Managing Delirium with Fluvoxamine Treatment for Non-Cardiac Surgery (MD FluNCS): A Feasibility Trial

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Protocol Version # **1**

Protocol Date: **16.05.2022**

Ethics Statement

The study will be conducted in accordance with the *National Statement on Ethical Conduct in Human Research* (2007), the *CPMP/ICH Note for Guidance on Good Clinical Practice* and consistent with the principles that have their origin in the Declaration of Helsinki. Compliance with these standards provides assurance that the rights, safety and well-being of trial participants are respected.

Contents

Summary

Study title:	MD FluNCS
Protocol version	V 1 Dated 16.5.2022
Objectives	
Primary objective	Pilot study to assess the feasibility of a large multicentre randomised trial of perioperative fluvoxamine in the prevention of postoperative delirium
Secondary objectives	
	1) Obtain the trial enrolment rate per month
	2) Reasons for screening failure/enrolment refusal into the trial
	3) Assess the influence of perioperative fluvoxamine on the rate and severity of delirium on POD1–4
	4) Assess the rate and severity of adverse effects of fluvoxamine
	5) Examine the number of missed study drug doses due to adverse effects
	6) Assess the ability to acquire EEG recordings on POD1+2
	7) Differences in EEG slow wave activity (0.5–6Hz) on POD1+2 with perioperative fluvoxamine
	8) Assess the ability to acquire plasma biomarkers IL-8 and NfL on POD1+2
	9) Group differences in levels of plasma IL-8 and NfL on POD1+2
	10) Assess the fraction of completed 3D-CAM assessments
	11) Influence of perioperative fluvoxamine on Delirium Rating Scale -Revised 98, 3D-Confusion Assessment Method-S, Richmond Agitation and Sedation Score on POD1–4
	12) Influence of perioperative fluvoxamine on postoperative pain scores
	13) Influence of fluvoxamine on postoperative change in cognition, disability or depression scores.
	14) Differences in C-Reactive Protein (CRP), White Cell count (WCC) and troponin.
Study design	Double blind placebo-controlled randomized controlled feasibility trial
Planned sample size	46
Selection criteria	
	Elective non-cardiac, non-intracranial surgical patients who are older than 60 years old with an expected length of hospital stay of >2 days

Study procedure	
	Patients will be randomised to: (1) 100 mg fluvoxamine the night before surgery, AM and PM on the day of surgery, and AM and PM on POD1, or (2) placebo control
Statistical considerations	This pilot study is powered for a 25% recruitment rate in approached patients with a 95% confidence interval of 13%.
Duration of the Study	1 year

1. BACKGROUND AND INTRODUCTION

1.1. DISEASE/PROPOSED INTERVENTION BACKGROUND

Delirium is a disturbance in attention, cognition, and consciousness, an acute physiological consequence of medical events, such as hospital admission, surgery, sepsis, and pharmacological intervention.[1] It is characterised by a sudden onset and fluctuating course not otherwise explained by a pre-existing neurological disorder or medical condition. [2,3] Common in older adults, it affects up to 50% of those in hospital with a healthcare burden estimated at $152 billion per annum in the USA.[4] Perioperative delirium has been associated with increased mortality,[5] comorbidity,[6,7] functional and neurocognitive decline,[8,9] hospital readmission,[10] and institutionalisation.[11] A recent meta-analysis (k=71) found older inpatients with delirium experienced a mortality risk three times that of those without delirium.[5]

The pathogenesis of postoperative delirium involves systemic inflammation[12,13] where inflammation drives changes in synaptic activity, revealed as electroencephalogram slowing[14], and consequent cognitive impairment. There is a proportional relationship between delirium severity and postoperative inflammation (notably IL-8)[12,13], suggesting a causal relationship. Inflammation also correlates with neuronal (neurofilament light and total tau)[13,15,16] and myocardial injury (troponin)[15] suggesting that blocking inflammation may protect against perioperative organ injury. Strategies to mitigate this rise in inflammation are urgently required.

Our animal and translational studies suggest that systemic inflammation drives a central inflammatory response, likely involving breakdown of the blood–brain barrier, and subsequent prostaglandin-mediated EEG slowing.

1.2. RATIONALE FOR PERFORMING THE STUDY

One strategy to suppress inflammation is through agonism of sigma-1 receptors which leads to suppression of pro-inflammatory cytokine release. Through modulation of the endoplasmic reticulum stress response via inositol response element-1 (IRE-1), sigma receptor agonism suppresses the transcription of proinflammatory cytokines,

suppressing the immune response. Many drugs target sigma-1 receptors, but the selective serotonin reuptake inhibitor, fluvoxamine, is a safe and potent agonist. Recent animal data shows that the powerful anti-inflammatory actions of fluvoxamine improve survival in sepsis animal models (20mg/kg intraperitoneal)[18], including reductions in inflammatory cytokine mediators. *In vitro* assays shows that fluvoxamine reduces the upregulation of cyclooxygenase-2 that drives inflammation-associated prostaglandin synthesis[19]. It also suppresses cytokine release from human blood[18]. It exerts direct anti-neuroinflammatory actions in a parkinsonian disease model[20], a multiple sclerosis model[21] and neuroprotection in a stroke model (20mg/kg)[22]. We have previously demonstrated in humans that fluvoxamine reduced clinical deterioration from COVID-19 in two RCTs,[23,24] likely though its anti-inflammatory effects. Fluvoxamine has also been used to treat delirium in a series of case reports based on older adults and/or intensive care unit patients, underscoring its potential utility in the setting of delirium[25].

Fluvoxamine pharmacokinetics

Fluvoxamine pharmacokinetics (PK) are relatively stable with age and with deteriorating renal function, though caution is warranted in patients with hepatic failure. The serum half-life is approximately 21 hours. Due to the lipid soluble nature of the drug, the drug becomes concentrated in the brain[26] with a brain half-life twice that for plasma. These pharmacokinetic properties are ideal for an anti-inflammatory agent that may target the brain, reducing the central inflammatory response. Notably, postoperative neurocognitive decline is associated with both infiltration of circulating monocytes (consistent with a key role of IL-8 in delirium) and activation of microglia.[27] Furthermore, fluvoxamine's slow redistribution from the brain may be ideal for reducing neuroinflammation and delirium severity even after discontinuation. Overall, these data suggest a concrete pathophysiologic pathway that could be pharmacologically attenuated through anti-inflammatory effects of fluvoxamine (**Figure 1**).

Currently, there are no established prophylactic perioperative medications that mitigate delirium risk. Furthermore, the role of inflammation in precipitating delirium has not been fully elucidated. The anti-neuroinflammatory effects of fluvoxamine have the potential to address both needs. Just as recent data suggest that fluvoxamine could be repurposed as a low-cost well-tolerated intervention for COVID-19,[28] perioperative administration has the potential to target a reduction of inflammation and injury within the brain.

Previous randomized controlled trials of prophylactic interventions to treat delirium have shown modest effectiveness. A reduction of systemic inflammation through the administration of corticosteroids[29] has not led to reductions in delirium, despite the extensive observational evidence to support neuroinflammatory hypotheses of delirium. Systemic corticosteroids may precipitate delirium and confer unwanted side effects on surgical wound healing, overall immunity, and hemostasis. Alternative prophylactic approaches have targeted sleep structure (e.g., dexmedetomidine) or symptoms (e.g., haloperidol).

Here, we target a putative pathway of delirium pathogenesis that may be both necessary in the perioperative setting and sufficient outside of the surgical arena.

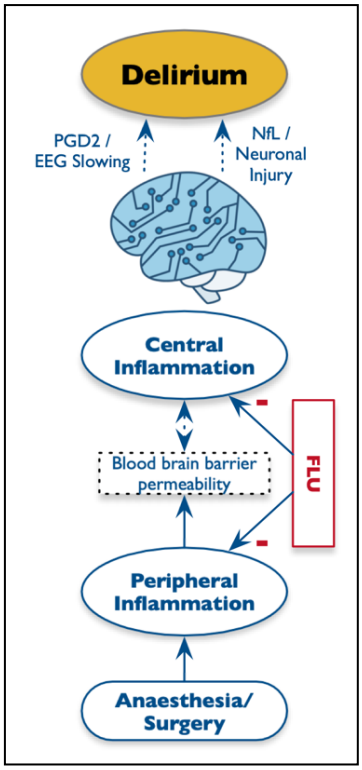


Figure 1. **Schema of the putative neuroinflammatory pathway targeted by this proposal.**

FLU = fluvoxamine

Thus, this potential therapeutic approach has potential generalizability to different clinical settings.

The 3 aims we will address in this study are: **Aim (1)** Evaluate the feasibility of recruiting participants; **Aim (2)** evaluate the feasibility of administering perioperative fluvoxamine in a placebo-controlled trial; and **Aim (3)** evaluate the feasibility of collecting participant outcomes. Completion of this feasibility trial will provide strong preliminary data and an established multisite transdisciplinary team towards a competitive grant application.This future grant proposal would encompass a transcontinental RCT to evaluate the effectiveness of perioperative fluvoxamine at reducing postoperative delirium incidence and severity. Data from this feasibility study would serve as key preliminary data. Synthesizing enrollment rates (**Aim 1**), rates of protocol adherence for study drug administration (**Aim 2**), rates of tolerance of AEs (**Aim 2**), rates of collection of outcome measures (**Aim 3**), estimates of EEG SWA/NfL/IL-8 variance (**Aim 3**), and a minimal clinically significant effect of fluvoxamine at reducing delirium severity of 20%, we will calculate the anticipated numbers of eligible and approached patients needed for this future trial. Based on existing data, the RCT would likely target enrollment of 280 patients, based on a minimal clinically important effect size of a 20% reduction in delirium severity. This innovative investigation would include mechanistic sub-studies to further enhance our understanding of delirium pathogenesis and longer-term implications on cognition and quality of life. The sub-studies will focus on how inflammation disrupts normal brain electrophysiological activity, alters circadian biology, and induces neurotoxicity in delirium.

2. HYPOTHESIS

We hypothesize that >25% of approached patients will be enrolled in the study. We also hypothesize that >80% enrolled patients will be adherent to oral fluvoxamine or placebo doses, and >90% of interpretable outcome measures will be obtained.

3. STUDY OBJECTIVES

3.1. PRIMARY OBJECTIVES:

Assessing the enrolment rate of approached patients in this pilot study to determine the feasibility of a larger trial

3.2. SECONDARY OBJECTIVES

The safety and tolerability of perioperative fluvoxamine.

The incidence of delirium (3D-Confusion Assessment Method (CAM) or CAM ICU)

Severity of delirium (Delirium Rating Scale-Revised-98 (DRS-R-98))

POD1+2 changes in IL-8 and NfL

Rate of successful biomarker collection on POD1+2

EEG SWA on POD1+2

Rate of successful EEG data collection on POD1+2

Postoperative pain score

Postoperative RASS score

Change in cognition and disability at 30 days postoperatively

Blood loss

Thromboelastography differences on the day of surgery prior to incision at RPAH only

Differences in CRP, WCC or troponin at RPAH only

4. STUDY DESIGN

4.1. DESIGN

Double blind randomized controlled trial.

4.2. EXPECTED PARTICIPANT NUMBERS

46 participants at Royal Prince Alfred Hospital, Sydney, Australia and University of Washington, St Louis, USA

4.3. DURATION OF THE STUDY

1 year

4.4. ENDPOINTS

PRIMARY ENDPOINTS

Trial enrolment rate

SECONDARY ENDPOINTS

The safety of perioperative fluvoxamine
The incidence of delirium on POD1–4 (3D-Confusion Assessment Method (CAM) or CAM-ICU)
Severity of delirium on POD 1–4 (Delirium Rating Scale Revised-98 DRS-R-98))
Rate of protocol adherence
Rate of completed 3D-CAM assessments
Peak delirum severity on POD1–4
Collection rate of biomarkers (IL-8 + NfL) and EEG recording on POD1+2
EEG slow wave activity (0.5–6Hz) on POD1+2
POD1+2 changes in IL-8 and NfL
RASS score on POD1–4

Postoperative pain score
Change in cognition and disability at 30 days postoperatively
Blood loss
Thromboelastography on the day of surgery prior to incision at RPAH only
CRP, WCC and troponin

4.5. CENTRE

Royal Prince Alfred Hospital

5. STUDY PARTICIPANTS

5.1. INCLUSION CRITERIA

Inclusion Criteria:

Elective non-cardiac, non-intracranial surgery

Requiring at least a 2-day stay in the hospital

Age >60 years old

Sex: Females and Males

Willingness to Provide informed consent and participate and comply with study requirements

English speaking to permit informed consent, cognitive and delirium assessments.

5.2. EXCLUSION CRITERIA

Exclusion Criteria:

Non-english speaking

Participants who may have received an investigational new drug within the last 7 days/weeks.

Participants who lack capacity to provide informed consent.

Participants with prior known intolerance/allergy to SSRIs or fluvoxamine

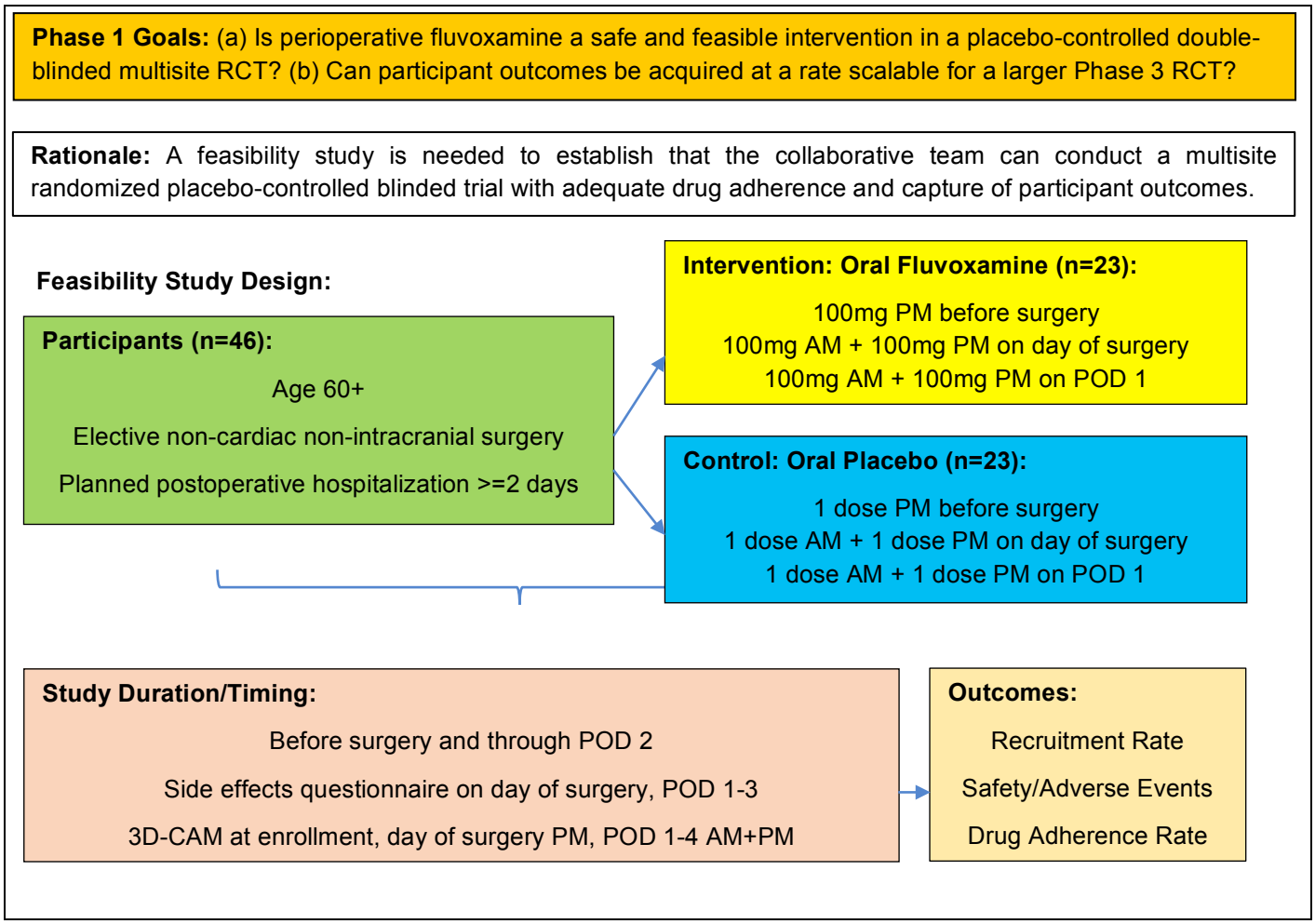
Planned postoperative ventilation

Patients on medications that interact with fluvoxamine: hepatic metabolism by CYP1A2 (theophylline, clozapine, tizadine, olanzapine), metabolism inhibited by fluvoxamine (diazepam, alprazolam, phenytoin), sigma-1

agonists/antagonists (donepezil, sertraline), risk of serotonin syndrome (St John's Wort, selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs)

6. STUDY PROCEDURES

6.1. STUDY FLOW CHART



Forty-six surgical patients will be randomized 1:1 to a prospective interventional parallel arm double-blinded placebo-controlled trial. All patients will undergo baseline cognitive screening, 3D-CAM assessment, and DRS-R-98 scoring at the enrolment visit. The intervention arm will receive five doses of oral fluvoxamine capsules, 100mg the night before surgery, 100mg twice daily on the day of surgery and on POD 1; pharmacokinetic modeling predicts high sigma-1 receptor binding at POD 1-2, coinciding with anticipated peak delirium incidence.[30] A placebo capsule will be administered at the same schedule for those in the control arm.

Outcome measures include: (1) Feasibility: Incidence and reasons for screen failures and withdrawals, (2) Safety/feasibility: incidence/severity/relatedness of adverse events, number/reasons of missed study drug administrations, (3) Feasibility: Incidence and reasons for missed outcome measurements, (4) Feasibility: Delirium incidence/severity (3D-CAM-S) at enrollment, POD 1-4 (both AM and PM), (5) Feasibility: IL-8 and NfL on POD 1 AM and POD 2 AM, and (6) Feasibility: awake EEG SWA on POD 1 AM and POD 2 AM.

6.2. INVESTIGATION PLAN

6.2.1. METHODOLOGY

Interventions	Enrolment Visit	Visit 1 (Intraop)	Visit 2 (PM day of surgery)	Visit 3 (POD1)	Visit 4 (POD2)	Visit 5 (POD3)	Visit 6 (POD4)	Visit 7 (POD 30)
Participant Consent	✓							
Inclusion / Exclusion criteria	✓							
Physical examination	✓			✓				
Cognitive screen[#]	✓						✓	✓
Adverse Event & Serious Adverse Event Assessment				✓	✓	✓		
Delirium Rating Scale-Revised-98[&]	✓		✓	✓	✓	✓	✓	
Richmond Agitation/Sedation Scale & VAS (pain)^	✓		✓	✓	✓	✓	✓	
EEG monitoring*				✓				
3D-Confusion Assessment Method - S[&]	✓		✓	✓	✓	✓	✓	
Satisfaction Questionnaire^							✓	
Blood sample collection		✓		✓	✓			
C-Reactive Protein, Troponin, White cell count+		✓		✓	✓	✓	✓	

[#]*[&]^Not SOC

[#]The preoperative cognitive screen will include the modified telephone interview of cognitive status (TICS-M) and verbal fluency and completion of the WHO Disability Assessement Schedule (WHODAS) and Geriatric Depression Sclae 15 (GDS15). Total time will be approximately 25 minutes.

[&]The 3D-CAM-S and DRS98 are questionnaires that allow for accurate diagnosis of delirium. These are conducted twice daily postoperatively (between 6.00 to 10.00 and 16.00 to 20.00).

NOTE: average score or worst score be used for analysis

^If Patient RASS score low/unable to conduct a delirium assessment – data missing or re-assessed within 2 hours.

*Visit 3 EEG collection will include a 256 electrode compumedics EEG will conducted on postoperative days 1 or 2 (if patient is comatose on POD1 it will be deferred to POD2) by trained research staff using a saline cap. The recording will last 40 minutes

+Blood samples for CRP, Troponin and WCC will be collected when feasible from pre-exisiting access lines and during routine blood collection to minimise invasive procedures and risk of infection. Blood samples will be collected by accredited members of the research team or ward/ICU staff.

6.2.2 ADVERSE EVENTS/SERIOUS ADVERSE EVENTS

Rates of nausea, diarrhea, headache, and insomnia will be evaluated from evening before surgery through POD 3 for individuals in both the intervention and control arms. These rates will be tabulated for all events, with consideration of severity and potential relatedness to fluvoxamine or drug-drug interactions.

6.3. STUDY PROCEDURE RISKS

Fluvoxamine has been associated with nausea, vomiting, drowsiness, dizziness, loss of appetite, insomnia, weakness, bruising, tremors and sweating. Anaesthetic doctors will be contacted prior to surgery to inform them of patient participation, they will be informed of an increased risk of nausea and vomiting in order to administer prophylactic antiemetics if required.

SSRIs are considered safe in the perioperative period and are continued perioperatively. SSRIs have been associated with increased bleeding risk, largely based on theoretical actions of serotonin on platelets, however this is not considered a clinical problem[31]. We will report blood loss to the DSMB after every 10 patients randomized.

The following risks are deemed very rare:

Small risk of serotonin syndrome if fluvoxamine is co-administered with other strongly serotonergic medications e.g. SSRIs, MAOIs, TCAs, tramadol, triptans etc.
Small risk of clinically relevant pharmacokinetic interactions through CYP1A2 e.g. increasing levels of warfarin, phenytoin, carbamazepine, reducing level of clopidogrel
Very small risk of inducing hyponatraemia in vulnerable elders (if required post-operation sodium levels will be monitored)

All risks will be outlined in the Patient Information and Consent Sheet and discussed during the consent process.
All patient medications will be screened prior to enrolment in study and participants will be asked to list their current medications.

6.4. PARTICIPANT RECRUITMENT AND SCREENING

Non-cardiac, non-intracranial surgical patients at Royal Prince Alfred Hospital and Washnington University will be recruited who are aged over 60 years old. Screening and recruitment will take place through the pre-admission clinic in conjuction with the anaesthetic assessment. All screening, recruitment and study activities including the pre-procedural interventions will be managed by anaesthetic research staff and anaesthetic doctors prior to and on the day of surgery.

If a patient displays cognitive dysfunction during pre-operative screening and enrolment, they will not meet eligibility criteria and will not be enrolled in trial. Based on patient pre-operative history this may be reported to the PI and if required discussed with treating team.

Will participants be screened?	Yes
If yes, what data will be collected? (NB, if participant is not eligible, will data collected be destroyed or kept?) This should be mentioned in PIS/CF)	Patients will be screened via the theatre lists to determine eligibility based on type of procedure and age. ASA status will be determined for eligibility at this time. Screening logs will not be collected.
Who will make initial contact with participants?	The initial contact with the patient will be made by a member of the anaesthetic department in the pre-admission clinic. Following this the anaesthetic doctor or a member of the research team will contact the patient to discuss involvement in the trial.
Who will perform the consent process? How will this be carried out?	Prior to obtaining consent the research team member will ensure the participant is capable of providing legal consent – based on their literacy, ability to understand the study and ensuring they are not influenced by power dynamics. Informed consent will be obtained prior to surgery by a member of the research team. eConsent will be obtained using RedCap if feasible. Paper copies will be kept in the participants medical records, a copy will be given to the participant and one will be stored in a locked file within the department of anaesthetics.
Will participants be consented verbally/explicitly/using eConsent?	eConsent will be used when feasible, alternatively paper based consent forms will be used as noted above.
Will participants be given a specific time period to consider participating?	Yes, participants will be given time in between their visit to the pre-admission and their day of surgery to consider participating and before providing informed consent.
Review of existing databases or databanks (please identify the database/databank and	RedCap will be used to obtain eConsent and collect/transcribe data collected during this study.

the custodian)	
Review of clinic files (please include who will be reviewing these files, for example a research coordinator).	Clinic files will be reviewed by the Clinical Research Coordinator (Department of Anaesthetics) and the principal investigator.
Advertisements (please include where the advertisement will be placed for example, in a newspaper, poster in a clinic or hospital foyer, radio announcements, website etc.)	Currently there is no plan for advertising.
Information Letter to Medical practitioners	No, the treating surgical team will be informed during the recruitment and screening process to ensure they support their patient's involvement.
Explain how potential participants will be screened for the study	Participants will be screened via the surgical lists for JL theatres.
Any other potential recruitment methods.	N/A

6.5. PARTICIPANT ENROLMENT

Participants will be enrolled into the study after the informed consent process has been completed and the participant has been assessed to meet all the inclusion criteria and none of the exclusion criteria. Study participants will receive a study enrolment number and this will be documented in the participant's medical (or personal) record and on all study documents.

During patient enrolment a member of the study team will disucss this with the treating team, anaesthetic doctor and post-operative ward staff. If any issues are raised during this time, they will be referred to the PI for ongoing discussion.

6.6. INFORMATION AND CONSENT

Informed consent will be obtained from eligible patients prior to their enrolment in the trial. Patient Information Consent Form will be signed by the participant and a copy will be provided to the patient/person responsible as well a copy filed in their medical record. The original consent form will be stored with the study file in a secure locked location.

6.7. RANDOMISATION PROCEDURE

Subjects will be computer randomized using the RedCAP database randomisation module. Members of the research team dispensing or transferring drugs will not be the same team members performing assessments.

Blinding

This study will be double-blinded. All delirium assessments will be conducted by members of the research team not involved in transferring or dispensing study drug. The clinical teams will not be informed of group assignment but may be unblinded if concerns arise about the care of individual patients. The delirium assessment team will always remain blinded to group intervention.

All data analysis will be conducted by separate members of the research team and all information will be de-identified.

6.8. END OF STUDY TREATMENT/WITHDRAWAL PROCEDURE

The study will end 30 days after surgery.

If at the 30-day cognitive screening, there is measured cognitive decline, this will be reported to the PI and if required discussed with the treating medical team, the patient and/or their GP for ongoing care.

6.9. PATIENT WITHDRAWAL

Patients or persons responsible may withdraw through proxy consent or if their treating physician believes it in their best interest to not continue.

7. OUTCOMES

7.1. DEFINITION OF OUTCOMES

Delirium severity will be defined using the Delirium Rating Scale Revised-98 (DRS-R-98)

Delirium incidence will be defined using the 3D-CAM and administered as described.[32,33].

Acquisition of EEG recordings and quantification of awake EEG SWA (EEG power 0.5-6 Hz) will proceed as published previously by our group.[14]

Blood will be processed with quantitation of IL-8 and NfL as we have previously described.[34] At Royal Prince Alfred Hospital patients will have CRP, WCC and troponin sent as SOC.

Rates for enrollment will be calculated with denominators of total eligible and total approached for consent. The rate of screen failures will provide information on the surgical volume and coordinator staff required. A high number of study refusals due to concerns of study drug or type/number of outcome assessments will provide valuable information on revising the study design and/or administration of study procedures for a future investigation. Enrollment rates of <25% based on total approached for consent will warrant revision of study design or additional sites in a future larger scale trial.

Rates of adherence will be computed based on the intake of each dose of study drug, with adherence defined as at least 80% of doses taken (4 of 5 total doses). Reasons for not taking study medication will be classified into the following categories: 1) forgetfulness, 2) misunderstanding, 3) interference with medical care, 4) possible side effects, 5) fear/stress, 6) lack of time.

Rates of data acquisition for CAM assessments, EEG recordings, and IL-8 sampling will be compiled at each time point. Less than 90% collection rate for interpretable outcome measures will constitute a “no go” signal, warranting revision of schedule of activities or pipeline for processing biomarkers.

Adverse events (AE) of nausea, diarrhea, headache, and insomnia will be evaluated from evening before surgery through POD 3. A high rate of AEs directly related to the study drug (>30%) combined with an overall adherence rate of <80% will constitute a “no go” signal for a larger clinical trial.

Postoperative pain scores will be determined using the visual analogue scale (VAS)

Patients at RPAH, will have a thromboelastograph sent prior to start of surgery to monitor platelet function.

Change in cognition and disability at 30 days postoperatively

Blood loss

8. STATISTICAL CONSIDERATIONS

8.1. SAMPLE SIZE OR POWER CALCULATION

Based on an estimated 25% enrollment rate, then n=184 screen-positive patients will provide sufficient power to measure this proportion with a 95% confidence interval width of 13%. From our preliminary data, we expect successful enrollment of 46 patients across 2 sites over 9 months. This will allow estimation of the proportion of patients who will complete at least 80% of doses of fluvoxamine with a 95% confidence interval width of 23%, assuming a completion rate of 80%.

8.2. PROVIDE A DETAILED ANALYSIS PLAN

The DRS-R-98 score, 3D-CAMS, TICS-M, Verbal fluency, WHODAS and GDS15 will be analyzed by Mann-Whitney or t-test depending on distribution.

The incidence of delirium (on 3D-CAM), will be analysed by Fisher’s exact test.

EEG analysis will be conducted by pwelch calculation of power bands and Mann-Whitney or t-test depending on distribution.

The biomarkers (IL-8 and NfL [and CRP, WCC and troponin]) will be log transformed and will be analyzed by Mann-Whitney or t-test depending on distribution[15].

Rates of data loss will be established using point estimates and sample variance will be estimated in intention to treat analyses.

For all analyses, a P below 0.05 will be considered statistically significant.

9. DATA COLLECTION

9.1. PARTICIPANT REGISTRATION

Participants will be registered/enrolled for the trial at the time of consent and will be provided with a study ID. The participant will be randomised to interventional group or placebo.

9.2. FORMS AND PROCEDURE FOR COLLECTING DATA

All data will be collected on a paper Case Report File (see appendix) or recorded directly to an electronic CRF. Any paper CRFs will be de-identified and labelled with patient ID number and data will be transcribed to REDCAP database. All paper documents will be securely stored in a locked cabinet as per legal requirements. Paper documents will be destroyed 15 years post-study.

9.3. CASE REPORT FORMS AND SCHEDULE FOR COMPLETION

A case report form will be provided in the the appendix. This study is completed 30-days after surgery.

9.4. DATA FLOW

Protocol → CRF Design → Patient data collected in CRFs → Patient data in CRFs converted into raw data sets → Raw data sets → Create Tables/Listings/Figures → Create Analysis → Report

10. QUALITY CONTROL AND ASSURANCE

10.1. CONTROL OF DATA CONSISTENCY

All data will be collected by research staff (see CRF). Data will be collected on paper CRFs and de-identified using patient study ids. All data will be transcribed to RedCap with permission to access only granted to study doctors and staff.

If feasible eCRFs will be used to ensure direct entry to improve efficiency and reduce entry errors, reduce data queries, missing data and maximise completed data.

10.2. PROTOCOL AMENDMENTS

All protocol ammendments will be submitted to the HREC for approval prior to use. Trial sites will follow their local governance protocols to gain approval to commence this trial.

11. ETHICS

11.1. INVESTIGATOR AUTHORISATION PROCEDURE

Ethics and Governance approval will be obtained via the local HREC and governance offices prior to commencement of the study.

11.2. PATIENT PROTECTION

Research doctors and staff will ensure that the study is completed in accordance with the guidelines set out in the *National Statement on Ethical Conduct in Human Research* (2007) (the *National Statement*) and the *CPMP/ICH Note for Guidance on Good Clinical Practice* and any other relevant legislation/guidelines.

12. SAFETY

12.1. ADVERSE EVENT REPORTING

Adverse event assessesments

Adverse even assessments will be done at study visits 2, 3, 4, 5 and 6- this will invcude a basic assessment of the patient for post-operative complications, infections and side effects of the study drug. Side effects can include but are not limited to:

Headache, nausea, dry mouth, dizziness, fatigue, sweating or restlessness.

If the patient experiences distressing or dangerous side effects the research personal will discuss this with the PI and treating team and cease the study drug if necessary.

Adverse event

The Australian Clinical Trial Handbook (*The Handbook*) defines an adverse event (drugs) as:

> any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign, symptom, or disease temporally associated with the use of a medicinal (investigational/experimental) product, whether or not related to this product. [1]

Adverse drug reaction

The Handbook defines an adverse drug reaction as:

> For unapproved medicines: all noxious and unintended responses to a medicinal product related to any dose should be considered ADVERSE DRUG REACTIONS. The phrase "responses

[1] http://www.tga.gov.au/industry/clinical-trials-handbook.htm (definitions of adverse events are on 28-29).

to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility.

For marketed medical products: a response to a drug which is noxious and unintended and which occurs normally used in man for prophylaxis, diagnosis or therapy of diseases of for modification of physical function.[2]

Serious adverse event (SAE) or Serious Adverse Drug Reaction is defined as:

Any untoward medical occurrence that at any dose:

- results in death;
- is life-threatening, (NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event/reaction which hypothetically might have caused death if it were more severe)
- requires in-patient hospitalisation or prolongation of existing hospitalisation;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect; or
- is a medically important event or reaction.[3]

An adverse event or serious adverse reaction can also be any event or experience which compromises the ethical acceptability of the protocol. This can be a non-medical event for clinical trials that are not medical or testing drugs or devices, such as those clinical trials conducted in different fields such as psychology.

12.2. SERIOUS ADVERSE EVENT REPORTING

All serious adverse events will be reported immediately to the sponsor and the HREC. The reports will be followed by a detailed written report. Follow-up reports will identify the participant/s by unique code assigned to participants (rather than by name).

12.3. DATA SAFETY AND MONITORING BOARD (DSMB)

A DSMB compromising of independent experts will be assigned prior to trial commencement.

12.4. EARLY TERMINATION

[2] Ibid.
[3] Ibid.

If early termination of the research project is required the Principal Investigator Professor Robert Sanders will communicate with the HREC and Governance offices. All policies and procedures will be followed and documented.

13. BLINDING AND UNBLINDING

This study is using a placebo control for the main study.

14. CONFIDENTIALITY AND STORAGE AND ARCHIVING OF STUDY

Electronic data will be stored in RedCAP and only accessible to those who are deemed to require access to the data for analysis purposes. Any staff who no longer require access to the online data will be removed from the database.

Paper CRFs will be kept in a locked secure file cabinet within the locked Department of Anaesthetics and keys will be kept in a safe location for those who require access. All documents will be held for 15 years as per legal requirements.

15. TRIAL SPONSORSHIP AND FINANCING

This trial is sponsored by the University of Sydney (under review) and is funded internally by the Department of Anaesthetics at Royal Prince Alfred Hospital and University of Washington.

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17. APPENDICES

1)Data Collection Sheet/CRF and Patient Satisfaction Survey (see attachment)