorbid Functioning
CVLT-II - The California Verbal Learning Test 2nd edition
FBC – Full Blood Count
ELFT – Electrolytes and Liver Function Tests

Figure Legend

Figure 1: Flow chart of the CoMET Trial

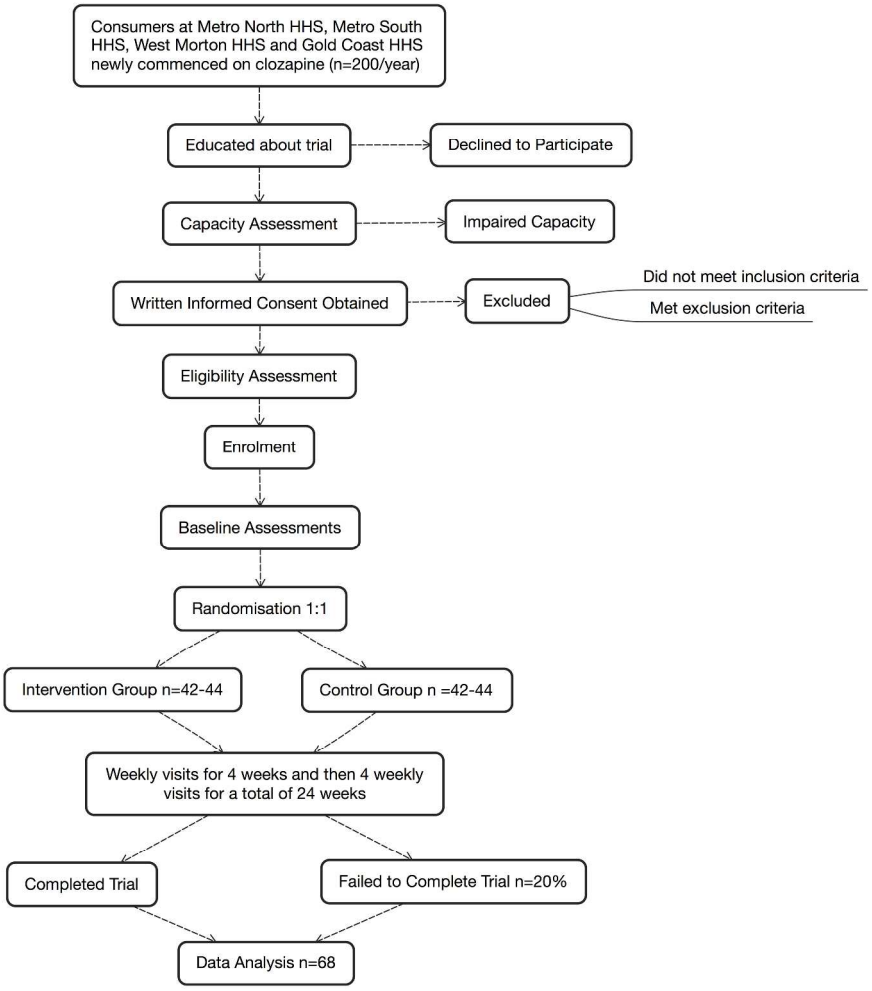


Figure 1

340x381mm (300 x 300 DPI)

Appendix 1 Inclusion/Exclusion Criteria

Inclusion Criteria

Patients will be invited to participate in the study if they meet all of the following criteria:

1. Aged between 18 and 64 years (inclusive)
2. Fulfil the DSM-IV criteria practice for schizophrenia or schizoaffective disorder, based on the Diagnostic Interview for Psychosis (DIP)
3. Have received oral clozapine for a period of no more than 2 weeks
4. Agree to participate, have capacity to consent and are able to follow the study instructions and procedures
5. Fasting Blood Glucose Level ≤6.0 mmols (confirmed within the previous two weeks of commencing clozapine)
6. BMI ≥18 and ≤40

Exclusion Criteria

Patients will be excluded from the study if they meet any one of the following criteria:

1. Known allergies to Metformin or any part of the formulation of the investigational product
2. Obesity induced by other endocrinologic disorder (e.g Cushing Syndrome, Hypothyroidism)
3. Current use of any weight-lowering therapy including: pramlintide, sibutramine, orlistat, zonisamide, topiramate or phenteremine (either by prescription or as part of a clinical trial)
4. Diagnosis of Type 1 or Type 2 Diabetes mellitus or already on metformin
5. Participants treated with corticosteroids or other hormone therapy (except oestrogens or thyroxine) for greater than 10 days (as they may lead to change in weight)
6. Chronic kidney disease (eGFR<60mL/min)
7. Previous surgical treatment of obesity
8. BMI ≤18 or BMI ≥40
9. Any concomitant disease or condition that according to the investigator's assessment makes the patients unsuitable for trial participation
10. People who are unable to understand or communicate in English
11. For female participants, those currently pregnant, or planning to become pregnant or lactating or no acceptance to the use of effective contraception during the study period
12. Inability to follow the study instructions and procedures

Appendix 2 SAE

Definition of a Serious Adverse Event (SAE)

A serious adverse event is any untoward medical occurrence that, at any dose:

a) results in death

b) is life threatening*

c) requires in-patient **hospitalisation or prolongation of an existing hospitalisation.

Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d) results in disability/incapacity, or

e) is a congenital abnormality / birth defect.

f) Any event deemed by the investigator as being a significant medical event.

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

** The term “hospitalisation” is the definition of a subject admitted to a hospital/inpatient (irrespective of the duration of physical stay), or not admitted to a hospital/not inpatient, but stays at the hospital for treatment or observation for more than 24 hours. Hospitalisations for administrative, trial related and social purposes do not constitute AEs and should therefore neither be reported as AEs or SAEs. Likewise, hospital admissions for surgical procedures planned prior to trial inclusion are not considered AEs or SAEs.

Appendix 3 Withdrawl Criteria

Participant Withdrawal by the Investigator

Participants will be withdrawn from the study by the Investigator, prior to completion of treatment, under the following conditions:

- Non-adherence with study medication for seven or more consecutive days
- Non-adherence with or self-ceased clozapine for 7 or more consecutive days
- Non-adherence of more than 50% of study medication on pill count.
- Clozapine ceased due to medical reasons with no planned re-challenge within 7 days of ceasing
- Development of a serious adverse event assumed to be associated with the study medication
- Cessation of effective contraception or confirmed pregnancy
- Development of T2DM
- Continual inability to provide informed consent

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | Item No | Description | Addressed on page number |
|---|---|---|---|
| **Administrative information** | | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | 1 |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry | 17 |
| | 2b | All items from the World Health Organization Trial Registration Data Set | |
| Protocol version | 3 | Date and version identifier | 2 |
| Funding | 4 | Sources and types of financial, material, and other support | 18 |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | 19 |
| | 5b | Name and contact information for the trial sponsor | 18 |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | 18 |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | 17 |

| | | | |
|---|---|---|---|
| **Introduction** | | | |
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | ____4-6____ |
| | 6b | Explanation for choice of comparators | ___4-6_____ |
| Objectives | 7 | Specific objectives or hypotheses | ___6_____ |
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) | ____7_____ |
| **Methods: Participants, interventions, and outcomes** | | | |
| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | _____7_____ |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | _7 and Appendix_ |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | ____9_____ |
| | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) | __9_____ |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | ____9_____ |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | _____9_____ |
| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | ____10_____ |
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | _____11_____ |

| | | | |
|---|---|---|---|
| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | 13 |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | 8 |
| **Methods: Assignment of interventions (for controlled trials)** | | | |
| Allocation: | | | |
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | 8 |
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | 8 |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | 8 |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | 8 |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | 8 |
| **Methods: Data collection, management, and analysis** | | | |
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | 11 |
| | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | 12 & 16 |

| | | | |
|---|---|---|---|
| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | 13 |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | 13-14 |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | 14 |
| | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | 14 |
| **Methods: Monitoring** | | | |
| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | 17 |
| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | |
| Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | 15 |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | |
| **Ethics and dissemination** | | | |
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | 17 |
| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | |

| | | | |
|---|---|---|---|
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | ___8_____ |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | _____ |
| Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | ____13____ |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | ___19_____ |
| Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | _____ |
| Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | _____ |
| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | ____17_____ |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers | _____ |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | _____ |
| **Appendices** | | | |
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates | _____ |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | _____ |

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.