N-acetyl cysteine (NAC) augmentation in Obsessive-Compulsive Disorder (OCD): A 24-week, randomised, double blind placebo controlled trial

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Principal Investigator: Prof. Jerome Sarris

Chief investigators: Prof Chee Ng, Prof Gerard Byrne, Prof David Castle, Dr. David Camfield

Associate Investigators: Ms. Georgina Oliver, Professor Michael Berk, Dr. Scott Blair West, Dr. Olivia Dean, Mr. Nathan Dowling, Dr. Ranjit Menon, Dr. Jenifer Murphy, Dr Suneel Chamoli, Prof Susan Rossell, Dr. Chad Bousman, Dr. Mark Boschen, Dr Vlasios Brakoulias

Medical Monitors: Prof Chee Ng, Dr. Scott Blair-West, Dr. Ranjit Menon, Prof Gerard Byrne, Dr Suneel Chamoli, Dr. Carolyn Ee

Sites: The Melbourne Clinic, Royal Brisbane and Women's Hospital & The National Institute of Complementary Medicine

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SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable NHMRC clinical trial and ICH guidelines.

Site Investigator:

Signed: _____ Date: _____

Name
Title

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LIST OF ABBREVIATIONS

ACL	Australian Clinical Labs
AE	Adverse Event/Adverse Experience
BAI	Beck Anxiety Inventory
BIS-11	Barratt Impulsivity Scale version 11
CBT	Cognitive Behavioural Therapy
CGI - I/S	Clinical Global Impression scale - improvement/severity
CRF	Case Report File
CTC	Clinical Trial Coordinator
DQES v2	Dietary questionnaire for epidemiological studies version 2
ERP	Exposure response prevention
GCP	Good Clinical Practice
GMP	Goods Manufacturing Practice
HAM-D	Hamilton depression rating scale
ICH	Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IICF	Informant Information Consent Form
IP	Investigational Product
IRB	Institutional Review Board
N	Total number of participants in population
NAC	N-acetylcysteine
OCD	Obsessive-Compulsive Disorder
PGI – I/S	Patient Global Impression scale - improvement/severity
PI	Principal Investigator
PICF	Participant Information Consent Form
RA	Research assistant
RCT	Randomised, controlled trial
SAFTEE	Systematic assessment for treatment emergent side effects
SCID-5-CT	Structured clinical interview for DSM-5 Clinical Trial version
SDS	Sheehan Disability Scale
SNP	Single nucleotide polymorphisms
SOP	Standard Operating Procedure
TR-OCD	Treatment refractory OCD
WHOQOL-BREF	World Health Organisation Quality of Life-BREF
Y-BOCS	Yale-Brown Obsessive-Compulsive Scale

PROTOCOL SUMMARY

Title: N-acetylcysteine augmentation (NAC) in Obsessive-Compulsive disorder (OCD): A 24 week, randomised, double blind, placebo controlled trial

Phase: III

Population: Male and female adults (18-75 years old) with Obsessive-Compulsive Disorder (N = 200) located in Australia.

Number of Sites: (3) The University of Melbourne (The Melbourne Clinic); The University of Queensland (Royal Brisbane and Women's Hospital); Western Sydney University (National Institute of Complementary Medicine; NICM)

Study Duration: 2016 - 2019

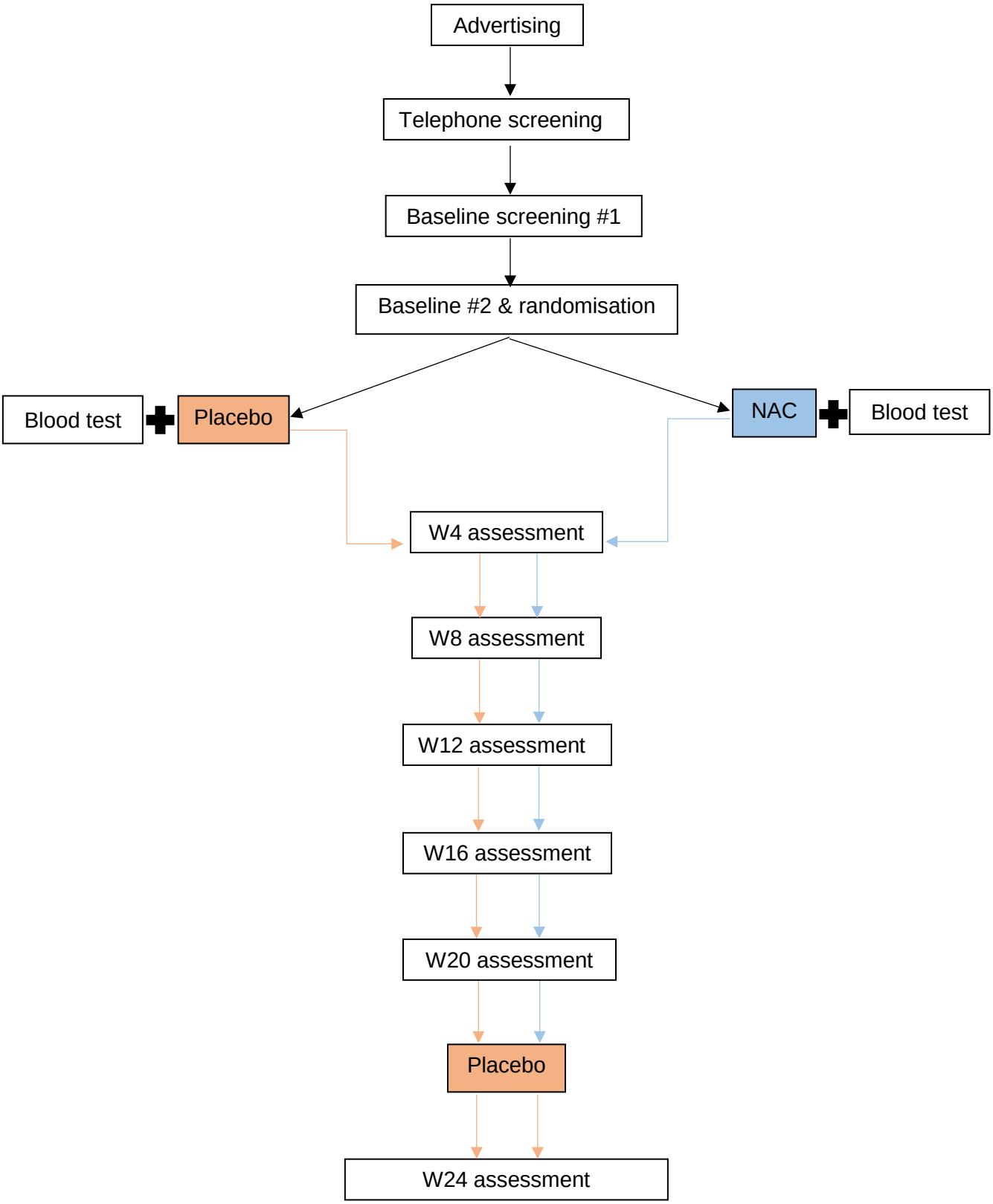
Subject Participation Duration: 24 weeks

Description of Agent: N-acetylcysteine (NAC) is an acetylated form of the essential amino acid cysteine. NAC possess glutamate modulating activity and is the rate limiting substrate for glutathione (GSH) production, a potent endogenous antioxidant. Participants will take NAC or matching placebo (capsule form) orally in doses between 2,000mg – 4,000mg per day, depending on individual treatment response.

Description of Study Design: 20 week, randomised, double blind placebo controlled trial with a 4-week, single blinded, placebo run out

Estimated Time to Complete Enrollment: 3.5 years

Schematic of Study Design:



Assessment Schedule

	Baseline 1	Baseline 2	W4	W8	W12	W16	W20	W24
PICF	X							
Demographics	X							
Medical hx	X							
Treatment hx/review	X	X	X	X	X	X	X	X
Caffeine, drug & alcohol intake	X		X	X	X	X	X	X
Blood pressure		X	X	X	X	X	X	X
NetSCID-5		X						
Qualitative review			X	X	X	X	X	X
Y-BOCS sx checklist	X	X*	X	X	X	X	X	X
Y-BOCS	X	X*	X	X	X	X	X	X
DOCS	X		X	X	X	X	X	X
SIGHD-17	X		X	X	X	X	X	X
BIS-11	X							

	Baseline 1	Baseline 2	W4	W8	W12	W16	W20	W24
BAI	X		X	X	X	X	X	X
SDS	X		X	X	X	X	X	X
WHOQOL-BREF	X				X		X	
DQES v3.2		X						
CGI-I			X	X	X	X	X	X
CGI-S		X	X	X	X	X	X	X
PGI-S	X		X	X	X	X	X	X
PGI-I			X	X	X	X	X	X
SAFTEE			X	X	X	X	X	X
BMI		X						
Blood collection		X**						

*The Y-BOCS will be administered at baseline 2 if this appointment occurs more than seven days after baseline I visit **completed at any time point before conclusion of the study

1 KEY ROLES

Individuals:	**Principal Investigator:** Professor Jerome Sarris **Chief Investigators:** Professor Chee Ng, Professor Gerard Byrne, Professor David Castle, Dr. David Camfield **Associate Investigators:** Professor Michael Berk, Dr. Scott Blair West, Dr. Olivia Dean, Mr. Nathan Dowling, Dr. Ranjit Menon, Dr. Jenifer Murphy, Ms. Georgina Oliver, Dr Suneel Chamoli, Prof Susan Rossell, Dr. Chad Bousman, Dr. Mark Boschen, Dr Vlasios (Bill) Brakoulias **Medical Monitor:** Dr. Scott Blair West, Professor Chee Ng, Dr. Ranjit Menon and Professor Gerard Byrne, Dr Suneel Chamoli, Dr. Carolyn Ee
Institutions:	The Professorial Unit, The Melbourne Clinic (University of Melbourne) The Royal Brisbane and Women's Hospital (The University of Queensland) National Institute of Complementary Medicine; NICM (Western Sydney University)

2 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

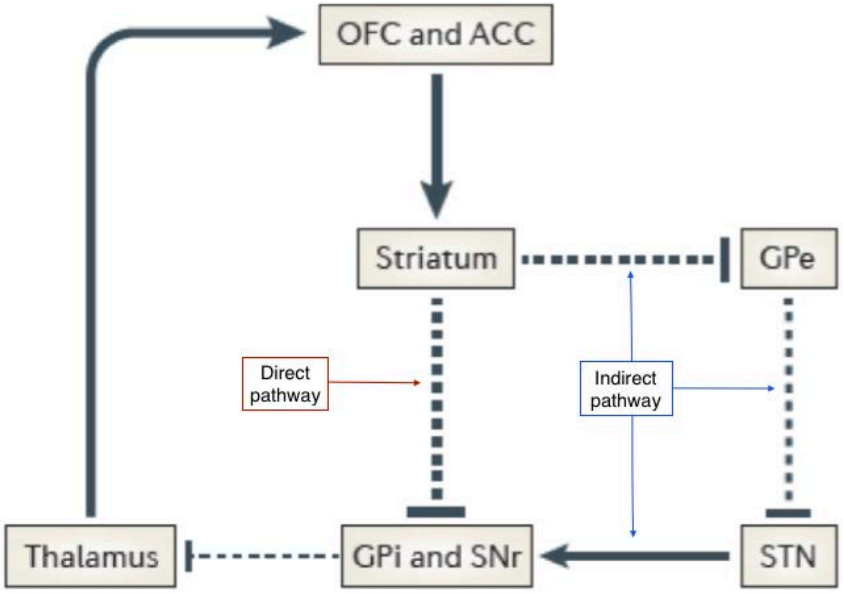
Obsessive-Compulsive Disorder (OCD) is a debilitating neuropsychiatric disorder with an Australian prevalence of 1.9% (Slade, Johnston, Oakley Browne, Andrews, & Whiteford, 2009). It is characterised by repetitive and intrusive thoughts, urges or images (obsessions) and subsequent repetitive behaviours (compulsions), typically performed to mitigate the distress of the obsessions. The disorder is diverse in its symptomatic expression and ranges in severity; however, OCD is often chronic in nature, extremely debilitating and can greatly impair quality of life (APA, 2013; Subramaniam, Soh, Vaingankar, Picco, & Chong, 2013). Current first-line treatments for OCD are selective serotonin re-uptake inhibitors (SSRIs), often at higher doses than typically necessary for major depressive disorder, as well as psychological interventions, including exposure-response prevention (ERP) behavioural therapy. Additional augmentation strategies are often utilised including the use of anti-psychotics, the tricyclic antidepressant clomipramine (also used effectively as a monotherapy) and more recently, glutamatergic agents (McGrath et al., 2014). Despite these treatments eliciting beneficial effects in several cases, particularly when pharmacological and psychological strategies are employed concurrently, it is estimated that at least 40% of patients do not experience adequate responses to these therapies, and a greater portion still may continue to experience significant symptoms (Knopp, Knowles, Bee, Lovell, & Bower, 2013; McGrath et al., 2014; Pallanti, Grassi, & Cantisani, 2014).

2.1.1 OCD neurobiology and glutamate

Disturbed functioning of the cortical-striatal-thalamic-cortical (CSTC) circuits in the brain is regarded as the core pathophysiological feature of OCD, and remains one of the prime foci of neurobiological investigations (Harrison et al., 2013; Ting & Feng, 2011). These circuits appear hyperactive in OCD sufferers compared to healthy controls (Baxter et al., 1988; Nordahl et al., 1989; Swedo et al., 1989), become accentuated with symptom provocation (Adler et al., 2000; Breiter et al., 1996; Rauch et al., 1994), and attenuate with successful treatment for OCD symptoms (Benkelfat et al., 1990; Saxena et al., 2002).

The beneficial effects of clomipramine (with strong effects on the serotonergic system) for OCD was observed in clinical trials in the late 1970s, which promoted neurobiological investigations towards the serotonergic system neurotransmitter system (Ananth, Solyom, Bryntwick, & Krishnappa, 1979; Goodman, Grice, Lapidus, & Coffey, 2014). However, disparities within resulting neuroimaging studies, coupled with treatment resistance amongst patients to serotonin pharmaceutical agents, encouraged research towards other neurotransmitter systems, including dopamine and glutamate (Goodman, Grice, Lapidus, & Coffey, 2014). A converging body of genetic, neuroimaging, preclinical and clinical evidence highlights the contributing role of disturbances within the glutamate system and OCD (Pittenger, Bloch, & Williams, 2011) – summarized in Table 2.1. However, various limitations and disparities exist in the currently available studies. For instance, sample sizes within the neuroimaging studies are often small and heterogeneous with respect to OCD chronicity, severity, co-morbid psychiatric disorders and medication status, all of which may affect observed neurobiological activity. Furthermore, difficulties in specifically assessing glutamate neurotransmitter activity may confound interpretation of these findings. For example, proton magnetic resonance spectroscopy (^{1}H MRS) measures glutamate in a complex with glutamine (i.e. Glx), and does not differentiate between glutamate's structural and neurochemical properties (Pittenger, Bloch, & Williams, 2011). Thus, "glutamate abnormalities are considered potentially important in OCD, but technically difficult to assess" (Brennan, Rauch, Jensen, & Pope Jr., 2013). In addition, several other neuroimaging studies fail to show significant differences in Glx activity throughout various regions of the brain between people with OCD and healthy controls (Brennan, Rauch, Jensen & Pope, 2013; Simpson et al., 2015). Regardless, the available evidence does provide additional support for the heterogeneous neurobiological aetiology of OCD and the well recognised frontal striatal model of the disorder, which postulates heightened activity of direct neural pathways over indirect, both of which operate under glutamatergic neurotransmission (see Figure 2.1). Thus, regulation of glutamate transmission may be a beneficial treatment strategy for some patients with OCD.

Figure 2.1 **Involvement of glutamate in the cortical-striatal-thalamic-cortical circuitry**



Adapted from Pauls, Abramovitch, Rauch, & Geller, 2014

Note. Solid black lines depict glutamate pathways and dashed lines depict GABA pathways. It is suggested that people with OCD have lower threshold activation for this system, which results in excessive activity of the direct pathway (striatum activation increases GABA signals to the globus pallidus interna (GPi) and substantia nigra (SNr)). This activity results in increased glutamatergic signals to the orbital frontal cortex (OFC) & anterior cingulate cortex (ACC), heightening the direct pathways positive feedback mechanisms. In OCD, increased tone of the direct pathway inhibits the modulating activity of the indirect pathway (glutamatergic signalling from the subthalamic nucleus (STN) to the GPi and SNr) and thus, results in disturbed glutamate neurotransmission.

Table 2.1 Summary of evidence for glutamate's role in OCD

Study Focus	Finding	Citation
Genetic	• Polymorphisms of an NMDA subunit associated with OCD susceptibility	Arnold et al., 2004
	• Glutamatergic gene variations associated with increased volume of the right ACC, left OFC and thalamus in psychotropic-naive paediatric OCD patients	Arnold et al., 2009
	• Strong evidence for variations in SLC1A1 gene (glutamate transporter gene) in OCD	Reviewed by Stewart et al., 2013
Preclinical	• Stimulation of glutamatergic neurons in the OFC and VMS induced OCD like behaviour	Ahmari et al., 2013
	• Stimulation of cortical-limbic glutamate output induces OCD like behaviour	McGarth et al., 2000
Neuroimaging Studies	• PET studies suggesting glutamate hyperactivity evident by increased glucose metabolism in glutamatergic neurons of adults with OCD versus healthy controls	Baxter, et al., 1988; Swedo, et al., 1989
	• ^{1}H MRS study demonstrating reduced levels of Glx in the ACC in psychotropic naïve paediatric sample	Rosenberg et al., 2004
	• ^{1}H MRS study demonstrating greater levels of Glx in the right OFC correlating with symptom severity	Whiteside et al., 2006
	• ^{1}H MRS study demonstrating reduced levels of Glx in the ACC in a cohort of females, independent of medication status	Yucel et al., 2008
	• ^{1}H MRS study demonstrating increased levels of Glx in the left caudate nucleus in a paediatric cohort. Glx levels decreased after successful SSRI treatment	Arnold et al., 2009
	• ^{1}H MRS study demonstrating decreased levels of tNAA in the pACC versus controls. Levels significantly increased after 4-weeks of intensive CBT and correlated with OCD symptom improvement	O'Neil et al., 2012
	• PET imaging study demonstrating a positive correlation with mGluR5 DVR and obsession sub-score of the Y-BOCS	Akkus et al., 2014
	• Single voxel MRS study demonstrating decreased glutamate levels in mPFC and right thalamus in unmedicated OCD patients significant over healthy controls	Zhu et al., 2015
	• ^{1}H MRS study in paediatric sample of OCD + ASD demonstrated higher levels of glutamate in the ACC but not the striatum in both conditions versus healthy controls	Naaijen et al., 2017

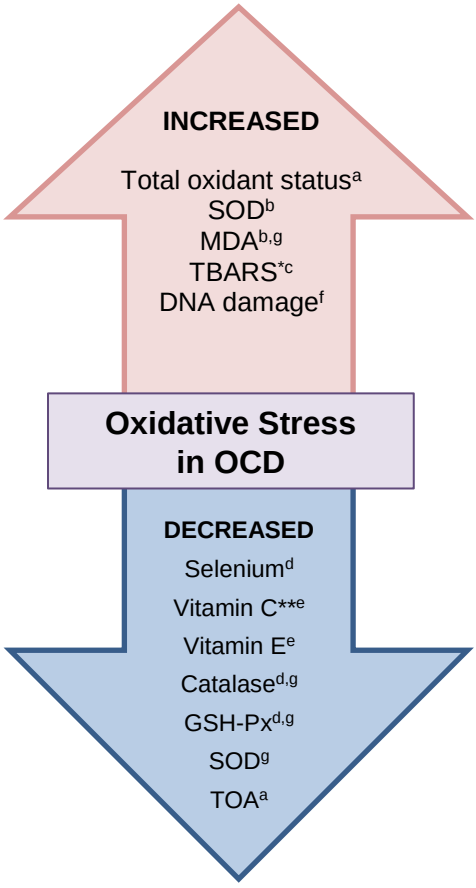
CSF studies	• High levels of glutamate in the CSF of psychotropic naive adults with OCD, independent of age, gender, clinical severity or chronicity • High levels of glutamate in CSF of adults with OCD. Higher binding of autoantibodies in the basal ganglia and thalamus of brain	Chakrabarty, Bhattacharyya, Christopher & Khanna, 2005 Bhattacharyya et al., 2009

ACC = anterior cingulate cortex; ASD = autism spectrum disorder; CSF = cerebral spinal fluid; DVR = distribution volume ratio; Glx = glutamate glutamine complex; 1H MRS = proton magnetic resonance spectroscopy; mGluR5 = metabotropic glutamate receptor 5; mPFC = medial prefrontal cortex; MRS = magnetic resonance spectroscopy; OCD = Obsessive-Compulsive Disorder; OFC = orbital frontal cortex; pACC = pregenual anterior cingulate cortex; PET = positron emission tomography; tNAA = N -acetyl-aspartate + N -acetyl-aspartyl-glutamate; VMS = ventromedial striatum; SSRI = Selective-serotonin reuptake inhibitor; Y-BOCS = Yale-Brown Obsessive Compulsive Scale

2.1.2 Oxidative stress in OCD

Various studies highlight greater levels of oxidative stress, lipid peroxidation and disturbances in antioxidant defense systems in blood samples of individuals with OCD versus healthy controls (see Figure 2.2) (Behl, Swami, Sircar, Bhatia, & Banerjee, 2010; Ersan, Bakir, Erdal Ersan, & Dogan, 2006; Kandemir, Abuhandan, Aksoy, Savik, & Kaya, 2013). Of interest, one study demonstrated that higher levels of oxidative stress correlated with symptom severity (Chakraborty, Singh, Dasgupta, Mandal, & Nath Das, 2009). Nevertheless, due to the cross-sectional design of these studies, and absence of longitudinal data, whether oxidative stress is a cause or consequence of OCD pathophysiology is yet to be identified. In addition, and similarly to the neurobiological investigations regarding glutamate, other studies fail to demonstrate significant difference over healthy controls (Alici et al., 2016). Of interest, it has been postulated that the apparent oxidative stress and impaired antioxidant defense mechanisms may be the result of excess levels of glutamate to inducing excitotoxicity and neuronal cell death (Onley, 1969; Sattler & Tymianski, 2001).

Figure 2.2 Summary of evidence of antioxidant disturbances in OCD



Note. GSH-Px = glutathione peroxidase; MDA = malondialdehyde; SOD = superoxide dismutase; TBARS = thiobarbituric acid; TOA = total antioxidant status

[a]Kandemir, Abuhandan, Aksoy, Savik, & Kaya, 2013; [b]Behl, Swami, Sircar, Bhatia, & Banerjee, 2010; Ersan et al., 2006; Kuloglu et al., 2002; Ozdemir et al., 2009; Shohag et al., 2012; [c]Chakraborty et al., 2009; [d]Ozdemir et al., 2009; [e]Ersan et al., 2006; Shohag et al., 2012. [f]Alici et al., 2016; [g] Shrivastava, Kar, Sharma, Mahdi, & Dalal, 2017

*Positively correlated with symptom severity **Trend only observed in Ersan et al., 2006 study, did not reach statistical significance.

2.2 Rationale

2.2.1 N-acetylcysteine (NAC)

N-acetylcysteine (NAC) is an acetylated form of the essential amino acid cysteine and has been used medicinally for over 50 years, initially in emergency departments for the treatment of paracetamol toxicity. NAC is considered a cysteine pro-drug which has been found to attenuate the synaptic release of glutamate in subcortical brain regions (via glutamate metabotropic autoreceptor 2/3 activation) and restore extracellular concentrations of glutamate in the nucleus accumbens (Baker et al., 2003; Madayag et al., 2007). The latter mechanism is postulated to be particularly beneficial for attenuation of compulsive behaviours, which both preclinical and clinical studies have highlighted NAC's ability to improve (Deepmala et al., 2015; Hurley et al., 2016; Kupchik et al., 2012; Madayag et al., 2007). Further, cysteine is the rate-limiting step for the potent endogenous antioxidant glutathione (GSH) and supplementation of NAC has been found to increase GSH in the bloodstream and brain (Lavoie et al., 2008, Dean, 2011; Das et al., 2013). Further, NACs modulation of glutamate and involvement in the production of GSH are believed to facilitate its neuroprotective effects and ability to enhance neurogenesis (Samuni, Goldstein, Dean, & Berk, 2013).

2.2.2 Pilot studies

Within the last 10 years, various case reports and clinical studies highlight promising, yet mixed effects of NAC for both pediatric and adult OCD (reviewed in Deepmala, 2015). However, many of these studies were underpowered (N = 40-50) and involved participants with varying severities and presentations of OCD, including treatment resistant populations.

To date, four RCTs investigating NAC for OCD in adult populations have been published. Two studies from Iran have revealed positive effects, the first highlighted a significant effect for NAC (2,400mg/day) over placebo from week-8, adjunctive to stable SSRIs or clomipramine, for improving symptoms in participants with OCD (N = 48, 75% women) (Afshar et al., 2012). Of note, the researchers classified these participants as treatment refractory, defined as failing to receive clinical benefits from two, 12-week courses of SSRIs or clomipramine. Another research group from Iran published additional positive effects in 2016, highlighting the ability of NAC augmentation (2,000mg/day) to potentiate the therapeutic effects of fluvoxamine (200mg) over

placebo + fluvoxamine over 10-weeks (Paydary et al., 2016). A third RCT was conducted in Brazil involving 40 adult patients who had failed to respond to at least one SSRI or clomipramine trial lasting for minimum 12 weeks (Costa et al., 2017). All participants experienced a reduction in their OCD symptoms (as per the Y-BOCS), however, NAC (3,000mg per day maximum dose from week-3 of the study) was not significant over placebo at the end of the 16-week intervention. In addition, our own pilot study (N = 44) published in 2015 revealed a non-significant effect for 3,000mg of NAC over placebo after 16-weeks (Sarris et al., 2015). A significant effect for improving compulsive symptoms was observed at week-12, however, this effect dissipated by week-16 end point. Our sample included participants with ranging severities and chronicity of OCD, and a post-moderator analysis revealed that NAC was more beneficial in less chronic presentations of OCD (<17 years duration), as well as those who were under the age of 34 (Sarris, Oliver, Camfield, & Dean, 2016). Further, previous clinical trials have revealed that NAC at doses beyond 3,000mg have elicited symptom improvement in attention-deficit hyperactivity disorder (ADHD), as well with lengthier administration of NAC (up to 6 months) in bipolar disorder (Berk et al., 2008; Berk et al., 2012; Garcia et al., 2013). Given these findings, and the many questions which remain regarding the benefits of NAC for differing symptom dimensions of OCD, treatment status, gender and required dose, a larger scale study to provide power to investigate these facets is warranted.

2.3 Potential Risks and Benefits

2.3.1 Potential Risks

The risks of participating include a breach of confidentially, side effects from taking the IP, discomfort when completing blood tests and/or the nature of the assessments involved in the study, including those conducted by the researcher as well as completed by the participants.

Participant's personal details will be collected during the baseline session of study (for contact purposes thereafter) and subsequent data will be de-identified. Although every effort will be made to maintain the anonymity of participants, a breach of confidentially is possible. See section 11.3 for further details regarding confidentially.

NAC may induce gastrointestinal side effects including mild abdominal pain or discomfort, heartburn, diarrhea, flatulence, nausea and cramps (Deepmala et al., 2015; Sarris et al., 2015).

Headaches, dizziness and skin rashes have also been reported in previous clinical studies (Ghanizadeh et al., 2017). However, specific to psychiatric research studies, only a small minority of participants have withdrawn due to side effects of NAC including a skin rash (n = 1), aggression (n = 1), severe heartburn (n = 1), neutropenia (with 6 grams of NAC, resolved when dose reduced to 2.4g; n = 1) and sensorineural deafness (n = 1) (Deepmala et al., 2015)

Participants may experience discomfort or bruising when having their blood taken during the study. The blood vessel may swell, or blood may clot in the blood vessel. Rarely, there could be a minor infection or bleeding.

Given that participants will be reviewing their mental, general and physical health in each of the study visits, some may find this psychologically distressing. To minimize these risks, all RAs involved in the assessment of participants will ensure that participants are adequately supported outside of the study, for example, advising them to maintain contact with their GP, psychiatrist and/or psychologist as required. In addition, participants who experience significant worsening in their mental health will be withdrawn from the study and referred for treatment. Further, during the informed consent discussion at baseline, the voluntary nature of the study and a participant's right to withdraw at any stage of the study will be highlighted.

2.3.2 Known Potential Benefits

Although the current available evidence of NAC in the treatment of OCD has revealed mixed results, several participants in previous clinical studies have experienced an improvement in their symptoms. Thus, in the current study, NAC (or placebo) may elicit a reduction in obsessive and compulsive behaviours for some individuals. Participants may also benefit from the knowledge that they are contributing to science and progressing the field of OCD research for other sufferers and their care givers. Participants will also be reimbursed for travel expenses totaling $140-$160 in the form of Coles/Myer gift cards ($20 at each scheduled study visit, $160 if all study visits are completed and if the baseline visits are completed on separate days). Upon completion of the 24-week study period, participants will have the option to receive three containers (120c in each container) of NAC free of charge.

3 OBJECTIVES

3.1 Study Objectives

This study seeks to elucidate the benefits of NAC augmentation (2-4 grams/day) compared to placebo in the treatment of OCD, in a 20-week, multicentre, randomised, double-blind, placebo controlled trial, with an additional 4-week, single blinded placebo run-out. The purpose of including a 4-week, placebo-run out is to asses any withdraw effects and/or sustained response of the NAC. It is hypothesised that NAC will be superior over placebo for improving OCD symptoms as measured by a reduction in Y-BOCS scores from baseline against each subsequent time point (W4, W8, W12, W16, W20 and W24). Additional benefits are anticipated for relieving anxiety as well as improving mood, functioning and overall quality of life. In addition, we will analyse the presence of single nucleotide polymorphisms (SNPs) related to glutamate and glutathione activity, which may serve as a predictor of treatment response to NAC in some individuals.

3.2 Study Outcome Measures

3.2.1 Primary Outcome Measures

The primary outcome measure is the Yale Brown Obsessive-Compulsive Scale (Y-BOCS) which assesses the impact, frequency and severity of both obsessive and compulsive symptoms in OCD. The Y-BOCS will be administrated at each time point during the 24-week study (baseline 1 session, baseline 2 if more than 7 days post baseline 1, W4, W8, W12, W16, W20 and W24).

3.2.2 Secondary Outcome Measures

The Structured Interview Guide for the Hamilton Depression rating scale, 17 item (SIGHD-17), Beck Anxiety Inventory (BAI), Sheehan Disability Scale (SDS), Dimensional Obsessive Compulsive Scale (DOCS), Clinical Global Impression scales (clinician and patient rated) will be used as secondary outcome measures at each time point (baseline, W4, W8, W12, W16, W20 and W24. The World Health Organisation Quality of Life (WHOQOL-Bref) will also be used as a secondary outcome measure which will be completed by participants at baseline, W12 and W20.

These measures will investigate the therapeutic effects of NAC for improving mood, anxiety, and quality of life. In addition, both the rater's and participants overall perspective of OCD severity and improvement with time will be assessed.

4 SUDY ENROLLMENT AND WITHDRAWAL

4.1 Subject Inclusion Criteria

Eligible participants must be:

- Between the ages of 18-75
- Have the desire and capacity to consent to the study and follow its procedures
- Have a primary diagnosis of OCD (NetSCID-5-CT, see section 6.1)
- Achieve a minimum of 16 on the Y-BOCS and no greater than 31 at time of entry into the study (a patient with Y-BOCS score higher than 31 will be referred for appropriate treatment).
- Taking psychotropic medication/s for their OCD, and continue to do so throughout the study period.
    - If using medication the dose must be stable, i.e. same dose of primary medication for minimum of 8-weeks (minimum 12-weeks if it is their very first medication trial). See Table. 5.2 regarding acceptable classes and doses of medications for the study

4.2 Subject Exclusion Criteria

Participants will be excluded from the study in the event of:

- Bipolar disorder*[a]
- Psychotic disorders*[a]
- Primary diagnosis of Obsessive-compulsive spectrum disorders including hoarding, body dysmorphic disorder, trichotillomania (secondary diagnosis permitted)
- Severe depression (as defined by HAM-D score of ≥24)
- Alcohol/substance abuse*
- Y-BOCS score of ≥32 (extreme OCD)
- Treatment refractory OCD (see Figure 4.1)

- Currently engaging in intensive psychological therapies for OCD (a 4-week washout will be required before reassessing eligibility), for example:
    - In-patient OCD programs
    - Intensive out-patient programs, for example 15-17 CBT sessions (involving ERP) conducted by a clinician within a 4-8 week period as outlined by Franklin, Abramowitz, Kozak, Levitt, & Foa, 2000; Simpson et al., 2013; Simpson et al., 2008
    - Online CBT courses, for example, 'This Way Up' or STOP by Swinburne University
- Medications with known or suspected negative interactions with NAC (see Table 4.2 for guidelines) as determined by the medical investigator/s

Table 4.2 Therapeutic agents that may interact with NAC

Agent	Mechanism	Strength of interaction	Evidence level
Activated charcoal	Strongly binds to up to 96% of orally ingested NAC (dose dependent)	Moderate	Clinical studies
Nitro-glycerine	NAC potentiates the activity of nitro-glycerine and causes hypotension	Major	Clinical studies
Insulin (inhaled preparations)	NAC (inhalation preparations) may affect absorption of rapid acting insulin when taken concurrently.	Moderate	Theoretical, - based on pharmacology
Chloroquine (Aralen)	NAC may prevent the build-up of heme inside cells and thus reduce Aralen's efficacy	Moderate	In vitro or animal study
>200mcg selenium	Selenium is required for GSH production and thus, may confound NAC activity	Moderate	In vitro or animal study
Anti-coagulant/anti-platelet medication	NAC may slow blood clotting (via nitric oxide activity) and therefore, potentiate the effects of these medications	Moderate	In vitro or animal study
Blood pressure medication	NAC may lower blood pressure via GSH's influence on nitric oxide activity. Further, NAC may potentiate hypotensive effects of ACE inhibitors	Moderate	In vitro or animal study

(Table sourced from MIMS & Natural Medicine Database, https://naturalmedicines.therapeuticresearch.com/; viewed April, 2018)

- Allergy to NAC, sulfur or any component of the IP
- Serious and unstable medical conditions (eg. cancer)
- Recent gastrointestinal ulcers
- Pregnancy and lactation[b]
- Participation in any other interventional study
- Cessation of primary medication for OCD

*Diagnosed by the NetSCID-5-CT. [a]Clinician diagnosed or, if self-reported/suspected by participant, a letter from a clinician confirming exclusion of diagnosis will be required [b]Female participants will be required to provide written consent at baseline that they will employ adequate contraception methods during the study period.

Figure 4.1 Treatment refractory OCD criteria

*Unsuccessful trial equates to minimum of 12 weeks of an SRI/clomipramine (where tolerated) within or above the specified dosage range (see Table 4.3) and ≤35% reduction in Y-BOCS score. In the event where a Y-BOCS score is not available to determine response, participants will be asked to describe their response to treatment as per CGI-I criteria (very much improved = 1 , much improved = 2, minimally improved =3, no change = 4 etc.) as suggested by Pallanti & Quercioli (2006) to gauge stages of response to treatment in OCD (see table 4.4). A reported score of ≥3 will be deemed an unsuccessful trial.

Table 4.3 Classes and dosages of medications to be trialed (minimum 12-weeks with inadequate response) for defining patients with TR-OCD

Medication	Dosage range (per day)
Fluoxetine	60-80mg
Sertraline	>200mg
Paroxetine	>60mg
Fluvoxamine	300-350mg
Citalopram	60-80mg
Escitalopram	30-40mg
Clomipramine	200-300mg
Duloxetine	60-120mg
Venlafaxine	150-375mg
Desvenlafaxine	100-400mg

(Bloch, McGuire, Landeros-Weisenberger, Leckman, & Pittenger, 2010; Sansone & Sansone, 2011)

Table 4.4 Guidelines for stages of response to treatment in OCD

Stages of response

Stage of response	Stage	Description
I	Recovery	Not at all ill; less than 8 on Y-BOCS
II	Remission	Less than 16 on Y-BOCS
III	Full response	35% or greater reduction of YBOCS and CGI 1 or 2
IV	Partial response	Greater than 25% but less than 35% YBOCS reduction
V	Non-response	Less than 25% YBOCS reduction, CGI 4
VI	Relapse	Symptoms return (CGI 6 or 25% increase in Y-BOCS from remission score) after 3+ months of "adequate" treatment
VII	Refractory	No change or worsening with all available therapies

(Pallanti & Quercioli, 2006)

4.3 Treatment Assignment Procedures

4.3.1 Randomisation Procedures

Randomisation of participants to treatment groups (for the first 20-weeks of the study) will be determined by computerised random allocation. Recruited eligible participants will be assigned a participant number and provided capsules according to a corresponding IP number. Participant numbers are provided sequentially and the randomisation code is set up in a 2 by 2 block design, with no group identifying them (to avoid potentially unblinding researcher's if participants were randomised to medication bottles labelled A or B).

The last four weeks of the study will be a single blinded placebo run-out (see section 5.12). All participants will be given placebo capsules at Week-20 (researchers unblinded) and told that they may either be receiving placebo or active treatment for the final four weeks of the study. They will continue the same dose of IP from the preceding four weeks (see Table 5.1 for titration strategy).

4.3.2 Masking Procedures

Blinding will be achieved by enlisting a person outside of the project to code the treatments and maintain the key to this code until data collection is completed. The codes will only be broken in an emergency, such as a serious adverse event that requires knowledge of the treatment being taken in order to manage a participant's condition.

4.3.3 Reasons for Withdrawal

Participants will be withdrawn from the study in the following events:

- Y-BOCS ≥32
- Severe deterioration of OCD*
- Suicidal ideation ≥3 on the SIGHD-17
- If a score of ≥ 24 on SIGHD-17 emerges during the study, clinical advice from the medical monitors will be sought to determine if withdrawal or referral is warranted
- Substantial treatment changes**

- Cessation of IP for >7 consecutive days
- Pregnancy
- Occurrence of serious medical condition as determined by the medical monitors, including gastrointestinal ulcers
- Emergence of serious side effects/SAE (to be determined by medical monitors on a case by case basis)
- Commencement of medication with known contraindications with NAC (see Table 4.2) at the discretion of the medical investigator/s
- Participants wishing to withdrawal from the study or withdrawal due to the discretion of the Investigators due to participant safety or similar reasons.

*RAs will notify medical monitors when a participant's Y-BOCS score increase of >35% from baseline. The participant's subsequent participation will be determined by the medical monitors on a case by case basis as well as appropriate referral suggestions (if withdrawn) as required. **For example, entry into an in-patient CBT program, introduction of new psychological therapies, introduction of a new medication, or cessation of medication used for their OCD.

4.3.4 Handling of Withdrawals

Participants will be asked to attend an exit visit in person to sign a withdrawal of consent form. Reasons for withdrawal will be detailed and recorded in the patients CRF by the RA. If participants are withdrawn from the study due to worsening of OCD symptoms (i.e. Y-BOCS ≥ 32) or mood (medical monitor's decision in cases of ≥ 24 SIGHD-17), referral back to their treating doctor for appropriate care will be advised. In cases of strong suicidal ideation/intent, the participant will be seen by one of the medical investigators of the study.

5 STUDY INTERVENTION/INVESTIGATIONAL PRODUCT

5.1 Study Product Description

5.1.1 Acquisition

NAC and placebo will be produced by Lipa Pharmaceuticals and both NAC and placebo will be supplied by Bioceuticals, in line with strict pharmaceutical Good Manufacturing Procedure (GMP).

5.1.2 Formulation, Packaging, and Labeling

Each opaque capsule will contain 500mg of NAC or microcelluose (placebo). The NAC and placebo capsules will be identical in colour, size and shape, and will be packaged in identical containers. Each container will contain 120 capsules. NAC has a strong sulfur odour, therefore, all IP will be contain a small sachet of NAC powder to mitigate any potential unblinding to the participant and RAs involved in assessments. An independent researcher will clearly label each participants IP series with a treatment number and best before date. The trial products will be stored in accordance with manufacturer's instructions which adopt Pharmaceutical Good Manufacturing Practice. Until dispensed to the participants, the IP will be stored in a securely locked area, only accessible to authorised personnel, in accordance with GCP drug storage requirements.

5.1.3 Product Storage and Stability

The IP will be kept in white, airtight containers and stored in a locked cupboard at each trial site. Participants will be advised to store their IP in a cool dry place and out of direct sunlight (below 25 °C).

5.2 Dosage, Preparation and Administration of Study Intervention/Investigational Product

All participants will commence the IP at a dose of two capsules, twice per day for the first eight weeks. The IP will be advised to be taken at least one hour away from other medications and after food, with water or orange juice and minimum of five hours between IP doses. All doses will be taken orally.

In cases of non-response (determined by < 35% reduction in Y-BOCS score from baseline), participants IP will be titrated by 500mg BID (1,000mg per day) from week-8, up to a maximum dose of 4,000mg per day (for example, see table 5.1 below). Note, participants may only increase their dose by 1,000mg per day and remain on this dose for the following four weeks before reassessing response and tolerance at the next study visit. If side effects are current/ongoing at a time point where titration may occur, for example, week-8, the medical investigators will determine if titration is appropriate for the participant. In the event that titration does occur, the RA will call the participant one week later to ensure tolerance to the higher dose. The medical investigators will be notified of any reported side effects and will determine if appropriate for the participant to continue on the titrated dose, or return to the previous tolerable amount.

Table 5.1 Example titration strategy of IP in cases of non-response* reported at each study visit

Visit period	Number of capsules	Dose of IP/day	Containers required
Baseline → Week-4	2 BID	2,000mg	1 x 120c
Week-4 → Week-8	2 BID	2,000mg	1 x 120c
Week-8 → Week-12*	3 BID	3,000mg	2 x 120c
Week-12 → Week-16*	4 BID	4,000mg	2 x 120c
Week-16 → Week-20*	4 BID	4,000mg	2 x 120c

Note *In cases of non-response (<35% reduction in Y-BOCS score from baseline) participants may increase the dose of IP by 1,000mg per day from these time points. Conversely, participants may reduce the dose of IP in the event of intolerable side effects, as determined by the participant or medical investigators.

5.3 Accountability Procedures for the Study Intervention/Investigational Product(s)

The IP will be shipped from Bioceuticals HQ in QLD to the Melbourne and Brisbane study sites by Australia Post or Express Courier. The IP will be ordered in amounts sufficient to randomise 20 participants and a new order for 20 new participants will be placed when levels reach no lower than stock required to randomize five new participants. When stock arrives to the designated study site, an RA will check off each unit against an invoice provided by Bioceuticals. Received stock will be logged in a password protected recruitment and tracking excel spreadsheet as well as a drug accountability folder specific to each study site.

5.4 Assessment of Subject Compliance with Study Intervention/Investigational Product

Participants will be asked to return their IP container from the previous 4-weeks with any remaining capsules left inside at each follow-up visit. The RA will give the container to a third party who will count any remaining capsules and record the value into the participants CRF. The days since last visit will be determined and the expected amount of capsules to be taken by the participant during this time calculated, for example, 28 days x 6 capsules per day (3,000mg of IP) = 168 capsules. This value will be subtracted from the amount of capsules that were in the container upon dispensing, and compared with the amount of capsules returned by the participant to determine compliance.

5.5 Concomitant Medications/Treatments

Participants must be receiving treatment for their OCD (pharmacotherapy and/or psychological interventions) to be permitted eligible for the study (see table 5.2 for permitted medications). The dosages and duration of the medications below must be stable i.e. be employed for a minimum of 8-weeks at consistent dosages and within the recommended therapeutic range for OCD (as specified in table 5.2). If the participant is currently trialing their very first medication, 12-weeks will be considered stable. In cases where participants are taking doses of medications outside of these ranges, for example, escitalopram 60mg/day or an augmented medication below the dosage range, the medical investigator/s at the clinical trial site in question will determine if participation in the study is appropriate.

Table 5.2 Medications and therapies that are permitted during the study

Medication and therapeutic dosage range for OCD (mg/day)			
SSRIs		**SNRIs/NaSSA/Other medications**	
Fluoxetine	20-80mg	Venlafaxine	150-375mg
Fluvoxamine	100-350mg	Desvenlafaxine	50-200mg
Sertraline	50-200mg	Duloxetine	60-120mg
Paroxetine	20-60mg	Mirtazapine	30-90mg
Escitalopram	10-40mg	Agomelatine	25-50mg
Citalopram	20-80mg		
Vortioxetine	10-30mg		
Antipsychotics		**Glutamate modulating agents**	
Risperidone	0.5mg-4mg	Memantine	5mg-20mg
Aripiprazole	6mg-30mg	Topiramate	50-200mg
Quetiapine	25mg-400mg	Lamotrigine	50-200mg
Asenapine	5-20mg	**TCA**	
Lurasidone	40-120mg	Clomipramine	50-300mg
Other			
Psychological interventions*	E.g. regular/consistent ERP, CBT		
Benzodiazepines*	Dose and frequency to be determined by medical monitors		

Note *Only when used as an adjunctive therapy (Bloch & Pittenger, 2014; Fornaro, 2011; Sansone & Sansone, 2011)

5.6 Advertising and enquires

The study may be advertised via the following mediums (where permitted)

- GP clinics & pharmacies affiliated with TONIC media (http://www.tonichealthmedia.com.au/)
    - Displaying of DL study brochures in health notice boards (O-NAC trifold DL brochure version 1)
    - Digital A3 image with study details displayed in health notice boards (see O-NAC A3 digital image version 1)
- Clinician referrals at TMC, RBWH and NICM
- Epworth Mental Health Clinic
- OCD Clinic – Brisbane
- Anxiety House - Brisbane
- St. Vincent's Hospital
- Facebook, Google and other social media advertising
- The Melbourne Clinic OCD in-patient program
- Swinburne University and other University psychology clinics
- Anxiety Recovery Centre Victoria
    - Seminars
    - Newsletters
    - Support groups
- A clinical trial recruitment company (e.g. TrialFacts)
- Community engagement including local GP offices, psychology practices, noticeboards and letterbox flyers
- Media releases and promotion including newspaper articles, radio interviews and television appearances

5.7 Pre-screening

Potential participants may enquire about the study via telephone or email, where an RA will explain the details of the study and answer any questions. If the person enquiring remains interested in the study, the RA will outline the information required to be gathered over the phone (e.g. age, medical history, current medication, history and current presentation of their OCD) to determine if the person meets general eligibility for the study. If they wish to continue with the specified pre-screening questions (by providing verbal consent), the RA will ask for the person's name, age, current medications, mental health diagnoses, medical history, brief treatment history and presenting symptoms. If they appear eligible after questioning, the PICF for the study will be sent and the person encouraged to read thoroughly and discuss the details with their treating doctor. A follow-up call will be made by the RA to assess interest and if willing, a baseline screening session will be made for the individual. Alternatively, enquiring individuals may complete an online pre-screening questionnaire (facilitated by REDCap software) which will ascertain similar information (see appendix for a copy of the REDCap pre-screening questionnaire and section 11.3.1 regarding REDCap confidentiality). Study staff will be notified by automated emails from REDCap when a pre-screening questionnaire is completed. A follow-up phone call will be made by the RA to clarify any necessary details highlighted in the questionnaire and let the person know if they are eligible to proceed with the study procedures. If so, the PICF will be sent and baseline booked as outlined above.

In cases where strong suicidal ideation or distress is apparent in people enquiring over the phone, the RA will encourage the person the make immediate contact with their treating doctor or psychologist or present to their nearest ER, by calling 000 if necessary. If necessary, RA's will contact emergency services if any safety concerns are voiced over the phone or if the RA is concerned about the welfare of any potential/current participants.

5.8 Baseline 1 session

Individuals that attend the baseline 1 session will meet with an RA who will discuss the PICF for the research study. An opportunity will be provided for the individual to ask any questions or raise any queries before signing the consent form. Consenting participants will be asked to provide demographic information, current and previous medications, a medical history as well as caffeine,

alcohol and drug intake over the last 3-months. A detailed description of the participants OCD, and any co-morbid mental health conditions, will be asked including its suspected onset, time of diagnosis, presentation and treatments employed since its occurrence. The Y-BOCS symptom checklist will then be administrated by the RA to determine the participant's current and most prominent obsessive and compulsive symptoms, as well as identifying symptoms experienced previously. The RA will then administer the Y-BOCS severity scale (based on the most prominent symptoms identified on symptom checklist) to ascertain the current severity of the OCD and determine eligibility. If eligible (scoring ≥16 and ≤31 on the Y-BOCS), the RA will administer the Y-BOCS question 11 to determine the participant's insight regarding their OCD symptoms, followed by the SIGHD-17. In cases where individuals do not meet me the inclusion criterial for the study, they will be outlined the reasons why and reimbursed $20 for their time. Referral to appropriate treatment will be advised where necessary, for example, back to their treating doctor or OCD support groups such as ARCVic. If the individual does meet eligibility criteria for the study thus far, they will be asked to complete the DOCS, BAI, BIS-11, SDS, PGI-S and WHOQOL-BREF. Participants may complete these self-reporting questionnaires on site or, if preferred, they may be taken home to complete. An appointment will be made to attend the baseline 2 session to complete remaining screening assessments and return completed self-reported questionnaires (if applicable). This appointment will ideally take place within the next 7 days where possible, however, if 7+ days later, the Y-BOCS will be re-administrated at the start of the baseline 2 session to re-assess eligibility.

5.9 Baseline 2 session

Upon return to the clinic, the RA will address any queries or concerns the participant may have since the first baseline visit. If they wish to continue in the study, the RA will administer the NetSCID-5 on a laptop to confirm a DSM-5 diagnosis of OCD and detect any co-morbid conditions, some of which may exclude the participant from the study (see section 4.2). Eligible participants' blood pressure, height and weight will be collected and self-reported questionnaires collected by the RA (if applicable). An ACL pathology slip will be given to participants consenting to provide a blood sample for the study and who prefer to complete the test off-site. They will be advised to complete the blood test at a time and ACL location of their convenience, ideally within the next four weeks. Alternatively, the blood sample can be collected on-site by an RA trained in venipuncture (see section 6.4). The participant will also be emailed a URL link containing the

DQES v3.2 and advised to complete online at home before the Week-4 study visit. If no internet is available at home, the participant will be provided with a laptop where they will complete the questionnaire on site with the RA. Upon conclusion of the final baseline session, the CGI-S will be completed by the RA.

The participant will be dispensed one IP container which will provide sufficient capsules for the following 4-weeks, as well as dosage instructions (verbally, on the IP container and an accompanying handout) and various contact numbers (study landline and after hours study mobile number, and TMC contact details in the event of an emergency/mental distress). They will also be provided with an estimated appointment calendar for the remaining follow-up visits.

A follow-up phone call will be conducted 7-10 days after the baseline 2 session to ensure compliance, tolerance and address any queries from the participant. The date and time of the Week-4 follow-up session will also be re-confirmed.

5.10 Follow-up visits

Participants will be required to attend follow-up visits at Week-4, 8, 12, 16, 20 and 24. In these sessions, participants will be asked to provide an overview since their last visit, particularly any noticeable changes in their OCD, mental health, functioning and/or quality of life. Changes in treatment (pharmacological and/or psychological), drug and alcohol consumption, medical conditions and the occurrence of side effects, if any, will also be ascertained. The Y-BOCS symptom checklist will be re-administrated by the RA to identify current obsessive and compulsive symptoms, followed by Y-BOCS severity scale (including question 11 regarding insight) and SIGHD-17. At each follow-up visit, the participant will also be asked to complete the DOCS, BAI, SDS, PGI-S, PGI-I and SAFTEE. Upon conclusion of each follow-up visit, the participants blood pressure will be taken and the CGI-I and CGI-S completed by the RA. In addition, at Week-12 and Week-20, the WHOQOL-BREF will also be completed by the participant.

Participants will also be reimbursed for travel expenses totaling $140-$160 in the form of Coles/Myer gift cards ($20 at each scheduled visit; $160 in total if all study visits are completed and if the baseline sessions are completed on separate days, reflecting additional travel costs incurred to the participant).

5.11 Final Study Visit

The final study visit will occur at Week-24, where the participants would have completed a single-blinded placebo run-out for the preceding 4-weeks (see section 5.12). In this final session, the RA will administer the Y-BOCS and SIGHD-17 and the participant will be given PGI-S, PGI-I, BAI, SDS and SAFTEE to complete. Participants will have the option of receiving three containers (120c in each) of NAC free of charge and advised to discuss with their treating doctor before use (a letter will also be provided to participants re-iterating this – see 'O-NAC Study completion letter' in appendix, approved by TMCREC 23 April, 2018).

5.12 Placebo run-out

The final four weeks of the trial will be reserved for the assessment of potential withdrawal effects and to investigate any sustained response that may occur after ceasing the NAC/placebo. This will be carried out my means of an additional four week single-blinded placebo run-out. The researchers will be aware that all participants will be transitioning onto placebo from Week-20 for the following four weeks, however, the participants will not be aware and continue under the assumption they may be receiving placebo or active treatment as they consented to in the baseline session. To uphold ethical standards whilst maintaining blinding, the PICF will state that the dose of NAC/placebo may change throughout the study to allow for titration and assessment of benefit/effect at various doses.

5.13 Withdrawal Visit

In the event of withdrawal, participants will be asked to detail their reasons for wishing to withdraw, or, if the decision of the researchers, the RA will record these reasons in the participants CRF. If willing, the participant will complete the Y-BOCS and SIGHD-17 with the RA and will complete the WHOQOL-BREF and SAFTEE. Finally, they will be asked to sign the withdrawal of consent form. If the participant specifies, all their data (including their stored genetic sample) can be destroyed and not included in the analysis. If not specified by the participant at the time of withdrawal, all their data will be used as outlined in the PICF.

5.14 Unscheduled Visit

Participants may be required to attend unscheduled study visits for the following reasons

- In the event of a SAE to assess impact, status and resolution of the event
- Necessity to withdraw participants from the study as per their wishes, or per protocol by the study investigators (see section 4.2)

All details of the visit will be recorded by the RA in the CRF, including reasons for the visit and future actions required regarding monitoring and following-up with the participant.

6 STUDY PROCEDURES/EVALUATIONS

6.1 Diagnostic assessments

The Structured Clinical Interview for DSM-5 (SCID-5) will be employed to confirm the presence of OCD and other comorbid mental health disorders as per DSM-5 criteria. The SCID-5 is a semi-structured, streamlined, clinician administrated instrument which assesses the presence of selected DSM-V mood disorders, anxiety disorders, substance use disorders, and personality disorders. The SCID-5 will be administered by the RA to the participant on an electronic tablet device or laptop using software called NetSCID (TeleSage, 2016).

The NetSCID is a relatively new tool that has been validated by 24 clinicians who administered the SCID (paper version) and/or NetSCID to 230 participants (Telesage, 2016). Validation studies are ongoing. When compared to the paper SCID, the NetSCID results in greater clinician satisfaction, fewer data entry and branching errors (TeleSage, 2016). The use of the NetSCID reduces the completion time by 30% compared to the paper version with data collected de-identified and scoring/coding of diagnoses instantaneous (TeleSage, 2016). Data from the NetSCID can be imported directly to a statistical package reducing data entry time and errors.

6.2 Clinical Evaluations

6.2.1 Qualitative review

At the beginning of each follow-up visit, participants will be asked to provide an overview of their month. Specifically, the RA will use the following semi-structured, open-ended questions to assist in gathering qualitative data:

- What, if any, changes have you noticed about your OCD over the past four weeks?
- What do you think has brought on these changes OR why do you think things have remained unchanged?
- Have you noticed differences in any other areas of your life over the past four weeks? (*can prompt with…*) For example, sleep, mood, energy, social life, work, stress…

Detailed notes will be taken by the RA during and after each visit, capturing as much information and narrative as possible provided verbally by the participant and also including the RAs own observations. The RA's impression of the participant's status and progress will also be detailed.

6.2.2 Yale Brown Obsessive-Compulsive Scale (Y-BOCS) – severity scale

The Y-BOCS (severity scale) was created in 1989 by Goodman and colleagues and is typically administrated as a 10-item instrument to provide a rating of severity regarding OCD symptoms. It is widely used in OCD clinical research and private practice and is well regarded as the gold standard for measuring the severity of both the obsessions and compulsions present in the disorder (Rapp, Bergman, Piacentini, & McGuire, 2016). Treatment sensitivity of the Y-BOCS has been demonstrated through its extensive use in clinical trials for OCD (Grabill et al., 2008). The Y-BOCS is a semi-structured, clinician administrated scale that asks the patients to reflect on the most prominent obsessive and compulsive symptoms separately over the past seven days, exploring frequency, impact/interference, distress caused and the person's effort to resist and ability to control the thoughts. A five point Likert scale ranging from 0-4 is used for each question, 0 equating to none or minimal impact/intensity and four of greatest severity. Scores are determined by the researcher based on the participant's self-reports as well as the researcher's own observations and interpretation during the session. The sum of the 10 items yields an overall score, which enables participant's OCD to be categorised as sub-clinical (0-7), mild (8-15), moderate (16-23), severe (24-31) and extreme (32-40). The Y-BOCS has demonstrated good criterion-related validity as patients diagnosed with OCD have received higher scores on the Y-BOCS compared to those with other anxiety disorders and healthy controls (Grabill et al., 2008). In addition, question 11 of the Y-BOCS will be administered at each visit which assesses the participant's insight into their obsessive and compulsive symptoms. A rating of excellent (=0), good (=1), mild (=2), poor (=3) and completely lacking insight (=4) can be determined on a Likert scale of 0 - 4, however, these scores are not included in the Y-BOCS total score.

6.2.3 Yale Brown Obsessive-Compulsive Scale (Y-BOCS) - symptom checklist

The Y-BOCS Symptom Checklist was developed by the same authors to augment the Y-BOCS severity scale (see section 6.2.2). It consists of 54 common obsessive and compulsive symptoms which are categorised into eight obsession subgroups, for example, aggressive obsessions (fear

might harm self or others; violent or horrific images), contamination obsessions (concerns or disgust with body waste or secretions; excessive concern with environmental contaminants) and obsessions with symmetry/exactness (concerns that another will have an accident unless things are in the right place); as well as seven compulsion categories including checking compulsions (checking locks, stoves, appliances; checking that did not/will not harm others), cleaning/washing rituals (excessive or ritualized handwashing) and repeating rituals (repeating or rewriting rituals). The checklist has been used to identify patients obsessive and compulsive symptoms in a dichotomous format (reported as 'yes' or 'no'), for symptoms endorsed at current as well as those experienced in the past. Current, more prominent symptoms are asked to be highlighted by the participant, thus enabling the Y-BOCS severity scale to reflect obsessions and related compulsions causing the most interference and/or distress to the patient. In this study, the symptom checklist will be administrated by the RA to the participant, rather than in self-report form.

6.2.4 Dimensional Obsessive-Compulsive Scale (DOCS)

The DOCS is a self-reporting measure developed in 2009 designed to capture dimensional or thematic aspects of OCD symptoms as well as their severity (Abramowitz et al., 2010). Each of the four categorised symptom dimensions 1) germs and contamination 2) responsibility for harm, injury or bad luck 3) unacceptable obsessional thoughts and 4) symmetry, completeness and exactness consists of 5-items addressing time, avoidance, distress, impairment and resistance towards both obsessions and compulsions. Patients are asked to rate each of these 20 items based on experiences in the past month on a Likert scale between 0 and 4, with higher scores reflecting greater severity. Benefits of the DOCS are its reported ability to assist in diagnoses of OCD (total scores greater than 18-20) and discriminate OCD from both healthy controls and patients with other anxiety disorders (Abramowitz et al., 2010). Whereas higher sub-scores on specified dimensions may indicate treatment targets or serve as a predictor of response in treatment intervention studies (Thibodeau, Leonard, Abramowitz, & Riemann, 2015). In addition, and unlike various other OCD measures, the DOCS captures avoidance behaviours common in individuals with OCD. The DOCS has excellent to good internal consistency ($\alpha = 0.89 – 0.90$) and demonstrates good convergent validity with the Y-BOCS ($r = 0.56$).

6.2.5 Structured interview guide for the HAM-D, 17 item (SIGHD-17)

The HAM-D is a 17-item, multidimensional scale designed for clinicians to administer and has been used extensively in clinical trial research (including OCD studies) since the 1960s to assess intervention efficacy (Baer & Blais, 2010; Moritz, Meier, Hand, Schick, & Jahn, 2004). Each item explores common features of depression including depressed mood, feelings of guilt, suicidality, somatic and psychological anxiety and sleep (onset, maintenance early morning wakening). Both the impact and frequency of each item is investigated over the previous 7-day period and a score rated on a Likert scale (ranging from 0-4 for most items) with larger magnitudes correlating with greater severity. Internal consistency appears to be greater when using the structured guidelines for the HAM-D (Williams, 1988), thus, the structured HAM-D (17-tem) will be employed in this study. Inter-rater reliability is high for the HAM-D total score (0.80-0.98), despite being poor for some of its individual items in some instances (Bagby, Ryder, Schuller, & Marshall, 2004). Suggested severities of depression as per the total HAM-D score (17-item) include no depression (0-7); mild depression (8-16); moderate depression (17-23); and severe depression (≥24) (Zimmerman, Martinez, Young, Chelminski, & Dalrymple, 2013).

6.2.6 Barratt Impulsivity Scale-11 (BIS-11)

The BIS-11 is a 30-item self-reporting measure designed to assess personality and behavioral constructs of impulsivity (Patton et al., 1995). It is suggested to be the most commonly employed self-reporting measure used specifically to assess impulsiveness in both research and clinical settings, with over 50 years of use since the creation of its first version in 1959 (Stanford et al., 2009). The BIS-11 consists of three factors of impulsivity 1) motor impulsiveness (11 items) 2) attentional (cognitive) impulsiveness (8 items) and 3) non-planning impulsiveness (11 items). The participant is asked to answer each item on a 4-point Likert scale (1 = rarely/never, 2 = occasionally, 3 = often, 4 = almost always/always). The BIS-11 will be employed in this study at baseline only and used to assess if the degree of impulsivity traits predict treatment response to NAC or placebo.

6.2.7 The Beck Anxiety Inventory (BAI)

The BAI is a 21-item self-reporting instrument which is used widely is clinical research both as a screening and outcome tool to determine the presence and severity of anxiety symptoms as defined by the DSM-IV (Beck & Steer, 1993). It was designed specifically to differentiate between anxiety and depressive symptoms, however, the BAI is advised not to be used as a diagnostic tool (Leyfer, Ruberg & Woodruff-Borden, 2006; Bardhoshi, Duncan & Erford, 2016). Each item assesses the presence and impact of physical and psychological symptoms of anxiety such as the occurrence of a 'racing or pounding heart', 'feeling unsteady' and 'fear that the worst may happen'. Participants are asked to answer each of the 21 items from experiences of the past 7-day period on a 4-point Likert scale, with 0 indicating 'not at all' and 3 ' severely', for example 'I could barely stand it'. A total score is obtained by adding all scores from each domain, with 0-7 denoting minimal anxiety, 8-15 mild anxiety, 16-25 moderate anxiety and 26-63 severe anxiety. A recent psychometric meta-analysis involving 192 studies from 1993 has highlighted the BAI to hold an excellent internal consistency ($\alpha = .91$, $k = 56$, $n = 25{,}917$, both clinical and non-clinical samples) and test-retest reliability in clinical samples of $r = .65$ ($k = 10$, $n = 2{,}101$, $Mdn = 6$ weeks) (Bardhoshi, Duncan & Erford, 2016).

6.2.8 World Health Organization-Quality of Life-BREF (WHOQOL-BREF)

The WHOQOL-BREF (Skevington et al., 2004) is a culturally appropriate quality of life (QOL) assessment instrument, which assesses an individual's perception of personal goals, standards and concerns, in the context of his/her culture and value systems. The WHOQOL-BREF is a reduced version of the original instrument, designed for use in clinical trials. It comprises 26 self-report items, including two benchmark items assessing overall QOL and general health. The remaining 24 items cover the domains of physical health, psychological health, social relationships, and environment. The WHOQOL-BREF also provides an overall score relating to QOL and general health. Individuals are asked to indicate "how good", "how satisfied", "how completely", "how often" or "how much" they experienced or felt relevant concerns over the past four weeks on a five-point Likert scale. The two benchmark items (overall QOL and general health) are calculated as a single score with a range of one to five. Domain scores are calculated by multiplying the mean score for all items included in each domain by a factor of four. Potential scores for each domain range from four to 20, with higher scores indicative of greater QOL.

Research indicates the WHOQOL-BREF is a valid and psychometrically sound instrument. Cross-sectional data obtained from a survey of adults (general population, in addition to hospital, rehabilitation, and primary care settings) carried out in 23 countries (*N* = 11,830) has indicated the WHOQOL-BREF has good psychometric properties of reliability (Cronbach's alphas ranging from .76 for social relationships to .87 for environment) and performs well in tests of validity (Fu et al., 2013; Skevington, Lotfy, & O'Connell, 2004).

6.2.9 Sheehan Disability Scale (SDS)

The Sheehan Disability Scale (SDS), developed in 1983, measures the extent in which three major domains (work, social life or leisure activities, and home life or family responsibilities) in an individual's life are impaired by their mental health symptoms. In this study, the scale will be employed as a self-reporting measure where participants will be asked to rate impairment on a 10-point visual analog scale which is anticipated to be completed within 1-2 minutes. A study involving 1,001 primary care patients highlighted that the inter-item correlations of the three SDS domains were fairly high (0.70 for work and family impairment, 0.72 for work and social impairment, and 0.79 for family and social impairment) (Leon, Olfson, Portera, Farber, & Sheehan, 1997). Consequently, the internal consistency was also high (alpha = 0.89 for the three item scale). Further, with effective treatment, the SDS appears to reflect chance over time and does not discriminate between active treatment (even in studies involving two active treatment arms) or placebo (Arbuckle et al., 2009; Leon et al., 1997).

6.2.10 Clinical Global Impression Scale (CGI)

The CGI was first developed for use in 1976 as part of a National Institute of Mental Health psychopharmacology study for schizophrenia (Guy, 1976). It is now widely used as a standard primary measure across various psychiatric conditions including depression, bipolar and OCD to assess treatment interventions (Berk, Copolov et al., 2008$_a$; Dean et al., 2014; Haghighi et al., 2013). The CGI is clinician rated and consists of two domains; the first rates the severity (CGI-S) of the participant's condition at baseline and each following visit, whilst the second domain rates the participant's perceived improvement (CGI-I) from baseline. The CGI-S scores range from 1-7, one being 'normal' and seven 'extremely ill'. The researcher rates the participant's primary condition in question each visit, based on their own observations and judgement, as well as self-reports obtained from the participant. The CGI-I assesses the clinical change compared to the

CGI-S score at baseline on a similar 1-7 scale, with one being ‘very much improved’ and seven ‘very much worse’. Conjointly, higher scores on the CGI equate to greater severity and worsening symptoms. The CGI is a valid outcome measure in psychiatry and has been supported in a study comparing over 600 hospital admissions and over 600 discharge rates, which were positively correlated with both CGI-I/S scores (*r* = .40 and .71 respectively; Berk, Ng et al., 2008). In addition, these results highlight this scale’s sensitivity to change.

6.2.11 Patient Global Impression of Change (PGI)

The PGI is a self-reported scale consisting of two parts which asks patients to rate the severity of the disease or disorder in question (the PGI-S) on a four point scale, for example, 1 = ‘normal’, 2 = ‘mild’, 3 = ‘moderate’ or 4 = ‘severe’; as well as its perceived improvement across the course of the intervention (the PGI-I) on a seven point scale (1 = very much better, 7 = very much worse). Congruent with the CGI, PGI-S and PGI-I scores of higher magnitude correlate with greater perceived severity and worsening of symptoms.

6.2.12 Dietary Questionnaire for Epidemiological Studies (DQES v3.2)

The DQES v3.2 is a modification of the Food Frequency Questionnaire (FFQ) developed by the Cancer Council in the late 1980s. It assesses the average intake of five food groups (1. Cereals, sweets & snacks 2. Dairy product, meats and fish 3. Fruit 4. Vegetables and 5. Alcoholic beverages) consumed over the last 12 months, and includes over 80 food items as well as approximate portion sizes. Each participant’s questionnaire will be analysed by the Nutritional Assessment Office of the Cancer Council Victoria to determine intake of energy, fat, (saturated fats and poly & mono unsaturated fats), fatty acids, cholesterol, protein, carbohydrates, sugars, starches, fibre, alcohol, various antioxidants, vitamins and minerals and glycaemic index and load of their diet. A URL will be provided for participants to complete the DQES v3.2 at home, alternatively, if they do not have internet access at home, they can complete the questionnaire on site on a study laptop.

6.3 Physical Examination

6.3.1 Blood pressure

Given NAC's potential hypotensive activity, participants will have their blood pressure (BP) taken automatically via a BP machine in each study visit. BP will be measured when participants are in a seated position, legs uncrossed, the BP cuff on their left arm and arm resting at heart level. BP will be categorized according to international guidelines, as seen in Table 6.1 below.

Table 6.1 International Blood Pressure Categorisations

Blood Pressure Classification	SBP mmHg		DBP mmHg
Hypotension	<90	or	<60
Normal	<120	and	<80
Prehypertension	120–139	or	80–89
Stage 1 Hypertension	140–159	or	or 90–99
Stage 2 Hypertension	≥160	or	≥100

6.3.2 BMI

Participants' height (m) and weight (kg) will be taken at baseline using a retractable tape measure and an electronic set of scales. These values will be used to calculate participants' body mass index (BMI; weight in kilograms/height in metres^2).

6.4 Clinical Laboratory Investigations

Participants may consent to providing a blood sample which will be analysed for single nucleotide polymorphisms (SNPs). Consenting participants can have their blood taken on site by an RA trained in venipuncture, or they will be given a pathology slip for ACL and asked to complete the blood test offsite at a time and ACL location of their convenience. A total of 5ml of blood will be extracted and collected in an EDTA tube by a venipuncture technician which will be couriered to ACL Molecular Genetics Lab and stored as whole blood at -80^{o}C. DNA will be extracted from this sample and analysed for various SNPs, names of which are yet to be confirmed by the study

investigators. No SNPs will be analysed until appropriate ethics committees have approved an amended SNP list in this protocol.

The samples will be stored for a period of up to five years after completion of the study and analysed to provide data for the current study, and possibly other research studies relating to OCD with appropriate ethics approval (where consent has been provided by participant).

7 ASSESSMENT OF SAFETY

7.1 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

7.1.1 Adverse Events

ICH E6 defines an adverse event (AE) as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product regardless of its causal relationship to the study treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the IP. The occurrence of an AE may come to the attention of study personnel during or by communication in between study visits or the participant presenting for medical care.

Dr Scott Blair-West, Prof Chee Ng and Dr. Ranjit Menon will be available for medical supervision relating to the participants in the study at The Melbourne Clinic. Prof Gerard Byrne and Dr. Suneel Chamoli will provide medical supervision at The Royal Brisbane and Women's Hospital and Dr. Carolyn Ee at Western Sydney University.

7.1.2 Serious Adverse Events

A serious adverse event (SAE) includes any untoward medical occurrence that:

- results in death;
- is life-threatening (including suicide attempts. NOTE: The term "life-threatening" refers to an event/reaction in which the patient was at risk of death at the time of the event / reaction; it does not refer to an event/reaction which hypothetically might have caused death if it were more severe);
- requires inpatient hospitalisation or prolongation of existing hospitalisation;
- congenial anomaly/birth defect
- results in persistent or significant disability/incapacity;
- is a medically important event or reaction

7.1.3 Screening for suicidality

Suicidality is screened by item-3 of the SIGHD-17 at each study visit (with the exception of the initial baseline 2 session, where the SCID-CT-5 will be used). Participants are also asked at the beginning of each follow-up visit regarding worsening of mood, OCD symptoms, thoughts of self-harm and suicidal ideation. Participants will be withdrawn from the study if item-3 on the SIGHD-17 is equal to or greater than 3 and if not at immediate risk, will be advised to make contact with their treating doctor. In cases of strong suicidal ideation and intent (for example, SIGHD-17 item-3 score of 4), the participant will be asked to wait with the RA until a risk assessment can be conducted by one of the medical investigators on site. If necessary, the participant will be directed to emergency services or 000 will be called for immediate transfer. The participants treating psychiatrist or physician will be contacted immediately.

7.1.4 Procedures to be followed in the Event of Abnormal Laboratory Test Values or Abnormal Clinical Findings

In the event of high or low blood pressure (see table 6.1), participants will be asked to have their BP taken again by the RA before completion of the study visit. Recent intake of caffeine, alcohol, medication and cigarettes, exposure to cold temperatures as well as recent stressors, or feelings or stress will be ascertained. If the 2nd reading appears abnormal, they will be advised to see their GP or treating doctor.

7.2 Reporting Procedures

Any AE or SAE may be reported by a participant in person during one of the study visits, or via phone as the event occurs. Participants will be advised at the baseline screening session (and in sessions thereafter) to contact the RA as soon as possible in the event of an AE or SAE. A landline number will be provided to participants to enable contact during business hours, however, if the event occurs after hours, they will be advised to call a specified research study mobile number which the principal investigator or CTC will keep with them at all times.

7.2.1 Serious Adverse Events

If any SAE (outlined in 7.1.2) occurs within the study they will be reported to all ethics committees (TMCREC, The University of Queensland Medical Research Ethics Committee and WSU Human Research Ethics Committee) within 48 hours of occurring using the initial SAE report form (see appendix). Subsequently, a follow-up SAE form (see appendix) will be submitted two weeks later to inform the ethics committee of the outcome of the event. The RA will keep appropriate contact with the participant throughout the period of the SAE and monitor after its resolution where applicable, and record all methods of contacts and details in their CRF.

7.2.2 Adverse Events

At the beginning of every follow-up visit, participants will be questioned non-specifically for any adverse events (AEs) as well as asked to complete a purpose-designed Symptom Checklist (the Systematic Assessment for Treatment Emergent Events; SAFTEE) to determine if a participant experienced an AE. Any verbally reported AEs or any symptoms on the SAFTEE marked as causing significant distress, including local and systemic reactions not meeting the criteria for a SAE, will be recorded in the participant's CRF. The information recorded in the CRF will be based on signs and symptoms reported by the participant or observed by the investigators. All AEs will be discussed with the study investigators in weekly teleconferences relating to the progress of the study and any necessary intervention for AEs will be decided by the medical investigators.

A description of each event, date and time of onset, assessment of severity, suspected relationship to study product (assessed only by those with the training and authority to make a diagnosis, which would include an MD or psychiatrist), and time of resolution/stabilization of the event. All AEs occurring during the study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution, and if a participant experiences an AE or an SAE during the treatment period that has persisted through to the last testing day, consent will be requested for continued contact with the participant until the AE or SAE has fully resolved. The status of the participant's condition will be recorded in their CRF each time contact is made.

Any medical condition that is present at the time that the patient is screened should be recorded in their medical history and not reported as an AE. However, if this condition deteriorates at any time during the study, it should be recorded as an AE.

7.2.3 Severity of Event

To quantify intensity, all AEs will be graded by the following:

- Mild: events require minimal or no treatment and do not interfere with the patient's daily activities.
- Moderate: events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- Severe: events interrupt a patient's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.
- Life threatening: any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that had it occurred in a more severe form, might have caused death.

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. Adverse events characterized as intermittent require documentation of onset and duration of each episode.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Considerations

A sample size of 200 participants (100 participants in each arm) are to be recruited and intention-to-treat principles will be applied to all data. A large sample of 200 participants is powered to detect a potential small to moderate effect size (*f* = 0.15) difference between NAC and placebo beyond treatment as usual, approximating a clinically significant 3 point reduction on the YBOCS (using all post-baseline data via intention-to-treat analysis). Based on an ANOVA model over seven time-points, a two tailed analysis with alpha=0.05, beta=0.80, and a critical F of 3.78; 200 participants (not including drop-outs) are required to detect a small to moderate effect size difference in Y-BOCS scale score between treatment and placebo.

The primary efficacy analysis will assess mean treatment group differences for the primary outcome measure (Y-BOCS) using a mixed-effects model, repeated measures approach (MMRM). Results from the analysis of dichotomous data (e.g. demographics data) will be presented as proportions with 95% confidence interval, and Fisher's Exact *p*-value where appropriate. Analysis of covariance (ANCOVA) will also be used to compare differences between treatment means in changes from baseline to week 20 last observation carried forward (LOCF) endpoint. The ANCOVA model will assess confounding covariates including intervention type (medication or psychological care), as well as age, gender, weight, physical activity levels, smoking and alcohol consumption.

Non-parametric statistics will be used when assumptions for parametric methods are violated. Effect sizes will be calculated using Cohen's d. All tests of treatment effects will be conducted using a two-tailed alpha level of 0.05 and 95% confidence intervals. Data will be analysed via SPSS 23.0.

9 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH E6, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of subjects.

The principal investigator, CTC, RAs and associated ethics committees will have access to patient CRFs for purposes of assessment, monitoring, safety and/or data entry. The principal investigator will also permit trial related monitoring, audits, IRB/IEC review and regulatory inspections by providing direct access to source/data documents. In addition, participants are also entitled to have access to their de-identified CRF via Australian and Victorian privacy laws. Participants wishing to access their file will be asked to contact the research staff and follow the regulations outlined by relevant government agencies.

10 QUALITY CONTROL AND QUALITY ASSURANCE

Standard Operating Procedures (SOPs) will be in place to ensure the trial is conducted in accordance with Good Clinical Practice (GCP). The clinical trials co-ordinator will routinely monitor the trial and ensure that it is being conducted in accordance with the protocol and GCP requirements. Additionally, the principal investigator, CTC and RAs involved in this study will have weekly teleconference meetings to discuss the progress and any issues that arise during the course of the study.

11 ETHICS/PROTECTION OF HUMAN SUBJECTS

11.1 Ethical Standard

The procedures outlined in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the principle investigator abides by GCP Guidelines and under the guiding principles detailed in the Declaration of Helsinki. The study will also be carried out in keeping with applicable local law(s) and regulation(s). This may include an inspection by the Regulatory Authority representatives at any time. The principal investigator must agree to the inspection of study-related records by the Regulatory Authority, and must allow direct access to source documents to the Regulatory Authority.

11.2 Informed Consent Process

Participants who complete a phone screening and meet the criteria for the study will be sent the PICF via email or post, advised to read it thoroughly and discuss with their treating doctor and/or psychologist. If they agree to attend the baseline session of the study, they will meet with an RA who will outline each section of the consent form with them. Opportunities for the participant to ask questions or raise concerns will be provided. If the participant understands and agrees with the information outlined in the PICF, they will be asked to sign it and thereby consent to participating in the study, along with the signature of the RA. Participants will have the option of selecting ‘yes’ or ‘no’ to participation in the genetic analyses of this study (see section 6.4.2) as well as future OCD studies. A dually signed copy of the PICF will be given to the participant to keep for future reference.

11.2.1 Referral to other research studies

Participants will have the option for their contact details to be stored on a password protected database to allow researchers to notify them of future OCD studies (with appropriate ethics committee approval). This option will be outlined to the participant by the RA at the baseline session and listed on the PICF, with participants being able to select ‘yes’ or ‘no’ to indicate their consent or desire to decline.

11.3 Subject Confidentiality

To maintain anonymity, participants will be allocated a numerical identifier. After consent is obtained, only these numbers will identify participants. All raw and analysed data from assessments and questionnaires will be assigned a code number and will not contain information that could enable identification of individual participants. Signed consent forms and participant identifying details will be kept together in a locked filing cabinet and stored separate from questionnaire and genetic data collected from participants throughout the study. A password protected, recruitment and tracking excel spreadsheet will be developed by the CTC and will contain participant contact details, IP allocation and study visit schedules. This information will not be accessible unless a justified scientific or ethical reason is provided to the director of the institute. In all publications and dissemination of findings, participants will be anonymous.

11.3.1 REDCap confidentially

REDCap is an electronic and secure data capturing program which was created in 2004 at Vanderbilt University. It is currently used in 2762 institutions across 119 countries, including The University of Melbourne where it is employed in 180+ research projects, many of which involve clinical research. REDCap is designed to comply with Health Insurance Portability and Accountability Act (HIPAA) regulations, which sets the standard for protecting sensitive patient data to uphold patient confidentiality. REDCap software will be used in this project to facilitate an online pre-screening questionnaire (see appendix) which enquiring individuals can complete at their own volition. Completed pre-screening questionnaires will be accessible to approved research staff via a central REDCap login (username and password).

12 DATA HANDLING AND RECORD KEEPING

The investigator is responsible to ensure the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

12.1 Data Capture Methods

Data will be collected primarily via handwritten notes in black pen only and stored in a CRF. Some measures (NetSCID-5-CT and DQES v3.2) will be captured on an electronic tablet device and results of SNP analyses will be stored on an excel spreadsheet created by ACL. All data collected electronically will be de-identified and collected using the participants designated participant code rather than the participant's name.

12.2 Types of Data

Data for this study will include participant demographic information, medical history, including mental health diagnoses, previous and current treatments and subsequent treatment changes, diet quality, caffeine, drug and alcohol intake, diet quality, change in outcome measures determined from clinician rated scales and self-reporting questionnaires (primarily mental health and quality of life related) and side effects. In addition, genetic data will be included.

12.3 Storage of data

Source documents will be kept in the participant's CRF and stored in a locked cabinet accessible only to the principal investigator, CTC and RAs working on the project. De-identified data from these files will be entered into an SPSS file (statistical analysis software) and backed up onto the University of Melbourne secure server ("M drive"). All electronic data will be verifiable against source documents. In addition, collected electronic data will be stored via the following methods and backed up onto UniMelb server where possible.

:

- REDCap pre-screening questionnaires: saved as password protected PDF documents on computers only accessible to study staff (e.g. the CTC, PI and RAs). A redacted copy will also be stored in the participant's CRF
- NetSCID-5-CT: reports saved as PDFs under individual participant codes (note, information within this report is de-identified). A copy will also be printed and stored in each CRF.
- DQES v3.2: stored with the Cancer Council (note, this data is de-identified) until requested for data analysis
- SNP reports: Sent from ACL in an excel spreadsheet with participant codes and D.O.B only

12.4 Study Records Retention

As per GCP guidelines, upon request of the IRB/IEC or regulatory authority, the principal investigator will make all requested trial-related records, including source documents, available for direct access. The study files and all source data will be retained for 15 years from the date of publication of study results, in accordance with university policy.

12.5 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, Good Clinical Practice (GCP), or Manual of Procedures requirements. The noncompliance may be either on the part of the subject, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3

5.1 Quality Assurance and Quality Control, section 5.1.1

5.20 Noncompliance, sections 5.20.1, and 5.20.2.

The PI may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to the trial participants without prior EC/IRB/favourable opinion. Details of the

implemented deviation or change, the reasons for it and, if appropriate, the proposed protocol amendment will be submitted to the EC/IRB as soon as possible. Any deviations from the protocol must be fully explained and documented by the investigator.

13 INSURANCE & FINANCES

This study is funded by the National Health and Medical Research Council (NHMRC; #APP1104460). A multi-institutional agreement (MIA) between The University of Melbourne, Western Sydney University and The University of Queensland has been initiated.

The trial will be covered by University of Melbourne insurance as the primary sponsor. The University of Queensland and Western Sydney University will also be required to provide insurance for site-specific cover.

14 PUBLICATION POLICY

There are no publication restrictions and this study will be published in international peer reviewed journals.

15 LITERATURE REFERENCES

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16 APPENDIX

Date:_ _____

ID: _____

Site:_____

O-NAC Serious Adverse Event Form

Study Title:	N-acetyl cysteine (NAC) augmentation in Obsessive-Compulsive Disorder (OCD): A 24-week, randomized, double blind placebo controlled trial
PI:	Prof Jerome Sarris
Site:	The Melbourne Clinic (TMC)
HREC number(s)	TMCREC: 279 UQMREC: 2016001720 WSU HREC: H12181
SAE definition:	A Serious Adverse Event is described as: Any untoward medical occurrence that at any dose: • Results in death • Is life threatening (at risk of death at the time of the event) • Requires inpatient hospitalisation or prolongation of existing hospitalisation • Results in persistent or significant disability/ incapacity, or • Is a congenital anomaly/ birth defect • Is a medically important event or reaction www.tga.gov.au

SAE Details

Event number:		**Participant ID**	
Report type:	Initial ❑ Outcome/Follow-up ❑		
Is the SAE related to a previous AE?	Yes ❑ No ❑		

	If yes, what was the date of the original AE? ____/_____/_____
Describe the original event *(if applicable)*	
Date (new) event started?	_____/_____/_____
Date event reported to researcher:	_____/_____/_____
Diagnosis:	*(If unknown, signs and symptoms are acceptable)*
Relevant diagnostic test/laboratory data:	

Medication given to treat event:	
Result	*(tick all appropriate boxes)* ❑ Patient died. Date: _____/_____/_____ ❑ Life threatening illness ❑ Required clinician visit ❑ Required hospitalization. Admission Date: ____/_____/____ Discharge Date: ____/_____/_____ ❑ Resulted in permanent disability/incapacity ❑ Other: _____
Action	❑ No action ❑ Other treatment given ❑ Study product interrupted. Total days _____ ❑ Study drug discontinued ❑ Participant withdrawn from study ❑ Other action**:** _____
Outcome	Date of outcome: _____/_____/_____ ❑ Completely recovered ❑ Recovered ❑ Condition improving ❑ Condition unchanged

	❑ Condition deteriorating ❑ Death. Date: _____/_____/_____
Severity	❑ Mild ❑ Moderate ❑ Severe
Causality	❑ Unrelated ❑ Possibly related ❑ Probably related ❑ Definitely related ❑ Unknown
Additional comments	
PI/Researcher name and contact number:	
Signature and date	____/_____/_____

16.2 REDCap Pre-screening questionnaire

Thank you for your interest in the N-acetylcysteine study for OCD with the University of Melbourne.

This questionnaire is used to assess whether you meet the key eligibility criteria for study participation.

Completion of the pre-screener does NOT guarantee that you will be eligible to participate.

Please complete the survey below. **Your answers will remain confidential.**

Your name (or initials if preferred)
* must provide value

Date of birth
* must provide value
Today D-M-Y
Please enter your date of birth

Postcode
* must provide value

Biological sex
* must provide value
- ◯ Female
- ◯ Male

reset

Best contact number
* must provide value

Email address
* must provide value

Confirm email address
* must provide value
Please confirm your email address

How did you hear about this research study?
* must provide value
For example, facebook, google, saw flyer at clinic

Have you been diagnosed with OCD?
* must provide value
- ◯ Yes
- ◯ No

reset

By whom?
* must provide value
For example, was it by a GP/psychiatrist/psychologist?

When were you diagnosed?
* must provide value
For example, how old were you? And/or what year were you diagnosed?

Do you currently take medication for your OCD?
* must provide value
- ◯ Yes
- ◯ No

reset

Please provide details of:
-the type of medication/s you take
-the dose of each medication
-how long you have been taking each medication

* must provide value

Expand

For example, lexapro 20mg for 6 months

Do you currently take any other prescription or over the counter medication?
This includes any vitamins, supplements or herbal remedies.

* must provide value

- ◯ Yes
- ◯ No

reset

For example, medication you take for another medical condition not specifically related to your OCD

Please provide details of:
-which medication/supplement
-the dose of this medication/supplement
-how long you have taken this medication/supplement for

Expand

Have you previously tried (other) medication for your OCD?

* must provide value

- ◯ Yes
- ◯ No

reset

Please list:
-all medications you have tried previously for your OCD
-the dose you took of each medication
-how long you were on them for (where possible)

* must provide value

Expand

Do you currently use any other treatment or therapies for your OCD?

* must provide value

- ◯ Yes
- ◯ No

reset

For example, sessions with a psychologist, group therapy, herbal medicine, nutritional supplements

Please provide details of:
-other therapies you use to help with your OCD
-how long you have been using them for

* must provide value

Expand

For example, see a psychologist every 2 weeks

Over the past month, what sort of symptoms have you experienced as part of your OCD?

Please provide as much detail as you're comfortable with

* must provide value

Expand

For example, intrusive/obsessive thoughts, needing to check things over and over, washing your hands excessively

How much time per day do these OCD symptoms occur?

* must provide value

For example, less than 1 hour or 50% of the day

On a scale of 0 to 10 (with 0 being 'no OCD symptoms' and 10 being the most severe OCD you have experienced) how bad has your OCD been this past week?

* must provide value

Have you been diagnosed with any other mental health disorders?

- ◯ Yes
- ◯ No

reset

For example, bipolar disorder, schizophrenia, ADHD or others

Please specify:
-which other mental health disorders you have been diagnosed with
-who diagnosed these conditions
-and when

Expand

For example, bipolar disorder by my psychiatrist 5 years ago

Do you have any medical conditions (previously and/or currently)?

* must provide value

- ◯ Yes
- ◯ No

reset

For example, high blood pressure, hypothyroidism, diabetes

Please provide details about: **-any medical conditions you currently have** **-any medical conditions you have had previously**	Expand For example, high blood pressure diagnosed 4 years ago which I take medication for
Do you have any allergies? * must provide value	○ Yes ○ No reset
Please provide details about any allergies you have	Expand For example, allergy to shellfish
Are you allergic to sulfur? * must provide value	○ Yes ○ No reset For example, sulfur based medications
Are you currently pregnant or breastfeeding? * must provide value	○ Yes ○ No reset
Are you currently using contraception? * must provide value	○ Yes ○ No reset
Please provide details	For example, OCP, condoms, IUD...
Do you drink alcohol? * must provide value	○ Yes ○ No reset
Please provide details. For example, how much, and how often do you drink alcohol? * must provide value	For example, 2 glasses of wine twice a week.

Is there anything else you'd like to add?	Expand
Please read the following statements carefully and select 'yes' if you understand them	
I understand that completing this questionnaire does NOT guarantee that I am eligible to participate in this study * must provide value	☐ YES
I understand that my doctor is the best person with whom to discuss treatment options regarding my mental health * must provide value	☐ YES
I understand that additional support for my OCD and mental health can be found here or I can call LIFELINE on 13 11 14 * must provide value	☐ YES
I understand that if I am in immediate distress I need to contact my treating doctor or dial '000' * must provide value	☐ YES

O-NAC Study Completion letter

N-acetylcysteine (NAC) augmentation in Obsessive-Compulsive Disorder (OCD)

The University of Melbourne
The Melbourne Clinic Professorial Unit
2 Salisbury St
Richmond
VIC 3121

Dear XXX,

On behalf of the research team I would like to extend a sincere thank-you for being involved in this study. We hope that taking part was informative and rewarding as it is invaluable to the research that we are conducting.

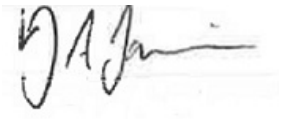
This study is expected to complete recruitment towards the end of 2019. After this time, and once all the data has been analysed, we will contact you to let you know if you were taking N-acetylcysteine (NAC) or placebo throughout your participation in the study, as well as a summary of the results.

If you have chosen to receive complementary samples of N-acetylcysteine (NAC) please seek advice from your treating doctor before using. You should only use NAC under the care of your GP/Psychiatrist. As you have now finished the study, your doctor is the best person to consult with regarding your general and mental health.

Involvement in our clinical trials including personal and medical information collected by researchers for recruitment and testing purposes is governed by The Melbourne Clinic Research Ethics Committee, and *The National Statement on Ethical Conduct in Human Research, 2007.*

If there are further queries regarding this study please contact the Research Site office on (03) 9487 4659 or via email: arcadia-research@unimelb.edu.au

Regards,



Jerome Sarris, O-NAC Chief Investigator

Honorary Research Fellow
The University of Melbourne
Faculty of Medicine, Department of Psychiatry
Melbourne, Victoria, Australia