**PROTOCOL TITLE**

Cannabidiol (CBD) for Clozapine Refractory Schizophrenia (CanCloz)

SHORT TITLE

Cadence CanCloz

**Protocol Number:**

Version: 2.2

Date: 23rd June 2022

**SPONSOR**

The University of Queensland

Brisbane St Lucia, QLD 4072

Australia

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**PROTOCOL AMENDMENT HISTORY**

|  |  |  |
| --- | --- | --- |
| **Version** | **Date** | **Primary Reason for change** |
| 1.0 | 12th May 2022 | Original |
| 2.0 | 13th June 2022 | HREC request for further information recommendations |
| 2.1 | 21st June 2022 | HREC request for further information recommendations |
| 2.2 | 23rd June 2022 | HREC request for further information recommendations |

 **SPONSOR SIGNATURE**

The undersigned parties agree that the protocol was written in accordance with the World Medical Association Declaration of Helsinki — Ethical Principles for Medical Research Involving Human Subjects (Fortaleza, Brazil 2013), the NHMRC National Statement on Ethical Conduct in Human Research (2007, updated 2018), and the Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice E6 (R2) (November 2016) — with introductory comments of the Australian Therapeutic Goods Administration.

|  |  |  |
| --- | --- | --- |
| Protocol Writer Name  | Signature  | Date  |
| Professor Dan Siskind |  |  |
| Andrea Baker |  |  |

I acknowledge and agree that I am responsible for conducting the study sponsored by QIMR Berghofer and will ensure that it is conducted to the above principles and QIMR Berghofer policy and procedures.

|  |  |  |
| --- | --- | --- |
| UQ Principal Investigator Name | Signature  | Date  |
| Professor Dan Siskind |  |  |

This clinical trial protocol has been reviewed and approved by the Sponsor.

|  |  |  |
| --- | --- | --- |
| The University of Queensland Approving Authority Name  | Signature  | Date  |
|   |  |  |

**CLINICAL INVESTIGATOR SIGNATURE**

I have received and read this protocol and all appendices. I agree to conduct the study in compliance with the protocol and all applicable legal and regulatory requirements including, but not limited to the following:

* World Medical Association Declaration of Helsinki – *Ethical Principles for Medical Research Involving Human Subjects*
* NHMRC *National Statement on Ethical Conduct in Human Research* (2007) incorporating all updates
* Notes for ***Guidance on Good Clinical Practice (CPMP/ICH/135/95)-Annotated with TGA comments (July, 2000 and Integrated Addendum to ICG E6(R1): Guidelines for Good Clinical Practice E6(R2) 9 November 2016)***

I will be responsible for oversight of all trial site personnel and activities and that the study will be conducted in accordance with the current HREC approvals.

I agree to inform all patients that the study interventions are being used for investigational purposes and I will ensure that the requirements related to obtaining informed consent are in accordance with International Council for Harmonisation (ICH) Guidelines for Good Clinical Practice (GCP) section 4.8 and local requirements.

I agree to report adverse events that occur in the course of the study to the Sponsor in accordance with ICH Guidelines for GCP section 4.11 and local requirements.

I have read and understand the information in the Investigator’s Brochures, including the potential risks and side effects of the study drug.

I agree to promptly report to the HREC all changes in the research activity and all unanticipated problems involving risk to patients. I will not make any changes to the conduct of the study without HREC and Sponsor approval, except when necessary to eliminate apparent immediate harm to patients.

I agree to maintain adequate and accurate records and make those records available in accordance with ICH Guidelines for GCP section 4.11 and local requirements.

I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.

I understand that the study may be terminated or enrolment suspended at any time by the Sponsor, with or without cause, or by me if it becomes necessary, to protect the best interest of the patients.

Signature: Date:

Investigator Name: Professor Dan Siskind

**ABBREVIATIONS AND DEFINITIONS OF TERMS**

|  |  |
| --- | --- |
| AE | Adverse Event |
| AQOL | Australian Quality of Life |
| bd | Twice a day |
| CBD | Cannabidiol  |
| CGI | Clinical Global Impression  |
| CIB | Clinical Investigators’ Brochure |
| CRF | Case Report Form |
| CTN | Clinical Trial Notification |
| GAF | Global Assessment of Functioning |
| GCP | Good Clinical Practice |
| HAM-A | Hamilton |
| 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 |
| NOAEL | No Observable Adverse Effect Level |
| PANSS | Positive and Negative Syndrome Scale |
| PK | Pharmacokinetic |
| SAE | Serious Adverse Event |
| SANS | Scale for the Assessment of Negative Symptoms  |
| SD | Standard Deviation |
| TAU | Treatment as usual |
| TGA | Therapeutic Goods Administration |

**Table of Contents**

[Cadence CanCloz 1](#_Toc103355897)

[1. Contacts 9](#_Toc103355898)

[1 Introduction 12](#_Toc103355899)

[1.1 Cannabidiol 12](#_Toc103355900)

[1.2 Rationale for the Use of Cannabidiol (CBD) in Clozapine Refractory Schizophrenia 12](#_Toc103355901)

[1.3 Safety profile of Cannabidiol (CBD) 13](#_Toc103355902)

[2 Objectives 14](#_Toc103355903)

[2.1 Primary Objectives 14](#_Toc103355904)

[2.2 Secondary Objectives 14](#_Toc103355905)

[2.3 Tertiary (Exploratory) Objectives 15](#_Toc103355906)

[**2.4 Safety Objective** 15](#_Toc103355907)

[3 Study Design 15](#_Toc103355908)

[4 Study Population 16](#_Toc103355909)

[4.1 Number of participants 16](#_Toc103355910)

[4.2 Inclusion Criteria 16](#_Toc103355911)

[4.3 Exclusion Criteria 16](#_Toc103355912)

[5 Participant Information and Informed Consent 17](#_Toc103355913)

[5.1 Screening assessment 17](#_Toc103355914)

[6 Study Assessments and Procedures 18](#_Toc103355915)

[6.1 Clinical Measures 18](#_Toc103355916)

[6.2 Biomarkers 19](#_Toc103355917)

[6.3 Study Procedures 23](#_Toc103355918)

[6.4 Study Restrictions 23](#_Toc103355919)

[6.5 Safety Assessments 23](#_Toc103355920)

[**6.5.1** **Adverse Events** 23](#_Toc103355921)

[6.5.2 Other Safety Assessments 24](#_Toc103355922)

[7 Investigational Product 24](#_Toc103355923)

[7.1 Description of Investigational Product 24](#_Toc103355924)

[7.2 Dose Justification 24](#_Toc103355925)

[7.3 Comparator Justification 25](#_Toc103355926)

[7.4 Administration 25](#_Toc103355927)

[7.5 Randomisation Procedure 25](#_Toc103355928)

[7.6 Frequency of visits and follow up 26](#_Toc103355929)

[7.7 Blinding and Unblinding Procedure 26](#_Toc103355930)

[7.8 Product Labelling 26](#_Toc103355931)

[7.9 Handling and Storage of Study Drugs 27](#_Toc103355932)

[7.10 Accountability 27](#_Toc103355933)

[8 Adverse Events (AE) and Serious Adverse Events (SAE) 28](#_Toc103355934)

[8.1 Definition of an Adverse Event (AE) 29](#_Toc103355935)

[8.2 Definition of a Serious Adverse Event (SAE) 30](#_Toc103355936)

[8.3 Time Period, Frequency, and Method of Detecting AEs and SAEs 30](#_Toc103355937)

[8.4 Recording of AEs and SAEs 31](#_Toc103355938)

[8.5 Prompt Reporting of SAEs 31](#_Toc103355939)

[8.6 Expeditable Events (SUSAR’s) 32](#_Toc103355940)

[8.7 Evaluating AEs and SAEs 32](#_Toc103355941)

[8.7.1 Assessment of Intensity 32](#_Toc103355942)

[8.7.2 Assessment of Causality 33](#_Toc103355943)

[8.8 Follow-up of AEs and SAEs 34](#_Toc103355944)

[8.9 Overdose 34](#_Toc103355945)

[8.9.1 Reporting of Overdose 35](#_Toc103355946)

[8.10 Pregnancy 35](#_Toc103355947)

[8.11 Post-study AEs and SAEs 35](#_Toc103355948)

[8.12 Risk Management Process 36](#_Toc103355949)

[**8.13** **Vital signs (will be recorded at baseline, weeks 4, 8 and 12)** 43](#_Toc103355950)

[**8.13.1** **Pulse and blood pressure** 43](#_Toc103355951)

[**8.13.2** **Body Measurements** 43](#_Toc103355952)

[**8.13.3** **Weight and Height** 43](#_Toc103355953)

[**8.13.4** **Waist Circumference** 43](#_Toc103355954)

[**8.14** **Laboratory assessments** 44](#_Toc103355955)

[**8.14.1** **Blood samples** 44](#_Toc103355956)

[9 Participant Completion and Withdrawal 45](#_Toc103355957)

[9.1 Participant Completion 45](#_Toc103355958)

[9.2 Participant Withdrawal by the Investigator 45](#_Toc103355959)

[9.3 Participant Withdrawal 45](#_Toc103355960)

[9.4 Early Termination of the Study 45](#_Toc103355961)

[10 Case Report Form (CRF) 46](#_Toc103355962)

[11 Data Analysis and Statistical Considerations 46](#_Toc103355963)

[11.1 Hypotheses 46](#_Toc103355964)

[11.2 Endpoints 46](#_Toc103355965)

[11.3 Sample Size and Power 47](#_Toc103355966)

[11.3 Statistical Analysis 48](#_Toc103355967)

[12 Data Management 48](#_Toc103355968)

[12.1 Documentation 48](#_Toc103355969)

[12.2 Archiving 49](#_Toc103355970)

[13 Responsibility 49](#_Toc103355971)

[13.1 Sponsor 49](#_Toc103355972)

[13.2 Monitoring and Quality Assurance 49](#_Toc103355973)

[13.3 Roles and Responsibilities of the Data Safety Monitoring Board 49](#_Toc103355974)

[14 Responsibility 50](#_Toc103355975)

[14.2 Ethical Considerations 50](#_Toc103355976)

[14.3 Human Research Ethics Committee (HREC) 51](#_Toc103355977)

[14.4 Informed Consent 51](#_Toc103355978)

[14.5 Participants (18-64 years inclusive) 51](#_Toc103355979)

[14.6 Protocol Modifications 52](#_Toc103355980)

[14.7 Protocol Compliance, Deviations and Serious Breaches of GCP 52](#_Toc103355981)

[14.8 Data Capture 52](#_Toc103355982)

[14.9 Essential Document Maintenance, Access and retention 52](#_Toc103355983)

[14.10 Confidentiality 53](#_Toc103355984)

[15 Participant Reimbursement 53](#_Toc103355985)

[15.1 Emergency Contact with Investigators 54](#_Toc103355986)

[15.2 Notification of Primary Care Physician and Treating Psychiatrist 54](#_Toc103355987)

[15.3 Investigator Indemnification 54](#_Toc103355988)

[15.4 Intellectual Property (IP) and Licencing 54](#_Toc103355989)

[15.5 Publication Policy 54](#_Toc103355990)

[15.6 Protocol Amendments 56](#_Toc103355991)

[15.7 Version Control 57](#_Toc103355992)

[15.8 Archives: Retention of Study Records 57](#_Toc103355993)

[16 References 58](#_Toc103355994)

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# Introduction

## Cannabidiol

The two most common phyto-cannabinoids in *Cannabis sativa* plant species are delta-9-tetrahydrocannabinol (TCH) and Cannabidiol (CBD). The latter is known for its more anxiolytic profile, sparing disturbances in perception and thought processing. 1

The endocannabinoid system is a strong neuromodulatory system, with as effects on inflammation, cell proliferation and apoptosis, pain modulation, memory and learning, and fear, amongst other functions.2 Endocannabinoids bind to presynaptic receptors, including CB1 and CB2, to potentiate retrograde signals that regulate the release of other neurotransmitters, such as dopaminergic, serotonergic, adrenergic, cholinergic and c-aminobutyric acid (GABA).3, 4. CB1 receptors are most densely found in the brain, including in the basal ganglia, cerebellum, hippocampus, while CB2 receptors are more prominent in the peripheral nervous system, peripheral organs and immune system.2

CBD has a strong potential for neuropsychiatric therapeutic use as it acts on the central nervous system via neuroreceptors including CB1, serotonin 5-HT1A receptor, and the transient receptor potential (TRP) vanilloid type 1 (TRPV1) receptor.5 Recent studies have explored the role of CBD to target the endocannabinoid system to improve mood and anxiety, epilepsy, chronic pain, movement disorders (such as Parkinson’s disease), nausea and inflammation associated with metabolic syndrome, malignancy, atherosclerosis etc.4, 5. Following animal and in vivo studies, it is suggested that CBD is non-toxic, with minimal (usually mild) side effects.6 CBD has shown promise as a treatment in for mental disorders, including anxiety, insomnia and post-traumatic stress disorder.7 There is early evidence to suggest CBD may have a role in reducing symptoms of psychosis. 8

## Rationale for the Use of Cannabidiol (CBD) in Clozapine Refractory Schizophrenia

Approximately 3% of the population are affected by psychosis, characterised by disturbance in cognition, affect, perception and behaviours.9 These psychotic conditions, such as schizophrenia, can be difficult to treat, even with optimal therapy. Approximately one third of people with schizophrenia have treatment resistant schizophrenia (TRS).10 TRS is defined as ongoing symptoms and functional impairment despite two adequate and adherent trials of different antipsychotics.11

Whilst antipsychotic drugs and supportive therapies reduce symptom burden and relapse rate, many patients continue to have ongoing symptoms and concomitant cognitive and social disabilities, poor physical health and curtailed life expectancy.12 Currently, the most effective antipsychotic for TRS is clozapine, which leads to reductions in positive symptoms and hospitalisations.13, 14 Even so, only 40% of people with TRS trialled on clozapine meet clinical response criteria.15 For people with clozapine resistant schizophrenia, there are few agents available to augment treatment, and they have limited effectiveness.16

Since the first case report of CBD in the treatment of schizophrenia, there have been three randomised placebo controlled trials among people with schizophrenia, albeit not among people with clozapine resistant schizophrenia.17-21 A 6-week double blind parallel group trial with 88 participants with partially responsive schizophrenia, not trailed on clozapine, compared adjunctive CBD 1000 mg/day to placebo.19 This study found significantly superior reductions in positive psychotic symptoms among the CBD group. A 4-week double blind RCT among 42 participants of 600-800mg daily CBD compared to the standard antipsychotic drug amisulpride showed improvement in psychotic symptoms with both treatments, with lower adverse drug reactions in the CBD arm.21 However a double blind 6-week RCT among 36 treatment-responsive patients with schizophrenia did not find a difference in psychotic symptoms between CBD 600mg/day compared to placebo18.

To date, there have been no trials of CBD among people with clozapine resistant schizophrenia. Given the personal and societal cost of clozapine resistant schizophrenia, this research project has the potential to identify CBD, if found to be effective, as a novel, safe adjunctive treatment for clozapine refractory schizophrenia.

## Safety profile of Cannabidiol (CBD)

CBD has been well tolerated at different doses, across several clinical trials. A trial by Taylor and colleagues in healthy controls, showed that single CBD doses of 1500, 3000, 4500 or 6000 mg were well tolerated.22 In patients receiving multiple doses (750 and 1500 mg twice daily) for 6 days, CBD was also well tolerated, with no subjects leaving the trial due to adverse events.22 McGuire et al. trialled doses of 1000mg of CBD in patients with schizophrenia, in addition to their usual antipsychotic medications, for 6 weeks. The positive psychotic symptoms were lower in the treatment group, with similar adverse events as those of the placebo group, showing good tolerance for CBD.19 Treatments of psychosis using CBD have been seen to effectively reduce positive symptoms with minimal side efects.23

There is a suggestion that CBD may inhibit CYP1A2, CYP2B6, CYP2C9, CYP2D6 and CYP3A4 enzymes, which could potentially impact the metabolism of other psychotropic medications, as well as some antiepileptics, antibiotics, antifungals, digoxin, statins and other medication classes that are metabolised by CYP450 cytochromes.23, 24 Monitoring for adverse events associated with these comedications is required.24 Clozapine is mostly metabolised by CYP1A2, accounting for 70% of variation in clearance, with CYP2D6 responsible for the remainder of n-demethylation. 25. As such, clozapine levels will be monitored as part of the study protocol.

Two mouse studies of two and twelve weeks respectively, showed CBD did not affect physiological parameters (e.g., temperature, blood pressure, electrolytes, heart rate) or psychomotor function (e.g., ataxia, rigidity, tremor, gait disturbance).23, 26 Animal studies have suggested that CBD drug-drug interactions are not dose related, and may occur with both high or low doses.27

# Objectives

Using a randomised, placebo-controlled double-blind parallel-group trial; the primary objective in this study is to examine the clinical efficacy of an add-on treatment of CBD in patients with clozapine refractory schizophrenia.

## Primary Objectives

The Primary objective of the study is to determine the impact of a 12 week treatment of CBD on the total PANSS scores in patients with clozapine refractory schizophrenia compared to placebo.

## Secondary Objectives

To determine the impact of (1000mg daily) of CBD treatment over 12 weeks on the Positive and Negative Syndrome Scale (PANSS) subscales, depression (Calgary Depression scale), Anxiety (HAM-A), Sleep (Pittsburgh Sleep Quality index), Quality of Life(AQoL-8D), change in weight and metabolic syndrome components or its components (waist circumference, HbA1c, High Density Lipoprotein (HDL), Low Density Lipoprotein (LDL), Body Mass Index (BMI), triglycerides, blood pressure hip waist ratio, liver function tests, NAFLD and FIB-4 scores, heart rate, diet and appetite (Food Craving Inventory), physical activity (SIMPAQ), endpoint clozapine and norclozapine levels compared to baseline, neurocognitive measures (Verbal Memory and Learning, Digit Sequencing Task, Symbol Coding task, Semantic and Letter Fluency, Trail Making task, HAM-A, Test of Premorbid Functioning and Calgary Depression Scale), compared to individuals taking placebo.

To determine the safety and tolerability over 12 weeks of (1000mg daily) of CBD in patients with clozapine refractory schizophrenia as measured by SAFETEE-SI, reported adverse events and dropouts compared to placebo.

## Tertiary (Exploratory) Objectives

To examine changes between baseline and the 12 week end point of CBD and CBD metabolites (7-COOH-CBD, 6-OH-CBD, 7-OH-CBD) and THC and metabolites (checking for possible illicit cannabis use).

**2.4 Safety Objective**

To assess the preliminary safety and tolerability of CBD weekly for 12 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-group trial to examine the clinical efficacy and safety of add-on treatment of CBD in patients with clozapine refractory schizophrenia. The study will recruit 40 individuals with clozapine refractory schizophrenia who will be randomised at the point of obtaining written informed consent.

Participants will be given 1000mg daily of CBD or placebo, in addition to their normal routine care. Routine care is defined as 'individualized combinations of psychopharmacology, behavioural interventions, rehabilitation and associated clinical services in keeping with Queensland Health standards of care'.

A battery of validated clinical measures will be conducted at baseline (i.e. week 0 and end point, week 12) and physical health measures will be at baseline (i.e. week 0, 4, 8 and 12). Adverse events will be recorded 2 weekly (i.e. 0,2,4,6,8,10 and 12) and trial medication will be distributed to participants 2 weekly (i.e. 0,2,4,6,8 and 10). Randomisation will be carried out using a computer-generated randomization table. Participants, recruiters, Queensland Centre for Mental Health Research (QCMHR) staff and clinical staff will be blinded to the intervention. Participants will receive either active treatment (1000mg CBD) or placebo in a 1:1 ratio.

# Study Population

Forty (40) eligible participants with treatment refractory schizophrenia, will be recruited through the mental health services at Metro North, West Moreton, Metro South and Gold Coast Hospital and Health Services.

## Number of participants

The study will consist of a total of 40 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 for schizophrenia or schizoaffective disorder, based on the Diagnostic Interview for Psychosis (DIP)
3. Total PANSS score ≥60
4. Have received oral clozapine for a period of at least 18 weeks with a clozapine level of >350mg/ml
5. Agree to participate, has capacity to consent and 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. Pregnancy, lactation, or if sexually active, no effective contraception (applies to both male and female participants)
2. Clinical blood test findings that might compromise participant safety or confound the trial results
3. Active current substance misuse including amphetamine and cannabis use
4. Other prescribed cannabinoids
5. Severe disturbance, such that the person is unable to comply with either the requirements of informed consent or the treatment protocol
6. Any concomitant disease or condition that according to the investigator’s assessment makes the patients unsuitable for trial participation
7. Cessation of clozapine

# Participant Information and Informed Consent

Consent will only be obtained from participants who are deemed to have capacity to provide informed consent. Capacity will be determined by collaboration between the treating clinician and delegated West Moreton HHS - Queensland Centre for Mental Health Research (QCMHR) research assistants and will comply with the guidelines within the NHMRC National Statement on Ethical Conduct in Human Research 2007. All QCMHR mental health research clinicians receive extensive training on capacity to consent as part of their professional development.

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

QCMHR Research staff will receive notification from the approved recruiting sites, that a potential participant has provided verbal consent to be contacted for further study information. QCMHR Research staff will then seek verbal consent to complete an assessment of inclusion/exclusion criteria. This verbal consent will be documented in the screening CRF. The screening assessment will be conducted by delegated employed West Moreton HHS - QCMHR research assistants who are experienced mental health clinicians. The screening assessment will take place at the participants home residence (adhering to table 2 risk analysis matrix), or at their usual mental health clinic, the choice is theirs. It will take approximately one hour to complete and will determine eligibility to participate in the trial.

All participants will receive verbal information about the study, the screening process and what participation involves. Participants will also be given written information in the form of a PICF, which will be easily understandable and have a clear simple format including short sentences.

Participants who meet all inclusion criteria and none of the exclusion criteria will be invited to participate in the study. The formal consent process will be conducted by QCMHR Research staff who all have extensive mental health experience and will discuss the information sheet with each participant and a friend or family member if desired, at length. The participant will have the opportunity to ask questions and have those questions answered to their satisfaction. 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. There is no time frame on how long a participant has to consider participation.

# Study Assessments and Procedures

## 6.1 Clinical Measures

A battery of validated clinical measures will be conducted at baseline (i.e. week 0 and end point, week 12) and physical health measures will be at baseline (i.e. week 0, 4, 8 and 12). Adverse events will be recorded 2 weekly (i.e. 0,2,4,6,8,10 and 12) and trial medication will be distributed to participants 2 weekly (i.e. 0,2,4,6,8 and 10). The clinical measures will be undertaken by QCMHR research staff who will be supervised by the QCMHR Research Manager. The QCMHR Research staff members are experienced mental health clinicians who are trained in administering these measures. These clinical measures will be administered at the participants choice of either the mental health clinic or their home residence.

In the event a participant cannot be seen on a scheduled date, the Protocol allows for the participant to be seen within 5 days either side of the scheduled date. This will not impact on the study outcomes nor meet the criteria for a deviation.

**Efficacy measures include:**

Positive and Negative Syndrome Scale (PANSS) total score will be used as the primary outcome measure which is a widely used scale for measuring symptom severity of patients with schizophrenia.

Secondary outcome measures will include the following clinical assessments:

* PANSS subscales including Positive, Negative and General Psychopathology, widely used scale for measuring symptom severity of patients with schizophrenia
* Test of Premorbid Functioning (TOPF) 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.
* Clinical Global Impression (CGI) which is used to measure symptom severity, treatment response and the efficacy of treatments in treatment studies of patients with schizophrenia.
* 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.
* BACS (Brief Assessment of Cognition in Schizophrenia) – Verbal memory and Learning – measures verbal recall.
* BACS – Digit Sequencing task – measures working memory
* BACS – Symbol Coding Task 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.
* BACS – Semantic and letter 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.
* Hamilton Anxiety Scale (HAM-A) measures the severity of anxiety symptoms
* Calgary Depression Scale assesses depression independently of symptoms of psychosis in schizophrenia

## 6.2 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 genetic testing or other investigations of bio specimens reveals a result which is potentially clinically actionable, the Investigator 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 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**

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

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **VISIT** | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| **Screening** | **Baseline** |   |   |   |   |   |   |
| **WEEK** |   | 0 | 3 | 5 | 7 | 9 | 11 | 13 |
| **Study medication period (12 weeks)** |   |   |   |   |   |   |   |   |
| **SCREENING AND CONSENT** |   |   |   |   |   |   |   |   |
| Assessment of current medication | x | x | x | x | x |  x | x | x |
| Informed consent  | x |   |   |   |   |   |   |   |
| Ongoing capacity | x | x | x  | x  | x | x | x | x |
| Inclusion / exclusion criteria | x |   |   |   |   |   |   |   |
| Urine pregnancy test (females only) | x |   |   |   |   |   |   |   |
| Drug distribution (fortnightly) |   | x | x | x | x | x | x |  |
| **SAFETY**  |   |   |   |   |   |   |   |   |
| Adverse events trial medication |  |  x |  x |  x | x | x | x | x |
| SAFTEE-SI\* |  | x | x | x | x | x | x | x |
| **EFFICACY** |   |   |   |   |   |   |   |   |
| Height |  | x |   |   |   |   |   |   |
| Body weight |  | x |  | x |  | x |  | x |
| Waist circumference & hip/waist ratio |   | x |  | x |  | x |  | x |
| Heart Rate |  | x |  | x |  | x |  | x |
| Blood pressure |  | x |  | x |  | x |  | x |
| HDL, LDL, Triglycerides, Total Cholesterol |   |  x |   |   |   |   |  | x |
| HbA1c  |   | x |   |   |   |   |  | x |
| **VISIT** | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|  | **Screening** | **Baseline** |   |   |   |   |   |   |
| **WEEK** |   | 0 | 2 | 4 | 6 | 8 | 10 | 12 |
| PANSS TOTAL SCORE |   | x |   | x  |   |  x |  | x |
| GAF |   | x |   |   |   |   |  | x |
| SIMPAQ |   | x |   |   |   |   |  | x |
| AQOL |   | x |   |   |   |   |  | x |
| CGI |  | x |  |  |  |  |  | x |
| TOPF |   | x |   |   |   |   |  | x |
| BACS Verbal Memory and Learning |   | x |   |   |   |   |  | x |
| BACS Digit Sequencing Task |   | x |   |   |   |   |  | x |
| BACS Symbol Coding Task |   | x |   |   |   |   |  | x |
| BASC Semantic and Letter Fluency |  | x |  |  |  |  |  | x |
| HAM-A |  | x |  |  |  |  |  | x |
| Calgary Depression Scale |  | x |  |  |  |  |  | x |
| Trail Making Test |   | x |   |   |   |   |  | x |
| Food Craving Inventory |   | x |   |   |   |   |  | x |
| **OTHER** |   |   |   |   |   |   |   |   |
| Trial medication compliance |   |   |  x |  x |  x | x  |  x |  x |
| Blood (other) - FBC (WCC, Neutrophils, lymphocytes) ELFT, clozapine/nor clozapine levels |   | x |   |   |   |  |  |  x |

## 6.3 Study Procedures

Dispensing of CBD to participants will occur once consent has been obtained and after the screening phase and randomisation has occurred. A delegated Research Pharmacist at the Princess Alexandra Hospital Pharmacy will dispense medication for all sites in accordance with the pharmacy manual. For each randomised participant, the entire 12 weeks of study medication will be provided to QCMHR delegated research nursing staff. Upon receiving the study medication, two designated QCMHR research nursing staff will document using the IP Accountability Log. Two designated QCMHR research nursing staff will also sign out the study medication for each randomised participant using the IP Accountability Log. The study medication will be distributed to the participant on a fortnightly basis by delegated QCMHR research nursing staff in line with this protocol (section 7.4). There will be a total of 6 dispensations per participant. The QCMHR Research Manager will be responsible for completing the IP Accountability Log at the end of the study, for each randomised participant. These logs will be filed in the master site file.

## 6.4 Study Restrictions

Participants are restricted from using other prescribed cannabinoids during the study.

## 6.5 Safety Assessments

All patients recruited in this study will be active cases at Metro North, Metro South, Gold Coast and West Moreton Hospital and Health Services. The QCMHR Research team will liaise with clinical staff to ensure that participants have undergone a routine physical health screen.

Female participants will have a urinary pregnancy screen at baseline prior to inclusion, and during the study if indicated.

**6.5.1 Adverse Events**

An Adverse Event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered an investigational product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product. This includes any newly occurring event, or a pre-existing condition that has increased in severity or frequency since the administration of the investigational product.

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 changes in their health. See Section 8 for full details on adverse event reporting.

### 6.5.2 Other Safety Assessments

If the participant is of child-bearing potential and sexually active, urine pregnancy tests will be conducted at baseline or when clinically appropriate.

# Investigational Product

## Description of Investigational Product

Linnea SA (Switzerland Company) has been contracted to manufacturer the study medication in accordance with cGMP guidelines.

Active: CBD 1000mg size 0 hard capsules will be compounded in identical form

|  |  |
| --- | --- |
| 1000mg CBD | 5 capsules in the pm  |
| Placebo | 5 capsules in the pm |

Placebo: size 0 hard capsules containing MCT oil only. Capsule shell consisting of water, gelatin and glycerine.

## Dose Justification

Based on previous trials, oral doses of 600-1000 mg/day of CBD have been used. Results of these trials suggest that CBD doses around 1000 mg/day may be required in people with schizophrenia in order to see improvement in symptoms. Bergamaschi et al reviewed adverse effects of a wide range of CBD doses in treatment trials. They found that even oral doses of up to 1500 mg/day were well tolerated, without effects on psychomotor activity, mood, or homeostatic activity27. Side effects such as fatigue, diarrhoea and changes in appetite/weight were most commonly reported following use of CBD25.

Accordingly, daily oral CBD 1000mg will be administered for 12 weeks. The CBD will be provided by Linnea SA, a Switzerland Good Manufacturing Practice (cGMP) accredited vendor.

## Comparator Justification

This study will use a placebo manufactured by Linnea SA (size 0 hard capsules containing MCT oil only. Capsule shell consisting of water, gelatin and glycerine.), 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. Therefore, the use of an adjunct therapy has been selected to ameliorate these ethical concerns as both the experimental and control groups will receive standard medical care (Treatment as Usual).

## Administration

|  |  |
| --- | --- |
| 1000mg CBD | 5 capsules in the pm  |
| Placebo | 5 capsules in the pm |

## Randomisation Procedure

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

The investigational products will be manufactured by Linnea SA in accordance with current Good Manufacturing Practice (cGMP) which is a 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 manufacturer and to the Princess Alexandra Hospital Pharmacist. The Princess Alexandra Hospital Pharmacist will hold the closed randomisation list and be the only one who has the ability to unblind in accordance with the unblinding manual. In the case of emergency where it is crucial the medical staff knows whether the participant is on CBD or placebo, participants will be provided with contact information (i.e. 24 hour mobile number 0439088922) for unblinding.

## Frequency of visits and follow up

Participants will be clinically assessed at baseline (i.e. week 0 and end point, week 12) and physical health measures will be at baseline (i.e. week 0, 4, 8 and 12). QCMHR Research Team will also contact participants once a week between face-to-face assessments by phone to monitor compliance and adverse events. Refer to Table 1 Schedule of Visits and Assessments.

## Blinding and Unblinding Procedure

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

Only 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 Pharmacist via the 24 hour number. All cases of emergency unblinding will be documented in the participants CRF and recorded on a Serious AE Form (if the participant meets the SAE criteria) 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.

|  |
| --- |
| **KEEP OUT OF REACH OF CHILDREN****FOR CLINICAL TRIAL USE ONLY****CBD STUDY**Study ID Cannabidiol or Placebo () Capsules.Qty Capsules Store below 30°CFor Oral Administration.Directions for use: Swallow five (5) whole capsules in the evening for 14 days.**Batch No: Exp Date:** **BOTTLE No: XX**Investigators Name: Professor Dan SiskindSubject Number: \_\_\_\_\_\_\_\_\_\_\_\_Sponsor: The University of Queensland(m) 0439088922 |

## Handling and Storage of Study Drugs

Prior to dispensing, all study medication will be kept securely locked, in a dry, restricted access location in a temperature-controlled room (20-25°C) at Queensland Centre for Mental Health Research. Temperature will be monitored using a temperature data logger and will be recorded on a weekly basis filled in the master site file. Any temperature excursions identified will be discussed with the manufacturer and managed according to their advice and recorded in the master site file. Only delegated members of the QCMHR Research Team will have access to the investigational products.

## Accountability

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

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

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), batch 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)

An Adverse Event (AE) means any untoward medical occurrence in a patient or clinical investigation subject administered an investigational product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product. This includes any newly occurring event, or a pre-existing condition that has increased in severity or frequency since the administration of the investigational 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: Anorexia, vomiting, allergic reactions

## 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 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.

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

All adverse events will be reported and recorded between the time of consent and the final visit (week 7) in the participants CRF.

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?”*

AEs should be monitored until resolution or until they are clearly determined to be due to aparticipant’s stable condition or intercurrent illness.

Investigators are not obligated to actively seek AEs or SAEs in participants after the study follow-up period. However, if the investigator learns of any SAE at any time after a participant has been withdrawn from the study, and he/she considers the event reasonably related to the investigational product, the investigator will promptly notify the Sponsor. AE logs will be submitted to the sponsor at n=15, n=40 and or end of study.

The sponsor will provide the site with annual safety reports in accordance with the NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods (November 2016).

## 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. AE’s will be recorded using MeDRA coding. 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 QIMR Berghofer (sponsor) by contacting the medical 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 emailed to the Research Office and UQ Principal Investigator within 24 hours of first becoming aware of the event.

UQ (Sponsor)

UQ Principal Investigator: Professor Dan Siskind

AND

Research Ethics and Integrity (Sponsor Representative)

Email: c.rosemeyer@uq.edu.au

Phone: +61 7 3365 4583

If the site investigator does not have all information regarding an SAE, ***he/she will not wait to receive additional information before notifying the sponsor*** 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.

The sponsor will ensure all SAEs are reviewed by their Principal Investigator and Medical Monitor and any outcome recorded. The site will be notified of any significant safety findings.

The sponsor will be responsible of notifying any relevant safety events to the TGA consistent with the NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods 2016 guidelines and TGA requirements.

## Expeditable Events (SUSAR’s)

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

## Evaluating AEs and SAEs

### Assessment of Intensity

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

**Mild:** sign or symptom that is easily tolerated by the Participant, causing minimal discomfort and not interfering with everyday activities.

**Moderate:** sign or symptom that is sufficiently discomforting to interfere with normal everyday activities.

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

**Life threatening**: sign or symptom results in a potential threat to life

**Fatal**: fatal sign or symptom results in death

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.

**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**

The Principal Investigator, in consultation with the Sponsor, will assess all reported SAEs for expectedness. This assessment will be performed with reference to applicable product information (e.g. Investigator's Brochure for an unapproved investigational product).

**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).

Adverse events that are causally related to the study product, and that are both serious and unexpected will be reported to the Therapeutic Goods Administration by the Sponsor in accordance with expedited reporting requirements.

## 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 each face to face contact (2 weekly) and during phone calls (in between weeks).

All AEs and SAEs will be followed until resolution, until the condition stabilises, until the event is otherwise explained, or until the Participant is lost to follow-up. Once resolved, the appropriate AE/SAE Case report Form (CRF) page(s) will be updated.

## Overdose

An overdose is defined as a dose taken by a patient 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.

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 patient 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 using the pregnancy report form. 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.

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 and will follow the participant up until the end of the pregnancy.

## Post-study AEs and SAEs

A post-study AE/SAE is defined as any event that occurs outside the AE/SAE detection period as defined in Section 8.3 “Time Period, Frequency, and Method of Detecting AEs and SAEs” of the protocol.

For participants that have experienced AE’s and SAE’s during the trial, we will follow-up until resolution and/or liaise with the treating team to optimize ongoing care as appropriate. For participants who experience a post study AE, a member of the research team will contact the participant to find out details of the event. These will be managed as per the previously described AE and SAE processes.

## Risk Management Process

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

It will ensure that risk and uncertainly 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). Participation in this trial is low risk in terms of CBD being safe. There are risks that are associated with participation of any trial (issues of confidentiality breach, discomfort from venesection, no benefit from the investigational product). The benefits that we anticipate range from none to receiving enriched care as a result of the follow up by a member of the research team. In addition, participants receive a small gift voucher to renumerate them for their time. The wider benefit is that the participants are supporting a study that will provide more information about a potential treatment for schizophrenia.

**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 clinically assessed at baseline, and every second week for 12 weeks. We will also contact participants once a week between face-to-face assessments by phone or other electronic means 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 expresses suicidal ideation. | 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 following advice from the treating team in managing the situation. 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. | 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. |
| 6. | Overdose | An overdose would include any dose greater than the highest daily dose included in the protocol or prescribing information.  | Possible | Minor-Moderate | Medium-High | For all overdoses the Serious AE Form will be completed and reported to the sponsor within 24 hours from the time that the Investigator or delegated research staff was notified of the overdose.Participants will be provided with 14 days’ supply at each face to face visit.Research staff will conduct a pill count at each face to face visit.Research staff will conduct medication compliance questionnaire at each face to face visit and phone contact.Any identified issues with medication compliance will be discussed at weekly team meetings. Senior research staff (including Project Manager and Chief Investigator) will determine the most appropriate plan of action if required. |
| 7. | 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. |
| 8. | 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. |

* 1. **Vital signs (will be recorded at baseline, weeks 4, 8 and 12)**
		1. **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.

* + 1. **Body Measurements**

Body measurements will include weight, height and waist circumference.

* + 1. **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).

* + 1. **Waist Circumference**

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.

* 1. **Laboratory assessments**

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 8.3).

* + 1. **Blood samples**

Samples will be drawn at week 0 (baseline), and 12 (end point), for assessment of white cell count, neutrophils, lymphocytes, 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, and 12. In addition to the standard metabolic monitoring we will be collecting HbA1c at weeks 0, and 12 and measuring CBD and THC levels. 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 12 weeks of dosing and associated assessments and blood tests.

## Participant Withdrawal by the Investigator

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

* Non-compliant with study medication for seven consecutive days
* Non-adherence of more than 50% of study medication on capsule count
* Development of a serious adverse event assumed to be associated with the study medication
* Cessation of effective contraception or confirmed pregnancy
* Lost to follow up
* Death
* Discontinuation of the study by the Sponsor, a Regulatory Authority, or a Human Research Ethics Committee
* Investigator’s decision to remove the participant from the study
* 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 Sponsor, Principal Investigator(s), Human Research Ethics Committee (HREC) and Regulatory Authorities independently reserve the right to discontinue the study at any time for safety or other reasons. This will be done in consultation with the Sponsor where practical. In the occurrence of premature trial termination or suspension, the above mentioned parties will be notified in writing by the terminator/suspender stating the reasons for early termination or suspension (with the exception of the sponsor’s responsibility for notifying the Regulatory Authorities). After such a decision, the Sponsor and the Investigator will ensure that adequate consideration is given to the protection of the subjects’ interests. The investigator must review all participating subjects as soon as practical and complete all required records.

# 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 UQ (Sponsor) for data analysis. In the CRF, participants will only be identified by their participant number in order to retain participant confidentiality.

All study related documents and records are to be retained for a minimum of fifteen years after trial completion. Written agreement from the Sponsor must precede destruction of the same.

# Data Analysis and Statistical Considerations

## Hypotheses

Those participants allocated to the active arms (1000mg daily) of CBD treatment will have meaningful difference in total PANSS score of at least 5 units (SD = 14.3) at week 12 compared to individuals taking placebo.

## Endpoints

| **OBJECTIVES** | **ENDPOINTS** | **JUSTIFICATION FOR ENDPOINTS** |
| --- | --- | --- |
| **Primary** |  |  |
| The Primary objective of the study is to determine the impact of 1000mg daily, CBD treatment over 12 weeks on the total PANSS scores in patients with treatment refractory schizophrenia compared to placebo.  | Reduction in Total PANSS scores at day 84 in the intervention groups compared to placebo | The study is of adequate duration to determine if CBD reduces the PANSS scores in people with treatment refractory schizophrenia.  |
| **Secondary** |  |  |
| To determine the minimal dose (1000mg daily) of CBD treatment over 12 weeks on PANSS subscales, GAF, CGI, TOPF, AQOL, Calgary Depression Scale, HAM-A, BACS Verbal memory, Digit Sequencing task, Symbol Coding task and Semantic and Letter fluency compared to individuals taking placebo. | Reduction in PANSS sub scales, GAF, CGI, TOPF, AQOL, Calgary Depression Scale, HAM-A, BACS Verbal memory, Digit Sequencing task, Symbol Coding task and Semantic and Letter fluency at day 84 in the intervention group compared to placebo | The study is of adequate duration to determine if CBD changes these secondary symptom measures in people with treatment refractory schizophrenia.  |
| To determine the safety and tolerability over 12 weeks of the dose (1000mg daily) of CBD in patients with treatment refractory schizophrenia as measured by reported adverse events compared to placebo  | Limited reported adverse events at day 84 related to the intervention dose compared to placebo | The study is of adequate duration to determine if CBD causes adverse effects in people with treatment refractory schizophrenia.  |

## 11.3 Sample Size and Power

The study is powered based on the primary outcome of endpoint PANSS score. With a difference in endpoint PANSS of 2.8, and a standard deviation of 6.5, a two-sided α =0.025, and power of 0.8 with repeated measures using Analysis of Covariance (ANCOVA) as the planned analysis we would require 40 participants.

We anticipate that 40% of the ~1600 South-East Queensland clozapine clinic attendees will have clozapine refractory schizophrenia. Of these 640, we anticipate a 30% agreement to participate rate, based on our previous studies in this population.

## Statistical Analysis

The effect of the CBD intervention relative to placebo on the outcome of 12-week PANSS score will be analysed in an ANCOVA model with baseline PANSS as the covariate. Supplementary analyses using linear regression will additionally adjust for (i.e., include as a covariate) study centre. Participants for whom 12-week PANSS measurements are missing will not be included in the primary analyses of the primary outcome. Depending on the patterns of missing data, appropriate post hoc sensitivity analyses will be performed. Change in PANSS measurements over time (across the three 4-weeky visits) will be analysed using linear mixed effect regression models adjusted for baseline PANSS. Other secondary outcomes will be analysed using regression models as appropriate for the outcome. Number needed to treat will be calculated on proportions of participants in each arm who achieve >20% reduction in PANSS.

# 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 Case Report Form (CRF) also known as source data, 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 each site.

De-identified data from the CRFs will be entered into REDCap, which is a secure 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.

# Responsibility

## Sponsor

## Monitoring and Quality Assurance

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.

The Research centre (Queensland Centre for Mental Health Research) 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.

**13.3 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.

**13.3 Roles and Responsibilities of the Data Safety Monitoring Board**

After the first 10 participants have been recruited and then at the end of study (40 participants), review and evaluate accumulated trial data for participant safety, trial conduct and progress and, where appropriate, efficacy.

• Make recommendations to the CADENCE-CanCloz investigators concerning the modification, continuation and/or termination of the trial.

• Maintain the confidentiality of its internal discussions and activities as well as the contents of the reports and data provided to it.

• Review and approve major post-activation modifications to trial (if any) proposed by the trial investigators

The DSMB will perform the following activities:

• Prior to start of the trial the DSMB will meet (teleconference or via email discussion) to review the trial protocol.

After the first 10 participants have been recruited and then at the end of study (40 participants), the DSMB will:

* evaluate the progress of the trial including assessments of data quality, participant recruitment, accrual and retention, participant risk versus benefit, and other factors that can affect trial outcome.
* review all adverse events (i.e. mild, moderate, severe or life-threatening events) whether they are related or unrelated to the administration of trial drug.

• The DSMB will review all Serious Adverse Events (SAE) which are considered to be probably or definitely related to the trial medication as they are reported (see approved safety reporting protocol).

# Responsibility

**14.1 Investigator**

## 14.2 Ethical Considerations

The investigator will ensure that this study is carried out in accordance with the World Medical Association Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects, the NHMRC National Statement on Ethical Conduct in Human Research (2007) incorporating all updates and the -Notes for Guidance on Good Clinical Practice (CPMP/ICH/135/95)-Annotated with TGA comments (July, 2000 and Integrated Addendum to ICG E6(R1): Guidelines for Good Clinical Practice E6(R2) 9 November 2016).

## 14.3 Human Research Ethics Committee (HREC)

This protocol, the written Participant Information and Consent Form and any other written material that will be provided to participants will be submitted to Metro South HREC for approval prior to participant accrual. If approval is suspended or terminated by the HREC, the investigator will notify the Sponsor immediately.

It is the responsibility of the investigator to report study progress to the HREC at least annually, or as otherwise required by the HREC.

The investigator will be responsible for reporting serious adverse events and other applicable safety information to the HREC in accordance with the guidelines of the HREC.

## 14.4 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.42

### 14.5 Participants (18-64 years inclusive)

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

It will be pointed out to participants that they can withdraw from the study at any time without prejudice and will not affect their current care. The 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 Case report Form (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.

## Protocol Modifications

The Investigator must not modify the protocol without first obtaining the agreement of The University of Queensland in writing. No changes to the protocol may be implemented without prior approval of The University of Queensland and the appropriate HREC, unless where required to eliminate immediate risk to study participants.

It is the responsibility of the Investigator to submit the amendment to the appropriate HREC for approval and provide a copy of the written HREC approval to the Sponsor. Protocol amendments should be signed by each investigator and the original signature page(s) should be forwarded to the Sponsor. Any training that is required by the amendment must be documented by the investigator and relevant site personnel. If a protocol amendment requires changes to the Participant Information and Consent Form, the revised Participant Information and Consent Form must be approved by the appropriate HREC.

## Protocol Compliance, Deviations and Serious Breaches of GCP

All deviations from the approved protocol will be documented and reported to the Sponsor. Those deviations deemed to have a potential impact on the integrity of the study data, patient safety or the ethical acceptability of the trial will be classified as protocol violations and reported to the HREC as per HREC guidelines. The sponsor is responsible for reporting serious breaches to the reviewing HREC within 7 calendar days of confirming a serious breach has occurred and provide follow-up reports when required. The sponsor will notify the sites principal investigator within 7 days of confirming a serious breach has occurred.

## Data Capture

The investigator or appropriately delegated study staff member will enter all protocol-required data into a Case Report Form (CRF) for each participant enrolled in the study. The investigator or study staff member should ensure that all data entered into the CRF is consistent with source documents and entered within a timely manner.

**14.9 Essential Document Maintenance, Access and retention**

The research site will maintain adequate and accurate records for this study, in compliance with ICH GCP Section 8. The investigator is responsible for maintaining the Investigator Site File, comprising the signed protocol / amendments, informed consent forms, CRF, curriculum vitae, financial disclosure forms, training records, Site Signature and Delegation Log and other applicable documents and correspondence.

Upon request, the investigator(s) / institution(s) will permit direct access to source data / documents for trial-related monitoring, audits, HREC review and regulatory inspection(s) by the Sponsor (or their appropriately qualified delegate) and Regulatory Authorities. Direct access includes examination, analysis, verification and reproduction of records and reports that are important to the evaluation of the trial.

The investigator should ensure that all study documents and records are stored securely throughout the duration of the study. All study related documents and records are to be retained for a minimum of fifteen years after trial completion. Written agreement from the Sponsor must precede destruction of the same.

**14.10 Confidentiality**

Authorised personnel from The University of Queensland or its representatives, responsible HREC(s) or regulatory authorities may review medical records of study participants for monitoring or audit purposes to ensure compliance with this protocol and all applicable regulatory and legal requirements.

These parties will not disclose the identity of any research participant to a third party, unless permitted or required by law. All study participants will be assigned a unique identifier and no identifying information is to be entered by the Investigator or study staff on any CRF, document or biological specimen provided to the Sponsor.

The investigator agrees that all study documents provided by the Sponsor will not be shared

with third parties unless specific prior permission is granted in writing by The University of Queensland or such disclosure is required by federal or other laws or regulations.

## 15 Participant Reimbursement

Participants will be reimbursed for out of pocket expenses, inconvenience and time involved by the provision of prepaid gift cards (e.g. Coles-Myer, K-Mart etc). We will provide a $20 gift card at the baseline visit and weeks 2, 4, 6, 8, 10 and 12 (total reimbursement $140). If the study is terminated by the Investigator prior to completion, or a participant withdraws or is withdrawn from the study before completion, a pro-rata payment will be made at the discretion of the Investigator.

## 15.1 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.

## 15.2 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. A copy will be retained by the study site for verification by the Study Monitor.

## 15.3 Investigator Indemnification

The University of Queensland adheres to the Medicines Australia “Guidelines for Compensation for Injury Resulting from Participation in a Company-Sponsored Clinical Trial,” and holds a No-Fault Compensation for Clinical Trials insurance policy. The study sponsor agrees to indemnify the investigator(s) from any claims for damages for unexpected injuries, including death, that may be directly caused by the participant’s participation in the study, but only to the extent that the claim is not caused by the fault or negligence of the participants or investigator(s), hospital, institution, ethics committee.

The University of Queensland (Sponsor) will enter into a Clinical Trial Agreement with Metro North, Metro South, Gold Coast and West Moreton Hospital and Health Services (HHS) who will be involved in the study, based on the standard Medicines Australia format.

## 15.4 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.

## 15.5 Publication Policy

A publication policy relating to abstracts submitted for conference oral and/or poster presentation, peer reviewed scientific articles, letters, editorials and comments based on data arising from the study.

1. **Definition of Authorship**

The project will employ the authorship framework developed by the Australian Vice Chancellors' Committee and the National Health and Medical Research Council:

*“Authorship is participation in conceiving and/or executing and/or interpreting at least that part of a publication in a co-author's field of expertise, sufficient for him/her to take public responsibility for it.*

*Authorship should be based on: substantial contribution to concept and design, or analysis and interpretation of data; drafting of the article or revising it critically for important intellectual content; and final approval of the version to be published.*

*Participation solely in the acquisition of funding or the collection of data does not justify authorship.”*

1. **Entitlement to Authorship**

All Chief and Associate Investigators (CIs and AIs) will have the opportunity to nominate to contribute to ‘core’ publications arising from this study (i.e., those addressing the major pre-specified aims of the study). This assumes a contribution to the writing of the paper.

For ‘non-core’ publications (e.g., those addressing secondary aims; student-led papers), the lead author, in consultation with PI Warren, will determine the reasonably inclusive subgroup of CIs and AIs to be offered the opportunity to contribute and co-author.

Other research staff (e.g., research nurse, research assistants) will have the opportunity to be a contributing author on papers which they contribute to substantially (i.e., going beyond data collection and management into analysis and/or writing of the paper).

Authors should ensure that the work of research students, research assistants and technical officers not on the authorship list, is properly acknowledged.

1. **Order of Authorship List**

Ordering of subsequent authorship will be determined by the proposer/lead author based on contribution and amount of input. The proposed order will then be discussed with PI Warren for confirmation.

1. **Removal from Authorship List**

In the event that an author leaves or reduces their input into the manuscript writing process, their rights and contributions regarding authorship will be discussed and agreed with the lead author. Changes to the authorship list will be discussed by the remaining research team.

1. **Acknowledgement**

A written acknowledgement of the funding by the Metro South Health Research Support Scheme will be included in all publications, newsletters and other materials that are published.

1. **Submission and Correspondence with Scientific Journals:**
	1. All authors should agree on the target journal and scientific conference the manuscript/abstract is to be submitted to or the appropriate ‘non-scientific’ publication (e.g., newspaper article).
	2. The lead author will coordinate the submission and responses to reviewer comments in consultation with co-authors.
	3. Before any article is submitted for publication, the manuscript will be ‘signed-off’ by the Writing Committee or by circulation to all investigators. This includes the completion of the appropriate forms of authorship as required by the journal and the academic institute(s).
	4. Overlap between papers should be minimised. All proposed papers should be scrutinised for potential overlap, and this should be identified and minimised by appropriate changes before the paper(s) are submitted.

## 15.6 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.

## 15.7 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-15

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.

## 15.8 Archives: Retention of Study Records

All study related documents and records are to be retained for a minimum of fifteen years after trial completion. Written agreement from the Sponsor must precede destruction of the same.

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