**PROTOCOL TITLE**

Dose finding clinical trial of sodium benzoate in people with treatment refractory schizophrenia

SHORT TITLE

Cadence DISCOVERY

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**STUDY ACKNOWLEDGMENT/CONFIDENTIALITY**

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

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

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

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

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

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**ABBREVIATIONS AND DEFINITIONS OF TERMS**

|  |  |
| --- | --- |
| AE | Adverse Event |
| AQOL  bd | Australian Quality of Life  Twice a day |
| CGI | Clinical Global Impression |
| CIB | Clinical Investigators’ Brochure |
| CRF | Case Report Form |
| CTN | Clinical Trial Notification |
| DAAO | D-amino acid oxidase |
| GAF | Global Assessment of Functioning |
| GCP | Good Clinical Practice |
| HDRS | Hamilton Depression Rating Scale |
| 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 |
| NMDA | N-methyl-D-aspartate |
| 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 |

# Introduction

Psychotic disorders are syndromes characterized by disturbances to cognition, affect, perception and behaviour. Approximately three percent of the population will be affected by psychosis at some point in their lives; onset is commonly in the second or third decade of life with males at higher risk. The pharmacological treatment of psychotic disorders has seen little innovation in recent decades. Since the advent of antipsychotic medication, the prognosis for those diagnosed with schizophrenia has largely remained unchanged with the majority of people experiencing persistent disability, severe physical and mental health problems and premature mortality. This is due to current treatments being only partially effective and having a high burden of adverse effects leading to low adherence. Furthermore, schizophrenia is all too commonly considered a unitary disease rather than a heterogeneous syndrome requiring individualized care. Finally, clinical outcomes are compromised by the silo approach to treating mental illness in psychiatry and there is a need to ensure better collaborations with other medical specialties to provide enhanced multidisciplinary care.

To reduce the personal, social and economic burden associated with psychotic disorders it is of utmost important to investigate novel methods of increasing the efficacy of pharmacological treatment.

## Building a clinical trials platform

The Cadence Clinical Trial Platform which Professor James Scott co-established in 2012 with Professor John McGrath has provided Queensland with capacity to undertake research into exciting novel interventions for schizophrenia and other mental disorders. This enables people in Queensland living with mental illness to participate in cutting edge clinical trials. It has been through clinical trials that outcomes have improved in cardiovascular disease and cancer. It will be through medical research that people with schizophrenia and other serious mental disorders can enjoy improvements in clinical care.

In order to grow research capacity in Queensland mental health services, Professor James Scott in collaboration with QIMR Berghofer’s clinical expertise, will harness the resources of hospital and health services and the hard work and good will of clinicians who spend their days providing care for people with serious mental illness. With the academic and clinical partnerships well established in Queensland, we have the opportunity to conduct studies that will translate to better outcomes for those with serious mental illness. Mentoring the next generation of clinician researchers will retain the best and brightest in our public mental health services. Our inter-specialty and interdisciplinary collaboration has resulted in the identification and treatment of an autoimmune cause of psychosis. This is an example par excellence of the future of psychiatry where work with other specialties in combination with multidisciplinary research teams (medical, nursing and allied health) will lead to individualized treatments that will optimize the care for people with serious mental illness.

## Novel interventions for psychosis

Schizophrenia affects 1 in 200 people, commonly occurring in adolescents and young adults with only 1 in 7 people fully recovering, leaving the majority with significant disability [1]. Antipsychotic medications modulating dopaminergic activity are only partially effective in reducing symptoms and improving functioning in people with schizophrenia. It is now recognised that the pathophysiology underlying schizophrenia extends beyond dopaminergic dysregulation. Hypofunction of the N-Methyl-D-Aspartate (NMDA) receptors [2] is another proposed mechanism which is not addressed by currently available antipsychotic medications.

Options for enhancing NMDA function are limited to agonists or modulators of the glycine binding site, as increasing glutamate levels causes excitotoxicity of neural cells. The D-amino-acids, D-serine and D-alanine, act as a full agonist of the glycine binding site and have shown some promise as an adjunct therapy for treatment of schizophrenia.[3]

A limiting factor with the use of D-serine and D-alanine as an adjunct treatment is they are oxidized by a flavoenzyme, D-amino acid oxidase (DAAO)[4]. This process both limits the bioavailability of these amino acids, lessening their effectiveness, and increases products that are potentially nephrotoxic in high dosages.[5, 6] This limitation has led to interest in compounds that may inhibit the activity of DAAO, and thus lead to an accumulation of endogenous D-alanine. One inhibitor of DAAO is the widely used food preservative sodium benzoate. Experimental animal studies have confirmed that sodium benzoate diminishes DAAO’s ability to oxidize D-serine and D-alanine, resulting in increased cerebral concentration of these D-amino acids.[7]

## Rationale for the Use of Sodium benzoate for the treatment of schizophrenia

In 2018-19, Professor James Scott lead an RCT (N=100) of adjunctive benzoate versus placebo in people receiving treatment in four Queensland Early Psychosis Services. Both groups improved significantly on the primary outcome of the total symptom score of the Positive and Negative Syndrome Scale for Schizophrenia (PANSS) but there was no significant difference between those receiving benzoate and those in the placebo arm (t= -0.49, p=0.63). However, benzoate was safe, well tolerated and highly acceptable to patients [8].

Early psychosis patients are much more responsive to treatment than people with persistent schizophrenia and the addition of benzoate to their treatment did not confer additional benefits. This contrasts previous research reporting benefits of benzoate in patients with schizophrenia. Two clinical trials from Taiwan have shown benzoate has strong efficacy and tolerability in people with persistent schizophrenia.[9, 10]. The studies however were limited by small sample sizes (N=52 and 60), short duration (6 weeks) and uncertainty regarding the appropriate dose of sodium benzoate. The dose finding study guiding these trials was conducted on five people with schizophrenia where 1 g/day provided clinical benefits and lower doses did not [10]; thus 1g/day was used in the first study. The second study [9] compared adjunctive benzoate 1g and 2g/day with placebo and reported that the higher dose exerted the greatest benefit. There has been no definitive dose finding study.

A further uncertainty is benzoate’s mechanism of action. It may exert its clinical effects either by increasing the availability of D-amino acids [2] or by reducing oxidative stress [9]. D-amino acids are agonists of N-methyl-D-aspartate (NMDA) receptors and hypofunction of these has been implicated in schizophrenia [2]. Alternatively, benzoate has antioxidant properties. Oxidative stress is another pathway which is associated with schizophrenia [11] and the redox properties of sodium benzoate may contribute to the clinical benefits of this compound that have been reported in people with psychosis [9]. The mechanism of action requires further research.

Encouraged by excellent open label responses to benzoate in some patients with treatment refractory schizophrenia, we conducted an RCT of 1 g/day adjunctive benzoate vs placebo in 100 people with early schizophrenia over 12 weeks. Both groups had substantial reductions in symptoms but there was no between group difference in treatment response [8]. The plasma concentration of D-Amino Acids was unchanged between baseline and 12 week end point in both the benzoate and the placebo groups and there was no between group difference in amino acid concentrations. These results raise issues as to whether the 1g/day dose used in the study was appropriate. Further, this study was conducted in people who had early illness and were very treatment responsive. We showed benzoate did not offer additional benefits in this clinical population. We hypothesise that benzoate given at the correct dose to people with treatment refractory schizophrenia will be an effective treatment.

Sodium benzoate is extremely safe with doses of 500mg/kg per day given for inborn errors of metabolism [12]. This study will undertake essential research to inform correct benzoate dosage and mechanism of action providing essential data for a future large scale NHMRC funded clinical trial of sodium benzoate in people with treatment refractory schizophrenia.

## Safety profile of sodium benzoate

There is a substantial body of safety information available for sodium benzoate because it has potent antimicrobial properties in acidic conditions; it is an ideal food preservative for products such as salad dressings, carbonated drinks, jams, fruit juices and other condiments. It is also used in some cosmetics and medications. On labels, the inclusion of sodium benzoate is indicated by the code E211. The U.S. FDA has classified sodium benzoate as ‘Generally Recognized As Safe’ and regulates the concentration of sodium benzoate to 0.1% by weight in food products and 1% concentration in medicines.[13, 14] The current acceptable daily intake of 0.5 mg/kg body weight is suggested by the joint committee by the Food and Agriculture Organization of the United Nations and the World Health Organization.[15] It is noted that intake estimations from several counties gave averaged 0.18-2.3mg/kg body weight, however, individuals in China can consume up to 14mg/kg body weight per day from diet alone (i.e. 980 mg per day in a 70 kg person).[16]

The International Programme on Chemical Safety (IPCS) published a report on sodium benzoate (and a related compound benzoic acid) in 2000 detailing the potential health effects of sodium benzoate in animal studies. Testing in rodents revealed a low rate of toxicity with mean lethal dose (LD50) values of >1940mg/kg body weight. Drawing evidence from two long term studies (12-16 months) in rodents, there was no evidence to suggest sodium benzoate had carcinogenic properties. Likewise, studies of the precursors of benzoic acid – benzyl acetate, benzyl alcohol, and benzaldehyde suggest that a carcinogenic effect of sodium benzoate is unlikely. The results of genotoxic activity were inconclusive in the IPCS report, and there was no consistent abnormal findings based on the Ames test. Based on *in vitro* studies of human lymphoblastoid cell lines, the evidence suggests that sodium benzoate at very high concentrations does have genotoxic effects. Sodium benzoate does have embryotoxic and fetotoxic effects, however these are only evident at dosage levels high enough to cause severe maternal toxicity. A No Observable Adverse Effect Level (NOAEL) of approximately 1310 mg/kg body weight for teratogenic effects in rodents was established.[17]

The acute toxicity of oral sodium benzoate in humans is low. There is evidence that some atopic individuals may be sensitive to food additives and preservatives (benzoate is a food preservative). [18] Thus, we will screen and exclude participants with a past history of allergies or intolerance of any food additives.

While the use of sodium benzoate for treatment in psychiatric disorders in humans is a contemporary procedure, it has also been used since the late 1970’s to treat patients with urea cycle enzymopathies that cause hyperammonaemia. [12, 19] The therapeutic dose administered to treat hyperammonaemia over several years is in the range of 250-500 mg/kg body weight per day, which equates to 17,500-35,000mg per day for a body weight of 70kg. It is noted that at this dose level, the clinical signs of toxicity are rare and are limited to anorexia and vomiting, especially after large intravenous bolus injections with 100% bioavailability.

# Objectives

Using a randomised, placebo-controlled double-blind parallel-group trial; the primary objective in this study is to determine the dose of sodium benzoate which maximises the clinical benefits in patients with treatment refractory schizophrenia.

## Primary Objectives

To determine the minimal dose (1000mg daily or 2000mg daily or 4000mg daily) required of sodium benzoate treatment over 6 weeks to maximise reduction in total PANSS scores in patients with treatment refractory schizophrenia compared to individuals taking placebo.

## Secondary Objectives

To determine the minimal dose (1000mg daily or 2000mg daily or 4000mg daily) required of sodium benzoate treatment over 6 weeks to maximise improvements in Positive and Negative Syndrome Scale (PANSS) subscales, Global Assessment of Function (GAF), Clinical Global Impression (CGI), Patient Global Impression of Improvement (PGI-I), compared to individuals taking placebo.

To determine the safety and tolerability of the three doses (1000mg daily or 2000mg daily or 4000mg daily) of sodium benzoate under investigation.

## Tertiary (Exploratory) Objectives

To examine changes in biochemical markers and correlate these with clinical outcomes. Exploration of changes in plasma amino acids (D-alanine, L-alanine, D-serine, L-serine, glycine and glutamate), plasma concentrations of sodium benzoate and plasma catalase will be undertaken.

# 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 sodium benzoate for treatment in patients with treatment refractory Schizophrenia. The study will include 52 individuals with treatment refractory schizophrenia.

Participants will be given 1000mg daily (500mg bd) or 2000mg daily (1000mg bd) or 4000mg daily (2000mg bd) of Sodium Benzoate 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'.

Face to face clinical assessments will be at baseline (week 0) and weeks 2, 4 and 6. Weekly phone contact will occur in between face to face visits. Randomisation will be carried out using a computer-generated randomization table. Participants, recruiters, research and clinical staff will be blinded to the intervention. Participants will receive either active treatment (1000mg, 2000mg or 4000mg) or placebo in a 1:1:1:1 ratio.

# Study Population

Fifty-two (52) participants will be recruited through the mental health services at Metro North and West Moreton Hospital and Health Services.

## Number of participants

The study will consist of a total of 52 participants.

## Inclusion Criteria

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

1. Aged between 18 and 64 years (inclusive).
2. Fulfil the DSM-IV criteria practice for schizophrenia, based on the Diagnostic Interview for Psychosis.
3. Have had the diagnosis of schizophrenia for at least 12 months duration
4. Have a Positive and Negative Syndrome Scale (PANSS) total score ≥70
5. Have received antipsychotic medications for a period of at least one continuous month prior to assessment for the study and remained symptomatic despite taking antipsychotic therapy
6. 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. Known allergies to sodium benzoate (E211) or any part of the formulation of the

investigational product.

1. Suspected allergies or known adverse reactions to food preservatives in general.
2. Comorbid physical illnesses that would impair the participants’ ability to complete the trial.
3. People who are unable to understand or communicate in English.
4. For female participant, those currently pregnant, or planning to become pregnant or lactating during the study period.
5. Inability to follow the study instructions and procedures.

# Participant Information and Informed Consent

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

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

## Screening assessment

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

# Study Assessments and Procedures

**6.1 Clinical Measures**

A battery of validated clinical measures, physical health measures (blood pressure, waist circumference, height, weight and Body Mass Index (BMI)) and adverse events will be conducted at baseline, weeks, 2, 4 and 6.

**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.
* 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.
* Patient Global Impression (PGI) is a global index that is used to rate the response of a condition to a therapy (transition scale).

## 6.2 Biomarkers

Biochemical markers will be examined to determine the pathway by which benzoate exerts clinical effects. Exploration of changes in plasma amino acids (D-alanine, L-alanine, D-serine, L-serine, glycine and glutamate), plasma concentrations of sodium benzoate and concentration of plasma catalase will be undertaken. For those participants who consent to this part of the study, a blood sample will be collected via venepuncture at baseline and week 6. In the event a participant does not consent to this part of the study they will not be excluded from participating.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Visit** | 0  Screening  Phase | 1  Baseline | 2 | 3 | 4 | 5 | 6 | 7 |
| **WEEK** |  | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| **Study medication period(6 weeks)** |  |  |  |  |  |  |  |  |
| **SCREENING AND CONSENT** |  |  |  |  |  |  |  |  |
| Assessment of current medication | X | X | X | X | X | X | X |  |
| Informed consent | X |  |  |  |  |  |  |  |
| Ongoing capacity |  | X | X | X | X | X | X | X |
| Inclusion / exclusion criteria | X |  |  |  |  |  |  |  |
| Urine pregnancy test (females only) | X |  |  |  |  |  |  |  |
| Drug dispensation (after randomisation) |  | X |  | X |  | X |  |  |
| **SAFETY** |  |  |  |  |  |  |  |  |
| Adverse events |  |  | X | X | X | X | X | X |
| Physical health and metabolic measures |  | X |  | X |  | X |  | X |
| **EFFICACY** |  |  |  |  |  |  |  |  |
| PANSS TOTAL SCORE | X | X |  | X |  | X |  | X |
| GAF |  | X |  | X |  | X |  | X |
| CGI |  | X |  | X |  | X |  | X |
| PGI |  | X |  | X |  | X |  | X |
| **OTHER** |  |  |  |  |  |  |  |  |
| Drug compliance |  |  | X | X | X | X | X | X |
| Blood test (amino acid analysis) |  | X |  |  |  |  |  | X |

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

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

## 6.3 Study Procedures

Dispensing of sodium benzoate to participants will occur once consent has been obtained and after the screening phase and randomisation has occurred. A delegated Research Pharmacist at the Royal Brisbane and Women’s Hospital will dispense medication for all sites. For each randomised participant, the entire 6 weeks of study medication will be provided to QCMHR delegated research staff. The study medication will then be distributed to the participant on a fortnightly basis by delegated research staff in line with this protocol (section 7.4). There will be a total of 3 dispensations per participant.

## 6.4 Study Restrictions

There are no restrictions to participants during the study in terms of concomitant medications, exercise or ambulation.

## 6.5 Safety Assessments

All patients recruited in this study will be active cases at Metro North and West Moreton Hospital and Health Services. The study 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**

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

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

### 6.5.2 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.

**6.6 Pharmacokinetics**

The following information is sourced directly from the Concise International Chemical Assessment Document 26 “Benzoic Acid and Sodium Benzoate”, World Health Organization [15].

After oral ingestion of benzoic acid and sodium benzoate, there is a rapid absorption (of undissociated benzoic acid) from the gastrointestinal tract in experimental animals or humans. One hundred percent absorption can be assumed from the general literature when sodium benzoate is administered orally. In humans, the peak plasma concentration is reached within 1–2 hours [20]. In the acid conditions of the stomach, the equilibrium moves to the undissociated benzoic acid molecule, which is believed to be absorbed rapidly. Benzoate from sodium benzoate changes from the ionized form to the undissociated benzoic acid molecule. As a result, the metabolism and systemic/toxic effects of benzoic acid and sodium benzoate can be evaluated together.

After oral and dermal uptake, sodium benzoate is metabolized in the liver by conjugation with glycine, resulting in the formation of hippuric acid. Elimination half-life of sodium benzoate ranges from 0.75 to 7.4 hours (drugs.com). The rate of biotransformation in humans is high: after oral doses of 40, 80 or 160 mg sodium benzoate/kg body weight, the transformation to hippuric acid was independent of the dose — about 17–29 mg/kg body weight per hour, corresponding to about 500 mg/kg body weight per day.[20] Hippuric acid is rapidly excreted in urine. In humans, after oral doses of up to 160 mg/kg body weight, 75–100% of the applied dose is excreted as hippuric acid within 6 hours after administration, and the rest within 2–3 days.[20]

The limiting factor in the biosynthesis of hippuric acid is the availability of glycine. The utilization of glycine in the detoxification of benzoate results in a reduction in the glycine level of the body. Therefore, the ingestion of benzoic acid or its salts affects any body function or metabolic process in which glycine is involved; for example, it leads to a reduction in creatinine, glutamine, urea, and uric acid levels.

Another metabolite of benzoate is the benzoyl glucuronide. For example, the dog excretes considerable amounts of this metabolite in the urine (20% after a single dose of 50 mg/kg body weight). In healthy adults, up to 97% of the dose of sodium benzoate is excreted as hippuric acid in the urine within 6 hours [20]

## 6.7 Pharmacodynamics

The desired pharmocodynamic outcome of sodium benzoate relates to its ability to inhibit D-amino-acid-oxidase (DAAO). DAAO is an enzyme that metabolizes D-amino-acids, such as D-serine and D-alanine. Sodium benzoate binds to the D-amino-acid-oxidase active site, which inhibits its ability to metabolize D-amino-acids. Consequently, by inhibiting DAAO, this results in increased concentrations D-amino acids. As D-serine and D-alanine are full agonists of the glycine binding site of the NMDA receptor, the increased cerebral concentrations of these D-amino acids result in increased NMDA function. There is also some evidence that sodium benzoate may reduce oxidative stress [9] which is another proposed mechanism for the onset and persistence of schizophrenia [11].

# Investigational Product

## Description of Investigational Product

Active: 3 doses of Sodium benzoate (125mg, 250mg and 500mg) capsules will be compounded in identical form

Placebo: Microcrystalline cellulose in matched gelatine capsule

## Dose Justification

With respect to the use of sodium benzoate as a food, the Joint Food and Agriculture Organization of the United Nations (FAO) / World Health Organization (WHO) Expert Committee on Food Additives, established a preliminary acceptable daily intake of up to 5mg/kg body weight for sodium benzoate.[21] This translates to 350mg per day for a 70kg person.

With respect to individuals with urea cycle disorders, the recommended dose of sodium benzoate is between 250-500mg/kg per day or approximately 17500mg-35000mg per day for a 70kg person. It is noted that serious side effects at this dosage are rare and limited to occasional cases of anorexia and vomiting.[15]

With respect to the choice of doses of sodium benzoate being examined, we are guided by the dose used by Lane and colleagues [10] who reported clinical efficacy with 1000mg per day. A later study by Lin and colleagues [9] reported benefits of 2000mg sodium benzoate per day that were larger than those from 1000mg per day. No studies in people with schizophrenia have used doses of 4000mg per day. Limited side effects are seen in the use of very high doses of up to 500mg/kg/day in patients with urea cycle disorders [12] which gives us confidence to prescribe up to 4000mg per day for the purposes of establishing the most appropriate dose for the treatment of schizophrenia.

## Comparator Justification

This study will use a placebo adjunct to routine care (routine care in this study is defined as 'individualized combinations of psychopharmacology, behavioural interventions, rehabilitation and associated clinical services in keeping with Queensland Health standards of care for psychosis’) as a comparator condition. The Declaration of Helsinki affirms that placebo-controlled trials should only be used in the absence of existing proven therapy. 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

Sodium Benzoate – 3 doses of Sodium benzoate (125mg, 250mg and 500mg), (with meals-reminder aid) capsules will be used in the study.

Placebo – identical-appearing microcrystalline cellulose gelatine capsules will be used in the study.

## Randomisation Procedure

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

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

The randomisation will be double-blind. An independent Biostatistician will generate the randomisation list which will be provided to the 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 the case of emergency where it is crucial the medical staff knows whether the participant is on sodium benzoate or placebo, participants will be provided with contact information (i.e. 24 hour number) for unblinding.

## Frequency of visits and follow up

Participants will be clinically assessed at baseline, week 2, 4 and 6. The study 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 study personnel, research pharmacist and the patient. Sodium benzoate and placebo capsules will be identical in packaging, appearance, colour and taste. Treatment allocations will not be disclosed to the Investigator or any study personnel before the database is locked, unless in the case of an emergency requiring unblinding. Unblinded participants will be withdrawn from the study.

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 on a Serious AE Form and reported to Metro North Hospital and Health Service (Sponsor) within 24 hours.

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

## Product Labelling

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

## Handling and Storage of Study Drugs

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

## Accountability

The designated Research Pharmacist will dispense study medication into the care of the delegated research staff, who will then sign that he/she has received the study medication for the study. The study drug will be kept in a securely locked area 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 research assistants. 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) and quantity of the drug dispensed to the participant.

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

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

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

## Definition of an Adverse Event (AE)

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

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

Examples of an AE **include**:

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

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

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

In this study, AEs may include the following documented side effects: 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 recorded between the time of consent and the final visit (week 7). Each Participant will be monitored regularly by the investigator and study personnel for adverse events occurring throughout the study. The research assistant will enquire about AEs by asking the following non-leading questions:

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

*“How are you feeling?”*

At subsequent scheduled visits, participants will be asked:

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

## Recording of AEs and SAEs

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

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

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

## Prompt Reporting of SAEs

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

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

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

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

## Expeditable Events (SUSAR’s)

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

## Evaluating AEs and SAEs

### Assessment of Intensity

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

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

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

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

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

### Assessment of Causality

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

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

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

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

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

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

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

**8.7.3 Assessment of Expectedness**

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

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

## Follow-up of AEs and SAEs

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

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. In addition, any pregnancies brought to the attention of the Investigator after this period, and where it is known that study medication was taken at the time of conception, will also be reported.

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

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

## 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.

## 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).

**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 6 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 assisting in the participant accessing appropriate support (e.g. emergency services)  Previously identified high risk patients and recent risk assessments will be discussed at weekly team meetings and their management reviewed by senior research staff (including Project Manager and Chief Investigator).  Research staff will be given support and feedback on risk assessments and their management to improve skills throughout the project. |
| 4. | 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. |
| 5. | 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. |
| 6. | 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. |

# Participant Completion and Withdrawal

## Participant Completion

Participants are considered to have completed the study if they complete 6 weeks of dosing.

## 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
* Continual inability to provide informed consent.

## Participant Withdrawal

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

## Early Termination of the Study

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

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

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

# Case Report Form (CRF)

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

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

# Data Analysis and Statistical Considerations

## Hypotheses

Those participants allocated to the active arms (1000mg daily or 2000mg daily or 4000mg daily) of Sodium Benzoate treatment will have significant reductions in PANSS total score at week 6 compared to individuals taking placebo.

## Endpoints

### Primary

To identify the minimal dose (1000mg daily or 2000mg daily or 4000mg daily) required of sodium benzoate treatment over 6 weeks to maximise reduction in total PANSS scores in patients with treatment refractory schizophrenia compared to individuals taking placebo.

### Secondary

To identify the minimal dose (1000mg daily or 2000mg daily or 4000mg daily) required of sodium benzoate treatment over 6 weeks to maximise improvements in Positive and Negative Syndrome Scale (PANSS) subscales, Global Assessment of Function (GAF), Clinical Global Impression (CGI), Patient Global Impression of Improvement (PGI-I), compared to individuals taking placebo.

### 11.2.3 Tertiary

Biochemical markers will be examined to determine the pathway by which benzoate exerts clinical benefits. Exploration of changes in plasma amino acids (D-alanine, L-alanine, D-serine, L-serine, glycine and glutamate), plasma concentrations of sodium benzoate and plasma catalase, a measure of oxidative stress will be undertaken.

## Sample Size and Power

The primary analysis will be a mixed effect repeated measures analysis comparing total PANSS scores across 4 time points (baseline, 2, 4, and 6 weeks) across 4 dose groups (placebo, 1000mg, 2000mg, and 4000mg). Based on our previous study total PANSS score had a standard deviation of around 15 for all subjects, and closer to 10 for cases with baseline PANSS scores > 75. The autoregressive (AR(1)) correlation between weeks was estimated at 0.815. Assuming a decrease in PANSS scores similar to our previous study, of 7 point in the first 2 weeks and an additional 3 points per 2-week period thereafter, this study has at least 80% power to detect an effect size of 0.55 between treatments. Power calculations were performed in PASS (v 2020 Power Analysis and Sample Size Software (2020). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass) using the repeated measures platform.

## Statistical Analysis

All data will be analysed using SAS 9.4. We will compare demographic and clinical differences between the groups at baseline (Fisher exact test for nominal variables and Mann-Whitney test or independent sample t test for continuous variables). Efficacy will be assessed according to standard Intention to Treat (ITT) analytic procedures (i.e. for those who do not complete the 6 week study period, we will carry forward their last observation on the study outcomes). Mean changes in clinical assessment will be assessed using mixed-model repeated-measure (MMRM) methods with treatment, week, and treatment-week interaction as fixed effects and intercept as the only random effect; baseline value will be the covariant. The MMRM analyses will be performed using the SAS PROC Mixed procedure. P values will be based on 2-tailed tests with significance levels of 0.05.

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

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

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

## Archiving

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

# Monitoring and Quality Assurance

An independent Study Monitor will conduct study documentation review to monitor key features of the study prior to commencement, during and after study completion. These site visits will enable the Monitor to maintain current, personal knowledge of the study through review of the CRFs, comparison of CRF entries against the electronic data base (REDCap) and discuss the conduct of the study with the Investigator. The Monitor will be responsible for monitoring adherence to the approved study protocol, regulatory compliance including GCP and completion of the CRF. The organisation, supply of study materials and quality assurance of the clinical trial is the responsibility of the Investigator or its designee.

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

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

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

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

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

**13.1 Data Safety Monitoring Board**

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

# Investigator Responsibility

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

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

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

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

# Study Report

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

# Administrative Procedures

## Ethical Considerations

Information on side effects of the Investigational Product and reference formulations is summarised in the Investigator’s Brochure. The monitoring and safety guidelines are outlined in the Monitoring Guidelines for the study. This study will be carried out according to the Declaration of Helsinki, the NHMRC National Statement on Ethical Conduct in Research Involving Humans (2007) and the Notes for Guidance on Good Clinical Practice as adopted by the Australian Therapeutic Goods Administration (2000) (CPMP/ICH/135/95) and the ICH GCP Guidelines.

## Ethical Review Committee

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

## Regulatory Authorities

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

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

## Informed Consent

Our criteria will ensure that recruited participants will be sufficiently competent to consent and participate in the study or to refuse consent. Current research provides evidence that while psychotic symptoms may be present, these do not robustly predict an individual’s functionality in daily life and capacity to make decisions, and whilst strongly correlated with cognitive impairment, do not reflect an enduring inability to understand information related to research participation.42

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

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.

## 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 and 6 (total reimbursement $80). For those participants who consent to the blood test an extra $10 will be provided at the baseline visit and week 6 (total reimbursement $100). If the study is terminated by the Investigator prior to completion, or a participant withdraws or is withdrawn from the study before completion, a pro-rata payment will be made at the discretion of the Investigator.

## Emergency Contact with Investigators

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

## Notification of Primary Care Physician and Treating Psychiatrist

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

## Investigator Indemnification

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

The Metro North Hospital and Health Service (Sponsor) will enter into a Clinical Trial Agreement with Metro North Hospital and Health Services (HHS) involved in the study, based on the standard Medicines Australia format.

## Intellectual Property (IP) and Licencing

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

## Publication Policy

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

## Protocol Amendments

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

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

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

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

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

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

## Version Control

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

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

## 16.13 Protocol Compliance

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

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

Whilst the Chief Investigator has overall responsibility for the conduct of the study, the appointed site Investigators will have the responsibility to ensure all study personnel at their sites comply with GCP, National Statement on Ethical Conduct (2007), Australian Code for the Responsible Conduct of Research and local policies and procedures.

## 16.14 Archives: Retention of Study Records

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

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