**PROTOCOL TITLE**

The efficacy of Metformin as an adjunctive treatment to attenuate weight gain and metabolic syndrome in patients with schizophrenia or schizoaffective disorder newly commenced on clozapine

SHORT TITLE

CADENCE-CoMET

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**DOCUMENT HISTORY**

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| **Version** | **Date** | **Summary of change** |
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| 1.1 | 24 January 2018 | Removal of two exclusion criteria |
| 1.2 | 28 May 2018 | Addition of text to the study objectives and study design in the Protocol. Addition of staff member to the Protocol |
| 2.0 | 31 August 2018 | Addition of abdominal and brain MRI for Metro South and Metro North participants only |

**STUDY ACKNOWLEDGMENT/CONFIDENTIALITY**

By signing this Protocol, the Investigator(s) acknowledges and agrees:

The Protocol contains all necessary details for conducting the study. The Investigator will conduct this study as detailed herein, in compliance with Good Clinical Practice and the applicable regulatory requirements, 1 and will make every reasonable effort to complete the study within the time designated.

The Protocol and all relevant information on the drug relating to pre-clinical and prior clinical experience, which was furnished by the Sponsor (the University of Queensland) will be made available to all physicians, nurses and other personnel who participate in the conduct of this study. The Investigator will discuss this material with them to assure that they are fully informed regarding the drug(s) and the conduct of the study.

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The conduct and results of this study will be kept confidential. The results of this study may be published. Upon completion of the Study, it is the intention of the parties to prepare a joint publication regarding or describing the Study and all the results there from and both parties shall co-operate in this regard.

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**ABBREVIATIONS AND DEFINITIONS OF TERMS**

|  |  |
| --- | --- |
| AE | Adverse Event |
| ANCOVA | Analysis of Covariance |
| ATP | Adult Treatment Panel |
| CIB | Clinical Investigators’ Brochure |
| CRF | Case Report Form |
| CTN | Clinical Trial Notification |
| GCP | Good Clinical Practice |
| HHS | Hospital and Health Service |
| Hr | Hour |
| HREC | Human Research Ethics Committee |
| IEC | Independent Ethics Committee |
| IPCS | International Programme on Chemical Safety |
| NHMRC | National Health and Medical Research Council |
| NSAID | Non-steroidal anti-inflammatory drug |
| PI | Product Information |
| PK | Pharmacokinetic |
| SAE | Serious Adverse Event |
| SD | Standard Deviation |
| T2DM | Type 2 Diabetes Mellitus |
| TAU | Treatment as usual |
| TGA | Therapeutic Goods Administration |
| XR | Extended release |

# Introduction

Life expectancy for people with schizophrenia is 16.4 years shorter than for the general population1 with 35.1% of excess deaths attributable to cardiovascular disease and type 2 diabetes mellitus (T2DM).1 People with schizophrenia are at risk of developing cardio-metabolic disease for several reasons including a genetic predisposition to developing diabetes,2 reduced physical activity3, poor diet4, and the use of antipsychotic medications.5

Although antipsychotic medications are a core component of treatments for schizophrenia,6 approximately 20% of patients are treatment refractory, defined as non-response to adequate trials of at least two different antipsychotics.7 In this situation, clozapine is the most effective medication8 although, unfortunately, it is associated with the highest rates of metabolic syndrome of all antipsychotics. 5

Schizophrenia can lead to cognitive deficits, which do not always respond to treatment with antipsychotic medications.9 These cognitive deficits can impact capacity for meal planning10, and influence dietary choices, leading to a poor diet.4

Metabolic syndrome is defined as having at least three of five abnormal results from the following parameters: waist circumference (Men > 102cm, Women > 88cm), fasting glucose (5.6 mmol/l), High Density Lipoprotein (HDL) cholesterol (Men 1.04mmol/l, Women 1.29 mmol/l), Triglycerides (1.7 mmol/l), and blood pressure (≥130/≥85 mmHg).11 A recent meta-analysis reported that 51.9% of people on clozapine had metabolic syndrome compared to 28.2% for olanzapine and 27.9% for risperidone5. In a ten-year follow up of people commenced on clozapine in the USA, 43% developed diabetes with a mean weight gain of over 13.5kg.12

Although there is increasing evidence for the efficacy of physical activity interventions for people with schizophrenia3, poor rates of uptake remain a barrier to their effectiveness. As a result, there has been growing interest in other interventions such as oral medication.

Among users of all anti-psychotics, there is increasing evidence for metformin for the management of weight gain.13 Metformin is a biguanide antihyperglycaemic commonly used in the management of T2DM.14 It reduces fasting glucose and triglyceride levels while increasing high-density lipoprotein (HDL).15 Its antihyperglycaemic properties are mostly attributed to suppression of hepatic gluconeogenesis and increased peripheral insulin sensitivity14. It can lead to mild weight loss in people without diabetes who are not on antipsychotic medications.16

There is also evidence that metformin increases the production of Glucagon-like Peptide (GLP-1), an intestinal epithelium produced peptide, following food consumption.17 In turn, GLP-1 stimulates insulin secretion while inhibiting glucagon secretion, and also appears to regulate appetite by inducing satiety.18 Metformin’s role in GLP-1 regulation is of particular relevance for people on clozapine as clozapine disrupts the glucagon-like peptide (GLP-1) pathway in the intestinal epithelium, thereby reducing GLP-1 levels.19 As such, it is possible that metformin may have greater benefits for people on clozapine than for other anti-psychotics.

Although treatment or prevention of clozapine induced obesity is not a Therapeutic Goods Administration (TGA) indication for use of metformin, a recent meta-analysis showed that metformin can lead to a greater than 3kg weight loss among people already obese on clozapine.20 There is an absence of robust evidence for effective treatments to avert clozapine associated weight gain and metabolic syndrome when people are first commenced on clozapine.

This research protocol aims to examine the role of metformin to attenuate weight gain among people newly commenced on clozapine.

## Safety profile

Metformin Extended Release (XR) has been extensively used for the treatment of T2DM. It is well tolerated. The Diabex XR brand of Metformin XR will be used in this trial. The following adverse effects are described in the Diabex XR PI; 21

**Adverse Effects**

|  |  |  |  |
| --- | --- | --- | --- |
| **Disorder** | **Frequency** | **Symptoms** | **Additional information** |
| Gastrointestinal Disturbance | Very common (>1/10) | nausea, vomiting, diarrhoea, loss of appetite, abdominal pain and anorexia. | These are the most common side effects and often resolve spontaneously after a few weeks and can be reduced by slowly titrating the medication |
| Taste Disturbance | Common (≥ 1/100, <1/10) |  |  |
| Metabolism and Nutrition Disorders | Uncommon (≥ 1/1000, <1/100) Very Rare (< 1/10 000)  | decreased Vitamin B12Lactic Acidosis | Some reports of reduced TSH levels in patients with hypothyroidism |
| Skin and Subcutaneous Tissue Disorders | Very Rare (<1/10 000) | erythema, pruritis and urticaria |  |
| Hepatobiliary Disorders | not known |  | Isolated reports of liver function test abnormalities and hepatitis which resolved upon discontinuation of metformin |

Metformin can cause a metallic taste however this side effect is unlikely to be as common in clinical practice as the Diabex XR PI reports. Taste disturbance is very rarely mentioned in the literature in association with metformin. In fact, the Australian Medicines Handbook22 does not even mention taste disturbance as a side effect of metformin. The most common side effect of metformin mentioned in the literature is still gastrointestinal side effects. 5% of people cease metformin because they can not tolerate these side effects which include diarrhoea, flatus, nausea and abdominal discomfort.23 These side effects can be reduced by taking metformin with the evening meal and slowly increasing the dose. In addition, as mentioned in the PI, most of these side effects resolve in the first few weeks.

In regard to the combined use of metformin XR and clozapine: There are no known pharmacokinetic interactions between metformin and clozapine so they can be safely used together.22 The tolerability of the combination of metformin and antipsychotics was explored by Wu et al.24 They found that metformin was well tolerated in females with first episode schizophrenia taking various antipsychotics including clozapine. In addition, the side effects reported were very similar in the placebo and metformin groups.

**Contraindications** (As per Diabex XR Product Information) 21

• Hypersensitivity to metformin hydrochloride or to any of the excipients.

• Diabetic ketoacidosis, diabetic pre-coma.

• Renal failure or renal dysfunction (creatinine clearance < 60 mL/min).

• Acute conditions with the potential to alter renal function such as:

- Dehydration

- Severe infection

- Shock

- Intravascular administration of iodinated contrast agents (see Precautions)

• Acute or chronic disease which may cause tissue hypoxia such as:

- Cardiac failure

- Recent myocardial infarction

- Respiratory failure

- Pulmonary embolism

- Shock

- Acute significant blood loss

- Sepsis

- Gangrene

- Pancreatitis

 • Major surgery (see Precautions)

 • Severe hepatic insufficiency, acute alcohol intoxication, alcoholism.

 • Lactation, pregnancy.

**Precautions**

**Lactic acidosis**

As described in the PI, 21 Lactic acidosis is a rare, but serious (high mortality in the absence of prompt treatment), metabolic complication that can occur due to metformin accumulation. Reported cases of lactic acidosis in patients on metformin have occurred primarily in diabetic patients with significant renal failure. The incidence of lactic acidosis can and should be reduced by assessing other associated risk factors such as poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency and any condition associated with hypoxia.

**Diagnosis**

The risk of lactic acidosis must be considered in the event of non-specific signs such as muscle cramps with digestive disorders such as abdominal pain and severe asthenia.

Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain and hypothermia followed by coma. Diagnostic laboratory findings are decreased blood pH, plasma lactate levels above 5 mmol/L, and an increased anion gap and lactate/pyruvate ratio. If metabolic acidosis is suspected, metformin should be discontinued and the patient should be hospitalised immediately (see over dosage-Treatment).

In addition to the information from the PI it is also important to note that the Cochrane Database Systematic Review25 concluded there was no evidence from prospective comparative trials to show that metformin is associated with an increased risk of lactic acidosis, or with increased levels of lactate, compared to other anti-hyperglycaemic agents.

**Renal function**

As metformin is excreted by the kidney, it is recommended that creatinine clearance and/or serum creatinine levels be determined before initiating treatment and regularly thereafter:

• At least annually in patients with normal renal function,

• At least two to four times a year in patients with serum creatinine levels at the upper limit of normal and in elderly subjects.

Decreased renal function in elderly subjects is frequent and asymptomatic. Special caution should be exercised in situations where renal function may become impaired, for example when initiating antihypertensive therapy or diuretic therapy and when starting therapy with a non-steroidal anti-inflammatory drug (NSAID).

**Administration of iodinated contrast materials**

The intravascular administration of iodinated contrast materials in radiologic studies can lead to renal failure. This may induce metformin accumulation and may expose the patient to lactic acidosis. Therefore, metformin must be discontinued either 48 hours before the test when renal function is known to be impaired or from the time of the test when renal function is known to be normal; and may not be reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal (see Precautions-Interactions with other medicines).

**Surgery**

Metformin hydrochloride must be discontinued 48 hours before elective surgery. Therapy may be restarted no earlier than 48 hours following surgery and only after renal function has been re-evaluated and found to be normal.

**Other precautions**

• All patients should continue their diet with a regular distribution of carbohydrate intake during the day. Overweight patients should continue their energy-restricted diet.

• The usual laboratory tests for diabetes monitoring should be performed regularly.

• Metformin hydrochloride alone does not cause hypoglycaemia; however caution is advised when it is used in combination with other antidiabetic agents (sulphonylureas, glinides, insulin).

**Combinations Requiring Precautions for Use**

**Medicines with Intrinsic Hyperglycaemic Activity**

[E.g. glucocorticoids, thyroid products and tetracosactides (systemic and local routes), β2-agonists, danazol, chlorpromazine at high dosages of 100 mg per day and diuretics].

More frequent blood glucose monitoring may be required, especially at the beginning of treatment. If necessary, adjust the metformin dosage during therapy with the respective medicinal product and upon discontinuation.

**ACE-Inhibitors**

ACE-inhibitors may decrease the blood glucose levels. Therefore, dose adjustment of metformin hydrochloride may be necessary when such medicinal products are added or discontinued.

**Anticoagulants**

Metformin increases the elimination rate of vitamin K antagonists. Consequently, the prothrombin time should be closely monitored in patients in whom metformin and vitamin K antagonists are being co- administered. Cessation of metformin in patients receiving vitamin K antagonists can cause marked increases in the prothrombin time.

**Beta-blockers**

Co-administration of metformin and beta-blockers may result in a potentiation of the anti- hyperglycaemic action. In addition, some of the premonitory signs of hypoglycaemia, in particular tachycardia, may be masked. Monitoring of blood glucose should be undertaken during dosage adjustment of either agent.

**Calcium Channel Blockers**

Calcium channel blockers may affect glucose control in diabetic patients; regular monitoring of glycaemic control is recommended.

**Hypoglycaemic Agents**

Metformin alone does not cause hypoglycaemia; however, caution is advised when it is used in combination with other hypoglycaemic agents (sulfonylureas, glitinides, and insulin).

**Nifedipine**

A single-dose, metformin-nifedipine drug interaction study in normal healthy volunteers demonstrated that co-administration of metformin and nifedipine increased plasma metformin Cmax and AUC by 20% and 9%, respectively, and increased the amount of metformin excreted in the urine. Tmax and half-life of metformin were unaffected. Nifedipine appears to enhance the absorption of metformin. Metformin had minimal effects on the pharmacokinetics of nifedipine.

**Diuretics, especially Loop Diuretics**

May increase the risk of lactic acidosis due to their potential to decrease renal function.

**Cimetidine**

Reduced clearance of metformin has been reported during cimetidine therapy, so a dose reduction should be considered.

**Thyrotropin**

Reduction of thyrotropin (TSH) serum levels has been reported in diabetic patients with hypothyroidism when metformin therapy is initiated.

**Renal function**

Since Metformin XR has been approved further studies have suggested that it is safe to use in patients with moderately reduced renal function. Because of this post-approval clinical study the European Medicines Agency released updated recommendations on the 14th October 2016 advising that metformin is safe to be used in patients with moderately reduced kidney function (eGFR 30-59mL/min).26

To reduce the likelihood of patients experiencing adverse events during the study Diabex XR will be titrated over 3 weeks up to a dose of 2000mg. Patients with chronic kidney disease (eGFR<60mL/min) will also be excluded. If IV contrast is required, the study compound will be ceased and restarted 48 hours later.

## Rationale for the Use of Metformin

The current pharmacological and behavioural treatment approaches for reducing clozapine-associated weight gain are limited and inconclusive. A recent meta-analysis of 17 studies has found that adjunctive ziprasidone, sibutramine, modafinil, phenylpropanolamine or atomoxetine did not show benefit for clozapine-associated weight gain.27 Treatment with fluvoxamine, metformin and topiramate as adjunctive pharmacological agents are mildly effective to attenuate clozapine-induced weight gain, although data is based on one to three trials for each intervention and the reliability of available studies is limited by methodological limitations and small sample sizes.27 Use of topiramate and fluvoxamine is also limited by their adverse effect profile and concerns over the safety and tolerability of their combination with clozapine.27 Two studies report 16-weeks of treatment with orlistat has beneficial effects in decreasing body weight in men (2.36-2.39 kg) but not in women.28,29 Orlistat is poorly tolerated with more than 1% of users reporting flatus from dietary fat, faecal incontinence/urgency, oily fatty stools, headache and fatigue.22

A recent meta-analysis examined the effect of metformin vs placebo on weight gain and metabolic syndrome in people taking clozapine who did not have Diabetes Mellitus. They identified that metformin was superior to placebo in terms of weight loss (-3.12kg, 95%CI -4.88kg to -1.37kg) and BMI (-1.18kg/m2, 95%CI -1.76kg/m2 to -0.61kg/m2).20 This meta-analysis also found that metformin significantly improved three out of the five components of the metabolic syndrome; waist circumference, fasting glucose and triglycerides. Whilst these results are promising there are many patients taking clozapine who have gained considerably more weight than this. In an American study with a 10 year follow of clozapine users, 43% patients developed diabetes and the mean weight gain was 13.5kg.12 Because of the numerous detrimental adverse effects associated with being overweight and the metabolic syndrome, it would be beneficial to patients with schizophrenia if weight gain could be prevented. To date, no study has examined the effects of any medication on the prevention of weight gain in patients who are newly commenced on clozapine. This study aims to explore whether co-commencement of metformin with clozapine in patients with schizophrenia will attenuate weight gain and metabolic syndrome.

The physiological mechanisms underlying clozapine-induced weight gain remain unclear; however, recent rat models suggest that the incretin hormone, glucagon-like peptide 1 (GLP-1) may play a role. GLP-1 decreases glucagon secretion, stimulates insulin secretion, delays gastric emptying and lowers food intake.18 In an obese rat model, clozapine acutely reduced GLP-1 production.30 Consequently, clozapine induced a preference for high fat, high sugar foods in rats, leading to obesity and additive impairments in glucose tolerance. GLP-1 agonists have been shown to reduce food intake and cause weight loss in people with and without T2DM.17 Metformin has been shown to increase GLP-1 and also to decrease food intake in pre-clinical and clinical trials.17 Thus it has been hypothesised that metformin’s effect on weight gain is mediated by GLP-1.This may explain why it is effective in reducing weight gain in patients receiving clozapine.

Therefore, in consideration of this data and the physiological mechanism of action, the use of metformin may represent a novel approach to preventing weight gain in overweight patients newly commenced on clozapine.

Whilst clozapine is the antipsychotic with the most propensity for weight gain, olanzapine also has a high propensity for weight gain. A Cochrane review identified that clozapine caused the most weight gain with olanzapine coming in second when compared to other atypical antipsychotics.31

# Objectives

Using a randomised, placebo-controlled, double blind parallel trial design; the primary objective in this study is to examine the clinical efficacy of add-on treatment of metformin to attenuate weight gain among clozapine naïve people who are newly commenced on clozapine or people who have not used clozapine in the last 12 months.

## Primary Objectives

To determine if 24 week treatment of metformin (2000mg once daily) versus placebo will attenuate weight gain compared to individuals taking placebo, adjusted for baseline weight (Analysis of Covariance-ANCOVA).

## Secondary Objectives

To determine if 24 week treatment of Metformin versus placebo has comparative changes in: rate of conversion to T2DM (fasting 2hr glucose tolerance test and HbA1c), development of metabolic syndrome or its components (waist circumference, fasting glucose, High Density Lipoprotein (HDL), Low Density Lipoprotein (LDL),Body Mass Index (BMI), triglycerides, blood pressure, hip waist ratio), insulin resistance as measured by homeostatic model assessment (HOMA) using fasting glucose and insulin, liver function tests, clozapine/norclozapine ratio, heart rate, diet and appetite (Food Craving Inventory), physical activity (SIMPAQ and IPAQ), proportion with weight gain of 5% or more at endpoint versus baseline, Global Assessment of Function (GAF), Positive and Negative Syndrome Scale (PANSS) and rates of drop out between the groups.

## 2.3 Tertiary (Exploratory) Objectives

To collect DNA for future collaboration studies related to metabolic syndrome changes from baseline to endpoint in those on active treatment.

We will test cognition at baseline and at 24 weeks. We hypothesis that people with more greatly impaired cognition may have more difficulty making healthy food and exercise choices, and as such, this may moderate weight gain.

## 2.4 Safety Objective

To assess the preliminary safety and tolerability of Metformin daily for 24 weeks for people with schizophrenia or schizoaffective disorder newly commenced on clozapine.

Outcomes will be:

a. number of dropouts between the intervention and control arm

b. number of adverse drug reactions in the intervention and control arm

c. scores from a structured qualitative interview with participants about their experience with study drug using the Systematic Assessment for Treatment Emergent Events – Systematic Inquiry (SAFTEE-SI).

d. serum bicarbonate and lactate for evidence of lactic acidosis

e. B12 deficiency

# Study Design

The design is a randomised, placebo-controlled, double-blind parallel trial to examine the clinical efficacy of add-on treatment of metformin to attenuate weight gain among clozapine naïve people who are newly commenced on clozapine or people who have not used clozapine in the last 12 months. The study will include 86 individuals with schizophrenia or schizoaffective disorder newly commenced on clozapine.

Participants will be given as tolerated either 2g/d (titrated 500mg week one, 1g week two, 2g for duration of study) of metformin or placebo in addition to their normal routine care. Routine care is defined as 'individualized combinations of psychopharmacology, behavioural interventions, rehabilitation and associated clinical services in keeping with Queensland Health standards of care'.

Initially participants will be seen weekly for the first 4 weeks for physical observations and to assess any adverse reactions to trial medication titration. Face to face clinical assessments and physical measures will be at baseline (week 0) and weeks 4, 8, 12, 16, 20 and 24. Randomisation will be carried out using a computer-generated randomization table blocked in groups of four. Participants will receive either the intervention or placebo in a 1:1 ratio.

# Study Population

Eighty-six (86) participants will be recruited through mental health services (i.e. inpatient units, clozapine clinics and continuing care units) in four Queensland Hospital and Health Services: (a) Metro North HHS, (b) Metro South HHS, (c) West Moreton HHS, (d) Gold Coast HHS.

## Number of participants

The study will consist of a total of 86 participants.

## 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)

1. 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)
2. Diagnosis of Type 1 or Type 2 Diabetes mellitus or already on metformin
3. Participants treated with corticosteroids or other hormone therapy (except oestrogens or thyroxine) for greater than 10 days
4. Chronic kidney disease (eGFR<60mL/min)
5. Previous surgical treatment of obesity
6. BMI ≤18 or BMI ≥40
7. Any concomitant disease or condition that according to the investigator’s assessment makes the patients unsuitable for trial participation
8. People who are unable to understand or communicate in English
9. 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
10. Inability to follow the study instructions and procedures

# Participant Information and Informed Consent

Consent will only be obtained from patients who are deemed to have capacity to provide informed consent. Capacity will be determined by collaboration between the treating clinician and delegated research assistant and will comply with the guidelines within the NHMRC National Statement on Ethical Conduct in Human Research 2007.

During the consenting process, all participants will be informed that they have the right to withdraw consent from the study at any time without prejudice and withdrawal from the study will not affect their current or future care. Revocation of consent forms will be completed for those participants who choose to withdraw from the study.

## Screening assessment

After verbal consent is provided, an assessment of inclusion/exclusion criteria will commence. Participants who meet all inclusion criteria and none of the exclusion criteria will be invited to participate in the study and the formal consent process will commence. For those who consent to participate, they will be enrolled in the study and randomized.

As part of the Cadence clinical trials platform, we wish to acknowledge and respect potential participants’ enthusiasm and interest in research. Thus, individuals who do not meet the inclusion criteria for Cadence studies are invited to be registered on the Queensland Centre for Mental Health Research (QCMHR) participant data register. A separate patient information consent form will be provided to those participants who are interested in this option.

# Study Assessments and Procedures

A battery of validated clinical measures, physical health measures (blood pressure, heart rate, waist circumference, hip waist ratio, height, weight and BMI) will be conducted at baseline, weeks, 4, 8, 12 and 16, 20 and 24. Adverse events will be conducted at weeks 4, 8, 12, 16, 20 and 24. Physical health measures and assessment of adverse drug reactions will be conducted weekly for the first 4 weeks whilst titration of trial medication occurs.

**Efficacy measures include:**

Weight will be used as the primary outcome measure.

Secondary outcome measures will include the following:

* rate of conversion to T2DM (fasting 2 hour glucose tolerance test and HbA1c)
* metabolic syndrome components (waist circumference, HbA1c, fasting glucose, HDL, LDL, triglycerides, blood pressure, hip waist ratio)
* homeostatic model assessment (HOMA) of insulin resistance and secretion based on fasting glucose and insulin
* metabolic bloods and liver function tests
* diet and appetite (Food Craving Inventory)
* proportion with weight gain of 5% or more at endpoint versus baseline

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.

Abdominal and brain MRI scans

We aim to recruit 10 participants from Metro South and Metro North (only) to participate in a brain and abdominal MRI which will be conducted at baseline and week 24. The scans do not involve any form of contrast medium and is an optional extra intervention to this study.

Although change in weight is an important marker of cardiovascular risk, it is important to identify changes in metabolically active adiposity e.g. visceral adipose tissue (VAT) and hepatic steatosis (HS), relative to storage adiposity e.g. subcutaneous fat (SC). MRI provides the most accurate direct measure of cross-sectional areas and volumetric measures of VAT and SC and HS. VAT and HS are both predictive of cardiovascular risk, including strong prediction of vascular inflammation independent of other cardiovascular risk factors. It has a strong association with metabolic syndrome in patients with schizophrenia and insulin resistance specific to people on clozapine compared with other measures of weight/body mass. HS decreases 50% following a 5% decrease in body mass, is sensitive to pharmacology treatment and is predictive of cardiovascular risk.

Metformin has been proven to protect a variety of cells from stress. Both GABAergic and glutamatergic brain circuits modulate hypothalamus-pituitary-adrenal (HPA)-axis activity, and stress in turn affects glutamate and GABA levels. Prefrontal cortices, including the anterior cingulate cortex (ACC) contribute to stress perception and regulation.

This feature of the study will be clearly outlined in the consent form. In the event that a person objects to the abdominal and brain MRI they will not be excluded from participating in the trial.

## Biomarkers

We will be collecting peripheral blood at baseline for DNA analysis, to examine putative genetic markers associated with change in weight among trial participants. We will genotype using the Infinium Omni2.5-8 (Illumina Inc.) which will genotype over 2 million common SNP variants for each participant. This comprehensive genomic profiling will allow us to examine SNP associations with any metformin-associated weight loss for each participant.

The remainder of the blood sample will be stored indefinitely for future research. However, future studies involving the stored blood samples will require approval from a Human Research Ethics Committee. This feature of the study will be clearly outlined in the consent form, and participants will be informed that DNA and sera samples may be used in future years by national and international collaborative, after approval from a Human Research Ethics Committee.

In the event that a person objects to any biological samples being collected and stored, they will not be excluded from participating in the trial.

**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 |   |   |   |   |   |   |   |   |   |
| Urine pregnancy test (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 |
| 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 HDL, LDL, Triglycerides, Total Cholesterol |   |  x |   |   |   |   |  x |   |   |  x |
| HbA1c  |   | x |   |   |   |   | x |   |   | x |
| OGTT |   | x |   |   |   |   |   |   |   | x |
| **OTHER** |   |   |   |   |   |   |   |   |   |   |
| Heart Rate |   | x |  x |  x |  x |  x | x |  x |  x | x |
| PANSS TOTAL SCORE |   | 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 Modalities Test |   | x |   |   |   |   |  |   |   | x |
| 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 (WCC, Neutrophils) ELFT, (Serum bicarbonate) part of routine ELFT and lactateclozapine/nor clozapine levels |   | x |   |   |   |   | x |   |   | x |

**Assessment schedule can vary plus or minus five days for operational convenience**

## Study Procedures

Dispensing of trial medication to participants will occur once consent has been obtained and after the screening phase and randomisation has occurred. A delegated Research Pharmacist at the Princess Alexandra Hospital will dispense medication for all sites. For each randomised participant, the entire 24 weeks of study medication will be provided to QCMHR delegated research staff. The study medication will then be distributed to the participant initially on a weekly basis for the first 4 weeks while titration occurs and then monthly basis by delegated research staff in line with this protocol (section 7.4). There will be a total of 9 dispensations per participant.

## Study Restrictions

There are no additional restrictions (apart from previously documented exclusion criteria) to participants during the study in terms of concomitant medications, exercise or ambulation.

If a participant develops T2DM at week 12 based on results from the HbA1c, the participant will be unblinded, withdrawn and referred back to the treating team for ongoing management.

## Safety Assessments

All patients recruited in this study will be active cases at Queensland Hospital and Health services. The study team will liaise with clinical staff to ensure that participants have undergone a routine physical health screen as part of clozapine commencement.

**6.4.1 Adverse Events**

The Investigator and designated study personnel will monitor each participant for adverse events during the study. All adverse events reported between consent and final follow-up visit will be recorded in the case report form (CRF). The investigator or designee will ask the participant non-leading questions in an effort to detect adverse events e.g. “Have you felt unwell or different in any way since your last visit”.

In addition, participants will be encouraged to spontaneously report any unusual feelings or sensations. See Section 8 for full details on adverse event reporting.

### 6.4.2 Other Safety Assessments

BHCG is routinely conducted as part of clozapine commencement. If this has not been completed and the participant is of child-bearing potential and sexually active, urine pregnancy tests will be conducted at baseline or when clinically appropriate.

### 6.4.3 Pharmacokinetics

Metformin XR has been extensively used clinically. As such the pharmacokinetics have already been thoroughly investigated and therefore pK data will not be collected during this study.

The following information on pharmacokinetics has been taken from the product information for Diabex XR.21

**Pharmacokinetics**

**Absorption**:

After an oral dose of the extended release tablet Diabex XR 500, metformin absorption is significantly delayed compared to the immediate release tablet with a Tmax at 7 hours (Tmax for the immediate release tablet is 2.5 hours).

Steady state bioequivalence data of Diabex XR 750 and of Diabex XR 1000 are not available.

The bioequivalent products show the following properties:

At steady state, similar to the immediate release formulation, Cmax and AUC do not increase in proportion with the administered dose. The administration of two, three, or four tablets Diabex XR 500 (500 mg tablets) results in a 1.8, 2.4, and 3.0 increase for Cmax  and a 2.0, 2.7, and 3.2 fold increase in AUC.

The AUC after a single oral administration of 2000 mg of metformin extended release tablets, administered as four tablets of 500 mg Diabex XR 500, is similar to that observed after administration of 1000 mg of metformin immediate release tablets twice daily.

Intrasubject variability of Cmax and AUC of metformin extended release is comparable to that observed with metformin immediate release tablets.

Although the AUC is decreased by 30% following single dose administration of Diabex XR 500 administered as four tablets of 500 mg in fasting conditions, both Cmax and Tmax are unaffected.

Metformin absorption from the extended release formulation is not altered by meal composition.

No accumulation is observed after repeated administration of up to 2000 mg of metformin administered as four tablets of 500 mg Diabex XR 500.

**Distribution:**

Plasma protein binding is negligible. Metformin partitions into erythrocytes. The blood peak is lower than the plasma peak and appears at approximately the same time. The red blood cells most likely represent a secondary compartment of distribution. The mean volume of distribution Vd ranged 63– 276 L.

**Metabolism**:

Metformin is excreted unchanged in the urine. No metabolites have been identified in humans.

**Excretion**:

Renal clearance of metformin is > 400 mL/min, indicating that metformin is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent terminal elimination half-life is approximately 61⁄2 hours. When renal function is impaired, renal clearance is decreased in proportion to that of creatinine and thus the elimination half-life is prolonged, leading to increased levels of metformin in plasma.

Please refer to the product information for Diabex XR in Appendix A for more information on the pharmacokinetic parameters from healthy volunteers.

## Pharmacodynamics

Metformin XR has been extensively used clinically. As such the pharmacodynamics have already been thoroughly investigated and therefore pharmacodynamic samples will not be collected during this study.

## The following information on pharmacodynamics is taken from the product information for Diabex XR: 21

Diabex XR 500 is an oral anti-diabetic agent. Metformin is a biguanide with antihyperglycaemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia.

Metformin may act via 3 mechanisms:

1) Reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis.

2) In muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilisation.

3) Delay of intestinal glucose absorption.

Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase.

Metformin increases the transport capacity of all types of membrane glucose transporters (GLUT).

In humans, independently of its action on glycaemia, metformin has favourable effects on lipid metabolism. This has been shown at therapeutic doses in controlled, medium-term or long-term clinical studies: metformin reduces total cholesterol, LDL cholesterol and triglyceride levels.

In regards to the unapproved TGA indication for the prevention of weight gain in overweight patients newly commenced on clozapine; there has not been any nonclinical or clinical studies to date that have examined metformin’s ability to prevent clozapine induced weight gain. Smith et al30 identified that clozapine reduces GLP-1 production in rats, resulting in preference for high fat diet and weight gain. GLP-1 decreases glucagon secretion, stimulates insulin secretion, delays gastric emptying and lowers food intake.18 Metformin has exhibited an opposite effect on GLP-1. In vitro studies have indicated that metformin inhibits the degradation of GLP-1.17 This suggests that metformin is able to prevent clozapine induced weight gain via its GLP-1 mediated effects on appetite.

Metformin’s ability to reduce appetite has been demonstrated in a number of animal trials. Matsui et al32 found that metformin reduced the consumption of a high fat diet for 2 hours after a single dose in mice.Elevated GLP-1 levels were found in the mice 1 hour after the metformin was given. After nine weeks of treatment the metformin treated mice consistently consumed less of the high fat diet and lost weight when compared to the control mice. Rouru et al33 found that after one and two weeks of treatment with metformin genetically obese Zucker rats consumed less food and lost weight compared to controls. The effect was stronger in obese rats compared to lean rats.

## These results have been carried over into clinical studies and several studies have demonstrated that metformin can reduce food intake and increase GLP-1 in humans.17

# Investigational Product

## Description of Investigational Product

Active: Diabex 500mg XR commencing at 500mg per day taken orally at night with food for the first week. The dose of metformin will be increased as tolerated to 1000mg at week 2 and 2000mg at week 3, up to a maximum of four 500mg Diabex XR tablets (2000mg) for the duration of the study.

Placebo: Patients in placebo arm will also be given one tablet in the first week and increased to 2 tablets in week 2 and 4 tablets in week 3 as tolerated up to a maximum of four tablets for the duration of the study.

## Dose Justification

In a recent meta-analysis the mean metformin dose used in randomised controlled trials (RCT’s) that compared metformin to placebo in people without diabetes mellitus who were on clozapine ranged from 250mg to 1500mg.20 Many RCT’s studying the effects of metformin on antipsychotic induced weight gain have begun with a daily dose of 500mg and titrated the dose if tolerated to 1000-1500mg.24, 34, 35, 36, 37, 38 This is consistent with the recommended dosing range for treatment of T2DM. The product information for Diabex XR suggests starting at 500mg and titrating up to 2000mg based on serial blood glucose measurements.21 A study by Chiu et al36 compared metformin doses of 500mg and 1000mg in clozapine-treated schizophrenia patients. 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 therapy.

Based upon these studies and the product information recommendations the starting dose of diabex XR will be 500mg per day taken orally at night with food. The dose will be titrated as tolerated by 500mg in the first week, 1000mg in week 2 and 2000mg in week 3, with a maximum of 2000mg for the duration of the study.

## Comparator Justification

This study will use a placebo adjunct to routine care (routine care in this study is defined as 'individualized combinations of psychopharmacology, behavioural interventions, rehabilitation and associated clinical services in keeping with Queensland Health standards of care for psychosis’) as a comparator condition. The Declaration of Helsinki affirms that placebo-controlled trials should only be used in the absence of existing proven therapy.39 Therefore the use of an adjunct therapy has been selected to ameliorate these ethical concerns as both the experimental and control groups will receive standard medical care (Treatment as Usual).

## Administration

Metformin – diabex XR 500mg tablets will be used in the study.

Placebo – identical appearing tablets (containing Microcrystalline Cellulose, Colloidal Silicon Dioxide, Sodium Starch Glycolate, Sodium Stearyl Fumarate) will be used in the study.

## Randomisation Procedure

Participants will be randomised once written consent has been obtained and the baseline assessments have been completed. Participants will be randomised to one of the treatment groups, using blocks of 4 via a computer-generated randomization table. Participants will receive either active treatment or placebo in a 1:1 ratio.

The investigational products will be manufactured in accordance with current Good Manufacturing Practice (GMP) in a suitable TGA licensed facility. Princess Alexandra Hospital Pharmacist will hold the randomisation code, and provide a 24 hour number to unblind participants if required. Participants will be randomised strictly using a chronological process. Participants will be allocated a unique identification number which will be linked to the specific site number. If a participant withdraws from the study then the participant number will not be re-used nor will the participant be allowed to re-enter the study.

The randomisation will be double-blind. An independent Biostatistician will generate the randomisation list which will be provided to the Princess Alexandra Hospital Pharmacist. The independent Princess Alexandra Hospital Pharmacist will hold the closed randomisation list and be the only one who has the ability to unblind. In the case of emergency where it is crucial the medical staff knows whether the participant is on metformin or placebo, participants will be provided with contact information (i.e. 24 hour number) for unblinding.

## Frequency of visits and follow up

The majority of clozapine initiation takes place as an inpatient. Research staff will initially conduct weekly visits for the first four weeks to assess physical measures and any identified adverse drug reactions related to the titration of the trial medication. The titration regime will be discussed weekly with the Coordinating Principle Investigator or delegate and the Endocrinologist or delegate.

Repeated measures which include clinical assessments and physical measures which will be conducted at baseline, week 4, 8, 12, 16, 20 and 24. Participants will be regularly telephoned during the trial to enhance retention. Refer to Table 1 Schedule of Visits and Assessments.

## Blinding and Unblinding Procedure

All medication will be blinded to the study personnel and the patient. Metformin and placebo tablets will be identical in packaging, appearance, colour and taste. Treatment allocations will not be disclosed to the Investigator or any study personnel before the database is locked, unless in the case of an emergency requiring unblinding. Unblinded participants will be withdrawn from the study.

In the event of a medical emergency which the investigator feels cannot be adequately managed without knowing the identity of the study medication, will the treatment code be unblinded for a particular participant. If a participant develops T2DM at week 12 based on results from the HbA1c then the participant will be unblinded and referred back to the treating team for ongoing treatment.

This will be done by the Princess Alexandra Hospital Pharmacist via the 24 hour number. All cases of emergency unblinding will be documented on a Serious AE Form and reported to The University of Queensland (Sponsor) within 24 hours.

After the completion of all participants in the study (last patient last visit), participants will be notified which arm of the study they took part in.

## Product Labelling

The labelling of study medication will comply with local regulatory GCP and TGA requirements and medication dispensing guidelines.

## Handling and Storage of Study Drugs

Prior to dispensing, all study medication will be kept securely locked, in a dry, restricted access location at room temperature (20-25°C). Only delegated members of the study team will have access to the investigational products.

## Accountability

The designated Research Pharmacist will dispense study medication into the care of the delegated research staff, who will then sign that he/she has received the study medication for the study. The study drug will be kept in a securely locked area and provided to the participants according to the protocol (section 7.4). Participants will be requested to return all unused study medication (i.e. unopened bottles or tablets not taken) and empty bottles to the delegated research assistants. All unused supplies of study medication will be accounted for and documented by the designated Research Pharmacist. Compliance with study medication will be calculated at each visit by means of self-report and a tablet count. This data will be used to calculate compliance with medication for analysis purposes.

All material supplied is for use only in this clinical study and should not be used for any other purpose. The Investigator is responsible for investigational product accountability, reconciliation and record maintenance. In accordance with all applicable regulatory requirements, the Investigator or designated site staff will maintain investigational product accountability records throughout the course of the study. These persons will document the amount of investigational product received from the Manufacturer, the amount supplied and/or administered to and returned by participants.

An investigational product dispensing Log will be kept current and will contain the following information:

* the identification of the participant to whom the drug was dispensed;
* the date(s) and quantity of the drug dispensed to the participant.

The inventory will be available for inspection by study monitors during the study. Drug supplies including participant returns will be collected at the end of the study by the study monitor, returned by the Investigator or designee to the sponsor or authorised for destruction. When requested in writing by the Sponsor, unused drug supplies may be destroyed by the Investigator or delegate provided such disposition does not expose humans to risks from the drug. Records will be maintained by the Investigator of any such alternate disposition of the investigational product. These records will show the identification and quantity of each unit disposed of, the method of destruction (taking into account the requirements of local law), and the person who disposed of the investigational product. Where investigational product is destroyed on-site, a record of destruction will be issued. Such records will be submitted to the Sponsor for reconciliation purposes.

# Adverse Events (AE) and Serious Adverse Events (SAE)

The investigator will be responsible for the detection and documentation of events meeting the criteria and definition of an adverse event (AE) or a serious adverse event (SAE) as provided in section 8.1. During the study, when there is a safety evaluation, the investigator or delegated research staff will be responsible for detecting AEs and SAEs, as detailed in this section of the protocol.

## Definition of an Adverse Event (AE)

Any untoward medical occurrence in a participant or clinical investigation participant, temporarily associated with the use of a medicinal product, whether or not considered related to the medicinal product.

For the current study, an AE is defined as any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Examples of an AE **include**:

* Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
* New conditions detected or diagnosed after investigational product administration even though it may have been present prior to the start of the study.
* Signs, symptoms, or the clinical sequelae of a suspected interaction.
* Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational product or a concurrent medication (overdose *per se* should not be reported as an AE/SAE).
* Acute episode of psychosis

Examples of an AE **do** **not include** a/an:

* Medical or surgical procedure (e.g. endoscopy, appendectomy); the condition that leads to the procedure is an AE.
* Situations where an untoward medical occurrence did not occur (social and/or convenience admission to hospital).

In this study, AEs may include the following documented side effects: nausea, vomiting, diarrhoea abdominal pain, loss of appetite, taste disturbance, allergic reactions.

The term AE is used to include both serious and non-serious AEs.

## 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.

Medical and scientific judgement will be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

In this study, psychiatric hospitalisations would be an SAE as it requires hospitalization – but this will not be reported to HREC, as this is an expected event during the course of a patient’s illness and is unlikely to be related to the investigational product.

## Clinical Laboratory Abnormalities and Other Abnormal Assessments as AE’s and SAE’s

Deterioration as compared to baseline in protocol-mandated laboratory values and vital signs should only be reported as AEs if they fulfill any of the SAE criteria or if they are medically relevant (ie. symptomatic, require corrective treatment or are the reason for discontinuation of treatment with the investigational product). Hypoglycaemic episodes (based plasma glucose concentrations or self- report) will be recorded as per section 6.4.1.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (e.g., anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE. Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

## Time Period, Frequency, and Method of Detecting AEs and SAEs

All adverse events will be recorded between the time of consent and the final visit (week 24). Each Participant will be monitored regularly by the investigator and study personnel for adverse events occurring throughout the study. The research assistant will enquire about AEs by asking the following non-leading questions:

At the first scheduled visit (pre-dosing) participants will be asked:

*“How are you feeling?”*

At subsequent scheduled visits, participants will be asked:

*“Since your last visit, have you had any health problems?”*

## Recording of AEs and SAEs

When an AE/SAE occurs, the investigator or delegate will review all documentation (e.g. hospital progress notes, laboratory, and diagnostic reports) relative to the event. The investigator or delegate will then record all relevant information regarding an AE/SAE in to the CRF.

For each adverse event, start and stop dates, action taken, outcome, intensity (see Section 8.7.1) and relationship to study product (causality) (see Section 8.7.2) will be documented. If an AE changes in frequency or intensity during a study, a new entry of the event will be made in the CRF.

All details of any treatments initiated including concomitant medications due to the adverse event will be recorded in the Case Report Form (CRF).

## Prompt Reporting of SAEs

Once an investigator becomes aware that an SAE has occurred in a study Participant, he/she will immediately notify the University of Queensland (sponsor) by contacting the study monitor via telephone to notify him/her of the event. The SAE form must be completed as thoroughly as possible with all available details of the event, signed by the investigator (or appropriately qualified designee), and faxed to the study monitor within 24 hours of first becoming aware of the event.

If the investigator does not have all information regarding an SAE, ***he/she will not wait to receive additional information before notifying the study monitor*** of the event and completing the form. The form will be updated when additional information is received.

 The investigator will always provide an assessment of causality at the time of the initial report as described in Section 8.7.2, “Assessment of Causality”. If data obtained after reporting indicates that the assessment of causality is incorrect, then the SAE form may be appropriately amended, signed and dated, and resubmitted to the Sponsor.

In accordance with current QH guidelines, the investigator must also notify the Reviewing Ethics Committee or Site Governance Office of any SAEs according to the guidelines of the Ethics Committee.

## Expeditable Events (SUSAR’s)

Expeditable events are those adverse events that are **CAUSALLY** related to the study product, **AND** that are both **SERIOUS** (see Section 8.2) and **UNEXPECTED** (see Section 8.7.3). These events are deemed Suspected Unexpected Serious Adverse Reactions. Reporting timeframes to the TGA and other regulators will be conducted in accordance with the relevant guidelines.

## Evaluating AEs and SAEs

### Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study. The assessment will be based on the investigator’s clinical judgement. The intensity of each AE and SAE recorded in the Case Report Form (CRF) will be assigned to one of the following categories:

**Mild:** An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.

**Moderate:** An event that is sufficiently discomforting to interfere with normal everyday activities.

**Severe:** An event which is incapacitating and prevents normal everyday activities.

An AE that is assessed as severe should not be confused with an SAE. Severity is a category utilised for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. An event is defined as “serious” when it meets one of the pre-defined outcomes as described in Section 8.2 “Definition of an SAE”.

### Assessment of Causality

The investigator will assess the relationship between investigational product and the occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the investigational product will be considered and investigated.

The causal relationship to the study product assessed by the Investigator (or medically qualified delegate) will be assessed using the following classifications:

**Not Related** In the Investigator’s opinion, there is not a causal relationship between the study product and the adverse event.

**Unlikely** The temporal association between the adverse event and study product is such that the study product is not likely to have any reasonable association with the adverse event.

**Possible** The adverse event could have been caused by the study Participant’s clinical state or the study product.

**Probable** The adverse event follows a reasonable temporal sequence from the time of study product administration, abates upon discontinuation of the study product and cannot be reasonably explained by the known characteristics of the study Participant’s clinical state.

**Definitely** The adverse event follows a reasonable temporal sequence from the time of study product administration or reappears when study product is reintroduced.

**8.7.3 Assessment of Expectedness**

**Expected** An adverse reaction, the nature or severity of which is consistent with the applicable product information (e.g. Investigators’ Brochure) for an unapproved medicinal product).

**Unexpected** An adverse reaction, the nature or severity of which is not consistent with information in the relevant document (e.g. Investigators’ Brochure for an unapproved medicinal product).

## Follow-up of AEs and SAEs

All AEs and SAEs documented at a previous visit/contact and are designated as ongoing, will be reviewed at subsequent visits/contacts.

To ensure patient safety, all AEs, regardless of suspected causality, occurring between the time of consent and until the final dose of study drug will be recorded. Any SAEs experienced after this period should only be reported if the investigator suspects a causal relationship to the study drug. Each participant will be monitored regularly by the Investigator and study personnel for adverse events occurring throughout the study.

## Overdose

An overdose is defined as a dose taken by a participant in excess of the doses in the approved study protocol or available product information, either accidentally or intentionally, irrespective of whether it involves study medication or non-study medication. Overdose may be suspected or confirmed and may or may not be associated with clinical signs and symptoms.

Although hypoglycaemia has not been seen with ingestion of up to 85 g of metformin alone, lactic acidosis has occurred in such circumstances. Lactic acidosis does not appear to occur in metformin overdose in people who do not have T2DM. This disorder is a medical emergency and must be treated in hospital. The onset of lactic acidosis is often subtle and accompanied only by nonspecific symptoms, such as malaise, myalgia, respiratory distress, increasing somnolence and nonspecific abdominal distress. There may also be associated hypothermia, hypotension and resistant bradyarrhythmias with more marked acidosis. Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonaemia).

It would definitely include (but not be limited to) those events which based on the investigators clinical judgment were considered to be of medical concern and /or require clinical observation and /or medical intervention. An overdose would include any dose greater than the highest daily dose included in the protocol or available product information. Deviations to study drug administration (i.e. resulting from poor participant compliance) which do not meet the definition of an overdose, will be recorded in the study medication compliance section of the case Report Form (CRF) and not as Serious AE’s.

### Reporting of Overdose

For all overdoses the Serious AE Form will be completed and reported to the sponsor within 24 hours from the time that the Investigator or delegated research staff have been made aware of the event. See section 8.5 for all other Serious AEs. The documentation will include details of any associated signs/symptoms or if the overdose is asymptomatic, this will be stated.

## Pregnancy

Details of all pregnancies in participants that occur during the treatment period and the final follow-up visit will be documented and reported to the Investigator. In addition, any pregnancies brought to the attention of the Investigator after this period, and where it is known that study medication was taken at the time of conception, will also be reported.

Although pregnancies are not generally serious AE’s, the Serious AE Form will be completed and forwarded to the Investigator within 24 hours. This will provide a record of the initial notification of the pregnancy.

Pregnancy is an exclusion criterion for this study, therefore, participants who become pregnant during the study should discontinue the study medication immediately and will be withdrawn from the study. The Investigator or delegated research staff will contact the participants treating Physician and inform them of the pregnancy in writing.

## Risk Management Process

Table 2 below details the Risk Identification, Evaluation and Management plan for this study.

It will ensure that risk and uncertainty are appropriately managed for the duration of the study. The risk management process is in accordance with the NHMRC National Statement on Ethical Conduct in Research Involving Humans (2007).

**Table 2: Risk Analysis Matrix**

|  |  |
| --- | --- |
| **Consequence** |  **Response To Risk** |
|

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Likelihood** | **Negligible** | **Minor** | **Moderate** | **Major** | **Extreme** |
| Almost Certain |  |  |  |  |  |
| Likely |  |  |  |  |  |
| Possible |  |  |  |  |  |
| Unlikely |  |  |  |  |  |
| Rare |  |  |  |  |  |

 |

|  |  |  |
| --- | --- | --- |
|  | Very High | Immediate action required |
|  | High | Urgent attention or investigation required |
|  | Medium | Require specific attention |
|  | Low  | Manage through routine procedures |

 |

**Risk Identification, Evaluation and Management Plan**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Risk | Description | Possible Effects | Risk Management strategies |
| Likelihood | Consequence | Rating |
| 1. | Psychological discomfort during interview  | Participants may experience psychological discomfort when answering questions in the clinical interview | Possible | Minor-moderate | Medium | The PICF clearly states the potential risk of discomfort.Recruitment of experienced mental health clinicians who will be able to minimise and manage discomfort.Participants will be initially seen weekly for the first 4 weeks to assess adverse drug reactions and clinically assessed at baseline, and every four weeks for 24 weeks. We will also contact participants regularly between face-to-face assessments by phone where participants are given the opportunity to discuss any concerns/discomforts re previous appointment. Clinicians will direct and assist participants to gain support if required. |
| 2. | Inconvenience of participating in the trial | Participants may be inconvenienced by time taken to participate in the trial. | Possible | Negligible | Low | The PICF clearly states the battery of clinical assessments to be completed and the approximate time and frequency for clinical assessment visits.Participants will be given as many breaks as necessary throughout the clinical assessment visit.Participants will be reimbursed for their time involved in the trial.Participants will be reminded that the trial is voluntary and they can withdraw at any time. |
| 3. | History of self-harm/suicidal ideation | Participant has had past suicidal ideation/ DSH behaviour. | Possible | Moderate-severe | High | Recruitment of experienced mental health clinicians who are trained in conducting risk assessment and managing high risk situations.Research staff will have access to a clinically trained senior staff including a Project Manager and Chief Investigator who will assist research staff to conduct risk assessment and implement risk management plan if required i.e. notifying treating team and assisting in the participant accessing appropriate support (e.g. emergency services)Previously identified high risk patients and recent risk assessments will be discussed at weekly team meetings and their management reviewed by senior research staff (including Project Manager and Chief Investigator).Research staff will be given support and feedback on risk assessments and their management to improve skills throughout the project. |
| 4.  | Blood tests | Three blood samples will be taken from participants who consent to the procedure. Participants may experience some short term mild discomfort from the blood draw. Participants may experience minor complications such as local bruising and inflammation of the vein used. | Possible | Negligible | Low | The PICF clearly states the potential complications associated with the blood draws. Participants provide specific consent for this procedure which is identified on the consent form.Participants will be taken to recognised pathologies who have trained phlebotomists to conduct the blood draws.Participants are made aware they can refuse a blood draw at any stage throughout the study. |
| 5. | Overdose | An overdose would include any dose greater than the highest daily dose included in the protocol or prescribing information.  | Possible | Minor-Moderate | Medium-High | For all overdoses the Serious AE Form will be completed and reported to the sponsor within 24 hours from the time that the Investigator or delegated research staff was notified of the overdose.Participants will be provided with 4 weeks supply (bottle) at each face to face visit.Research staff will conduct a tablet count at each face to face visit.Research staff will conduct medication compliance questionnaire at each face to face visit and phone contact.Any identified issues with medication compliance will be discussed at weekly team meetings. Senior research staff (including Project Manager and Chief Investigator) will determine the most appropriate plan of action if required. |
| 6. | Home visits | Participants may be seen at home rather than in the clinic. Individuals with psychosis can often experience hallucinations and delusions which could result in unpredictable behaviour. | Possible | Minor-Moderate | Medium-High | First preference should be interview conducted at the clinic in a suitable interview room.Two staff will be required for home visits and will carry a mobile phone.Research staff will adhere to a sign in/out policy and advise the Project Manager of the address they will be attending.Any incidents from a home visit will be reported to the Project Manager and Chief Investigator and documented in the CRF or if required reported to Metro South HREC. |
| 7. | Transporting participants in QLD Health work vehicles | Research staff will be transporting participants to pathology appointments and may be required to transport participants to the interview site. * There may be risk associated with motor vehicle accident
* There may be risks associated with unpredictable behaviour of a patient whilst being transported.
 | Possible | Minor-Moderate | Medium -High | Research staff will have a current QLD Driver’s Licence and completed the mandatory Driver Safety E-Learning Course.Recruitment of experienced mental health clinicians who will be able to and manage unpredictable behaviour.Research staff will carry a mobile phone and adhere to a sign in/out policy and advise the Project Manager of the address they will be attending. |

## Physical examination

## All patients recruited in this study will be active cases at Queensland Hospital and Health services. The study team will liaise with inpatient staff, clozapine coordinators and Continuing Care Unit staff to ensure that participants have undergone a routine physical health screen which includes the following systems; respiratory, cardiovascular, gastrointestinal including mouth, musculoskeletal, central and peripheral nervous system, skin and lymph node palpation, as part of clozapine commencement.

## Any abnormal, clinical significant findings at screening must be recorded as a concomitant illness. Any changes in subsequent visits as compared to screening which fulfil the criteria for an AE must be recorded as an AE (see section 6.4.1).

## Vital signs

### Pulse and blood pressure

As per standardised procedure, participant’s systolic and diastolic blood pressure will be measured (after sitting for 5 minutes) in the sitting and standing position at all visits to the clinic. However, re-measurement of blood pressure is allowed if white coat syndrome is suspected. Caffeine, smoking and physical activity should be avoided within 30 minutes prior to the blood pressure measurement at all visits to the clinic.

Pulse will be recorded after resting for five minutes in a sitting position at all visits to the clinic.

### Body Measurements

Body measurements will include weight, height and waist circumference.

### Weight and Height

Weight will be recorded to the nearest 0.1 kg. Weight should be measured at screening and weekly for the first 4 weeks and then at each monthly face to face visit (4, 8, 12, 16, 20 and 24) using calibrated scales. The same pair of scales should preferably be used throughout the trial. Weight should be measured with an empty bladder, without shoes and only wearing light clothing. Weight measured at screening will only be used for the Investigator’s calculation of BMI, whereas weight measured at week 0 will be used as baseline for assessment of change in body weight.

Height without shoes will be recorded at screening.

BMI will be calculated as follows: BMI (kg/m2) = weight (kg)/height (m2).

### Waist Circumference

Waist circumference will be measured initially weekly for the first 4 weeks and then at each monthly face to face visit (4, 8, 12, 16, 20 and 24).

The waist circumference will be measured in the horizontal plane to the nearest 0.5 cm using a non-stretchable measuring tape. The participant should be standing with arms at their side and feet together. Participants should be measured in the standing position with an empty bladder and wearing only light clothing. The research assistant should request the participant locate the top of the hip bone and the base of the side of their ribs. The research assistant should then measure the space between these two points and locate the halfway measurement. The research assistant should then place the beginning of the tape at the point of the halfway measurement and request the participant hold the tape in place. The research assistant then places the tape measure evenly around the abdomen at this level and records the measurement. Participants should be asked to breathe normally and the measurement should be performed end of a normal expiration. The measuring tape should lie flat against the skin without compressing the soft tissue. Where possible the same research assistant should take the measurement for that participant to increase the likelihood of consistency of the measurement.

## Laboratory assessments

Any abnormal, clinically significant result identified at screening will be recorded as concomitant illnesses. Laboratory analysis results will be sent to the Investigator at each time point. The Investigator will report any abnormal results fulfilling the criteria for an AE according to this protocol (see section 6.4.3). Lipids, glucose and insulin will need to be performed after 8 hours of fasting.

### Blood samples

Samples will be drawn at week 0, 12, and 24, for assessment of white cell count, neutrophils, metabolic monitoring and biochemistry (eLFTs) as per the standard clozapine protocol. This study makes no changes to standard clozapine monitoring. Blood clozapine/norclozapine concentrations will be recorded at weeks 0, 12 and 24. In addition to the standard metabolic monitoring we will be collecting HbA1c and fasting insulin at weeks 0, 12 and 24 and OGTT at weeks 0 and 24.

Baseline blood samples will be conducted on participants who are either inpatients or outpatients in Community Care Units. Blood draws will be added to the routine weekly clozapine blood monitoring. Week 12 and 24 blood draws will, where possible be timed to co-occur with routine monthly clozapine blood monitoring.

# Participant Completion and Withdrawal

## Participant Completion

Participants are considered to have completed the study if they complete 24 weeks of dosing.

## 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 of more than 50% of study medication on tablet count
* 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

## Participant Withdrawal

All participants have the right to withdraw consent at any time without prejudice and this will not affect their ongoing care. This will be clearly discussed during the consenting process. If a participant decides to withdraw consent we will complete a revocation of informed consent form.

## Early Termination of the Study

The study may be terminated prematurely by the Coordinating and or Principal Investigator or his/her designee and the sponsor if:

* The number and/or severity of adverse events justify discontinuation of the study.
* New data becomes available which raises concern about the safety of the study drug, so that continuation might cause unacceptable risks to participants.

After such a decision, the Investigator or designee will contact all participants promptly, and written notification of study termination will be sent to the Reviewing Ethics Committee and relevant Governance Offices. A study closure advice will also be sent to the TGA on the approved form. The Australian Clinical Trial Registry entry will also be updated accordingly.

# Case Report Form (CRF)

A Case Report Form (CRF) will be completed for each study participant summarising all clinical screening and study data that is to be provided to the University of Queensland (Sponsor) for data analysis. In the CRF, participants will only be identified by their participant number in order to retain participant confidentiality.

The completed CRF’s will be retained by the Investigators for a period of at least 15 years or the maximum time frame as determined by local regulations, whichever is the longest.

# Data Analysis and Statistical Considerations

## Hypotheses

Those participants allocated to the active arm metformin treatment will have lower mean body weight at week 24 compared to individuals taking placebo, adjusted for baseline body weight (ANCOVA).

## Endpoints

### Primary

24 week treatment of metformin (2000mg) versus placebo will attenuate weight gain compared to individuals taking placebo, adjusted for baseline body weight (ANCOVA).

### Secondary

To determine if 24 week treatment of metformin versus placebo has comparative changes in rate of conversion to T2DM (fasting 2hr glucose tolerance test and HbA1c), development of the metabolic syndrome or its components (waist circumference, fasting glucose, High Density Lipoprotein (HDL), Low Density Lipoprotein (LDL),Body Mass Index (BMI), triglycerides, blood pressure, hip waist ratio), insulin resistance as measured by homeostatic model assessment (HOMA) using fasting glucose and insulin, liver function tests, clozapine/norclozapine ratio, heart rate, diet and appetite (Food Craving Inventory), physical activity (SIMPAQ and IPAQ), proportion with weight gain of 5% or more at endpoint versus baseline, Global Assessment of Function (GAF), Positive and Negative Syndrome Scale (PANSS) and rates of drop out between groups.

### 11.2.3 Tertiary

Collect DNA for future collaboration studies related to metabolic syndrome changes from baseline to endpoint in those on active treatment.

## Sample Size and Power

## The study is powered based on the primary outcome. The sample size calculation was based on the meta-analysis of metformin for clozapine obesity 19 (MD 3.12kg, SD = 8.8). With an α =0.05, and power of 0.8 with repeated measures (one baseline measure and six follow-up measures) using Analysis of Covariance (ANCOVA) as the planned analysis, we will require 34 participants per group (n = 68). Over a 24 week period we predict attrition of 20%. Thus, we will need to randomize approximately 86 participants.

## Statistical Analysis

We will adopt an intention-to-treat principle to analyse all outcomes (i.e. for those who do not complete the 24 week study period, we will carry forward their last observation on the study outcomes). For the primary outcome, we will be using repeated-measures ANCOVA analysis to assess for differences in the two group’s endpoint weight after adjusting for baseline weight. The significance level for the treatment effect will be set at the 0.05 level using two-sided test. For secondary outcome measures, we will be using paired t-test and Wilcoxon signed-rank tests to look at various metabolic syndrome components. We will also compare demographic and clinical differences between the groups at baseline using fisher exact or chi square test for categorical variables or two independent sample t-test for continuous variables.

# Data Management

## Documentation

A screening log will be utilized to track potential participants and also record the counts of individuals approached, consented, meeting inclusion/exclusion criteria, withdrawals, and completion (in keeping with standard CONSORT diagram requirements).

The CRF will comprise of the hard copy questionnaires, clinical assessments and measures. These de-identified data will be retained in a secure room, in a locked filing cabinet, at the lead site.

De-identified data from the CRFs will be entered into REDCap, which is a secure (encrypted to health service standard, housed on a server behind the University of Queensland firewall), web-based application for building and managing online surveys and databases. Delegated research assistants will be trained in, and responsible for entering data into the database.

Upon completion and resolution of monitoring and data management queries, the clinical trial database will be closed. All data will be exported into SAS software to enable statistical analysis.

A copy of the PICF will be stored in a secure room in a locked filing cabinet separate from the CRFs.

## Archiving

The Investigator, Project Manager or their delegate at each site will organise the retention of documentation relating to the study (source documents, informed consent forms, approvals) for a period of at least 15 years or the maximum time frame as determined by local regulations, whichever is the longest.

# Monitoring and Quality Assurance

The appointed HRECs will monitor research practice to assure adherence to the approved protocol and the NHMRC National Statement on Ethical Conduct in Human Research (2007).

In order to ensure the accuracy of data, direct access to source documents by the representatives of both the Study Monitor and regulatory authorities will be available.

The Investigator will submit to the Reviewing HREC, annual (or more frequent if requested) reports of the study.

The study coordinator or designated delegate will monitor data entered at each site and be responsible for resolving data entry errors and discrepancies.

Data quality will be ensured by performing data entry checks for consistency between the CRF and the data entry into REDCap database. These checks will be performed during data entry so that discrepancies can be resolved immediately. A data manager will later perform additional checks for completeness and plausibility of data. Resultant queries will be raised and resolved electronically by the data manager and the study centre.

The lead site will maintain a record of all personnel involved in the study including a Signature & Delegation Log which the Investigators will sign. In consultation with the lead site, each site will ensure that appropriate training is provided to study personnel, and that any new information of relevance to the performance of this study is forwarded to the staff involved in a timely manner.

**13.1 Data Safety Monitoring Board**

An independent Data Safety Monitoring Board (DSMB) will be established specifically to monitor safety data and study trends throughout the duration of the trial to determine if continuation of the trial is appropriate scientifically and ethically. The members of the DSMB serve in an independent capacity and will provide their expertise and recommendations to guide the clinical trial where required.

# Investigator Responsibility

Except where the Coordinating Principal Investigator’s signature is specifically required, it is understood that the term ‘Investigator’ as used in this Protocol and on the CRFs refers to the Coordinating Principal Investigator and the Principal Investigator or an appropriately qualified member of the staff that the Coordinating Principal Investigator designates to conduct the study. The Coordinating Principal Investigator is ultimately responsible for the conduct of all aspects of the study.

The study and its associated documents will be reviewed and approved by the appointed certified HREC and Research Governance (at all sites) before study start. A signed and dated letter that the ethics application has been approved by the appointed HREC and Research Governance Authority will be provided to the Sponsor before study initiation.

Prior to submission to appointed HREC and Research Governance, the investigator will sign the protocol signature page confirming his/her agreement to conduct the study in accordance with the protocol, GCP and other regulatory requirements locally applicable. All relevant data and records will be provided to study monitors, HREC and regulatory authorities as required. If an inspection of the clinical site is requested by a regulator, the investigator will inform the University of Queensland (Sponsor) immediately that this request has been received.

Each Investigator will comply with the local regulations regarding clinical trials and the Investigator responsibilities outlined in the ICH GCP guidelines.1

# Study Report

The Investigator will submit at least annual study reports to the reviewing HREC, or more frequent if needed.

# Administrative Procedures

## Ethical Considerations

Information on side effects of the Investigational Product and reference formulations is summarised in the Investigator’s Brochure. The monitoring and safety guidelines are outlined in the Monitoring Guidelines for the study. This study will be carried out according to the Declaration of Helsinki, the NHMRC National Statement on 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.1

## Ethical Review Committee

The National Ethics Application Form (NEAF) and associated documents will be submitted for approval to the appointed multi-site HREC and written approval obtained from both the appointed HREC and Governance Office, before volunteers are recruited and participants are enrolled. The Chief Investigator will submit the National Ethics Application Form and associated documents including Site Specific Applications from each site, to the appointed HREC and Research Governance. The Chief Investigator has overall responsibility to ensure all reports at each site are submitted in line with the appointed HREC reporting requirements.

## Regulatory Authorities

The study will be notified under the Clinical Trial Notification (CTN) scheme. The University of Queensland (Sponsor) will submit the CTN forms from each participating site. The trial will also be listed on the Australian and New Zealand Clinical Trials Registry.

In agreeing to the provisions of the Protocol, these responsibilities are accepted by the Investigators.

## Informed Consent

Our criteria will ensure that recruited participants will be sufficiently competent to consent and participate in the study or to refuse consent. Current research provides evidence that while psychotic symptoms may be present, these do not robustly predict an individual’s functionality in daily life and capacity to make decisions, and whilst strongly correlated with cognitive impairment, do not reflect an enduring inability to understand information related to research participation.40

Eligible participants (18-64 years) will be given a full explanation in lay terms, with a friend or family member present if desired, of the study aims, the discomfort, risks and benefits in taking part and a copy of the Participant Information Sheet Consent Form to review.

It will be pointed out to participants that they can withdraw from the study at any time without prejudice and will not affect their current care. The adult participants will have the opportunity to ask questions. A telephone number will be provided so that participants can call a research representative who will be able to respond to any questions they may have.

Each participant will acknowledge receipt of this information by giving written informed consent for participation in the study.. A notation that written informed consent has been obtained will be made on the participant’s CRF. The original, completed consent forms will be retained by the Investigator and a copy will be provided by the research staff to the participants.

In accordance with the National Statement, seeking the participants consent will include discussion of possibility that the participant may lose capacity to consent or to participate in the research, in which case, unless contrary to the participant’s best interests, their wishes about what should happen in that circumstance should be followed. In this circumstance, the Queensland Civil and Administrative Tribunal (QCAT) appointed guardian may be involved in trial-related decisions. Ongoing capacity will be assessed at every trial visit.

## Participant Reimbursement

Participants will be reimbursed for out of pocket expenses, inconvenience and time involved by the provision of prepaid gift cards (e.g. Coles-Myer, K-Mart etc). We will provide a $20 gift card at baseline, week 4, 8, 12, 16, 20 and week 24 (total reimbursement $140). If the study is terminated by the Investigator prior to completion, or a participant withdraws or is withdrawn from the study before completion, a pro-rata payment will be made at the discretion of the Investigator.

## Emergency Contact with Investigators

All participants will be provided with a Participant Emergency Contact Card with contact details of whom to contact in the case of an emergency including unblinding.

## Notification of Primary Care Physician and Treating Psychiatrist

With the consent of the participant, the Investigator will notify the primary care physician (provided that such a physician can be identified for the participant) and treating Psychiatrist of the participants’ involvement in the study. A letter will be sent to the physician and treating Psychiatrist stating the nature of the study, treatments, expected benefits or adverse events.

## Investigator Indemnification

The clinical trial insurance will reimburse participants for costs of medical care that occur as a result of complications directly related to participation in this study. The Investigator and insurance company will be notified as soon as possible if this occurs or where a causal relationship cannot be excluded. All SAE’s will be reported to the nominated insurance company.

The University of Queensland (Sponsor) will enter into a Clinical Trial Agreement with each of the four Hospital and Health Services (HHS’s) involved in the study, based on the standard Medicines Australia format.

## Intellectual Property (IP) and Licencing

The collection of data in this study is subject to Intellectual Property (IP) and Licencing agreements which will be documented in the Research Agreement.

## Publication Policy

Results will be disseminated in peer reviewed publications and published in international journals. There will be an undertaking to seek journals that have open access policies. Our findings will also be summarised in several brochures, including one designed for feedback to participants and Hospital and Health Services (HHS’s) who participate in the study. Only group data will be reported.

## Protocol Amendments

Any amendments to the protocol will be submitted to the appointed HREC by the Chief Investigator for approval. Any approved amendments by the appointed HREC will be forwarded by the Chief Investigator for submission to each Research Governance Office.

No changes (amendments) to the Protocol will be implemented without prior approval from the Reviewing Ethics Committee. If a Protocol amendment requires changes to the Informed Consent Form, the revised Informed Consent Form, prepared by the Chief Investigator, will be approved by the Reviewing Ethics Committee and site governance officers.

Once the final Protocol has been issued and signed by the Chief Investigator and the authorised signatories, it will not be informally altered. All protocol amendments will pass through appropriate approval steps before being implemented. Any change to the protocol constitutes an amendment.

Where the amendment affects the ongoing suitability of the study at a participating site, Research Governance approval will also be sought. The Research Governance Office will determine the ongoing suitability based on the amendment submitted.

The Chief Investigator will submit the amendment to the appointed HREC for their approval; written approval will be obtained. Completed and signed Protocol amendments will be circulated to all appointed site Investigators.

The original signed copy of amendments will be kept in the Study File with the original Protocol. Where an amendment to the Protocol substantially alters the study design or the potential risks to the participants, each participant’s consent to continue participation will be obtained.

## Version Control

Version control ensures that amendments to documents are tracked and verifiable and that the correct version of a document is in use according to the relevant ethical, regulatory or local approval.

All documents will be given a version number and date e.g. Version 1.0 15-Feb-17

Each amendment to a document will require a version number and date to be updated.

If this is a **significant change** e.g. change in the content of the document, then the version number will be increased by 1.0.

If it is a **minor change** e.g. contact details, then the number after the decimal point will be increased by 0.1.

## Protocol Compliance

Should there be questions or consideration of deviation from the Protocol, clarification will be sought from the Study Monitor. Any participant treated in a manner that deviates from the Protocol, or who is admitted into the study but is not qualified according to the Protocol, will be ineligible for analysis.

If an emergency occurs that requires a departure from the Protocol, the nature and reasons for the Protocol violation/deviation will be recorded in the CRF and the Chief investigator will notify the Reviewing HREC and /or Governance Office as soon as possible.

## Archives: Retention of Study Records

All CRF’s and study documentation will be kept by the Investigators for at least 15 years or the maximum time frame as determined by local regulations, whichever is the longest.

## Independent Evaluation of Clinical Trial

The Royal Brisbane and Women’s Hospital Foundation are funding a separate HREC approved Process Evaluation study which is being conducted by Associate Professor Sue Patterson. The aims of the Process Evaluation study is to generate evidence to support interpretation of the findings of the CoMET Trial and to contribute to the body of evidence needed to improve the efficiency of pragmatic randomised controlled trials.

As part of this Process Evaluation study, research staff from all sites will be invited to be interviewed about the design and implementation of the CoMET trial and perceived influences on implementation. Participants who have been recruited as part of the Process Evaluation study will only be recruited from the Royal Brisbane and Women’s Hospital.

Please note that staff who consent to be interviewed for the Process Evaluation study must not disclose information obtained about participants or their involvement in this clinical trial at any time. Participants who consent to participate in the CoMET trial and to be contacted for potential future research will be made aware that there is a Process Evaluation study being conducted and a member of the research team will contact them in due course.

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