**PROTOCOL TITLE**

Clozapine Obesity and Semaglutide Treatment (COaST). A randomised controlled multi-centre trial of semaglutide versus placebo for people with schizophrenia on clozapine with obesity inadequately responsive to metformin.

SHORT TITLE

CADENCE COaST

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| 1.1 | 11th May 2021 | Addition of text, inclusion/exclusion criteria |
|  |  |  |
| 2.0 | 14th July 2021 | Removal of metformin run-in phase, switch from oral to subcutaneous semaglutide |

**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 University of Queensland (Sponsor) will have access to source documents entered into the Case Report Form. The Case Report Forms and other data pertinent to this study are the sole property of the University of Queensland (Sponsor), who may utilise the data in various ways, such as for submission to government regulatory authorities, or in publication of the results of the study.

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 |

MTC Medullary thyroid carcinoma

# Introduction

Schizophrenia represents the most disabling and costly psychiatric disorder in terms of both human suffering and expenditure. People with schizophrenia die almost 20 years earlier than the general population, most commonly from avertable cardiometabolic disease. (1) Despite the prevalence and burden of obesity in schizophrenia, there are a dearth of effective treatment options, and metabolic comorbidity remains vastly undertreated. (2) Behavioural strategies for weight reduction in schizophrenia, though efficacious, are hampered by low uptake and high dropout. (2) Existing pharmacological agents to aid weight loss have either limited efficacy or unacceptable adverse drug reactions. (2)

Despite their effectiveness in treating the psychotic symptoms of schizophrenia, antipsychotic medications lead to obesity, diabetes and cardiovascular disease. (3) Antipsychotic induced weight gain is associated with decreased medication compliance, increased hospitalization and social care costs, stigma, and decreased quality of life. (3) Metformin is increasingly used as a first line agent for antipsychotic induced weight gain, but has limited efficacy, only leading to around 3% body weight reduction. (4) There is an urgent need for more efficacious cardiometabolic agents for people with schizophrenia.

Glucagon-like-peptide (GLP-1) is an endogenous peptide produced in the gastro-intestinal tract that aids glucose homeostasis. Our group found that antipsychotics impair endogenous GLP-1 production, leading to obesity. (5) Glucagon-like-peptide receptor agonists (GLP-1RAs), such as semaglutide have been shown to be safe and effective for glycaemic control and weight loss in people with and without type 2 diabetes. (6) In animal models(7) and human pilot data(8) we have shown that GLP-1RAs can also reduce antipsychotic-associated obesity and cardiometabolic disease.(9) Pre-clinical research on the impact of antipsychotics on the GLP-1 pathway suggests that weight loss with semaglutide may be even greater among people on antipsychotics. If that finding is confirmed, there is immediate potential for translation to clinical care.

To date, the management of antipsychotic-induced weight gain in current clinical guidelines includes cognitive behaviour therapy interventions, dietary changes, and switching of antipsychotic medication. (10, 11) However, it is not clinically appropriate for patients with treatment refractory schizophrenia to cease clozapine (the most effective medication against positive and negative symptoms) and begin a more weight-neutral but less efficacious agent.

Behavioural strategies for weight reduction in schizophrenia are only modestly effective, with low uptake and high dropout rates.(2) According to current Australian guidelines, unapproved medicines that are used in the treatment of other conditions and have evidence of a beneficial effect on weight (including, fluoxetine, topiramate, metformin and GLP-1 agonists) may be used when relevant comorbidities are present. (12)  Our meta-analysis of randomised controlled trials of metformin for reducing weight among people with schizophrenia on clozapine found only modest improvements (13, 14)(13, 14). (4) Overall, studies using current pharmacological and behavioural interventions for reducing clozapine-associated weight gain report only modest weight reduction, which is of substantially less magnitude than the weight gained by treatment with clozapine. (11) Furthermore, the reliability of available data is limited by methodological limitations and small sample sizes.

Absolute body weight change is only a partial measure of change in cardiometabolic risk. Visceral adiposity is more metabolically active than peripheral adiposity (15). As such, investigation of body composition through imaging techniques such as dual energy X‐ray absorptiometry (DEXA) can provide a more accurate estimation of the location of body weight change (15). DEXA uses very low dose energy, and as such is of very low risk to participants. (16) Previous studies of GLP1-RAs among people with antipsychotic obesity have suggested that GLP1-RAs may lead to a reduction of visceral rather than peripheral adiposity (17).

To reduce the personal, social and economic burden associated with cardiometabolic disorders that may develop secondary to weight gain, it is of significant benefit to investigate novel methods of treating clozapine-associated obesity. To date, GLP-1RAs show the best promise for treatment of clozapine associated obesity. There is an urgent need for a trial of Semaglutide versus placebo for clozapine associated obesity.

## Safety profile

**Semaglutide**

To our knowledge, there is no efficacy data available for the use of semaglutide in preventing weight gain in patients taking clozapine or other antipsychotics. However, there is efficacy data for use of Semaglutide in the general population with people with and without T2DM. The most commonly reported adverse events are nausea and diarrhoea which was mild to moderate in severity, and reduced over time (6). A full listing of adverse events of subcutaneous Semaglutide versus placebo from a trial among obese people without T2DM is provided in the table below.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Adverse Events Associated with Semaglutide vs Placebo** (from Wilding, John P.H., Rachel L. Batterham, Salvatore Calanna, Melanie Davies, Luc F. Van Gaal, Ildiko Lingvay, Barbara M. McGowan, Julio Rosenstock, Marie T.D. Tran, Thomas A. Wadden, Sean Wharton, Koutaro Yokote, Niels Zeuthen, and Robert F. Kushner. “Once-Weekly Semaglutide in Adults With Overweight or Obesity.” New England Journal of Medicine (2021) | | | | | | |
| **Adverse Event** | **Semaglutide (N = 1306)** | | | **Placebo (N = 655)** | | |
| No. of participants (%) | No. of events | Events/100 person-yr | No. of participants (%) | No. of events | Events/100 person-yr |
| Any adverse event | 1171 (89.7) | 9658 | 566.1 | 566 (86.4) | 3302 | 398.0 |
| Serious adverse events | 128 (9.8) | 164 | 9.6 | 42 (6.4) | 53 | 6.4 |
| Adverse events leading to discontinuation  of drug or placebo | 92 (7.0) | 123 | 7.2 | 20 (3.1) | 23 | 2.8 |
| Gastrointestinal disorders | 59 (4.5) | 78 | 4.6 | 5 (0.8) | 5 | 0.6 |
| Fatal events | 1 (0.1) | 1 | 0.1 | 1 (0.2) | 3 | 0.3 |
| Adverse events reported in ≥10% of participants§ | | | | | | |
| Nausea | 577 (44.2) | 1068 | 62.6 | 114 (17.4) | 146 | 17.6 |
| Diarrhea | 412 (31.5) | 766 | 44.9 | 104 (15.9) | 138 | 16.6 |
| Vomiting | 324 (24.8) | 636 | 37.3 | 43 (6.6) | 52 | 6.3 |
| Constipation | 306 (23.4) | 390 | 22.9 | 62 (9.5) | 73 | 8.8 |
| Nasopharyngitis | 281 (21.5) | 480 | 28.1 | 133 (20.3) | 216 | 26.0 |
| Headache | 198 (15.2) | 387 | 22.7 | 80 (12.2) | 104 | 12.5 |
| Dyspepsia | 135 (10.3) | 179 | 10.5 | 23 (3.5) | 30 | 3.6 |
| Abdominal pain | 130 (10.0) | 175 | 10.3 | 36 (5.5) | 41 | 4.9 |
| Upper respiratory tract infection | 114 (8.7) | 158 | 9.3 | 80 (12.2) | 116 | 14.0 |
| Safety focus areas | | | | | | |
| Gastrointestinal disorders | 969 (74.2) | 4309 | 252.6 | 314 (47.9) | 739 | 89.1 |
| Gallbladder-related disorders | 34 (2.6) | 42 | 2.5 | 8 (1.2) | 8 | 1.0 |
| Hepatobiliary disorders | 33 (2.5) | 40 | 2.3 | 5 (0.8) | 5 | 0.6 |
| Cholelithiasis | 23 (1.8) | 24 | 1.4 | 4 (0.6) | 4 | 0.5 |
| Hepatic disorders | 31 (2.4) | 37 | 2.2 | 20 (3.1) | 24 | 2.9 |
| Acute pancreatitis | 3 (0.2) | 3 | 0.2 | 0 | — | — |
| Cardiovascular disorders | 107 (8.2) | 134 | 7.2 | 75 (11.5) | 96 | 10.5 |
| Allergic reactions | 96 (7.4) | 108 | 6.3 | 54 (8.2) | 63 | 7.6 |
| Injection-site reactions | 65 (5.0) | 99 | 5.8 | 44 (6.7) | 82 | 9.9 |
| Malignant neoplasms | 14 (1.1) | 14 | 0.8 | 7 (1.1) | 7 | 0.8 |
| Psychiatric disorders | 124 (9.5) | 160 | 9.4 | 83 (12.7) | 113 | 13.6 |
| Acute renal failure | 3 (0.2) | 4 | 0.2 | 2 (0.3) | 2 | 0.2 |
| Hypoglycemia | 8 (0.6) | 15 | 0.9 | 5 (0.8) | 7 | 0.8 |

*Contraindications*(As per Ozempic Product Information)

* A personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2Known hypersensitivity to semaglutide or to any of the components in Ozempic
* History of pancreatitis with a GLP-1 analogue
* End-stage renal disease or severe renal impairment (creatinine clearance <30 mL/min).

## Rationale for the Use of Semaglutide

***Schizophrenia is associated with high rates of metabolic disorders:*** Life expectancy for people with schizophrenia in Australia is 16.4 years less than the general population(18) with 35.1% of excess deaths attributable to cardiovascular disease and diabetes mellitus.**(18)** Among a nationally representative sample of people with schizophrenia, 20.8% had type 2 diabetes mellitus (T2DM) while 54.8% had metabolic syndrome.**(19)** Possible explanations include genetic predisposition to developing diabetes, reduced physical activity, poor diet and the obesogenic effects of antipsychotic medications.(2)

***Weight gain is a major health problem among people with schizophrenia:*** Weight gain is the most distressing side effect reported by callers to mental health helplines(20) and is associated with poorer quality of life(21) and barriers to social engagement.(22) Weight gain also reinforces patients’ negative self-perceptions. These factors are associated with compromised adherence to treatment(20) leading to relapse and poor mental health outcomes. Furthermore, being obese increases the risk of all-cause mortality, with a body mass index (BMI) of >35 being associated with a 30% increase in mortality.(23) A multicentre weight loss intervention study showed losing 3kg was associated with a >50% reduction in the risk of developing T2DM among people with obesity.(24)

***The use of antipsychotics is associated with increased risk of obesity and metabolic disorders:*** Although antipsychotic medications are a core component of schizophrenia treatment, they are strongly associated with weight gain, metabolic syndrome and diabetes.(2) Commonly used antipsychotics, including risperidone, paliperidone, quetiapine, olanzapine and clozapine have a particular propensity for weight gain.(2)

***There is a lack of effective treatments for obesity in schizophrenia:*** Despite the prevalence and burden of obesity in schizophrenia, there are a dearth of effective treatment options, and metabolic comorbidity remains vastly undertreated.(25) Behavioural strategies for weight reduction in schizophrenia are only modestly effective, with low uptake and high dropout rates.(2) Our seminal and highly cited review of weight-loss strategies in this high metabolic risk population found insufficient evidence to recommend use of most examined pharmacological agents.(25) Only metformin has demonstrated sufficient evidence to support its use for weight reduction in schizophrenia, with our meta-analysis finding a mean weight loss of 3.12kg (95% CI -4.88 to -1.37).(4) It demonstrates a good safety profile and is not associated with increased dropout rates as compared to placebo.(4)

***Limitations of metformin:*** Despite its safety profile and modest weight loss properties, the seminal 2013 RCT (N=148) of metformin versus placebo for weight loss among people with schizophrenia on antipsychotics found that only 17% or participants achieved a clinically meaningful loss of body weight (≥5%).(26) Furthermore, metformin did not reduce visceral fat. Visceral fat is an independent predictor of risk for T2D and CVD.(27)

***The role of Glucagon-Like Peptide-1 (GLP-1) in glucose metabolism:*** Although the physiological mechanisms underlying the metabolic adverse effects of antipsychotics are not fully understood, our group’s preclinical models have suggested GLP-1 is a key mediator.(28) GLP-1 is an endogenous peptide synthesised in the intestinal mucosa.(29) GLP-1 decreases glucagon secretion and stimulates insulin secretion in a glucose-dependent manner, delays gastric emptying and appears to lower food intake by promoting satiety (Fig 1).(30)

**Semaglutide** is well-tolerated, with the main side effects being mild-to-moderate transient gastrointestinal effects, including nausea and vomiting (20%).(31) Less frequently, patients describe headache (8%), fatigue (4%), reflux (3%), and dizziness (3%). Major hypoglycaemia incidence is very rare (0.2%) and minor hypoglycaemia infrequent (2%) due to the glucose-dependent insulinotropic effect.(7) Current evidence suggests that GLP-1-RAs do not increase risk of pancreatitis.(32)

GLP-1 agonists have very well established glucose and body weight lowering properties in non-psychiatric patients with T2DM, with over 25 RCTs underlining their successful clinical application as antidiabetic agents.(7) A growing body of evidence supports that GLP-1 agonists cause clinically significant and sustained weight loss (~3.5kg over 24 weeks) for obese patients without T2DM(33) and may reduce the prevalence of prediabetes.(34) Through beta-cell protection, GLP-1-RAs may reduce risk of progression to T2DM.(35) GLP-1-RAs are associated with lower risk of cardiovascular mortality, non-fatal myocardial infarction, and non-fatal stroke among people at risk of, or with established cardiovascular disease.(36) Semaglutide has similar safety and tolerability to other GLP1-RAs, but greater weight loss efficacy (2.3-6.3 kg),(37) and has been shown to reduce visceral adiposity.(38)

***GLP-1 mediates metabolic disorders associated with antipsychotics:*** Antipsychotics acutely reduce GLP-1 secretion in rodents causing increased hepatic glucose output, higher glucagon levels and a preference for high fat and high sugar foods.(28) GLP-1-RAs, including semaglutide, normalise glucose tolerance and decrease body weight in rats treated with antipsychotics, providing mechanistic justification of their therapeutic potential in this context.(28) Metformin, however, only partially attenuates glucose dysregulation in animal models of antipsychotic metabolic abnormalities.(39)



There is equipoise in the published literature regarding the efficacy of GLP-1-RAs in RCTs on weight loss among people on antipsychotic medications. A Danish short duration (12 week) double-blind pilot RCT (n=40) by Ishøy et al looked at the GLP-1RA exenatide versus placebo for obesity among people on any antipsychotics and found equivocal results.(40) The disadvantage of this trial design was its short duration (long-acting subcutaneous exenatide was released from microspheres over 10 weeks, and would only have just reached steady state by study endpoint) and instead a 24 week trial would have been ideal. A 16-week RCT from another Danish research group used the daily sub-cutaneous GLP-1-RA, liraglutide, for people with schizophrenia on olanzapine or clozapine with pre-diabetes.(41) They found body weight decreased with liraglutide compared with placebo (-5.3 kg; 95% CI, -7.0 to -3.7 kg), along with significant reductions in waist circumference, systolic blood pressure, visceral fat and low-density lipoprotein (LDL). A limitation of liraglutide is its need for daily sub-cutaneous administration.

***Pilot data:*** In 2018,our group published a 24-week randomised open label pilot feasibility study of weekly subcutaneous exenatide (the only GLP-1RA available in Australia at the time) compared to usual care for obese people (BMI 30-45 kg/m2) with schizophrenia on clozapine with or without T2DM.(8) Twenty-eight participants were randomised to exenatide-weekly (14) or usual care (14). All 28 participants completed the study. Compared with usual care, participants on exenatide had greater mean weight loss (−5.29 vs −1.12 kg; p=0.015) and body mass index reduction (−1.78 vs −0.39 kg/m2; p=0.019), reduced fasting glucose (−0.34 vs 0.39 mmol/L; p=0.036) and glycated haemoglobin (HbA1c) levels (−0.21% vs 0.03%; p=0.004). Six people on exenatide achieved >5% weight loss versus one who received usual care (p=0.029). There were no significant differences in other metabolic syndrome components (blood pressure, triglycerides and HDL). Participants in the exenatide group reported transient nausea (n=8), vomiting (n=7), dizziness (n=7) and diarrhoea (n=7), however despite this none discontinued. These results suggest reasonable tolerability and a consistent and favourable pattern of improvements with exenatide.

Our group combined the data from the three published studies of GLP1-RAs among people with schizophrenia who were obese and taking antipsychotic medications into an individual patient data meta-analysis.(9) We found that body weight loss was 3.71 kg (95% CI = 2.44-4.99 kg) greater for GLP-1RA versus control (p<0.001), with significant improvements in waist circumference, body mass index, HbA1c, fasting glucose and visceral adiposity. A 5% or greater reduction in body weight was achieved by 36.9% of participants. This compares favourably to metformin which, as previously noted, was only associated with 17% of participants achieving ≥5% loss of body weight(26) (Fig 2).

# 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 semaglutide to reduce body weight among people who are on clozapine.

## Primary Objectives

To determine percentage change in body weight with 36 week treatment with subcutaneous semaglutide versus placebo, adjusted for baseline weight (Analysis of Covariance-ANCOVA).

## Secondary Objectives

To determine if 36 week treatment with subcutaneous semaglutide versus placebo has comparative changes in: 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, NAFLD and FIB-4 scores, clozapine/norclozapine ratio, heart rate, diet and appetite (Food Craving Inventory), physical activity (SIMPAQ), body composition (DXA), proportion with weight loss of 5% or 10% at endpoint versus baseline, change in body weight in kg, 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.

Given that the GLP-1 receptor is widely expressed in the human brain (42), and that there is a high density of GLP-1 receptors present cortical areas associated with memory formation, learning and emotional processing (43), it has been theorized that GLP1-RAs may have a pro-cognitive effect. In animal studies, GLP1\_RAs have been noted to reduce neuro-inflammation, improve cerebral metabolism, and aid neuro-regeneration (44, 45) (46).

We will test cognition at baseline and at 36 weeks to test the hypothesis that Semaglutide is associated with greater improvement in cognitive function than placebo. In addition, people with more greatly impaired cognition 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 subcutaneous semaglutide weekly for 36 weeks for people with schizophrenia or schizoaffective disorder treated with 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).

# Study Design

The design is a randomised, placebo-controlled, double-blind parallel trial to examine the clinical efficacy of add-on treatment of subcutaneous semaglutide to reduce body weight among people who are on clozapine. The study will include 80 individuals with schizophrenia or schizoaffective disorder currently prescribed clozapine.

# Study Population

Eighty (80) participants will be recruited through mental health services (i.e. inpatient units, clozapine clinics and continuing care units) in three Queensland Hospital and Health Services: (a) Metro North HHS, (b) Metro South HHS and (c) West Moreton HHS.

## Number of participants

The study will consist of a total of 80 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 or bipolar affective disorder, based on the Diagnostic Interview for Psychosis (DIP)
3. BMI ≥26kg/m2 and ≤40 at baseline
4. Have received oral clozapine for a period of at least 18 weeks
5. Have had less than 5% body weight increase or loss in the previous 3 months.
6. Agree to participate, have capacity to consent and are able to follow the study instructions and procedures

## Exclusion Criteria

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

1. Known allergies to Semaglutide or other GLP1 RA’s or any part of the formulation of the investigational product
2. Obesity induced by other endocrinologic disorder (e.g Cushing Syndrome, untreated Hypothyroidism)
3. Current use of any weight-lowering therapy including: pramlintide, sibutramine, orlistat, zonisamide, topiramate or phenteremine (either by prescription or as part of a clinical trial)
4. Diagnosis of Type 1 or Type 2 Diabetes mellitus as determined by an oral glucose tolerance test (OGTT)
5. Participants treated with corticosteroids or other hormone therapy (except oestrogens or thyroxine) for greater than 10 days
6. Chronic kidney disease (eGFR<60mL/min)
7. History of medullary thyroid adenoma or carcinoma, and patients with or family history of Multiple Endocrine Neoplasia syndrome type 2 (MEN 2)
8. History of pancreatitis
9. Previous surgical treatment of obesity
10. BMI ≤26kg/m2 or BMI ≥40 at baseline
11. Any concomitant disease or condition that according to the investigator’s assessment makes the patients unsuitable for trial participation
12. People who are unable to understand or communicate in English
13. For female participants, those currently pregnant, or planning to become pregnant or lactating or no acceptance to the use of effective contraception during the study period
14. Inability to follow the study instructions and procedures

# 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.

Participants who meet the inclusion criteria will be randomised using a computer-generated randomization table. Participants will receive either the intervention semaglutide or placebo in a 1:1 ratio for 36 weeks.

# 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 weekly for 36 weeks. During weekly injections participants will be monitored for side effects. Adverse events will be recorded weekly for the first 4- weeks than 4 weekly i.e. baseline, 1, 2, 3, 4, 8, 12, 16, 20, 24, 28, 32 and 36.

**Efficacy measures include:**

Percentage change in weight will be used as the primary outcome measure.

Secondary outcome measures will include the following:

* change in weight in kg
* 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 loss of 5% or more at endpoint versus baseline

Ancillary Measures

* clozapine/norclozapine ratio
* heart rate

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.
* 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.

**Dual-Energy X-ray Absorptiometry (DXA)**

We aim to recruit participants in a Dual-Energy X-ray Absorptiometry (DXA) scan which will be conducted at baseline and week 36. The scan does not involve any form of contrast medium and is an optional extra intervention to this study. DEXA is able to calculate body composition, and differentiate lean muscle, body adiposity and bone. Moreover, it can differentiate between visceral and peripheral adiposity.

Absolute body weight change is only a partial measure of change in cardiometabolic risk. Visceral adiposity is more metabolically active than peripheral adiposity (15). As such, investigation of body composition through imaging techniques such as dual energy X‐ray absorptiometry (DEXA) can provide a more accurate estimation of the location of body weight change (15). DEXA uses very low dose energy, and as such is of very low risk to participants. (16) Previous studies of GLP1-RAs among people with antipsychotic obesity have suggested that GLP1-RAs may lead to a reduction of visceral rather than peripheral adiposity (17).

This feature of the study will be clearly outlined in the consent form. In the event that a person objects to the Dual-Energy X-ray Absorptiometry (DEXA) they will not be excluded from participating in the trial.

## Biomarkers

In addition to the above clinical measures participants will have the option to provide a saliva sample at baseline to validate existing known correlates of clozapine and obesity, including variants in genes such as LEP and HTR2C. The DNA samples collected in this study will be used to validate associations between DNA SNPs and treatment refractory clozapine patient populations.

The saliva sample will be collected using a saliva collection tube. Participants will be asked to provide approximately 2mls of saliva into the collection tube. DNA will be extracted directly from the saliva sample and will be stored indefinitely for future unspecified testing of genetic material (i.e. DNA). The sample will be stored at QIMR Berghofer Medical Research Institute (QIMRB). However, future studies involving the stored DNA sample will require approval from a Human Research Ethics Committee. In the event that genetic testing or other investigations of bio specimens reveals a result which is potentially clinically actionable, we will contact the participant to discuss the findings and recommend they see their GP for further information and investigations as required. This feature of the study will be clearly outlined in the consent form, and participants will be informed that the DNA from the saliva sample 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 a saliva sample being collected and stored, they will not be excluded from participating in the study.

**Table 1: Schedule of Visits and Assessments (Intervention phase)**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **VISIT** | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
| **Screening** | **Baseline** |  |  |  |  |  |  |  |  |  |  |  |
| **WEEK** |  | 0 | 2 | 3 | 4 | 8 | 12 | 16 | 20 | 24 | 28 | 32 | 36 |
| **Study medication period (36 weeks)** |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **SCREENING AND CONSENT** |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Assessment of current medication | x | x | x | 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 | x | x | x |
| Inclusion / exclusion criteria | x |  |  |  |  |  |  |  |  |  |  |  |  |
| Urine pregnancy test (females only) | x |  |  |  |  |  |  |  |  |  |  |  |  |
| Drug administration (weekly injections)\* |  | x | x | x | x | x | x | x | x | x | x | x |  |
| **SAFETY** |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Adverse events trial medication |  | x | x | x | x | x | x | x | x | x | x | x | x |
| SAFTEE-SI\* |  | x | x | x | x | x | x | x | x | x | x | x | x |
| **EFFICACY** |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Height | x | x |  |  |  |  |  |  |  |  |  |  |  |
| Body weight\* | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Waist circumference & hip/waist ratio\* |  | x | x | x | x | x | x | x | x | x | x | x | x |
| Blood pressure\* |  | x | x | x | 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 |  |  |  | x |
| **OTHER** |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Heart Rate\* |  | x | x | x | x | x | x | x | x |  | x | x | x |
| PANSS TOTAL SCORE |  | x |  |  |  |  |  |  | x |  |  |  | x |
| GAF |  | x |  |  |  |  |  |  | x |  |  |  | x |
| SIMPAQ |  | 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 | x | x | x |
| Blood (other) - FBC (WCC, Neutrophils) ELFT, (Serum bicarbonate) part of routine ELFT and clozapine/nor clozapine levels |  | x |  |  |  |  | x |  |  | x |  |  | x |
| Optional DNA saliva sample |  | x |  |  |  |  |  |  |  |  |  |  |  |
| Optional DEXA |  | x |  |  |  |  |  |  |  |  |  |  | x |

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

**\*All participants will be seen weekly for 36 weeks for administration of subcutaneous semaglutide/placebo injection, physical measures and adverse events**

## Study Procedures

Trial medication will be dispensed weekly in the form of injection, to participants after randomisation has occurred. A delegated Research Pharmacist at the Princess Alexandra Hospital will dispense medication for all sites. For each randomised participant, the entire 36 weeks of trial medication will be provided to QCMHR delegated research staff. Trial medication will be administered weekly by delegated research staff in line with this protocol (section 7.4). Trial medication and placebo will be administered subcutaneously using blinded identical insulin syringes with Semaglutide or saline in equal volumes. There will be a total of 36 insulin syringes 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.

## 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 six monthly physical health screen as part of treatment as usual.

**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 report

**6.4.2 Pharmacokinetics**

**Semaglutide**

A summary of the pharmacokinetic information for subcutaneous semaglutide has been sourced from the PI for Ozempic. Absolute bioavailability of subcutaneous semaglutide is 89%. Maximum concentration of semaglutide is reached 1 to 3 days post dose. Similar exposure is achieved with subcutaneous administration of semaglutide in the abdomen, thigh, or upper arm. Steady-state exposure is achieved following 4-5 weeks of once-weekly administration. The mean apparent volume of distribution of semaglutide following subcutaneous administration in patients with type 2 diabetes is approximately 12.5 L. Semaglutide is extensively bound to plasma albumin (>99%). The apparent clearance of semaglutide in patients with type 2 diabetes is approximately 0.05 L/h. With an elimination half-life of approximately 1 week, semaglutide will be present in the circulation for about 5 weeks after the last dose. The primary route of elimination for semaglutide is metabolism following proteolytic cleavage of the peptide backbone and sequential beta-oxidation of the fatty acid sidechain. The primary excretion routes of semaglutide-related material are via the urine and feces. Approximately 3% of the dose is excreted in the urine as intact semaglutide.

# Investigational Product

## Description of Investigational Product

Active: 2.4mg (titrated – 0.25mg for 4 weeks, 0.5mg for 4 weeks, 1.0mg for 4 weeks, 1.7mg for 4 weeks, 2.4mg for the duration of the study) of subcutaneous semaglutide given using a blinded insulin syringe

Placebo: saline solution of matched volume given using a blinded insulin syringe

## Dose Justification

**Semaglutide**

Participants will be given a dose titration of 0.25mg subcutaneous semaglutide once weekly for a period of 4 weeks, then 0.5mg once weekly for a period of 4 weeks, then 1.0mg once weekly for a period of 4 weeks, then 1.7mg once weekly for a period of 4 weeks, then 2.4mg weekly thereafter.

Semaglutide is generally well tolerated with the most common side effects being nausea, vomiting, diarrhoea, constipation and dyspepsia. Adverse events are dose dependent and typically transient. Headache, increased pancreatic lipase levels, and increased amylase levels have been reported in treatment with semaglutide, and a meta-analysis reported infrequent acute pancreatitis (47). Overall, the risk of adverse events and treatment discontinuation is comparable to other GLP-1 agonists as found by a recent meta-analysis (48).

Due to the gastrointestinal effects of injectable semaglutide, this established a need for dose titration to increase tolerability. Two recent clinical trials of Semaglutide for obesity/overweight among people with, and without T2DM used a dose titration protocol of dose increases (as tolerated) every 4-weeks, starting at 0.25mg/week, 0.5mg/week, then 1.0mg/week, 1.7mg/week and then 2.4mg/week for the remainder of the trial. (6, 49). This dose regime has been used as the recommended titration in the product information of subcutaneous Semaglutide.

## Comparator Justification

This study will use a saline placebo administered subcutaneously in identical manner to the investigational product, with identical volumes.

Both semaglutide and placebo will be given as an 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. (50) 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), which includes information on diet and exercise.

## Administration

Semaglutide - 1.34mg/ml (titrated – 0.25mg (0.19ml) for 4 weeks, 0.5mg (0.38ml) for 4 weeks, 1.0mg (0.75ml) for 4 weeks, 1.7mg (1.3ml) for 4 weeks, 2.4mg (1.8ml) for the duration of the study) will be used in the study and administered subcutaneously using insulin syringes.

Placebo - saline solution of matched volume (titrated 0.19ml for 4 weeks, 0.38ml for 4 weeks, (0.75ml for 4 weeks, 1.3ml for 4 weeks, 1.8ml for the duration of the study) will be used in the study and administered subcutaneously using insulin syringes.

## 7.5 Randomisation Procedure

Randomisation will occur at time of recruitment to the study. Participants will be randomised (1:1 ratio) to add-on treatment with semaglutide or placebo via a computer-generated randomization table and will enter a 36-week double blind treatment phase.

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 semaglutide or placebo, participants will be provided with contact information (i.e., 24 hour number) for unblinding.

## Blinding and Unblinding Procedure

All medication will be blinded to the study personnel and the patient. Semaglutide and placebo syringes will be identical in packaging, appearance, and colour. 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.

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 refrigerated, restricted access location at temperature (2-8°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). All unused supplies of study medication will be accounted for and documented by the designated Research Pharmacist.

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:

Semaglutide: nausea, vomiting, diarrhoea, constipation and dyspepsia.

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 hospitalisation – 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 AEs and SAEs

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 (i.e. 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., anaemia versus low haemoglobin 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 36). 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 (SUSARs)

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.

**Semaglutide**

The most commonly reported adverse event with semaglutide overdose was nausea. All patients recovered without complications.

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 AEs, 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 (during open label metformin titration) to assess adverse drug reactions. After randomisation, clinically assessed at baseline, and every four weeks for 36 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. | Subcutaneous injection of study compound or placebo | Participants will receive a weekly subcutaneous injection of placebo or semaglutide | Possible | Negligible | Low | The PICF outlines the potential discomfort associated with the subcutaneous injections. Participants provide specific consent for this procedure which is identified on the consent form.  Injections will be given by clinical trial nurses specifically trained to give subcutaneous injections. |
| 6. | Saliva sample | Consenting participants will have the opportunity to provide a saliva sample at the baseline visit. May experience discomfort during this procedure. | Possible | Negligible | Low | Participants will be asked to expectorate into a small tube, approximately 2mls. Participants will be able to take as long as necessary to provide the sample and will be given strategies if experiencing any difficulty.  Participants will be informed they can withdraw from this procedure at any time. |
| 7. | 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.  Senior research staff (including Project Manager and Chief Investigator) will determine the most appropriate plan of action if required. |
| 8. | 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. |
| 9. | 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. |
| 10. | DEXA scan | Consenting participants will to take part in a DEXA scan at baseline and end point. Participants may experience discomfort from laying on the flat X-ray bed as still as possible for 10-20 minutes. | Possible | Minor - moderate | Low-medium | Experienced research staff will accompany participants for the scan and will advise the participant this procedure is voluntary and they can withdraw at any time. Experienced X-ray staff will be conducting the scan. |

## 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 will be measured weekly for 36 weeks 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 baseline.

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

### Waist Circumference

Waist circumference will be measured weekly for 36 weeks.

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, 24 and 36, 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, 24 and 36. In addition to the standard metabolic monitoring we will be collecting HbA1c and fasting insulin at weeks 0, 16 and 36 and OGTT at weeks 0 and 36. Blood draws will be added to the routine 4 weekly clozapine blood monitoring.

# Participant Completion and Withdrawal

## Participant Completion

Participants are considered to have completed the study if they complete 36 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 three or more weeks
* 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
* 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 semaglutide treatment will have a greater reduction of percentage body weight at week 36 compared to individuals taking placebo, adjusted for baseline body weight (ANCOVA).

## Endpoints

### Primary

36 week treatment of semaglutide versus placebo will lead to a greater reduction of percentage body weight at week 36 compared to individuals taking placebo adjusted for baseline (ANCOVA).

### Secondary

To determine if 36 week treatment of semaglutide versus placebo has comparative changes in change in weight in kg, rate of conversion to T2DM (endpoint 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, NAFLD and FIB-4 scores, clozapine/norclozapine ratio, heart rate, diet and appetite (Food Craving Inventory), physical activity (SIMPAQ), body composition (DXA), proportion with weight loss of 5% or 10% 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 from consenting participants via a saliva sample 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 36 week time point data from studies of Semaglutide 2.4mg for weight loss among people with overweight and obesity (without T2DM, Wilding et al 2021 (6) and with T2DM, Davies et al 2021 (49)), and informed by our pilot study of exenatide for clozapine obesity. The difference in the results between Wilding and Davies may be partially explained by the T2DM participants being on metformin. We anticipate that about half the sample will be on metformin at baseline.

Wilding et al 2021 (6) reported a baseline SD in weight of 21%, and a reduction of -3% for placebo and -13% for semaglutide. Davies et al 2021 (49) also reported a baseline SD in weight of 21%, and a reduction of -3% for placebo and -9% for Semaglutide.

With a baseline weight SD of 21%, and a 6.5% difference in weight at endpoint, an α =0.05, and power of 0.8 with repeated measures using Analysis of Covariance (ANCOVA) as the planned analysis we would require 32. Over a 36 week period we predict attrition of 20%. Thus, we will need to randomize approximately 80 participants.

## Statistical Analysis

We will adopt an intention-to-treat principle to analyse all outcomes (i.e. for those who do not complete the 36 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 change in percentage weight over the study period. 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 Human Research Ethics Application (HREA) 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 Human Research Ethics Application 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 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 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. Woolworths, K-Mart etc). During the major study visits participants will receive $50 at baseline, week 20 and 36. At weeks 4, 8, 12, 16, 24, 28 and 32, participants will receive $20 (total $290). We will provide an extra $30 for those participants who consent to taking part in the DEXA scan at baseline and endpoint (Total $60). 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 SAEs will be reported to the nominated insurance company.

The University of Queensland (Sponsor) will enter into a Clinical Trial Agreement with each of the three Hospital and Health Services (HHSs) 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 (HHSs) 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.

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