Title of Research project:

APPLICATION FOR IRB APPROVAL OF INTERVENTIONAL STUDIES
CHRISTIAN MEDICAL COLLEGE, VELLORE

Please complete and submit **Sections I to III**withall supporting documents.

SECTION I

Fluid Research Funding/External Funding (delete as appropriate)

If for external funding, please provide name of funding agency and the application for submission in the funding agency's format, in addition to this application.

1. **Title of Research Project:PRE**vention of **DEL**irium in **I**ntensive **C**are using low dose risperidone prophylaxis: a randomised placebo controlled trial (PREDELIC trial)
2. **Title of Study(for lay public):PRE**vention of **DEL**irium in **I**ntensive **C**are using low dose risperidone prophylaxis:
3. **Acronym, if any:** PREDELIC
4. **Unique protocol IDs (if allotted by Sponsor/ Clinical Trial Registration Number - please list as many as is relevant):** Not applicable
5. **Name of the Principal Investigator:** Dr Amita Jacob
   Designation / Department / Unit / of Principal Investigator: PG Registrar, Department of General Medicine, Christian Medical College, Vellore 632004 India
   Employment Number: 29553
   If Post Graduate Registrar / Fellowship: PG Registrar
   Enrollment date of PG Course: April 2016
   Completion date of PG Course: April 2019
   Address for communication (including telephone and fax numbers and email id):
   Dr Amita Jacob,
   Department of General Medicine, Christian Medical College, Vellore 632004 India
   Email: amita.jacob@gmail.com
   Mobile 9003540268

6. **Contact person for scientific queries** (including telephone and fax numbers and email id):
   Dr Amita Jacob,

Department of General Medicine, Christian Medical College, Vellore 632004 India
Email: amita.jacob@gmail.com
Mobile 9003540268

7. **Contact person for public queries** (including telephone and fax numbers and email id):

Dr Amita Jacob,
Department of General Medicine, Christian Medical College, Vellore 632004 India
Email: amita.jacob@gmail.com
Mobile 9003540268

8. **Name of Guide (for Post-Graduate Registrar /Fellowship) Dr. O.C Abraham**
   Employment Number:
   Address for communication Dr O.C Abraham, Department of General Medicine, Unit 4, Christian Medical College, Vellore
9. **Name and Designation of Co-Guide/ Co-Investigator (s), Employment Number and Department**

Dr J.V Peter, Medical ICU, Division of Critical Care, Christian Medical College, Vellore
Dr Binila Chacko, Medical ICU, Division of Critical Care, Christian Medical College, Vellore

10. **Any one of the investigators on this study should be certified in Good Clinical Practice (GCP),**
    Name: Dr. J.V Peter
    Date of Certification: available in Principal's office
    Department: Department of Critical Care
    Enclosed a copy of the certificate: No.
11. Permission letter from the HOU & HOD of each unit/department involved in the study. If Medical students, Nursing students & Allied Health students, nurses,are involved in the study a permission letter from the appointing authority has to be enclosed.

12. **Source/s of Monetary or Material Support**

Internal- Fluid /Major Research Grant : Fluid grant requested

External :

Departmental fund :

13. Primary Sponsor: Not applicable

14. **Secondary Sponsor:** Not Applicable

15. Countries of recruitment: India

16. Sites of the study (including departments where the study will recruit participants): Medical Intensive Care Unit and Medical High Dependency Unit, CMC, Vellore

17. **Has Drug Controller General of India (DCGI) clearance been obtained?** Not necessary. The drug risperidone to be used in this Randomized Controlled Trial has been licensed for use in India. It is used in a variety of clinical contexts including in the routine management of delirium in Intensive Care Units.

18. If this is a laboratory study if you have out sourced genetic test to an external laboratory. Please provide evidence of the laboratory credentials.
No. This is not a laboratory study.

19. Is this an invention or idea that you plan to register as a patent: Please mention: No

20. **In case there is an invention what are the benefits for the CMC as an institution in terms of patenting and royalties received?** Not applicable

21. Objectives of the study:

To examine the efficacy of risperidone in the prevention of delirium in an intensive care unit.

22. Brief Summary (in 250 words): The study will be a randomized, double-blind, placebo-controlled, prophylactic intervention trial in patients in the intensive care unit. We will include consecutive non-neurological ICU patients, aged ≥18 years with an expected ICU length of stay >1 day. The patients will be randomized in a 1:1 allocation ratio into intervention and control groups. The intervention group will receive prophylactic treatment with oral risperidone 1mg twice daily, and patients in the control group will receive placebo throughout the duration of stay in the ICU and will be followed up for a total period of 28 days. Patients will be screened daily for delirium using the CAM-ICU instrument- a validated tool for diagnosing delirium in ICU. In patients who develop delirium, the trial medication will be continued and patients will subsequently receive open label treatment with open label anti-psychotics at the discretion of the treating physician. All patients will be followed up for 28days days after enrollment. Data will be analysed using descriptive summary statistics as well as.

23.Health Condition or problem studied: Delirium in the intensive care unit

24. Study Type: Double-blinded, randomized controlled trial

25.Present Knowledge and relevant bibliography (Is there a justification for this trial? Please provide a brief review of the relevant literature and appropriate references)

Delirium is a prevalent and serious problem in patients admitted to in Intensive Care Units (ICUs). Prevalence as high as 60 to 70 %(Reade & Finfer, 2014; Salluh et al, 2010) has been reported and this problem has been found to be associatedwith worse short term and long term patient outcomes. There are several factors that make the ICU patient at risk for delirium-the most common being medications used for pain relief and sedation. A significant proportion of patients are distressed and agitated, which can precipitate accidental removal of endotracheal tubes or of intravascular catheters used for monitoring or administration of life-sustaining medications. Pain is the most common experience recalled by patients (Stein-Parbury& McKinley, 2000).

Delirium- a clinical syndrome

A significant proportion of patients in intensive care units present with the clinical syndrome of delirium, which is often under recognized and under diagnosed. The syndrome characterized by a disturbance of attention and awareness associated with neurocognitive dysfunction (E.g. deficits in memory, disorientation, language, visuospatial ability or perception), is often acute in onset (APA, 2013).

Causes

Delirium is a syndrome, that can have diverse medical causes (E.g. infections, metabolic disturbance, hepatic and renal failure) or be due to medication (E.g. benzodiazepines) or substance intoxication or withdrawal (E.g. alcohol). Multiple aetiologies for delirium can co-exist (Salluh et al, 2010; APA, 2013; Reade &Finfer, 2014).

Pathophysiology

The pathophysiology of delirium is dependent of its causation (Reade &Finfer, 2014). Consequently, it is difficult to characterize its specific pathology. The increased risk of delirium associated with the use of $GABA_A$ agonists and anticholinergic drugs has led to the belief that the GABAergic and cholinergic neurotransmitter systems play a contributory role. Cholinergic deficiency may be a final common pathway. Other hypotheses include excess dopaminergic activity and direct neurotoxic effects of inflammatory cytokines. Currently, these hypotheses are unproven, and hence, pharmacologic management strategies are largely empirical.

A positive association between the duration of delirium in the ICU and both cerebral atrophy and cerebral white-matter disruption has been documented using magnetic resonance imaging techniques (Gunther et al, 2012; Morandi et al, 2012). However, these

preliminary studies do not reveal the directionality of causation; delirium in the ICU either gives rise to alterations in brain structure or the presence of such changes increase susceptibility to delirium.

Despite the difficulties in diagnosing the underlying cause and pathophysiology, delirium is considered a commonly occurring and serious event in critically ill patients. As there is no diagnostic test (blood, electrophysiological, or imaging test) for delirium, its identification is purely clinical, making it a clinical diagnosis (Reade &Finfer, 2014).

Prevalence

Delirium is common in intensive care settings and its prevalence has ranged between 16%-89% (Reade &Finfer, 2014; Salluh et al, 2010). Advanced age, the presence of more than one condition associated with coma, treatment with sedative medications, a neurologic diagnosis, and increased severity of illness are risk factors.

Impact on outcome

Delirium has a significant impact on patients admitted to ICUs. The diagnosis of delirium in patients admitted to ICUs results in increased morbidity, duration of hospitalization and mortality (Salluh et al, 2010; Reade &Finfer, 2014). The diagnosis is associated with increased mortality (estimated as a 10% increase in the relative risk of death for each day of delirium (Pisani et al, 2009)) and decreased long-term cognitive function (van den Boogaard et al, 2012). Such a negative impact demands regular monitoring and requires early recognition and intervention with effective therapy.

Clinical subtypes

Delirium presentations have been categorized into hyperactive and hypoactive (APA, 2013). The hyperactive variety is characterized by increased levels of psychomotor activity that may be associated with lability or fluctuations of mood, agitation, and refusal to cooperate with medical care. Individuals with hypoactive delirium present with reduced psychomotor activity that may be accompanied by sluggishness and lethargy that approaches stupor and constitutes a more challenging clinical diagnosis. Clinical presentations can also present with a mixed level of activity with fluctuations in level or normal level of psychomotor activity with disturbance of attention and awareness. The condition is usually acute and lasts for a few hours or days. However, occasionally it can be persistent lasting weeks and months.

Recognition and diagnosis

Delirium is said to be unidentified in about 75% of patients with the condition in ICU (Reade &Finfer, 2014). On the other hand, active screening by research nurses have identified 64% of patients diagnosed with delirium by psychiatrists, neurologists or geriatricians (van Eijk et al, 2009).

Diagnostic criteria like the Diagnostic and Standard Manual IV (DSM IV) (APA, 1994) have been the clinical gold standard for diagnosis of delirium. The current DSM 5 (APA, 2013) criteria are for delirium are:

A. Disturbance in attention (i.e., reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment).
B. The disturbance develops over a short period of time (usually hours to a few days), represents an acute change from baseline attention and awareness, and tends to fluctuate in severity during the course of a day.
C. An additional disturbance in cognition (e.g. memory deficit, disorientation, language, visuospatial ability, or perception).
D. The disturbances in Criteria A and C are not better explained by a pre-existing, established or evolving neurocognitive disorder and do not occur in the context of a severely reduced level of arousal such as coma.
E. There is evidence from the history, physical examination or laboratory findings that the disturbance is a direct physiological consequence of another medical condition, substance intoxication or withdrawal (i.e. due to a drug of abuse or to a medication), or exposure to a toxin, or is due to multiple etiologies.

Instruments, which are used to identify delirium test cognitive domains of standard diagnostic criteria. Some of the scales used to identify delirium in ICUs include the following: (i) Confusion Assessment Method (CAM), (ii) Delirium Symptom Interview (DSI), (iii) Confusion Assessment Method for the Intensive Care Unit (CAM-ICU), (iv) Intensive Care Delirium Screening Checklist (ICDSC).

Delirium Detection Scale (DDS) and the Memorial Delirium Assessment Scale (MDAS) are employed to assess delirium symptom severity.

The CAM-ICU scale can be used even on non verbal ventilated patients in the ICU and has a pooled sensitivity of 80% with a sensitivity of 95.9% (Gusmao-Flores, 2012).Using a structured format, this tool evaluates four features, namely, acute onset or fluctuating course, inattention, disorganized thinking, and altered level of consciousness. When administered by bedside nurses with no formal psychiatric training, the CAM-ICU has been demonstrated to have high accuracy (sensitivity of 93% to 100% and specificity of 98% to 100%) and interrater reliability (K = 0.96) (Ely EW2001).

<u>Prevention of Delirium in ICU</u>

A variety of factors common in critically ill patients predispose to delirium. These include infection, pain, use of sedation, metabolic derangements, and hypoxemia. Hence, patients should regularly be evaluated and treated for the above to decrease its risk. Delirium prevention can be divided into pharmacologic and nonpharmacologic methods

Nonpharmacologic interventions

Sleep deprivation and disturbance of the circardian rhythm is a major risk factor for delirium. Interruptions in REM sleep are the most significant. Improvement in sleep quality by noise and light reduction and reducing night-time procedures was associated with improved sleep and a reduced incidence of delirium in the ICU (Van Rompaey, 2012; Kamdar 2013). Immobility is another risk factor for delirium that can be avoided by regular physical and occupational therapy (Shweickert& Kress, 2011). Other factors worsening delirium include visual and hearing impairments, cognitive impairments and dehydration.

Multi-component interventions including a repeated reorientation of the patient and provision of cognitively stimulating activities; non-pharmacologic sleep protocol; early mobilization activities and range of motion exercises; timely removal of catheters and physical restraints; use of eyeglasses, magnifying lenses, and hearing aids; and early correction of dehydration have been shown to be effective in older hospitalized patients (Inouye, 1999) and post-operative patients (Marcantonio, 2001) but have not been evaluated in the ICU. Many of these interventions are routinely employed in many ICUs. Schweickert WD et al in 2009 performed a randomised controlled trial in 104 ICU patients and foundthat early physical and occupational therapy almost halved the delirium rates. Even more recently, implementation of the ABCDE delirium prevention bundle,which incorporated awakening and breathing co-ordination, delirium monitoring and physiotherapy, was found to have a 20% decrease in delirium. (Balas MC 2014)

Pharmacological interventions

(i) Rational Use of sedation and analgesia
Deep sedation has been associated with a higher incidence of delirium (Shehabi et al, 2012; Kamdar, 2015). Benzodiazepines in particular seem to worsen delirium when given in high doses compare to other sedatives (Pandharipande, 2008) One of the reasons for higher doses of sedation is agitation due to pain. Hence adequate analgesics as well as daily pain monitoring is recommended for all ICU patients (Payen, 2009). The use of dexmedetomidine (Pandharipande, 2008; Jakob et al, 2012) for sedation have been associated with less ICU delirium that other sedatives. Ketamine also appears to improve rates of delirium in post-operative patients (Hudetz et al, 2009).

(ii) Pharmacological prophylaxis
Both Haloperidol and atypical antipsychotics have been successfully used to prevent delirium in the post-operative setting (Wang et al, 2012; Wang et al, 2013). However, evidence is limited in non-surgical patients and there have been no high-quality trials that are positive for delirium prevention with antipsychotics outside the postoperative period(Reade &Finfer, 2014).

Title of Research project:

Summary of Antipsychotic RCTs for prevention and management of delirium from literature

Authors	Study design	Dose, route	Outcome
Wang et al, 2012 Crit Care Med. 2012 Mar;40(3):731-9.	DB, PC, RCT in post operative patients	Haloperidol (0.5 mg intravenous bolus injection followed by continuous infusion at a rate of 0.1 mg/h for 12 hrs)	1. Primary end point - incidence of delirium within the first 7 days after surgery. 2. Secondary end points- time to onset of delirium, number of delirium-free days, length of intensive care unit stay, all-cause 28-day mortality, and adverse events. 3. Delirium was assessed using the confusion assessment method for the intensive care unit. 4. Drug superior to placebo
Prakanrattana&Prapaitrakool, 2007 Anaesth Intensive Care. 2007 Oct;35(5):714-9.	DB, PC, RCT in post operative patients	1 mg of risperidone sublingually when they regained consciousness	1. Primary outcome- incidence of delirium 2. Drug superior to placebo
Devlin et al 2010 Crit Care Med. 2010 Feb;38(2):419-27.	DB, PC, RCT in post operative patients in established delirium (n=36)	quetiapine 50 mg every 12 hrs or placebo. (dose increased to 50 to 100 to 150 to 200 mg every 12 hrs) if more than one dose of haloperidol was given in the previous 24 hrs	1. Primary outcome- time to resolution of delirium 2. Quetiapine superior to placebo
Girard et al 2010 Crit Care Med. 2010 Feb;38(2):428-37.	DB, PC RCT in ventilated surgical patients	Oral haloperidol (average total 15.0 [10.8–17.0] mg/day) or ziprasidone (average total 113.3 [81.0–140.0] mg/day) or placebo every 6 hrs for up to 14 days	1. primary end point was the number of days patients were alive without delirium or coma; 2. no difference
Skrobik et al 2004; Intensive Care Med. 2004 Mar;30(3):444-9.	DB Haloperidol vs olanzapine in delirious patients		1. reduction in delirium severity index 2. Haloperidol equal to olanzapine but with more side effects for hpl
Van den Boogaard et al 2013 Trials 2013:14:400	DB, PC RCT Protocol	Intravenous haloperidol 1mg q8H or 2 mg q8h vs placebo	1. Primary outcome 28 day survival 2. Secondary outcome – incidence of

			delirium, delirium outcome, haloperidol adverse effects
Meta analysis			
Zhang et al, 2013 Crit Care. 2013 Mar 18;17(2):R47	Meta-analysis of strategies to prevent delirium		Both typical (three RCTs with 965 patients, RR=0.71; 95% CI=0.54 to 0.93) and atypical antipsychotics (three RCTs with 627 patients, RR=0.36; 95% CI=0.26 to 0.50) decreased delirium occurrence when compared to placebos.
Reade &Finfer 2014 N Engl J Med 2014; 370:444-454	Review		Antipsychotic useful in prevention of delirium in ICU but based on small trials

Equivalence of **oral** antipsychotics: Haloperidol 2 mg = risperidone 3 mg= quetiapine 300 mg (from Maudsley Prescribing Guideline 2015; Delivery by intravenous route results in 3-5 time the oral dose a there is no first pass metabolism in the liver.

Prevention of delirium crucial; multiple strategies employed including monitoring, management of pain and agitation, use of sedation and analgesia (Reade &Finfer, 2014). The management of established delirium involves the use of low dose antipsychotic medication (e.g. halorperidol, risperidone, etc), benzodiazepines (midazolam, etc).

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Hudetz JA, Patterson KM, Iqbal Z, Gandhi SD, Byrne AJ, Hudetz AG, Warltier DC, PagelPS.Ketamine attenuates delirium after cardiac surgery with cardiopulmonary bypass.JCardiothoracVascAnesth. **2009** Oct;23(5):651-7. doi: 10.1053/j.jvca.2008.12.021. Epub**2009** Feb 23.

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Kamdar BB, Niessen T, Colantuoni E, King LM, Neufeld KJ, Bienvenu OJ, Rowden AM, Collop NA, Needham DM.Delirium transitions in the medical ICU: exploring the role of sleep quality and other factors.Crit Care Med. **2015** Jan;43(1):135-41. doi: 10.1097/CCM.0000000000000610.

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Van Rompaey K, Unuane D, Moens M, Duerinck J, Poppe K, Velkeniers B, D'Haens J. Long-term follow-up results of multimodal treatment with initial surgical approach for acromegaly in a single center.ActaNeurol Belg. 2013 Mar;113(1):49-54. doi: 10.1007/s13760-012-0128-8. Epub**2012** Sep 14.

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Wang W, Li HL, Wang DX, Zhu X, Li SL, Yao GQ, Chen KS, Gu XE, Zhu SN. Haloperidol prophylaxis decreases delirium incidence in elderly patients after noncardiac surgery: a randomized controlled trial*.Crit Care Med. **2012** Mar;40(3):731-9. doi: 10.1097/CCM.0b013e3182376e4f

Wang HR, Woo YS, BahkWM.Atypical antipsychotics in the treatment of **d**elirium. Psychiatry ClinNeurosci. 2013 Jul;67(5):323-31. doi: 10.1111/pcn.12066.

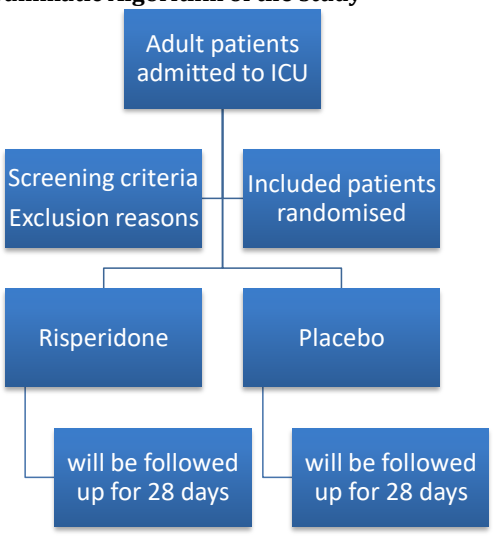
26. Preliminary work already done by the investigator in this problem: The investigator has worked in the medical ICU at CMC, Vellore, for one year before joining postgraduate training and is aware of routine diagnosis and management in ICU. The guide and co-guides are consultants who manage patients in ICU and have many years of experience in the field.

27. List of publications of the investigator in the field.
Nil

28. Structured abstract (Structured abstract should be in future tense)

The study will be conducted as a prophylactic, placebo-controlled, randomised controlled trial. Consecutive adult patients in the medical intensive care unit meeting the inclusion criteria will be enrolled at admission into ICU. Written informed consent will be taken from the individuals or the relatives of all participants. Patients will be allocated in a 1:1 ratio to treatment and control groups. The treatment group will receive low dose oral risperidone twice daily and the control group will receive placebo. All participants will be regularly screened for delirium using the CAM-ICU instrument and followed up till 28 days after enrolment.

29. Detailed diagrammatic Algorithm of the study



30. Methods in detail:

i. Intervention and Comparator agent:

Intervention: Oral Risperidone 1mg twice daily for the duration of their ICU stay
Comparator: Placebo daily for the same duration

ii. Key Criteria

Inclusion Criteria: Consecutive adults (18>years) admitted into the medical intensive care unit

Exclusion Criteria:

No informed consent obtained
Neurological disease (including post-cardiopulmonary resuscitation patients)
Coma due to drug overdose
Alcohol withdrawal syndrome
Antipsychotic therapy over the last 30 days
Pregnancy/breast feeding
Documented delirium prior to ICU admission
Difficulty in CAM-ICU ssessment (serious auditory or visual disorders, severely mentally disabled; serious receptive aphasia)
ICU-stay less than one day
Moribund and not expected to survive two days
Known allergy to Risperidone
Severe haemodynamic instability (vasopressor dose/inotrope dose>20mcg/min)
Liver failure
Renal failure (Stage 3 KDIGO)

Method of randomization:

i. **Method of allocation concealment:** The allocation sequence will be generated by the pharmacist and the study medication will be stored in sequentially labeled containers for use. Allocation will be concealed from the all investigators, participants and the treating physicians

ii. **Blinding and masking:** The patients, care providers and investigators were all blinded after assignment to treatment and control groups. Both treatment and placebo were administered in similar unmarked packaging.

iii. **Primary Outcome:** The incidence of delirium in the study patients.

iv. **Secondary Outcome/s:**

Ventilator free days

Self-extubation rate

Duration of ICU stay

Duration of hospital stay

Mortality at 28 days

v. Target sample size and rationale:(It may be suitable to have a statistician as a co-investigator)

Sample size was calculated using the following values:
Alpha 0.05
Beta 0.02
Delirium in controls group 50%
Delirium in intervention group 30%
Sample required 95 in each arm
Allowing for 20 % dropout- 108 patients in each arm

Kelsey et al., Methods in Observational Epidemiology 2nd Edition, Table 12-15

vi. Phase of trial: III

vii. Expected date of first enrolment: October 2016

viii. Estimated duration of trial: 2 years

ix. Protocol variations: Any rules for

a. interim analyses: nil
b. For withdrawal of participants: Severe haemodynamic stability, Adverse effects related to trial medication
c. For premature stopping of trial: not anticipated

x. Has a Data monitoring committee been appointed?No

xi. If yes: supply name and email address of contact person:

xii. Post Trial benefits and care: Has provision been made for post-trial access to the best proven intervention from this trial or best available care for participants after the study is completed?

Delirium is usually of acute onset and of short duration. We do not anticipate prolonged delirium in patients

xiii. Statistical Analyses:

a. Statistical methods to be used for the primary outcome; include description of methods to estimate the strength of the effect (e.g.: Odds ratios, relative risks, etc)

Data will be analyzed according to the intention-to-treat principle. Continuous variables will be described using mean and standard distribution or median and interquartile range depending on their distribution. Student t-test (for normally distributed data) or Mann Whitney U test (for non-normally distributed data) will be employed to assess the statistical significance of associations depending on the distribution. Categorical variables will be described using frequency and percentages and their statistical significance assessed using the chi-squared test. Survival analysis

using Kaplan- Meier curves will be used as graphical representation and the log rank test will be used to assess statistical significance. Cox proportional regression analysis will be used to test the differences in the development of delirium in the ICU and in 28-day survival for the use of risperidone versus placebo.

b. Methods for additional analyses, if indicated.Not applicable

c. **Name & designation of the statistician involved in your project for Statistical Analyses:**

30. **Complete budget plan for all studies**:
Cost of reproducing instruments and proforma Rs 4000*.00*
Cost of risperidone= Rs5000
Cost of placebo= Rs45000.00
Total= Rs54000.00

*For **FLUID research grant money cannot be allocated for travel of the investigators nor can job outsourcing** be covered with FLUID grants. Funding out of the institution can be given only for the special mission hospital grant*

*(From Fluid Research Fund, there are no grants for personnel except in a major grant application, funding is limited **Rs. 50,000/- per year** for two years for standard applications, **Rs. 2,00,000/- per year for two years for major applications**).Website link: http://172.16.11.136/Research/#. >Rules for Major Fluid Research Grants. Do not exceed the budget allocated to you. In case the budget is exceeded, the amount will have to be deducted from one of your departmental special funds. Stationary, printing material and paper should not exceed more than 20% of the allocated fluid grant.*

*Please mention below the **breakdown of budget requested:**(The budgets that are drawn up should be comprehensive and should mention all subject in detail (For example – laboratory investigation should mention the specific category without generalization.)*

32. **In case of major equipment purchase what is the agreement with the funding agency in terms of institutional ownership of the equipment?**
Not applicable

33. ***Enclose proforma for Data collection:***
Enclosed

34. If this is an application for Fluid Research Funding, please provide name and account number of any other Fluid Research grant held by the PI. Nil

S.	Study Tit	IRB Min. and d	Grant Sanctio amount/ Account	Duratio Ye	Study ongo comple

35. Informed Consent Documents (patient information sheet, investigator's brochure, drug information etc and informed consent document)please submit all translations with the proposal

Enclosed

36. Publication Plans: (List all potential authors and their likely contributions)

(Please tick √ appropriate box)

	Responsibilities								
Author(s) name	Research and Study design	Data collection &analysis	Laborato analysis	Interpretatio and conclusion	Preparatio of Manuscrip	Review of Manuscrip	Guide and critic revision	Administrati	Technica Support
A. Jacob	□	□		□	□	□		□	
Dr. O.C.Abra	□			□	□	□	□	□	□
DrJ.V.Peter	□			□	□	□	□	□	□
DrBinilaCha	□			□	□	□	□	□	□

37. Inter-departmental cooperation: (Please describe the arrangements with institutional diagnostic service units/departments that are being used for this research project, if applicable). The study will be done within the Medical Intensive Care and the Department of Medicine.

Information about the project has been sent to the various departments who admit patients to MICU/MHDU.

38.Signature of Principal Investigator: Amita Jacob

39. Signature of Guide/Head of the Department/ Unit: Dr O.C Abraham

40.Co-Investigators' Consent (all co-investigators have to sign this form or supply separate letters of consent):

I/We give my/our consent to be a Co-Investigator and provide my/our expertise to the project. I/We have approved this version of the protocol and have contributed substantially to its development.

Name	Department	Signature	Date
Dr. J.V Peter	**MICU**		
Dr. Binila Chacko	**MICU**		

Note: If the project is a resubmission a fresh copy of signatures needs to be obtained for IRB submission
Section II

APPLICATION FOR ETHICS APPROVAL FOR ALL INTERVENTIONAL STUDIES IN HUMAN PARTICIPANTS

1. **Please provide a brief summary of the justification, objectives and methods in lay language, avoiding technical terms.**
   Delirium is a state of confusion, decreased attentiveness and disorientation that is common among ICU patients. It has been found to be associated with poorer outcomes among critically ill patients. Hence, prevention and treatment of delirium is important in the ICU setting. Different pharmacological and non-pharmacological agents have been tried to prevent delirium. Risperidone is a newer antipsychotic with similar efficacy and improved safety compared to typical antipsychotics.
   The aim of this trial is to compare the efficacy of Risperidone for delirium prevention to placebo. We plan to randomly allocate the patients into 2 groups out of which one will receive Risperidone once daily and one will receive placebo. Patients will be regularly screened for development of delirium by clinical assessment with a validated questionnaire.

2. **Please describe if the study uses procedures already being performed on patients for diagnosis or treatment or if modified or novel procedures are to be used?**
   Risperidone is a newer atypical antipsychotic medication, which is commonly used in India for the treatment of psychosis and for delirium. It is known to be effective as well as a safe drug.

3. **Please describe what benefits might be reasonably be expected by the participant as an outcome of participation**
   Patient's receiving the treatment can expect a reduced incidence of ICU delirium as well as, possibly reduced length of ICU stays and improved outcomes at 28 days.

4. **Please describe what benefits to others or new knowledge might be expected as a result of this study**
   The data generated will increase medical and scientific knowledge as there is no evidence for the use of antipsychotic medication for routine prophylaxis to prevent delirium in patients admitted to ICUs

5. **Who are to be enrolled?**

   Adult patients admitted to the medical ICU with non-neurological disease

6. **If any vulnerable groups (e.g., pregnant women, children) are to be enrolled, please provide a justification for their inclusion.**
   Pregnant women and children are excluded from the trial

7. **Mention how you will ensure that there is no undue inducement for participation of economically disadvantaged persons among the likely participants in this study.**

The patients will be allowed to volunteer. Those who consent will also be allowed to withdraw their consent without any prejudice to their medical treatment.

8. **What are the potential risks to participants in this study?**
   Side effects with Risperidone use are uncommon, however they can includedizziness, headache. Rare complications include extrapyramidal side effects and ECG changes. All vital signs and side effects will be routinely monitored in the ICU and ward.

9. **Are the risks to participants reasonable in relation to the benefits that might reasonably be expected as an outcome to the participant or to others, or the importance of the knowledge that may reasonably be expected to result? Please provide a detailed description of the above.**

The very small dose of risperidone usually does not produce any significant risk as most of the side effect described are when it is given in much higher doses (e.g. 8 mg per day). 1mg is a small dose and if it can prevent the development of delirium, which causes increased duration of hospitalization, ventilation, high cost of care and high mortality, the benefit to the patient is substantial and the risks minimal.

10. **What is the risk of death from this study?**
    Negligible

11. **Regarding informed consent to obtained from research participants or their legally authorized representative(s):**

    a. **Does the informed consent document include all the required elements (See appendix IV)?**
       Yes
    b. **Are the participant information sheet and the consent document in language understandable to participants? (PLEASE PROVIDE WITH THIS SUBMISSION TRANSLATIONS IN ALL LOCAL LANGUAGES ANTICIPATED TO BE USED).**
       Yes
    c. **Who will obtain informed consent (PI, nurse, other?) and in what setting? Pricipal Investigator, in the ICU**
       Principal Investigator
    d. **If appropriate, is there a children's assent? If yes, please submit a copy of this form.**
       Not applicable
    e. **Is the EC requested to waive or alter any informed consent requirement?**
       No

12. **Is there provision of free treatment for research related injury? If yes, who will provide it?**
    The institution will provide for treatment of any side effects.

13. **Is there provision for compensation of participants for disability or death resulting fromresearchrelated injury? If yes, who will provide it?**
    No. The risk of such injury are negligible.

14. **Is the study covered by insurance? If yes, please provide insurance documents from an Indian insurance company.**
    No. The risk of such injury are negligible.

15. In addition to the overall budget in Section I, please provide details of the following

i) Justification, timing and amount of payments to study participants
ii) Justification, timing and amount of payments to investigators/departments
iii) Any other study related financial or in kind incentives to participants or study staff

The amount requested is small as risperidone is freely available in the market, and is inexpensive.

16. Please describe the plan for maintaining confidentiality of study participant information.

All study information will be confidential and will be maintained separately from the hospital records. It will be analysed and published without patient identification.

17. Please describe the plans for monitoring the safety of participants, reporting and managing adverse events. If this is an externally funded study with a Data Safety Monitoring Board, please provide the name and contact information of the DSMB chairperson.

The protocols in the ICU monitor vital signs of patients in real time with the use of electronic monitors. All patients are routinely assessed routinely and frequently during their stay in ICU. Side-effects will be picked up and managed immediately in the ICU by the treating physicians.

18. If an internal DSMB is being conducted kindly nominate the person from your specialty act as a neutral referee (This person should not be an investigator in this study)

19. If applicable; please provide all significant previous decisions (e.g., those leading to a negative decision or modified protocol) by other ECs or regulatory authorities for the proposed study (whether in the same location or elsewhere) and an indication of the modification(s) to the protocol.

Nil

20. If appropriate, has permission from the Drug Controller General of India been obtained?

Not necessary as the drug is licenced, manufactured, used routinely in clinical practice and in ICUs to manage delirium, agitation and psychosis.

21. If this is international collaborative research, has permission from the Health Minstry's Screening Committee been obtained? NA

22. For exchange of biological material in international collaborative studies, please provide a Memorandum of Understanding (MOU)/ Material Transfer Agreement (MTA) between the collaborating partners. NA

23. Declaration (to be signed by all investigators)

By signing this form we give our consent to provide our expertise to the project. In addition:

a. We confirm that all investigators have approved this version of the protocol and have contributed substantially to its development.
b. We confirm that all potential authors are included in this protocol.
c. We also affirm that we shall register the trial in the Clinical Trials Registry- India (http://ctri.nic.in) in accordance with the details submitted here and submit the registration details before getting final IRB approval and enrolling the first participant.
d. We confirm that we shall submit any protocol amendments, adverse events reports, progress reports (if required) and a final report and participate in any audit of this study.
e. We confirm that we shall conduct this study in accordance with the Declaration of Helsinki; the ICMR Guidelines for Biomedical Research in Human Subjects 2006, with any subsequent amendments; Schedule Y of the Drugs and Cosmetics Act; GCP guidelines; and all applicable laws of the Republic of India.
f. We agree to submit the results of this study for publication to a peer reviewed journal, within two years of completion.
g. We declare that we have no conflicts of interest that may affect the conduct or reporting of this study (OR) we declare the following conflicts of interest below.
h. We are aware of the institution's policies regarding scientific misconduct and agree to abide by them.

Title of Research project:

24. Signature of Principal Investigator

25. Signature of Guide/Head of the Department/ Unit

26. Co-Investigator's Consent (all co-investigators have to sign this form or supply separate letters of consent)

Name	Department	Signature	Date
Dr.J.VPeter	**Medical ICU**		
Dr.O.CAbraham	**Medicine unit IV**		
Dr.BinilaChacko	**Medical ICU**		

Conflicts of interest if any:

Note: If the project is a resubmission a fresh copy of signatures needs to be obtained for IRB submission.

Title of Research project:

SAMPLE INFORMATION SHEET & CONSENT FORM

Section III

CHECKLIST FOR PROTOCOLS SUBMITTED TO IRB OF CMC VELLORE FOR INTERVENTIONAL TRIALS IN HUMANS

Please tick the appropriate boxes below to indicate that the following have been submitted and if not, please explain why:

1. Application form for protocols of interventional trials with all sections (I, and II) completed [Y]

2. Informed consent and participant information form in all relevant local languages (PDF format)[Y]

3. Names, affiliations and signatures of all investigators/co-investigators for the declaration [Y]

4. Signature of the Head of the department or unit as applicable (for interdepartmental studies, an agreement letter from concerned departmental heads is desirable, if they are not co-investigators). [N]

5. Recent curriculum vitae of all investigators, with qualifications, experience and relevant Publicationsduring the past five years. [Y]

6. If applicable, data on safety of proposed intervention and any drug/device or vaccine to be tested, including results of relevant laboratory, animal and human research. [NA]

7. If applicable, proposed compensation and reimbursement of incidental expenses and management ofresearch related and unrelated injury/ illness during and after research period. [NA]

8. If applicable (in study-related injuries), a description of the arrangements for insurance coverage forresearch participants and copy of insurance documents from an Indian insurance agency. [NA]

9. If applicable all significant previous decisions (e.g., those leading to a negative decision or modifiedprotocol) by other ECs or regulatory authorities for the proposed study and an indication of the modification(s) to the protocol made on that account. Thereasons for negative decisions should be provided. [NA]

10. Plans for publication of results, positive or negative, with names of proposed authors and their expected contributions. [Y]

11. All other relevant documents related to the study protocol, e.g., investigator's brochure for trial on drugs/ devices/ vaccines/ herbal remedies, and statement of relevant regulatory clearances. [Y]

12. If applicable, any material used for advertisement to recruit participants to the study - this may include flyers, brochures, posters, radio and TV advertisements. [NA]

13. For externally funded trials, details of Funding agency/ Sponsors and breakdown of fund allocation. [NA]

Title of Research project:

14. One hard copy and a soft copy on CD to research@cmcvellore.ac.inof all the above.[Y]

Please list below all additional documents that are being submitted along with this application including all appendices.

Title of Research project:

Format for Informed Consent Form for Subjects

Informed Consent form to participate in a research study

Study Title:

Study Number: _____

Subject's Initials: _____ Subject's Name: _____

Date of Birth / Age: _____

(Subject)

(i) I confirm that I have read and understood the information sheet dated _____ for the above study and have had the opportunity to ask questions. [ ]

(ii) I understand that my participation in the study is voluntary and that I amfree to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. [ ]

(iii) I understand that ***the Sponsor of the clinical trial, others working on the Sponsor's behalf (delete as appropriate)***, the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published. [ ]

(iv) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s).[ ]

(v) I agree to take part in the above study. [ ]

(vi) I am aware of the Audio-visual recording of the Informed Consent.[ ]
(Click here for Audio Visual guidelines)

Signature (or Thumb impression) of the Subject/Legally Acceptable

Date: ____/____/_____

Signatory's Name: _____ Signature:

Or

Title of Research project:

Representative: _____

Date: _____/_____/_____

Signatory's Name: _____

Signature of the Investigator: _____

Date: _____/_____/_____

Study Investigator's Name: _____

Signature or thumb impression of the Witness: _____

Date: _____/_____/_____

Name & Address of the Witness: _____

Title of Research project:

Notes for filling in this form

1. **Section I is required for Research Committee Approval. Section II is required for Ethics Committee Approval. Section III contains a checklist that should accompany this submission. Incomplete submissions will be rejected.**
2. The Senatus hasresolved that all clinical trials conducted in CMC should be prospectively registered before enrolment of the first participant in the CTRI. **Only items submitted in the proposal and approved by the Research and Ethics committees should be submitted to the CTRI.**
3. Please see **Appendix I-IV** of this form for detailed description of items required for submission of applications before filling this form. Appendix I contains the Clinical Trials Registry India: Dataset and Description; Appendix II: Instructions for registering trials in the CTRI; Appendix III: The Revised CONSORT Statement: CONSORT checklist (the full statement can be obtained from www.consort.org). Instructions for preparing informed consent documents based on Schedule Y (Drugs and Cosmetics Act) 2005, and a sample consent form are provided in Appendix IV. Website link: http://172.16.11.136/Research/Flow%20chart.html.
4. Please also read the **Standard Operating Procedure** of the IRB of CMC Vellore (available from the Research website) for additional guidance on policies and procedures that will be followed at CMC for IRB approval. Website link: http://172.16.11.136/Research/IRB_Polices.html.
5. For externally funded projects with commercial sponsors, please also **submit the receipt of payment of the non-refundable processing fee.**
6. Submission procedure
    - Project proposal,
    - Curriculum Vitae's
    - Information sheet and informed consent forms
    - The aforesaid in translated versions need to be **scanned into PDF format**.
    - **Signatures by all** investigators and the Guide/Head of the Department/Unit need to be scanned.
    - **Applications submitted after the due date will not be entertained.**
7. **It is mandatory to fill in the checklist (Section III)**

Completed application with all supporting documents (Hard and Soft copy (CD) should be submitted to **Institutional Review Board,Christian Medical College**

Title of Research project:

Office of Research, I st Floor, Carman Block, Bagayam, Vellore 632 002 India.

E-mail: research@cmcvellore.ac.in.
Tel: 0416 -2284294, 2284202 Fax: 0416 – 2262788, 2284481.
Hours for submission: 8.00 am to 5.00 pm (Monday – Friday)
8.00 am to 12.00 pm (Saturday)