Online Forms
National Ethics Application Form

Within which Jurisdictions will your research application be submitted to: *(tick all that apply)*

- [x] New South Wales
- [ ] Queensland
- [x] South Australia
- [ ] Victoria

HREC Application Reference Number:

1. TITLE AND SUMMARY OF PROJECT

1. Title

What is the formal title of this research proposal?
Randomised double-blind placebo-controlled phase III trial of oral melatonin for the prevention of delirium in hospital in people with advanced cancer

What is the short title / acronym of this research proposal (if applicable)?
Phase III RCT of melatonin for prevention of delirium in cancer

2. Description of the project in plain language

Give a concise and simple description (not more than 400 words), in plain language, of the aims of this project, the proposal research design and the methods to be used to achieve those aims.

This application is for a phase III randomised controlled trial that will evaluate the efficacy of daily prolonged release melatonin 2mg in preventing delirium in inpatients with advanced cancer.

The aim of the investigator-initiated, cooperative group trial is to determine the effectiveness of melatonin in preventing delirium (number of delirium-free days during a hospital admission achieved by reducing overall delirium occurrence, or reducing duration and severity of delirium if it occurs).

All inpatients with advanced cancer in participating palliative care and oncology units will be eligible to participate, unless they meet the specific exclusion criteria for the study (current delirium, contraindications to study intervention, short prognosis). Patients who consent will be randomised to receive either 2mg prolonged release melatonin or placebo daily at night for the duration of their inpatient admission or until delirium occurrence. The primary aim is to determine the effectiveness of melatonin in preventing delirium; by increasing the number of delirium-free days during a hospital admission (achieved by reducing overall delirium occurrence, or reducing duration and severity of delirium if it occurs). The secondary aims are to better understand what constitutes delirium risk and precipitants for people with advanced cancer, the toxicities associated with melatonin, and to explore the collateral benefits in sleep quality. The severity and duration of delirium, and its impacts will be evaluated if it occurs. Days in coma will also be measured as this may occur in severe irreversible delirium prior to death.

2. RESEARCHERS / INVESTIGATORS

1. Chief researcher(s)/investigator(s)
This question only applies to multi-centre research. If your research is not multi-centre, please leave this question blank. See Guidance Text (G) for the definition of a Chief Researcher

Chief researcher

	Title:	Forename/Initials:	Surname:
	Professor	Meera	Agar
Mailing Address:	University of Technology Sydney		

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	Level 3, 235 Jones Street
Suburb/Town:	Ultimo
State:	NSW
Postcode:	2007
Country:	Australia
Organisation:	Faculty of Health, SWSLHD Palliative Care Department
Department*:	Centre for Cardiovascular and Chronic Care, Clinical Trials, Palliative Care,
Position:	Professor of Palliative Medicine, Clinical Trial Director, Staff Specialist in Palliative Medicine
E-mail:	meera.agar@sswahs.nsw.gov.au
Phone (BH):	02 9514 4243
Phone (AH)*:	0430 212 912
Mobile*:	0430 212 912
Pager*:	
Fax:	

Is this person the contact person for this application?
(•) Yes ( ) No

Summary of qualifications and relevant expertise.
Qualifications: MBBS, Master of Palliative Care, FRACP, FAChPM, PhD.

Expertise: Dr Agar's areas of expertise include palliative care symptom management, palliative care research, study methodology, dissemination and translation of research findings into practice. She completed her Doctoral thesis on Delirium in advanced cancer. She was the chief investigator for the largest delirium treatment randomised controlled trial which recruited over 200 participants. She has been the site investigator for over 20 investigator led clinical trials in SWSLHD.

Please declare any general competing interests.
None

Name the site(s) for which this chief researcher / investigator is responsible.
Liverpool Hospital

Describe the role of the chief researcher / investigator in this project.
Dr Agar will be leading the conception, design, execution, analysis and preparation of manuscripts for publication of this project, and will provide leadership to the collaborative team. She will be involved in ensuring data quality. Dr Agar will also lead the dissemination plan for this work, which will include translation of the findings into policy development, clinical guidelines and new program work

Is the chief researcher / investigator a student? ( ) Yes (•) No

2. Principal researcher(s) / investigator(s)

Principal researcher / investigator 1

	Title:	Forename/Initials:	Surname:
	A/Prof	Gideon	Caplan
Mailing Address:	Barker Street		
Suburb/Town:	Randwick		
State:	NSW		
Postcode:	2031		
Country:	Australia		
Organisation:	Post-acute Services, Prince of Wales Hospital		
Department*:	Geriatric medicine		
Position:	Director		
E-mail:	g.caplan@unsw.edu.au		
Phone (BH):	02 9382 2470		

Phone (AH)*:

Mobile*:

Pager*:

Fax:

Is this person the contact person for this application?
○ Yes ◉ No

Summary of qualifications and relevant expertise
Qualifications - MBBS, FRACP

A/Prof Caplan has led several clinical trials of hospital in the home interventions, where delirium impacts where important outcomes. He also has undertaken research to understand the pathophysiology of delirium in older adults. He is the President of the Australasian Delirium Association, which is the group aiming to improve delirium research and care in Australia. He was an investigator on the recently completed RCT of antipsychotics for delirium treatment.

Please declare any general competing interests
nil

Name the site(s) for which this principal researcher / investigator is responsible.
not responsible for a specific site

Describe the role of the principal researcher / investigator in this project.
A/Prof Caplan will contribute experience and knowledge of delirium from a Geriatric Medicine perspective.

Is the principal researcher a student? ○ Yes ◉ No

Principal researcher / investigator 2

Title:	Forename/Initials:	Surname:
A/Prof	Peter	Lawlor

Mailing Address: 43 Bruyère Street

Suburb/Town: Ottawa

State: Ontario

Postcode: KIN 5C8

Country: Canada

Organisation: University of Ottawa, Canada

Department*: Division of Palliative care, Dept of Medicine, Bruyère Continuing Care

Position: Medical Director

E-mail: plawlor@bruyere.org

Phone (BH): 613-562-6262,Ext:1423

Phone (AH)*:

Mobile*:

Pager*:

Fax: 613--562--6371

Is this person the contact person for this application?
○ Yes ◉ No

Summary of qualifications and relevant expertise
Qualifications: MB B Ch BAO. MMed Sc (pathology). CCFP

Expertise: A/Prof Lawlor has considerable expertise in delirium research in palliative care settings both as a clinician and a researcher.

Please declare any general competing interests
nil

Name the site(s) for which this principal researcher / investigator is responsible.
not responsible for a specific site

Describe the role of the principal researcher / investigator in this project.

CI Lawlor will contribute expertise and experience in delirium prevention and treatment specifically in cancer, including leadership of a current phase II trial of melatonin for delirium prevention in Canada. CI Lawlor has committed to share data from this trial where instructive to the aims of the proposed study. He will attend team meetings via teleconference as required. He was an investigator on the recently completed RCT of antipsychotics for delirium treatment.

Is the principal researcher a student? ○ Yes ◉ No

Principal researcher / investigator 3

Title:	Forename/Initials:	Surname:
A/Prof	Delwyn	Bartlett

Mailing Address: 431 Glebe Point Road

Suburb/Town: Glebe
State: NSW
Postcode: 2037
Country: Australia
Organisation: Woolcock institute of Medical Research & The University of Sydney
Department*:
Position: Clinical Associate Professor & Health Psychologist
E-mail: delwyn.bartlett@sydney.edu.au
Phone (BH): 02 9114 4060
Phone (AH)*:
Mobile*:
Pager*:
Fax:

Is this person the contact person for this application?
○ Yes ◉ No

Summary of qualifications and relevant expertise
Delwyn Bartlett is a Clinical Associate Professor at the Central Clinical School of Medicine at the University of Sydney where she received her PhD in 2002. She is a registered psychologist who has been predominantly working in the area of sleep health and psychology since 1993. She treats patients with sleep disorders such as insomnia, sleep apnea, and parasomnias as well as depression and anxiety.

Please declare any general competing interests
nil

Name the site(s) for which this principal researcher / investigator is responsible.
not responsible for a specific site

Describe the role of the principal researcher / investigator in this project.
A/Prof Bartlett brings experience from sleep disorders, and input relating to circadian rhythm disorders and melatonin in this context

Is the principal researcher a student? ○ Yes ◉ No

Principal researcher / investigator 4

Title:	Forename/Initials:	Surname:
Prof	David	Currow

Mailing Address: 216 Daws Road

Suburb/Town: Daw Park
State: SA
Postcode: 5041
Country: Australia
Organisation: Flinders University
Department*: Discipline of Palliative and Supportive Services

Position: Professor
E-mail: david.currow@sa.gov.au
Phone (BH): +61 08 72218235
Phone (AH)*:
Mobile*:
Pager*:
Fax:

Is this person the contact person for this application?
○ Yes ◉ No

Summary of qualifications and relevant expertise
Qualifications: BMed, PhD, MPH, FRACP, FAChPM, FAHMS, GAICD

Please declare any general competing interests
nil

Name the site(s) for which this principal researcher / investigator is responsible.
not responsible for a specific site

Describe the role of the principal researcher / investigator in this project.
Prof Currow will be involved in the trial conduct, analysis and write up and brings extensive experience in palliative care clinical trials. He was an investigator on the recently completed RCT of antipsychotics for delirium treatment.

Is the principal researcher a student? ○ Yes ◉ No

Principal researcher / investigator 5

Title:	Forename/Initials:	Surname:
Dr	Jane	Nikles

Mailing Address: Building 71/918

Suburb/Town: RBWH Herston
State: QLD
Postcode: 4029
Country: Australia
Organisation: University of Queensland
Department*: UQ Centre for Clinical Research
Position: Senior Research Fellow
E-mail: uqjnikle@uq.edu.au
Phone (BH): 07 3346 5144
Phone (AH)*:
Mobile*:
Pager*:
Fax:

Is this person the contact person for this application?
○ Yes ◉ No

Summary of qualifications and relevant expertise
Qualifications: MBBS, FRACP, PhD

After graduating from medical training with first class honors and a University Medal in 1983, in 2006 she obtained a PhD on “Using n-of-1 trial methodology as a management tool in clinical practice” in the field of Population Health, which was awarded, as was her MBBS, from The University of Queensland. Dr Nikles is an experienced trial coordinator, at a senior experienced postdoctoral level. She has taken overall responsibility for past grants, including ensuring scientific rigour, meeting timelines, communicating with funding bodies, ensuring ethical conduct of research and completion within budget.

Experience especially relevant to the proposed project includes running RCTs of melatonin in other populations.

Please declare any general competing interests
nil

Name the site(s) for which this principal researcher / investigator is responsible.
not responsible for a specific site

Describe the role of the principal researcher / investigator in this project.
CI Nikles contributes experience as a general practitioner and clinical trials expert and as the only team member with experience of trialling melatonin. She will continue to contribute to the design and methods of the proposed study. She will attend team meetings as required via teleconference from Brisbane and will contribute to interpretation and reporting.

Is the principal researcher a student? ○ Yes ◉ No

Principal researcher / investigator 6

Title:	Forename/Initials:	Surname:
Prof	Jane	Phillips

Mailing Address: Level 3, 235 Jones St

Suburb/Town: Ultimo
State: NSW
Postcode: 2007
Country: Australia
Organisation: University of Technology
Department*: Centre for Cardiovascular and Chronic Care
Position: Director
E-mail: jane.phillips@uts.edu.au
Phone (BH): 02 9514 4822
Phone (AH)*:
Mobile*:
Pager*:
Fax:

Is this person the contact person for this application?
○ Yes ◉ No

Summary of qualifications and relevant expertise
Professor Phillips RN PhD is a palliative care nurse, and brings extensive experience in research in the palliative care setting, and has undertaken studies exploring delirium care in this context. She is the current chair of the palliative care clinical studies collaborative trials management committee, who will coordinate this study

Please declare any general competing interests
nil

Name the site(s) for which this principal researcher / investigator is responsible.
not responsible for a specific site

Describe the role of the principal researcher / investigator in this project.
Prof Phillips has had input into the trial design, and will continue to be involved in its conduct in particular operationalising the non-pharmacological elements of the study

Is the principal researcher a student? ○ Yes ◉ No

Principal researcher / investigator 7

Title:	Forename/Initials:	Surname:
A/Prof	Lawrence	Lam

Mailing Address: Level 3, 235 Jones St

Suburb/Town: Ultimo
State: NSW

Postcode:	2007
Country:	Australia
Organisation:	University of Technology
Department*:	Faculty of Health and Graduate School of Health
Position:	Professor of Public Health
E-mail:	lawrence.lam@uts.edu.au
Phone (BH):	
Phone (AH)*:	
Mobile*:	
Pager*:	
Fax:	

Is this person the contact person for this application?
○ Yes ◉ No

Summary of qualifications and relevant expertise
Qualifications: BSc (Hons), MAppPsych, MPH, Grad Dip Biostats, PhD

I have received training in many areas including Medical Sciences (Pharmacology), Psychology, Public Health, Epidemiology and Medical Statistics. I have obtained degrees including: B.Sc (Hons), Master in Applied Psychology, MPH, Grad Dip in Biostats, PhD in Epid and Biostats. I am an academic and a practising Epidemiologist, as well as a qualified Medical Statistician and a research Psychologist.

Please declare any general competing interests
nil

Name the site(s) for which this principal researcher / investigator is responsible.
not responsible for a specific site

Describe the role of the principal researcher / investigator in this project.
CI Lam is a senior biostatistician who will conduct all statistical analyses in the proposed research and lead reporting of analysis sections in publications. He has contributed to the design and methods of the proposed trial, including power estimate and sample size calculation. He will attend investigator meetings and liaise with the trials coordinator as required.

Is the principal researcher a student? ○ Yes ◉ No

Principal researcher / investigator 8

Title:	Forename/Initials:	Surname:
Ms	Nikki	McCaffrey

Mailing Address:	RoomM 55, A block Repatriaion General Hospital,Daws Road
Suburb/Town:	Daws park
State:	SA
Postcode:	5041
Country:	Australia
Organisation:	Flinders University
Department*:	Department Palliative & Supportive Services
Position:	Health Economist
E-mail:	nicola.mccaffrey@flinders.edu.au
Phone (BH):	08 8275 2882
Phone (AH)*:	
Mobile*:	
Pager*:	
Fax:	08 8275 2854

Is this person the contact person for this application?
○ Yes ◉ No

Summary of qualifications and relevant expertise
Qualifications: BSc(Hons), MSc, PGDip(HEc), PGDip(ClinPharm)

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Please declare any general competing interests
nil

Name the site(s) for which this principal researcher / investigator is responsible.
not responsible for a specific site

Describe the role of the principal researcher / investigator in this project.
I bring to the project team the necessary expertise to undertake and complete a cost effectiveness evaluation, including the modeling of costs, risks, harms and benefits of interventions, the choice and valuation of appropriate outcomes in palliative care and the impact of economic evaluation on health care policy. I am an expert health economist and have participated in the design of the study to allow for meaningful economic data analysis. I have contributed to the development of the research protocol and will continue to supervise the conduct of the economic aspect of this research and supervise the economic analyses. I will also participate in the preparation of manuscripts and dissemination of the results at national and international clinical research meetings.

Is the principal researcher a student? ○ Yes ○ No

Principal researcher / investigator 9

Title:	Forename/Initials:	Surname:
Prof	Wes	Ely

Mailing Address:	Centre for Health Services Research
	6th Floor, Medical Centre East 6109
	Vanderbilt University School of Medicine
Suburb/Town:	Nashville
State:	Tennessee
Postcode:	37232-8300
Country:	USA
Organisation:	Vanderbilt University
Department*:	Pulmonary and Critical Care Medicine
Position:	Associate Director of Aging Research
E-mail:	wes.ely@vanderbilt.edu
Phone (BH):	615-936-3395
Phone (AH)*:	
Mobile*:	
Pager*:	
Fax:	615-936-1269

Is this person the contact person for this application?
○ Yes ◉ No

Summary of qualifications and relevant expertise
Qualifications - BS, MPH, MD

Expertise - Dr. Ely's research has focused on improving the care and outcomes of critically ill patients with sepsis and respiratory failure, with special emphasis on the problems facing older patients in the ICU (e.g., delirium and cognitive impairment in the ICU, weaning from mechanical ventilation, neuropsychological deficits post ICU care, and quality of death in the ICU).

He was an author of the ACCP/AARC clinical practice guidelines for weaning from the ventilator and for the upcoming revised version of the SCCM guidelines for Pain, Anxiety and Delirium. Dr. Ely was one of the coordinating center physicians for the Phase III PROWESS international trial of rh-Activated Protein C (and subsequent open label investigations) for severe sepsis that eventually led to its becoming the first approved drug for this disease. He is currently the director of the Vanderbilt clinical trials coordinating center for studies related to delirium and sedation.

Please declare any general competing interests
nil

Name the site(s) for which this principal researcher / investigator is responsible.
not responsible for a specific site

Describe the role of the principal researcher / investigator in this project.
Prof Ely contributes to this project as a world leader in delirium research in intensive care with particular expertise in clinical trials and measurement. He will attend investigator meetings via teleconference as

required and contribute to interpretation and reporting of study findings. He will disseminate findings via the Vanderbilt Delirium website which he developed and implemented as a leading resource for both medical and lay readers interested in learning about delirium.

Is the principal researcher a student? ○ Yes ◉ No

3. Associate Researcher(s) / investigator(s)

How many known associate researchers are there? (You will be asked to give contact details for these associate researchers / investigators) 10

Do you intend to employ other associate researchers / investigators? ◉ Yes ○ No

Associate Researcher / Investigator 1

Title:	Forename/Initials:	Surname:
Dr	Tim	Luckett

Mailing Address:	Faculty of Nursing, Midwifery & Health Building 10, Level 7, UTS 235-253 Jones St
Suburb/Town:	Ultimo
State:	NSW
Postcode:	2007
Country:	Australia
Organisation:	University of Technology
Department*:	Centre for Cardiovascular and Chronic Care
Position:	Senior Research Fellow
E-mail:	tim.luckett@uts.edu.au
Phone (BH):	02 95144861
Phone (AH)*:	
Mobile*:	
Pager*:	
Fax:	

Is this person the contact person for this application?
○ Yes ◉ No

Summary of qualifications and relevant expertise
Qualifications - BSc (Hons), PhD

Expertise - Dr Tim Luckett is an experienced palliative care researcher and also has expertise in patient reported outcome measurement. He was the trial coordinator for the phase II pilot which was undertaken prior to this study

Please declare any general competing interests
None

Description of the role of the associate researcher / investigator in this project.
Dr Luckett has been involved in the trial design, and will be involved interpretation of results

Name the site at which the associate researcher / investigator has responsibility.
nil

Is this associate researcher / investigator a student? ○ Yes ◉ No

Associate Researcher / Investigator 2

Title:	Forename/Initials:	Surname:
Ms	Bev	Noble

Mailing Address:

Suburb/Town:
State: NSW
Postcode:
Country:
Organisation: Improving palliative care through clinical trials - NSW Palliative Care Clinical Trials group
Department*:
Position: Consumer representative
E-mail: bev.noble@bigpond.com
Phone (BH):
Phone (AH)*:
Mobile*:
Pager*:
Fax:

Is this person the contact person for this application?
○ Yes ◉ No

Summary of qualifications and relevant expertise
Ms Noble is a breast cancer survivor, and has also experienced the role of a carer first-hand. With a background in social welfare, Ms Noble is highly experienced in understanding and navigating the health system. She has an active interest in health policy development and improving the lives of cancer patients in Australia. Ms Noble has been the consumer representative for the NSW palliative care clinical trials group since its inception in 2009, and is on its management advisory committee. She joined Breast Cancer Action Group and Cancer Voices in 2000, where she holds a position on the executive committee. Ms Noble participates in the Partnership Council and the Clinicians Council as a consumer at the Chris O'Brian Lifehouse. She is also a consumer representative for Cancer Voices NSW Executive and Health Consumer Forum.

Please declare any general competing interests
nil

Description of the role of the associate researcher / investigator in this project.
Bev Noble was involved in the study pilot, and will be responsible for providing critical consumer input across all aspects of the trial.

Name the site at which the associate researcher / investigator has responsibility.
none

Is this associate researcher / investigator a student? ○ Yes ◉ No

Associate Researcher / Investigator 3

Title:	Forename/Initials:	Surname:
Dr	AnnMarie	Hosie

Mailing Address: level 3, Building 10, 235-253 Jones St

Suburb/Town: Ultimo
State: NSW
Postcode: 2007
Country: Australia
Organisation: University of Technology
Department*: Centre for Cardiovascular and Chronic Care
Position: Project Coordinator for The Stop Cancer PAIN Trial
E-mail: AnnMarie.Hosie@uts.edu.au
Phone (BH): 02 9514 4858
Phone (AH)*:
Mobile*:
Pager*:
Fax:

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Is this person the contact person for this application?
○ Yes ◉ No

Summary of qualifications and relevant expertise
RN PhD. Dr Hosie undertook her doctoral studies exploring the assessment, and management of delirium by nurses in the palliative care setting. She is on the committee of the Australasian Delirium Association.

Please declare any general competing interests
nil

Description of the role of the associate researcher / investigator in this project.
Dr Hosie will be involved in training at the sites, in particular in the non pharmacological prevention strategies

Name the site at which the associate researcher / investigator has responsibility.
Training at all sites

Is this associate researcher / investigator a student? ○ Yes ◉ No

Associate Researcher / Investigator 4

Title:	Forename/Initials:	Surname:
A/Prof	Brian	Le

Mailing Address:	Grattan Street
Suburb/Town:	Parkville, Melbourne
State:	VIC
Postcode:	3050
Country:	Australia
Organisation:	The Royal Melbourne Hospital
Department*:	Palliative Care
Position:	Director
E-mail:	brian.le@mh.org.au
Phone (BH):	+ 61 3 9342 7820
Phone (AH)*:	
Mobile*:	
Pager*:	
Fax:	+61 3 9342 4928

Is this person the contact person for this application?
○ Yes ◉ No

Summary of qualifications and relevant expertise
FRACP. A/Prof Le is an senior palliative care clinician and has extensive experience in palliative care clinical trials.

Please declare any general competing interests
nil

Description of the role of the associate researcher / investigator in this project.
A/Prof Le will be involved in study design, conduct, analysis and write up.

Name the site at which the associate researcher / investigator has responsibility.
Royal Melbourne Hospital/Peter MacCallum Cancer Centre

Is this associate researcher / investigator a student? ○ Yes ◉ No

Associate Researcher / Investigator 5

Title:	Forename/Initials:	Surname:
A/Prof	Jennifer	Philip

Mailing Address:	41 Victoria St
Suburb/Town:	Fitzroy

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State: VIC
Postcode: 3065
Country: Australia
Organisation: St Vincents Hospital
Department*: Palliative Medicine & Centre For Palliative Care
Position: Associate Professor, Deputy Director
E-mail: jennifer.philip@svha.org.au
Phone (BH): 61 3 9416 0000
Phone (AH)*:
Mobile*:
Pager*:
Fax: 61 3 9416 3919

Is this person the contact person for this application?
○ Yes ◉ No

Summary of qualifications and relevant expertise
FAChPM, PhD

Please declare any general competing interests
None

Description of the role of the associate researcher / investigator in this project.
A/Prof Philip will be involved in study design, conduct, analysis and write up.

Name the site at which the associate researcher / investigator has responsibility.
None.

Is this associate researcher / investigator a student? ○ Yes ◉ No

Associate Researcher / Investigator 6

Title:	Forename/Initials:	Surname:
Ms	Meg	Brassil

Mailing Address:

Suburb/Town:
State: QLD
Postcode:
Country:
Organisation: Palliative Care Clinical Studies Collaborative
Department*: Management Advisory Board
Position: Consumer Representative
E-mail: meg.brassil@bigpond.com
Phone (BH):
Phone (AH)*:
Mobile*:
Pager*:
Fax:

Is this person the contact person for this application?
○ Yes ◉ No

Summary of qualifications and relevant expertise
Ms Brassil brings personal experience of home and hospice based palliative care, and believes in the importance of evidence based clinical practice for people with advanced illness. Ms Brassil is a member of Health Consumers Association, consumer representative on State Palliative Care Clinical Network Steering Committee since 2010
and community representative on interview panels for the Graduate Entry Medical Program at Flinders University. Al Brassil has a Masters in Social Work and Diploma of Financial Planning. Ms Brassil is the PaCCSC consumer representative and has been in that role for over 6 years.

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Please declare any general competing interests
None

Description of the role of the associate researcher / investigator in this project.
Meg will be responsible for providing critical consumer input across all aspects of the trial.

Name the site at which the associate researcher / investigator has responsibility.
None

Is this associate researcher / investigator a student? ○ Yes ◉ No

Associate Researcher / Investigator 7

	Title:	Forename/Initials:	Surname:
	A/Prof	Peter	Martin

Mailing Address:	PO Box 281
Suburb/Town:	Geelong
State:	VIC
Postcode:	3220
Country:	Australia
Organisation:	Barwon Health
Department*:	Palliative Care
Position:	Regional Director
E-mail:	petermar@barwonhealth.org.au
Phone (BH):	(03)4215 5565
Phone (AH)*:	
Mobile*:	
Pager*:	
Fax:	(03) 4215 6390

Is this person the contact person for this application?
○ Yes ◉ No

Summary of qualifications and relevant expertise
MB BCh BAO, PGDipPM, MMed, FAChPM

Please declare any general competing interests
nil

Description of the role of the associate researcher / investigator in this project.
A/Prof Martin will be involved in study design, conduct, analysis and write up.

Name the site at which the associate researcher / investigator has responsibility.
none

Is this associate researcher / investigator a student? ○ Yes ◉ No

Associate Researcher / Investigator 8

	Title:	Forename/Initials:	Surname:
	Prof	Richard	Chye

Mailing Address:	170 Darlinghurst Rd
Suburb/Town:	Darlinghurst
State:	NSW
Postcode:	2010
Country:	Australia
Organisation:	St Vincents Hospital, Sydney
Department*:	Sacred Heart Health Service
Position:	Director, Sacred Heart Supportive & Palliative Care

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E-mail: richard.chye@svha.org.au
Phone (BH): 02 83829570
Phone (AH)*:
Mobile*:
Pager*:
Fax:

Is this person the contact person for this application?
○ Yes ○ No

Summary of qualifications and relevant expertise
FRACP FFPMANZCA FAChPM AdDipBusMgt GrdCertMgt

Please declare any general competing interests
nil

Description of the role of the associate researcher / investigator in this project.
Prof Chye will be the site investigator for Sacred Heart Health Service. He will also be involved in study design, conduct, analysis and write up.

Name the site at which the associate researcher / investigator has responsibility.
Sacred Heart Health Service

Is this associate researcher / investigator a student? ○ Yes ◉ No

Associate Researcher / Investigator 9

Title:	Forename/Initials:	Surname:
A/Prof	Shirley	Bush

Mailing Address: 43 Bruyère Street
Rm 282J

Suburb/Town: Ottawa
State: Ontario
Postcode: K1N 5C8
Country: Canada
Organisation: University of Ottawa
Department*: Division of Palliative Care, Department of Medicine
Position: Assistant Professor
E-mail: sbush@bruyere.org
Phone (BH): 613-562-6262 x1060
Phone (AH)*:
Mobile*:
Pager*:
Fax:

Is this person the contact person for this application?
○ Yes ◉ No

Summary of qualifications and relevant expertise
MBBS, MRCGP, FAChPM

Please declare any general competing interests
nil

Description of the role of the associate researcher / investigator in this project.
Dr Bush will be involved in study design, conduct, analysis and write up.

Name the site at which the associate researcher / investigator has responsibility.
nil

Is this associate researcher / investigator a student? ○ Yes ◉ No

Associate Researcher / Investigator 10

Title: Forename/Initials: Surname:

	Dr	Andrew	Teodorczuk

Mailing Address:

Suburb/Town: Newcastle
State:
Postcode:
Country: UK
Organisation: Newcastle University
Department*: Campus for Ageing and Vitality, Northumberland Tyne and Wear NHS Trust & School for Medical Education
Position: Consultant Old Age Psychiatrist and Senior Lecturer
E-mail: andrew.teodorczuk@newcastle.ac.uk
Phone (BH):
Phone (AH)*:
Mobile*:
Pager*:
Fax:

Is this person the contact person for this application?
○ Yes ◉ No

Summary of qualifications and relevant expertise
MD
MRCPsych
MBChB

Dr Teodorczuk has particular interest in delirium education and training. He is in process of relocating to a clinical academic position in Australia (Griffith University)

Please declare any general competing interests
nil

Description of the role of the associate researcher / investigator in this project.
Dr Teodorczuk will be involved in study design, conduct, analysis and write up. He will also assist in training at the sites in the non pharmacological elements of the study intervention.

Name the site at which the associate researcher / investigator has responsibility.
None

Is this associate researcher / investigator a student? ○ Yes ◉ No

Associate Researcher / Investigator 11

Title:	Forename/Initials:	Surname:
Dr	Peter	Allcroft

Mailing Address: Repatriation General Hospital
Daws Road

Suburb/Town: Daw Park
State: SA
Postcode: 5041
Country: Australia
Organisation: Repatriation General Hospital
Department*: Southern Adelaide Palliative Services
Position: Senior Medical Consultant
E-mail: allc@adam.com.au
Phone (BH): 08 8275 1732
Phone (AH)*:
Mobile*:

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Pager*:

Fax:

Is this person the contact person for this application?
○ Yes ◉ No

Summary of qualifications and relevant expertise
BM BS, FRACP. Senior consultant in palliative care and respiratory end of life medicine. Was the site investigator for recently completed clinical trial of antipsychotics in delirium

Please declare any general competing interests
none

Description of the role of the associate researcher / investigator in this project.
Dr Allcroft will act as site investigator for this project at the Repatriation General Hospital and Flinders Medical Centre in SA. He will have responsibility for the development, review and oversight of issues specific to the study. He will contribute to the ongoing oversight of the study implementation. As chief investigator he will contribute to the protocol development, oversight of the study implementation,
review of the key performance indicators, data analysis and manuscript preparation.

Name the site at which the associate researcher / investigator has responsibility.
Southern Adelaide Palliative Services, which includes Repatriation General Hospital and Flinders Medical Centre

Is this associate researcher / investigator a student? ○ Yes ◉ No

5. Other personnel relevant to the research project

5a. How many known other people will play a specified role in the conduct of this research project?

6

5b. Describe the role, and expertise where relevant (e.g. counsellor), of these other personnel.

Two research nurses at each site will assist with recruitment and data collection to the study. Study nurses must have experience in the care of people with life−limiting illnesses and have demonstrated skills and ability to adequately capture the clinical information required in the case report forms. The role of the study nurses will be to; initiate recruitment processes, screen referred patients, obtain informed consent, collect study data, enter data into the study database, liaise with clinical teams regarding implementation of the study protocol.

5c. Is it intended that other people, not yet known, will play a specified role in the conduct of this research project?

◉ Yes ○ No

6. Certification of researchers / investigators

6a. Are there any relevant certification, accreditation or credentialing requirements relevant to the conduct of this research?

○ Yes ◉ No

7. Training of researchers

7a. Do the researchers / investigators or others involved in any aspect of this research project require any additional training in order to undertake this research?

◉ Yes ○ No

What is this training?

All researchers, investigators and study staff will be provided with training in ICH Good Clinical Practice as well as the standard operating procedures that have been developed for the collaborative. A 1 day training workshop will be held prior to initiation of study recruitment to ensure all study staff are familiar with the study protocol, consent procedures and data collection requirements

How and by whom will the training be provided?
Training will be conducted by the PaCCSC National Manager and Project Officer, and the chief investigator (Dr Agar) all of whom have completed formal GCP training. Training will be conducted at a face−to−face workshop and then individually with site staff at each of the study sites. Training will be supplemented by manuals and standard operating procedures.
At the site initiation visit the pharmacy will be visited by the coordinating site project officer. At this time the pharmacy procedures will be clarified, the protocol reviewed in detail and a pharmacy manual provided. The manual has been
prepared with the input and advise of experienced trial pharmacists during the protocol development, and reviewed by 2 other pharmacists prior to finalisation.

How will the outcome of the training be evaluated?
Training will be evaluated by ongoing monitoring by the PaCCSC Project Officer, this will be via:
1. Compliance with Key Performance Indicators,
2. Site monitoring visits
3. Data management reporting of errors and query resolution rates
4. Adverse event reporting

3. RESOURCES

Project Funding / Support

1. Indicate how the project will be funded?

Type of funding.

[Please note that all fields in any selected funding detail column (with the exception of the code) will need to be completed.]

Funding	Confirmed or Sought?	
External Competitive Grant	○ Confirmed ◉ Sought ○ Not Sought	*Amount of funding* 821,661
Internal Competitive Grant	○ Confirmed ○ Sought ◉ Not Sought	
Sponsor	○ Confirmed ○ Sought ◉ Not Sought	
By Researchers Department or Organisation	◉ Confirmed ○ Sought ○ Not Sought	*Amount of funding* 30,000

1a. External Competitive Grant

Name of Grant / Sponsor	NHMRC/Cancer Australia/Cancer Council NSW National Breast Cancer Foundation
Code (optional)	
Detail in kind support	
Indicate the extent to which the scope of the grant and the scope of this HREC application are aligned:	if this grant was successful the trial could be opened at a further 9 sites across Australia.

1d. By Researchers Department or Organisation

Name of Grant / Sponsor	University of Technology Sydney
Code (optional)	
Detail in kind support	The sites have non-project linked clinical trials nurses, and will provide clinical trials nurse time to supplement recruitment to this study. A post-doctoral fellow (1.0 FTE) and Research assistant (0.6 FTE) working at UTS under supervision of the chief investigator Prof Agar will also provide support in the coordination of the trial. $30000 discretionary research funding will cover study intervention, database set up, pharmacy costs at the proposed sites. The sites also will be eligible for funding per participant recruited as part of the CINSW cancer institute clinical trial portfolio. Further discretionary funding is available for future years to support ongoing recruitment at the participating sites
Indicate the extent to which the scope of the grant and the scope of this HREC application are aligned:	100%

2. How will you manage a funding shortfall (if any)?

The trial will only open at the specific limited sites, until further funding is obtained. There will be no shortfall of funding for the proposed sites.

3. Will the project be supported in other ways eg. in-kind support/equipment by an external party eg. sponsor?

(•) Yes ( ) No

Describe the support and indicate the provider:
The sites have non project linked clinical trials nurses, and will provide clinical trials nurse time to supplement recruitment to this study. The palliative care clinical studies collaborative will provide infrastructure support - site initiation and monitoring, electronic data management systems and standard operating procedures.

4. Is this a study where capitation payments are to be made, and will participants be made aware of these payments to clinicians or researchers / investigators?

No capitation payments will be made.

Duality of Interest

5. Describe any commercialisation or intellectual property implications of the funding/support arrangement.

None

6. Does the funding/support provider(s) have a financial interest in the outcome of the research?

( ) Yes (•) No

7. Does any member of the research team have any affiliation with the provider(s) of funding/support, or a financial interest in the outcome of the research?

( ) Yes (•) No

8. Does any other individual or organisation have an interest in the outcome of this research?

(•) Yes ( ) No

Indicate the interested party and describe the interest:

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The manufacturers and distributors of the study drug, Circadin, have a potential financial interest if a new indication is supported by the study. The investigators will purchase the study drug from the manufacturers, with the company having no input into study design, no access to study data or restrictions to study results publication. The placebo will be manufactured by pharmaceutical packaging professionals.

9. Are there any restrictions on the publication of results from this research?

○ Yes ◉ No

4. PRIOR REVIEWS

Ethical Review

Some HRECs may require researchers to provide information additional to that contained in a NEAF proposal. For this reason, it is prudent to check whether the HRECs to whom you propose to submit this proposal require additional information.

Duration and location

1. In how many Australian sites, or site types, will the research be conducted?

4

2. In how many overseas sites, or site types, will the research be conducted?

0

3. Provide the following information for each site or site type (Australian and overseas, if applicable) at which the research is to be conducted

1
Site / Site Type Name: Liverpool Hospital
Site / Site Type Location: Cnr Goulburn and Elizabeth Street
Liverpool NSW 2170, NSW

2
Site / Site Type Name: Southern Adelaide Palliative Care Services
Site / Site Type Location: Repatriation General Hospital, Daws Road, Daw Park 5041, Adelaide, SA

3
Site / Site Type Name: Sacred Heart Health Service
Site / Site Type Location: Darlinghurst Road
Darlinghurst, NSW 2010

4
Site / Site Type Name: Flinders Medical Centre
Site / Site Type Location: Flinders Dr, Bedford Park 5042, Adelaide, South Australia

4. Provide the start and finish dates for the whole of the study including data analysis

Anticipated start date: 01/09/2016 *(dd/mm/yyyy)*
Anticipated finish date: 01/12/2020 *(dd/mm/yyyy)*

5. Are there any time-critical aspects of the research project of which an HREC should be aware?

○ Yes ◉ No

6. To how many Australian HRECs (representing site organisations or the researcher's / investigator's organisation) is it intended that this research proposal be submitted?

1
A list of NHMRC registered Human Research Ethics Committees (HRECs), along with their institutional affiliations and contact details is available on the NHMRC website at the following web address: http://www.nhmrc.gov.au/health_ethics/hrecs/overview.htm#d.

7. HRECs

HREC 1

Name of HREC:
South Western Sydney Local Health District (SWSLHD) Human Research Ethics Committee (EC00136)

Provide the start and finish dates for the research for which this HREC is providing ethical review:
Anticipated start date or date range: 01/09/2016 *(dd/mm/yyyy)*
Anticipated finish date or date range: 31/12/2020 *(dd/mm/yyyy)*

For how many sites at which the research is to be conducted will this HREC provide ethical review?
4

Site 1

Name of Site: Liverpool Hospital

Principal Researcher 1

Principal Researcher Name:
Professor Meera Agar

Site 2

Name of Site: Southern Adelaide Palliative Care Services

Principal Researcher 1

Principal Researcher Name:
Prof David Currow

Site 3

Name of Site: Sacred Heart Health Service

Principal Researcher 1

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Principal Researcher Name:
Prof Richard Chye

Site 4

Name of Site: Southern Adelaide Palliative Care Services

Principal Researcher 1

Principal Researcher Name:
Dr Peter Allcroft

Site 5

Name of Site: Flinders Medical Centre

Principal Researcher 1

Principal Researcher Name:
Dr Peter Allcroft

8. Have you previously submitted an application, whether in NEAF of otherwise, for ethical review of this research project to any other HRECs?

○ Yes ◉ No

9. HRECs

Research conducted overseas

Peer review

11. Has the research proposal, including design, methodology and evaluation undergone, or will it undergo, a peer review process?

◉ Yes ○ No

Provide details of the review and the outcome. A copy of the letter / notification, where available, should be attached to this application.
The protocol was reviewed at the annual research forum of the Palliative Care Clinical Studies Collaborative (PaCCSC) and accepted as an investigator-led collaborative trial for the collaborative to support. It also has undergone review by the PaCCSC scientific committee. This proposal is also currently under review for funding by the NHMRC/Cancer Australia.

5. PROJECT

1. Type of Research

Tick as many of the following 'types of research' as apply to this project. Your answers will assist HRECs in considering your proposal. A tick in some of these boxes will generate additional questions relevant to your proposal (mainly because the National Statement requires additional ethical matters to be considered), which will appear in Section 9 of NEAF.

The project involves:

- [ ] Research using qualitative methods
- [ ] Research using quantitative methods, population level data or databanks, e.g survey research, epidemiological research
- [x] Clinical research
- [ ] Research involving the collection and / or use of human biospecimens
- [ ] Genetic testing/research
- [ ] A cellular therapy
- [ ] Research on workplace practices or possibly impacting on workplace relationships
- [ ] Research conducted overseas involving participants
- [ ] Research involving ionising radiation
- [ ] Research involving gametes or use or creation of embryos
- [ ] None of the above

Does the research involve limited disclosure to participants?

○ Yes ◉ No

Does the research involve:

- [ ] Opt out approach
- [ ] Waiver
- [x] None of the above

Research plan

2. Describe the theoretical, empirical and/or conceptual basis, and background evidence, for the research proposal, eg. previous studies, anecdotal evidence, review of literature, prior observation, laboratory or animal studies.

Prevalence and incidence of delirium in advanced cancer:

Delirium is a complex neuropsychiatric syndrome with fluctuating symptoms and multifactorial aetiology, characterized by a disturbance in cognition, arousal and attention which occurs in the presence of an underlying medical condition. Delirium is associated with a spectrum of distressing symptoms (for example disorientation,

sleep wake disturbance, hallucinations, delusions, agitation, paranoia, and worsening physical function). Delirium is prevalent in patients with advanced cancer in both oncology and palliative care settings. Delirium prevalence on admission to hospital in patients with advanced cancer has been shown in several studies to range between 28% - 48%, and up to 90% in the hours to days before death. The incidence of new episodes of delirium during admission has been reported as ranging between 20% and 45%. Taken in combination this means potentially at least two thirds of inpatients with advanced cancer may have delirium at some point during hospitalisation.

Delirium is associated with significant morbidity and mortality

Delirium is associated with increased mortality regardless of underlying illness, a risk that extends to after discharge even if delirium has resolved, with occurrence of delirium in advanced cancer an independent predictor of mortality. Delirium, even if it is detected and treated is associated with significant morbidity and economic cost arising from increased length of hospital stay, postoperative complications, increased risk of functional and cognitive decline which often leads to the need for institutional care. There is also convincing evidence that people with both hypoactive and hyperactive delirium have an awareness of their symptoms and are highly distressed by the recollection of this when the delirium resolves, including two sentinel studies in cancer patients. Witnessing delirium is also highly distressing for caregivers and health professionals. Hence to make the most impact on outcomes delirium prevention is the key.

Current strategies for delirium prevention

Current accepted and evidence based delirium prevention strategies include complex multi-component non-pharmacological interventions; however the inclusion of cognitive and exercise based strategies make adherence unachievable for many advanced cancer patients suffering fatigue and functional decline. A less challenging multicomponent intervention developed for advanced cancer patients failed to demonstrate a difference in the incidence of delirium between two palliative care centres that received the intervention and seven that did not.

Why alternative strategy is needed.

Alternative and/or supplemental strategies for preventing delirium in advanced cancer are therefore needed, with robust evaluation via randomised controlled trials (RCTs). A supplemental pharmacological approach with an acceptable adverse effect profile is an attractive alternative; and melatonin shows particular promise. Clinical and laboratory data identify low melatonin levels and circadian desynchrony in delirium, and 3 RCTs have demonstrated support for melatonin as a safe preventative agent in the hospitalised elderly. The team has completed a phase II RCT (n=30) and established feasibility of trial methods and demonstrated potential for increase in delirium-free days and lower delirium incidence rate in the advanced cancer population.

3. State the aims of the research and the research question and/or hypotheses, where appropriate.

The aim of this investigator-initiated, cooperative group trial is to determine the effectiveness of melatonin in preventing delirium; by increasing the number of delirium-free days during a hospital admission achieved by reducing overall delirium occurrence, or reducing duration and severity of delirium if it occurs.

Primary objective

To determine if oral prolonged release melatonin when compared to placebo can increase the number of delirium-free days during a hospitalisation for advanced cancer patients.

Secondary objectives

to determine if oral prolonged release melatonin can:
1. reduce delirium severity and duration for those who develop a delirium episode;

2. reduce delirium incidence;

3. cause adverse effects, in particular sedation;

4. positively influence adverse events associated with delirium episodes, including:
i. length of hospital stay and inpatient resource utilisation;
ii. benzodiazepine and antipsychotic use (delirium or non-delirium indication);
iii. in-hospital complications (pressure areas, falls, thromboembolism, pneumonia, functional decline);
iv. days spent in coma and survival;
v. Patient and family distress;

5. provide other symptom benefits in the form of improved sleep quality.

4. Has this project been undertaken previously?

○ Yes ◉ No

Benefits/Risks

In answering the following questions (Q 5 – 11) please ensure that you address all issues relevant to the type of participants that will be involved in your research project. Refer for guidance to relevant chapters of the National Statement.

5. Does the research involve a practice or intervention which is an alternative to a standard practice or intervention?

◉ Yes ○ No

Explain how the practice or intervention differs from standard practice or intervention:
No pharmacological agents are currently used as standard practice to prevent delirium in inpatients with advanced cancer. We propose a new use for a drug (oral prolonged release melatonin 2mg) currently approved in Australia for treatment of insomnia.

There is a standardised protocol to provide non-pharmacological elements for delirium prevention adapted to each individuals ability/clinical condition, based on current best evidence for delirium prevention; and this will be offered to both arms of the study.

7. What expected benefits (if any) will this research have for the wider community?

Health services can no longer view delirium as 'inevitable' during hospital stays for people with advanced cancer; but instead a preventable cause of morbidity and mortality, and an important safety concern. Every day without delirium improves the quality of life for someone with advanced cancer. This is the first trial of its kind in cancer care, aiming to prevent delirium, or reduce its duration and severity to stall the cascade of functional and cognitive decline, morbidity, mortality and resultant health care costs. Melatonin use could be rapidly translated into practice, given the formulation already has Therapeutics Goods Administration registration for another indication. The health economic analyses will also inform cost effectiveness

8. What expected benefits (if any) will this research have for participants?

While we hypothesise that melatonin will increase the number of delirium-free days, this has yet to be tested so we cannot be sure of any benefits to those who participate.

9. Are there any risks to participants as a result of participation in this research project?

◉ Yes ○ No

10. Explain how the likely benefit of the research justifies the risks of harm or discomfort to participants.

The most important risk is from potential adverse effects of the study drug, melatonin. Previous studies including the phase II RCT by this investigator group suggest these effects to be uncommon or rare. In the phase II study 6 SAEs were reported and all were unrelated to the study medication. The specific exclusion criteria ensure those with a specific contraindication to melatonin, potential risk to unborn or lactating infant, or where melatonin metabolism is significantly altered or can interact with other medications are not included as participants in this study. The overall potential benefit of reducing delirium incidence and its significant impact outweighs the potential minimal risk of melatonin adverse events. The participants will be closely monitored for emergent side effects, and potential side effects even if they do occur (such as sedation) are usually reversible with cessation of the medication.

11. Are there any other risks involved in this research? eg. to the research team, the organisation, others

○ Yes ◉ No

12. Is it anticipated that the research will lead to commercial benefit for the investigator(s) and or the research sponsor (s)?

○ Yes ◉ No

16. Is there a risk that the dissemination of results could cause harm of any kind to individual participants - whether their physical, psychological, spiritual, emotional, social or financial well-being, or to their employability or professional relationships - or to their communities?

○ Yes ◉ No

Monitoring

17. What mechanisms do the researchers / investigators intend to implement to monitor the conduct and progress of the research project?

Peer review and site visits
Each study site will be visited by the PaCCSC project officer and chief investigator prior to recruitment commencement, when the site coordinator and study nurse will be assessed as appropriate, and trained in the data collection, data entry, and filing and other trial procedures in order to comply with Good Clinical Practice. Peer review will be undertaken via regular study nurse telephone links and ongoing assessment by the study investigator. The assessment will be recorded and a copy sent to the study site.

Monitoring visits
Internal monitoring of the study is described in detail in the PaCCSC Monitoring Standard Operating Procedure. Briefly, each study site will be visited by staff from the co−ordinating site at initiation, mid recruitment and study closure where all study procedures, recording, reporting and maintenance will be checked, including the pharmacy records. This will include data quality, protocol violations, adverse event reporting, participant existence and eligibility, and other aspects to determine Good Clinical Practice compliance.

Independent data and safety monitoring
The study will be monitored by an independent data and safety monitoring committee (IDSMB), as set out within the PaCCSC governance structure, and its standard operating procedures.The membership of the IDSMB is still to be formalised and the membership will be provided to the HREC.

18. Please detail your Data and Safety Monitoring Board (DSMB) and its nominee for this trial.

This study will have an independent Data Safety Monitoring Board, membership will include a palliative care clinician, statistician and clinician with experience in delirium that will be managed by the Palliative Care Clinical Studies Collaborative on a contract basis. Its primary role is to monitor Adverse and Serious Adverse Events, the board will not otherwise be involved in the study. The DSMB terms of reference will determine the frequency of this review. The exact names and qualifications of the IDSMB will be provided to the HREC when formalised.

The Data Safety Monitoring Board (DSMB) will be established to:
• review data from an ethical standpoint, with patient rights, safety and wellbeing being paramount
• report on trial continuation

Specifically, the Board will receive serious adverse events as part of the established reporting mechanism, an adverse event summary report of all adverse events, these will be discussed as a standing agenda item, with these discussions and any actions and outcomes minuted. The Board will also receive an updated literature summary at each meeting, which will outline any new published literature that may have an impact on the study in any way.

6. PARTICIPANTS

1. Research participants

The National Statement identifies the need to pay additional attention to ethical issues associated with research involving certain specific populations.

This question aims to assist you and the HREC to identify and address ethical issues that are likely to arise in your research, if its design will include one or more of these populations. Further, the National Statement recognizes the cultural diversity of Australia's population and the importance of respect for that diversity in the recruitment and involvement of participants. Your answer to this question will guide you to additional questions (if any) relevant to the participants in your study.

Tick as many of the following 'types of research participants' who will be included because of the project design, or their inclusion is possible, given the diversity of Australia's population. If none apply, please indicate this below.

If you select column (a) or (b), column (c) will not apply.

The participants who may be involved in this research are: ***If you select column (a) or (b), column (c) will not apply.***	**a) Primary intent of research**	**b) Probable coincidental recruitment**	**c) Design specifically excludes**
People whose primary language is other than English (LOTE)	☐	☑	☐
Women who are pregnant and the human fetus	☐	☐	☑
Children and/or young people (ie. <18 years)	☐	☐	☑
People in existing dependent or unequal relationships	☑	☐	
People highly dependent on medical care	☑	☐	
People with a cognitive impairment, an intellectual disability or a mental illness	☐	☐	☑
Aboriginal and/or Torres Strait Islander peoples	☐	☑	☐
People who may be involved in illegal activity	☐	☑	☐
None apply	☐		

You have indicated that it is probable that
- People whose primary language is other than English (LOTE)
- Aboriginal and/or Torres Strait Islander peoples
- People who may be involved in illegal activity

may be coincidentally recruited into this project. The National Statement identifies specific ethical considerations for these groups(s).

Please explain how you will address these considerations in your proposed research.
All these groups may meet the eligibility criteria. Current services at the study sites for cancer patients are offered to Indigenous patients and it is important that this group is included in the research. Some service consumers may also be involved in illegal activity without our knowledge. While some people whose primary language is other than English will be included, these must have adequate English (or have access to a health care interpreter) to complete assessments. Delirium in people with dementia is a specific clinical scenario where prevention strategies need to be individualised, hence this trial is not designed to evaluate the role of melatonin for this population. The safety of the study intervention is not established in pregnant or breastfeeding women, or children so these are specifically excluded. People who already have delirium are also excluded.

Participant description

2. How many participant groups are involved in this research project?

1

3. What is the expected total number of participants in this project at all sites?

220

4. Groups

Group 1

Group name for participants in this group:	Inpatients with advanced cancer
Expected number of participants in this group:	220
Age range:	18+

Other relevant characteristics of this participant group:
1 Diagnosis of advanced cancer defined by the intent of treatment being no longer curative;
2 Admission to an acute or subacute inpatient palliative care or oncology facility;
3 Capacity to give written informed consent
Why are these characteristics relevant to the aims of the project?
Having advanced cancer and being an inpatient render this group at risk of delirium.

Your response to question 1 at Section 6 - "Research Participants" indicates that the following participant groups are excluded from your research. If this is not correct please return to question 1 at Section 6 to amend your answer.

- Women who are pregnant and the human fetus
- Children and/or young people (ie. <18 years)
- People with an intellectual or mental impairment

5. Have any particular potential participants or groups of participants been excluded from this research? In answering this question you need to consider if it would be unjust to exclude these potential participants.

TGA information on melatonin recommends that it not be given to women who are pregnant or breast-feeding.

Services at participating sites are provided only to adult patients.

To establish whether melatonin has potential in increasing delirium-free days, it is important that participants do not have cognitive impairment to begin with. In practical terms, exclusion criteria will include a Short Blessed Test (SBT) score of 10 or more, a Delirium Rating Scale (DRS_R-98) score of ≥17.75 (the score cut off for a diagnosis of delirium), or a clinical assessment that a potential participant is unable to give informed consent.

Participant experience

6. Provide a concise detailed description, in not more than 200 words, in terms which are easily understood by the lay reader of what the participation will involve.

Patient participants will be asked to take one prolonged release tablet at 8pm every night and continued until delirium occurrence, discharge or three weeks if patient remains in hospital (e.g. while awaiting long-term care placement) after any acute medical issues imparting a delirium risk have been resolved. Depending on which group the participant is randomly allocated to, this tablet may be either melatonin or a placebo (dummy pill). Neither the participants nor their medical teams will know whether they have received melatonin or the placebo. Following consent, patients will be asked to give a 15ml blood sample to help understand the mechanism by which melatonin might increase delirium-free days; another sample will be taken if delirium develops. This part of data collection will be optional; patients can choose to participate in the study without giving blood. A nurse will screen once every 8 hour shift for delirium and a more formal assessment will be undertaken every 3 days. We will also measure participants' degree of sedation and sleep quality. Information will be collected from medical records regarding use of drugs and hospital service use. If participants develop delirium, we will monitor the severity and duration of the delirium episode. We will monitor participants closely for any adverse effects, all of which are uncommon/rare.

Relationship of researchers / investigators to participants

7. Specify the nature of any existing relationship or one likely to rise during the research, between the potential participants and any member of the research team or an organisation involved in the research.

The CI and all PIs are treating physicians at the study sites so may be responsible for the care of patients recruited to the study.

9. Describe what steps, if any, will be taken to ensure that the relationship does not impair participants' free and voluntary consent and participation in the project.

Research staff, medical or nursing, will clearly identify themselves and the purpose of their visit at their contact with the person as being part of the research process.

The investigators and study staff with designated study related duties will work to eliminate any concern of inappropriate influence—the presentation of the study will be as unbiased as possible, the information sheet and consent forms will be clear, and participants will be able to withdraw from the study at any time. All study procedures, including eligibility, baseline assessment and other data collection points, will be performed by a person not involved in the clinical care of the participant.

10. Describe what steps, if any, will be taken to ensure that decisions about participation in the research do not impair any existing or foreseeable future relationship between participants and researcher / investigator or organisations.

Participants will be cared for as individuals with specific needs; the needs of research will come second.

The consent process will clearly state that the participation will not have any effect of the clinical care relationship the may exist.

11. Will the research impact upon, or change, an existing relationship between participants and researcher / investigator or organisations?

○ Yes ◉ No

Recruitment

13. What processes will be used to identify potential participants?

All in-patients will be screened by the study nurse for their suitability to enter the study in consultation with the treating clinician and nursing staff. The study nurse will ask the clinician in charge for permission to approach potentially eligible participants. This referral will be recorded within both the CRF and the clinical file.

14. Is it proposed to 'screen' or assess the suitability of the potential participants for the study?

◉ Yes ○ No

How will this be done?
Screening will be undertaken through the following process:
1. Explain the study and provide the participant information sheet. Give the participant time and privacy to read and consider the information, and discuss with family members if requested.
2. Check to confirm the person is interested in participating, and obtain informed consent.
Complete the eligibility screening as per the case report form, some items will be obtained while in discussion with participants, while other items will be obtained by referring to the clinical file.

15. Describe how initial contact will be made with potential participants.

After checking with the clinical team to make sure the person meets the broad criteria for consideration of eligibility, that the person has given explicit permission to be seen by a researcher, and is well enough to be approached, the

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study nurse will introduce themselves to the person and explain the study.

16. Do you intend to include both males and females in this study?

◉ Yes ○ No

What is the expected ratio of males to females that will be recruited into this study and does this ratio accurately reflect the distribution of the disease, issue or condition within the general community?
1:1

17. Is an advertisement, e-mail, website, letter or telephone call proposed as the form of initial contact with potential participants?

○ Yes ◉ No

18. If it became known that a person was recruited to, participated in, or was excluded from the research, would that knowledge expose the person to any disadvantage or risk?

○ Yes ◉ No

Consent process

19. Will consent for participation in this research be sought from all participants?

◉ Yes ○ No

Will there be participants who have capacity to give consent for themselves?
◉ Yes ○ No

What mechanisms/assessments/tools are to be used, if any, to determine each of these participant's capacity to decide whether or not to participate?
The research team will undergo training in consent procedures to ensure that potentially elgible participants understand the information being provided and ask appropriate questions indicating understanding. A cognitive assessment (short blessed test and delirium assessment with DRS-R-98) will be used to support the assessment of capacity.

Are any of the participants children or young people?
○ Yes ◉ No

Will there be participants who do not have capacity to give consent for themselves?
○ Yes ◉ No

The following questions relate to participants who are able to provide consent and also to participants for whom consent may be provided by a person with legal authority to do so. When answering these questions you need to describe any differences in the processes followed, or the documentation used, for different groups of participants in your proposal, e.g. processes and documentation for users of facilities/services will differ from those for providers of those facilities/services. Where your proposal involves participants with an intellectual or mental impairment, or people in dependent relationships, additional questions about their consent appear at section 7 questions 19-20 and questions 15-18 respectively.

Describe the consent process, ie how participants or those deciding for them will be informed about, and choose whether or not to participate in, the project. Obtaining consent for this study will be a process of information exchange between the study staff, the potential participant and any other person the potential participant believes should be included in the discussion. The participant information sheet will be used as a basis for the discussion, which will cover all procedures, benefits, burdens and side effects expected during the study. The participant will be given the opportunity (in time and physical capacity) to consider the study and formulate questions, any questions will be addressed and answered fully. The participant will be given as much time as they need to consider and discuss the study with their family members. Prior to study commencement, during the site initiation visit, the study nurse, site coordinator and the investigator will be trained in consent procedures for this study, with the opportunity

to role play scenarios and develop a consent script to ensure all information is fully covered.
The consent form is completed by the study nurse in accordance with the requirements of the institutional ethics committee. The form is signed and dated by the participant in front of a witness.
If a participant or person on behalf of a participant chooses not to participate, are there specific consequences of which they should be made aware, prior to making this decision? None
Might individual participants be identifiable by other members of their group, and if so could this identification could expose them to risks? Participants may be identified as participating by other patients because of the study procedures. However, this identification will not expose them to any risk.
If a participant or person on behalf of a participant chooses to withdraw from the research, are there specific consequences of which they should be made aware, prior to giving consent? None.
Specify the nature and value of any proposed incentive/payment (eg. movie tickets, food vouchers) or reimbursement (eg travel expenses) to participants. None. The participants are all inpatients so there will be no travel expenses incurred.
Explain why this offer will not impair the voluntary nature of the consent, whether by participants' or persons deciding for their behalf. NA

Are the participants from which you are recruiting attending for therapeutic care? If yes please provide the details of this care Participants will include inpatients with advanced cancer on palliative care and oncology wards. They may be receiving care for a range of reasons, most commonly symptom control or for an acute medical illness related or unrelated to their cancer.

Do you propose to obtain consent from individual participants for your use of their stored data/samples for this research project?
(•) Yes ( ) No

7. Participants Specific

People in dependent or unequal relationships

You have indicated that the project involves persons in dependent relationships. You may need to reconsider your answers to Section 6 Questions 7-11 to ensure that the information provided is accurate and consistent.

15. Describe the dependent relationship between the participants and the researcher, members of the research team, and/or any person involved in the recruitment/consent process.

Participants may be patients of the study CI and PIs.

16. How will the process of obtaining consent enable persons in dependent relationships to give voluntary consent?

The study CI and PIs will not be the only study staff involved in the consent procedure. Their role however is crucial as delirium is a medical condition, and from experience from other studies in delirium it is important for an explanation about delirium, what it is, and how it relates to the participants individual medical circumstances to be undertaken by a medical practitioner involved in their clinical care. It will be made clear that participation is voluntary and will not effect patient care.

17. Will there be any specific risks to participants in this research project as a result of the dependent relationship?

( ) Yes (•) No

18. If a participant chooses to withdraw from the research, how will the ongoing dependant relationship with the participant be maintained?

Medical care will continue as normal with the exception of administration of melatonin/placebo and the study measures and monitoring.

8. CONFIDENTIALITY/PRIVACY

Answers to the questions in section 8.1 will establish whether an HREC will need to apply guidelines under federal or

State/territory privacy legislation in reviewing your application. Answers to questions in the remaining parts of section 8 will show how confidentiality of participants is to be protected in your research.

1. Do privacy guidelines need to be applied in the ethical review of this proposal?

Indicate whether the source of the information about participants which will be used in this research project will involve:

- [x] collection directly from the participant
- [ ] collection from another person about the participant
- [ ] use or disclosure of information by an agency, authority or organisation other than your organisation
- [x] use of information which you or your organisation collected previously for a purpose other than this research project

Information which will be collected for this research project directly from the participant

Describe the information that will be collected directly from participants. Be specific where appropriate.
Participants will need to undergo some blood tests to ensure eligibility (Full blood count, electrolytes and liver function, and INR if on warfarin) prior to commencement of the study.

They will also be asked to rate their sleep quality using the Insomnia Severity Index (ISI) every 5 days during their admission, which has established psychometric properties in cancer.

Patients will be screened for dementia at the beginning of the study using the 6-item Short Blessed Test (SBT). In addition, observational data will be taken as follows with the participant's knowledge: Participants will be screened for delirium and sedation on a daily basis using the Nursing Delirium Screening Scale (NuDESC) and the Richmond Agitation-Sedation Scale (RASS). They will be assessed more thoroughly every 3 days using the Delirium Rating Scale (DRS-R-98).

The information collected by the research team about participants will be in the following form(s). Tick more than one box if applicable.

- [x] individually identifiable
- [x] re-identifiable
- [ ] non-identifiable

Give reasons why it is necessary to collect information in individually identifiable or re-identifiable form
Identifiable data is required so that the data obtained can be linked to the trial interventions and will allow unblinded analysis to individual participant data. Henceforth, patients will be allocated an ID number and the data rendered re-identifiable for error checks and to enable data to be removed in the event a participant withdraws and does not want their earlier data to remain in the study.

Information which will be used for this research project which you or your organisation collected previously for a purpose other than this research project

1b. Indicate from which of the following you will be collecting information for this research project and indicate how many databases from each source.

Commonwealth	
State/Territory	4
Private Sector	

Organisations databases

1

Name of agency / organisation	Southern Adelaide Palliative Care Services

Database source:	○ A Commonwealth government department or agency ◉ A state/territory authority ○ A private sector organisation
Name/description of the database	Patient medical records.
Describe the information that will be collected. List all data items.	Sociodemographic data, clinical data (cancer type, stage), number of medications at baseline, subsequent prescriptions of benzodiazepines, antipsychotics, corticosteroids or opioids, identification of hearing impairment, comorbidities, diagnosis of depression, presence of indwelling bladder catheter, blood urea to creatinine ratio, number of room or bed changes during the admission, survival, delirium precipitants, medical complications associated with delirium such as falls, pressure areas, pneumonia, and health services utilization (length of stay and in-hospital resource utilisation)

The information used by the research team about participants will be in the following form(s). Tick more than one box if applicable.

- ☑ Identified
- ☑ Re-identifiable
- ☐ De-identified

Give reasons why it is necessary to use information in Identified or Potentially identifiable form
Identifiable data is required so that the data obtained can be linked to the trial interventions and will allow unblinded analysis to individual participant data. It may also need to be identified for removal in the event a participant withdraws.

2

Name of agency / organisation	Liverpool Hospital
Database source:	○ A Commonwealth government department or agency ◉ A state/territory authority ○ A private sector organisation
Name/description of the database	Patient medical records
Describe the information that will be collected. List all data items.	Sociodemographic data, clinical data (cancer type, stage), number of medications at baseline, subsequent prescriptions of benzodiazepines, antipsychotics, corticosteroids or opioids, identification of hearing impairment, comorbidities, diagnosis of depression, presence of indwelling bladder catheter, blood urea to creatinine ratio, number of room or bed changes during the admission, survival, delirium precipitants, medical complications associated with delirium such as falls, pressure areas, pneumonia, and health services utilization (length of stay and in-hospital resource utilisation)

The information used by the research team about participants will be in the following form(s). Tick more than one box if applicable.

- ☑ Identified
- ☑ Re-identifiable
- ☐ De-identified

Give reasons why it is necessary to use information in Identified or Potentially identifiable form
Identifiable data is required so that the data obtained can be linked to the trial interventions and will allow unblinded analysis to individual participant data. It may also need to be identified for removal in the event a participant withdraws.

3

Name of agency / organisation	Sacred Heart Health Service
Database source:	○ A Commonwealth government department or agency ◉ A state/territory authority ○ A private sector organisation
Name/description of the database	Patient medical records
Describe the information that will be collected. List all data items.	Sociodemographic data, clinical data (cancer type, stage), number of medications at baseline, subsequent prescriptions of benzodiazepines, antipsychotics, corticosteroids or opioids, identification of hearing impairment, comorbidities, diagnosis of depression, presence of indwelling bladder catheter, blood urea to creatinine ratio, number of room or bed changes during the admission, survival, delirium precipitants, medical complications associated with delirium such as falls, pressure areas, pneumonia, and health services utilization (length of stay and in-hospital resource utilisation)

The information used by the research team about participants will be in the following form(s). Tick more than one box if applicable.

- ☑ Identified
- ☑ Re-identifiable
- ☐ De-identified

Give reasons why it is necessary to use information in Identified or Potentially identifiable form
Identifiable data is required so that the data obtained can be linked to the trial interventions and will allow unblinded analysis to individual participant data. It may also need to be identified for removal in the event a participant withdraws.

4

Name of agency / organisation	Flinders Medical Centre
Database source:	○ A Commonwealth government department or agency ◉ A state/territory authority ○ A private sector organisation
Name/description of the database	Patient medical records
Describe the information that will be collected. List all data items.	Sociodemographic data, clinical data (cancer type, stage), number of medications at baseline, subsequent prescriptions of benzodiazepines, antipsychotics, corticosteroids or opioids, identification of hearing impairment, comorbidities, diagnosis of depression, presence of indwelling bladder catheter, blood urea to creatinine ratio, number of room or bed changes during the admission, survival, delirium precipitants,,medical complications associated with delirium such as falls, pressure areas, pneumonia, and health services utilization (length of stay and in-hospital resource utilisation)

The information used by the research team about participants will be in the following form(s). Tick more than one box if applicable.

- ☑ Identified
- ☑ Re-identifiable
- ☐ De-identified

Give reasons why it is necessary to use information in Identified or Potentially identifiable form
Identifiable data is required so that the data obtained can be linked to the trial interventions and will allow unblinded analysis to individual participant data. It may also need to be identified for removal in the event a participant withdraws.

1c. Will the information to be used in medical research?

◉ Yes ○ No

1d. Does this application include an attachment relevant to state/territory privacy legislation?

○ Yes ◉ No

1e. Is the information health information?

◉ Yes ○ No

Using information from participants

2. Describe how information collected about participants will be used in this project.

We plan to collect only enough personal information to give a general demographic and disease profile of the participant. The participant responses collected are limited to those that will address our primary and secondary aims.

3. Will any of the information be used by the research team be in identified or re-identifiable (coded) form?

◉ Yes ○ No

Indicate whichever of the following applies to this project:

☑ Information collected for, used in, or generated by, this project will not be used for any other purpose.

☐ Information collected for, used in, or generated by, this project will/may be used for another purpose by the researcher for which ethical approval will be sought.

☐ Information collected for, used in, or generated by, this project is intended to be used for establishing a database/data collection/register for future use by the researcher for which ethical approval will be sought.

☐ Information collected for, used in, or generated by, this project will/may be made available to a third party for a subsequent use for which ethical approval will be sought.

4. List ALL research personnel and others who, for the purposes of this research, will have authority to use or have access to the information and describe the nature of the use or access. Examples of others are: student supervisors, research monitors, pharmaceutical company monitors.

Investigators will have access to data by ID number only for the purposes of data monitoring and analysis.

The project officer will have access to all study data for the purposes for data checking, monitoring and preparation for analysis.

Site coordinators will have access to the local site case report forms and the data contained within for the purpose of data collection, data entry and data query resolution.

Data safety monitoring board will have access to de-identified data for safety and efficacy assessments.

Study auditors will have access to case report forms (by ID number only), and study files in order to audit the study.

Site research ethics committees will have access to local data for audit purposes.

Storage of information about participants during and after completion of the project

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5. In what formats will the information be stored during and after the research project? (eg. paper copy, computer file on floppy disk or CD, audio tape, videotape, film)

All data will be collected and stored on paper Case Report Forms and then entered in a onto an secure online password protected research electronic database. The data will be downloaded on a regular basis into a computer file with regular backup to CD for security.

Source data, such as investigations and medical examinations will be kept within the clinical record and will be retained according to hospital requirements.

6. Specify the measures to be taken to ensure the security of information from misuse, loss, or unauthorised access while stored during and after the research project? (eg. will identifiers be removed and at what stage? Will the information be physically stored in a locked cabinet?)

There will be differential access to the database, site staff (study nurses and site coordinators) will have access for data entry only, and will only be able to view the data for that participant at that time. The PaCCSC Project Officer will have access to the reporting, update, data corrections and download functions of the database.

Data entry will be by ID number only.

Each site will maintain an electronic file containing the participant information along with the allocated ID number. This will be stored on a password protected, network backup computer. Paper versions will be stored in a locked filing cabinet.

Signed consent forms will be kept in a locked filing cabinet, separate from the file linking the patient with the ID number.

9. The information which will be stored at the completion of this project is of the following type(s). Tick more than one box if applicable.

- [x] individually identifiable
- [x] re-identifiable
- [ ] non-identifiable

Give reasons why it is necessary to store information in individually identifiable or re-identifiable form.
Signed consent forms need to be kept for the required retention period consistent with international and national guidelines.

If the data can be re-identified using a code, specify the security arrangements and access for the code.
The identified data will be separated from the study data, so that the link between the participant and their data cannot be made by persons without authorised access.

10. For how long will the information be stored after the completion of the project and why has this period been chosen?

Records from our study will be maintained for 15 years after study completion, this meets national requirements for record retention of research materials.

11. What arrangements are in place with regard to the storage of the information collected for, used in, or generated by this project in the event that the principal researcher / investigator ceases to be engaged at the current organisation?

The information generated during this study remain the property of Investigator team and will be stored for the 15 years regardless of changes in the principal researcher work location.

Ownership of the information collected during the research project and resulting from the research project

13. Who is understood to own the information resulting from the research, eg. the final report or published form of the results?

Any Intellectual Property arising from this study shall be jointly owned by Investigators equally.

14. Does the owner of the information or any other party have any right to impose limitations or conditions on the publication of the results of this project?

◯ Yes ◉ No

Disposal of the information

15. Will the information collected for, used in, or generated by this project be disposed of at some stage?

◉ Yes ◯ No

At what stage will the information be disposed?
The information will be disposed of after the required retention period has passed and if there are no ongoing or outstanding analysis, questions or publications pending.
How will information, in all forms, be disposed?
Once the waiting period is complete, the files will be erased from the data base hard drive (the online data entry system), the CDs used for security backup of the data, and shred any paper copies. This includes the master list linking participant name and treatment number.

Reporting individual results to participants and others

16. Is it intended that results of the research that relate to a specific participant be reported to that participant?

◯ Yes ◉ No

Explain/justify why results will not be reported to participants:
The study's outcomes measures are all transparent to participants removing the need to provide individual feedback. At the completion of the study, a report detailing the study findings will be offered to all participants still alive or their relatives.

17. Is the research likely to produce information of personal significance to individual participants?

◉ Yes ◯ No

18. Will individual participant's results be recorded with their personal records?

◉ Yes ◯ No

19. Is it intended that results that relate to a specific participant be reported to anyone other than that participant?

◯ Yes ◉ No

20. Is the research likely to reveal a significant risk to the health or well being of persons other than the participant, eg family members, colleagues

◯ Yes ◉ No

21. Is there a risk that the dissemination of results could cause harm of any kind to individual participants - whether their physical, psychological, spiritual, emotional, social or financial well-being, or to their employability or professional

relationships - or to their communities?

◯ Yes ◉ No

22. How is it intended to disseminate the results of the research? eg report, publication, thesis

The Palliative Care Clinical Studies Collaborative (PaCCSC) which is conducting this study have developed a comprehensive dissemination strategy to ensure the findings of this study (either positive or negative) are used to inform clinical practice in Australia. Specific dissemination activities that will occur include:

o Publication in peer review journals
o Study summary outcomes on CareSearch.com.au
o Conference presentations
o Presentations to clinical meetings at each of the study sites.
o Presentation to key peak bodies.
o Specific consultation with leaders of clinical guidelines for delirium care

23. Will the confidentiality of participants and their data be protected in the dissemination of research results?

◉ Yes ◯ No

Explain how confidentiality of participants and their data will be protected in the dissemination of research results:
All information presented will be de-identified group data that will not allow the identification of individual participants

9. PROJECT SPECIFIC

Your responses to question 5.1 "Type of Research" and question 6.1 "Research participants" indicate that the HREC will require additional information which is specific to your research project. The following table indicates the question sets relating to the project that you will need to complete. If this is not correct please return to question 5.1 and 6.1 at to amend your answer.

- 9.1. Type of research/trial
- 9.2. Clinical research

9.1 Type of research/trial

1. The study involves:

☑ The administration of a drug / medicine (includes a complementary / alternative medicine)
☐ The use of a medical device
☐ The administration of human somatic cell gene therapy
☐ The use of a xenotransplant
☐ The use of stem cells (adult or embryonic) as therapy
☐ Other

2. The project will be conducted as follows:

Under the Clinical Trial Notification Scheme (CTN) ◉ Yes ◯ No

3. Provide the following details for the clinical trial protocol:

Protocol name:	Randomised double blind placebo controlled phase III trial of oral melatonin for the prevention of d
Protocol version number:	035/16 v 1.0
Protocol version date:	27/05/2016 *(dd/mm/yyyy)*

*If you intend to/have registered this trial in a publicly accessible register, please provide the details of it here*The trial will be registered online on the ANZ Clinical Trials Registry.

4. Provide the following details for the investigator's brochure/product information (as relevant):

Title of Investigator's Brochure:	Investigator's Brochure Circadin
Investigator's brochure version number:	1i
Investigator's brochure version date:	01/08/2010 *(dd/mm/yyyy)*

9.2 Clinical research

1. The study examines:

- [x] The administration of a drug / medicine (includes a complementary / alternative medicine)
- [ ] The use of a medical device
- [ ] Other

2. Provide the following details for the study protocol:

Protocol title:	Randomised double blind placebo controlled phase III trial of oral melatonin for the prevention of d
Protocol version number:	035/16 v 1.0
Protocol version date:	27/05/2016 *(dd/mm/yyyy)*

3. Provide a statement addressing the following as may be applicable to the project.

a) Method of randomisation
b) Whether the hypothesis offers a realistic possibility that the intervention is at least as effective as standard treatment
c) The justification for the use of placebo or non-treatment control group, including alternative effective treatments and any risk of harm in the absence of treatment.
d) How variations in response will be treated
e) Endpoints
f) Details of contingencies and management of these
g) Explain the arrangements in place to ensure there is adequate compensation for participants.

a) Randomisation schedules will be developed for each site using random number tables, generated at an independent centre (central registry). Randomisation will be stratified by location of inpatient admission (oncology or palliative care unit) given differing patient populations and service delivery models. Treatment for each patient will be allocated according to a block randomisation (blocks of 6) schedule held by the central registry in a 1:1 ratio. Block randomisation will ensure even allocation to each code in each site. The central registry will supply the schedule tables to each site pharmacy. Treatment allocation will not be disclosed to patient, study staff, treating clinicians or investigators. The study drug and placebo will be manufactured by an external facility and supplied to each site pharmacy in pre-prepared and coded bottles.

b) There are currently no standard measures taken to prevent delirium in inpatients with advanced cancer. Both arms will receive standardised multi-component non-pharmacological interventions. Components of inpatient care that may influence delirium risk will be standardised for sleep preservation, mobility, orientation and sensory deficit minimisation, individualised to the functional status of the participant. This includes assessment of patients' readiness for and coordination of exercise program, access to hearing aids /glasses, sleep preservation techniques and reorientation. Light exposure will be minimised from 2200 to 0630 hours to standardise light exposure, to help maintain their normal sleep pattern in the hospital environment, and to avoid nocturnal depletion of melatonin.

c) The aetiology of delirium is complex and poorly understood. While it is unlikely there may be a placebo effect in delirium prevention, the possibility cannot be ruled out. Risk of harm arises from potential side effects of melatonin outlined in detail elsewhere on the NEAF. These are all uncommon or rare and our exclusion criteria and monitoring are designed to avoid serious adverse events.

d) There may be a variance in delirium episodes (the primary outcome of interest) if the treatment is effective. Delirium episodes will be treated with standard supportive measures and medical treatment of the underlying precipitants individualised by the treating clinicians and in accordance with patients goals of care.

e) Endpoints will be:

Primary end point:
1. delirium-free days (before delirium onset for those who develop delirium)

Secondary end points:

1. Feasibility end points:
- Percentage of eligible patients screened who progress to randomized.

2. Efficacy

-Incidence of first episodes of delirium as defined by Diagnostic and Statistical Manual of Mental Disorders Version IV Text Revised (DSM-IV-TR) assessment by treating clinician confirmed by a DR-R-98 (total score ≥17.75)

-Sleep quality measured using Insomnia Severity Index at baseline every 5 days during admission.

3. Toxicity

-Delirium symptom and time profile, subtype and severity (measured by Delirium Rating Scale – Revised -98 (DRS-R-98)), time to delirium onset, and duration of delirium (number of days DRS-R-98 score ≥17.75);

-Sedation will be rated daily by observation using the Richmond Agitation-Sedation Scale - Palliative (RASS - Pal), developed by Al Bush.

4. Benzodiazepine and antipsychotic use

-Regular use and administration of ‘as required’ doses of all benzodiazepine and antipsychotics will be recorded daily, including the clinical indication.

5. Delirium risk factors

-Delirium risk factors will be recorded at baseline: age (>65 and >80 years of interest), cognitive impairment defined as SBT score >4, visual impairment, presence of infection, and use of physical restraint.(14) Risk factors which have uncertain/contradictory evidence will also be collected to advance the science for future work: primary or secondary brain malignancy, benzodiazepines (oral diazepam equivalents), corticosteroids (oral dexamethasone equivalents), opioids (oral morphine equivalents), hearing impairment, comorbidities (Charlson Comorbidity Index), diagnosis of depression, use of indwelling bladder catheter, number of room/bed changes during admission, multiple medications (number of medications), and high blood urea/creatinine ratio (>18).

f)If delirium develops, this will be treated according to standard practice which involves treating the underlying medical precipitant, non pharmacological strategies and the administration of anti-psychotics if required for specific symptoms. This treatment will be determined by the treating clinician. Administration of melatonin/placebo will be stopped but we will continue to monitor the type, severity and duration of the delirium episode.

g) Participants will not receive any compensation for participating in this study.

4. How many drugs will be used in this research project?

1

5. Provide the following information for each drug:

Drug 1

Approved name:	Melatonin
Trade name:	Circadin
Approved therapeutic indication, dose and duration in Australia:	Insomnia; 2 mg once daily for up to thirteen weeks
Dosage regimen:	2mg oral prolonged release once daily at 8pm.
	The adverse reactions were reported in clinical trials and were defined as possibly, probably or definitely related to treatment. A total of 9.5% of subjects receiving Circadin reported an adverse reaction compared with 7.4% of subjects taking placebo. Only those adverse events occurring in subjects at an equivalent or greater rate than placebo have been included. Uncommon Irritability, Nervousness, Restlessness, Insomnia, Abnormal dreams, Anxiety, Migraine, Lethargy Psychomotor hyperactivity, Dizziness, Somnolence, Abdominal pain, Abdominal pain upper, Mouth Ulceration, Dry mouth, Hyperbilirubinaemia, Dermatitis, Night Sweats, Pruritus, Rash, Pruritus Generalised, Dry Skin, Pain in extremity, Menopausal symptoms, Asthenia, Chest Pain, Glycosuria, Proteinuria, Liver Function Test Abnormal, Weight increased
Known adverse effects:	Rare Herpes zoster, Leukopenia, Thrombocytopenia, Angina Pectoris, Palpitations Hypertriglyceridaemia, Hypocalcaemia, Hyponatraemia, Mood altered, Aggression, Agitation, Crying, Stress Symptoms, Disorientation, Early morning awakening, Libido increased, Depressed mood, Depression, Syncope, Memory impairment, Disturbance in attention, Dreamy state, Restless Legs Syndrome, Poor quality sleep, Paresthesia, Visual acuity reduced, Vision blurred, Lacrimation increased, Vertigo positional, Vertigo, Hot flush, Gastrooeshophageal Reflux Disease, Gastrointestinal disorder, oral Mucosal Blistering, Tongue Ulceration, Gastrointestinal upset, Vomiting, Bowel sounds abnormal, Flatulence, Salivary hypersecretion, Halitosis, Abdominal Discomfort, Gastric disorder, Gastritis, Eczema, Erythema, Hand Dermatitis, Psoriasis, Rash Generalised, Rash pruritic, Nail disorder, Arthritis, Muscle, Neck pain, Night cramps, Priapism Prostatis, Fatigue, Pain, Thirst, Polyuria, Hematuria, Nocturia, Hepatic enzyme increased, Blood Electrolytes Abnormal, Laboratory Test Abnormal. The following precautions are listed in the information for melatonin: Drowsiness: Circadin may cause drowsiness. Therefore the product should be used with caution if the effects of drowsiness are likely to be associated with a risk to safety. Effects on ability to drive and operate machinery: Circadin has negligible influence on the ability to drive and use machines. Nevertheless, patients should avoid engaging in hazardous activities (such as driving or operating machinery) aftertaking Circadin. Autoimmune diseases: No clinical data exist concerning the use of Circadin in individuals with autoimmune diseases. Therefore Circadin is not recommended for use in patients with autoimmune diseases. Excipients: The tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the LAPP lactase deficiency or glucose-galactose malabsorption should not take this medicine. Effects on fertility: No significant effects on fertility or reproductive performance were observed in rats given oral melatonin prior to mating through to early gestation at doses over 900-fold the recommended clinical dose, based on body surface area. Use in pregnancy: Category B3. No significant effects on embryofetal development were observed in rats given oral

	melatonin during the period of organogenesis at doses over 900-fold the recommended clinical dose, based on body surface area. No clinical data on exposed pregnancies are available. In view of the lack of clinical data, use in pregnant women and by women intended to become pregnant is not recommended.
Known contra-indications/warnings:	Use in lactation: Maternal transfer of exogenous melatonin to the fetus via the placenta or milk has been demonstrated in several animal species including rats, hamsters, goats, monkeys and cows. A slight reduction in post-natal growth, viability and development was found in rats given oral melatonin during gestation through weaning at doses over 900-fold the recommended clinical dose, based on body surface area; the no-effect dose was over 250-fold the clinical dose. Endogenous melatonin has been detected in human breast milk, thus exogenous melatonin is likely excreted into human milk. The effects of melatonin on the nursing infant have not been established. Therefore, breast-feeding is not recommended in women under treatment with melatonin. Paediatric use: Circadin is not recommended for use in children and adolescents below 18 years of age due to insufficient data on safety and efficacy. Use in the elderly: Melatonin metabolism is known to decline with age. Across a range of doses, higher AUC and Cmax levels have been reported in older subjects compared to younger subjects, reflecting the lower metabolism of melatonin in the elderly. Carcinogenicity: An oral lifetime carcinogenicity study with melatonin in rats showed an increased incidence of thyroid follicular cell adenomas in males at doses around 700-fold the recommended clinical dose, based on body surface area. No neoplastic tissue histopathology was examined at lower doses and therefore the no-effect dose could not be determined. These effects were associated with liver enzyme induction in this species and are unlikely to be relevant to humans. Genotoxicity: Results from a standard battery of in vitro and in vivo assays showed no evidence of a genotoxic potential for melatonin. Interactions with other medicines: Pharmacokinetic interactions Hepatic enzymes - Melatonin has been observed to induce CYP3A in vitro at supra-therapeutic concentrations. The clinical relevance of the finding is unknown. If induction occurs, plasma concentrations of concomitantly administered drugs can be reduced. Melatonin does not appear to induce CYP1A enzymes in vitro at supra-therapeutic concentrations. Therefore, interactions between melatonin and other active substances as a consequence of melatonin's effect on CYP1A enzymes are not likely to be significant. Melatonin's metabolism is mainly mediated by CYP1A enzymes. Therefore, interactions between melatonin and other active substances as a consequence of their effect on CYP1A enzymes is possible: Quinolones - CYP1A2 inhibitors such as quinolones may give rise to increased melatonin exposure. Carbamazepine and rifampicin - CYP1A2 inducers such as carbamazepine and rifampicin may give rise to reduced plasma concentrations of melatonin. Fluvoxamine - Caution should be exercised in patients on fluvoxamine, which increases melatonin levels (17-fold higher AUC and 12-fold higher serum Cmax) by inhibiting its metabolism by hepatic cytochrome P450 (CYP) isozymes CYP1A2 and CYP2C19. The combination should be avoided. 5- or 8-methoxypsoralen - Caution should be exercised in patients on 5- or 8-methoxypsoralen (5 and 8-MOP), which increases melatonin levels by inhibiting its metabolism.

	Cimetidine - Coadministration of CIRCADIN with cimetidine resulted in a 1.7 fold increase in exposure to melatonin with no change in the exposure to cimetidine. Caution should be exercised in patients on cimetidine, a CYP2D inhibitor which increases plasma melatonin levels by inhibiting its metabolism.
Concurrent drugs to be avoided:	Cigarette smoking - Cigarette smoking may decrease melatonin levels due to induction of CYP1A2. Oestrogens - Caution should be exercised in patients on oestrogens (e.g. contraceptives or hormone replacement therapy), which increase melatonin levels by inhibiting its metabolism by CYP1A1 and CYP1A2. Other - There is a large amount of data in the literature regarding the effect of adrenergic agonists/antagonists, opiate agonists/antagonists, antidepressant medicinal products, prostaglandin inhibitors, benzodiazepines, tryptophan and alcohol, on endogenous melatonin secretion. Whether or not these active substances interfere with the dynamic or kinetic effects of Circadin or vice versa has not been studied. Pharmacodynamic interactions Alcohol - Alcohol should not be taken with Circadin, because it reduces the effectiveness of Circadin on sleep. The prolonged release characteristics of Circadin may be altered by alcohol, resulting in immediate release of melatonin. Hypnotics - Circadin may enhance the sedative properties of benzodiazepines and non-benzodiazepine hypnotics, such as zaleplon, zolpidem and zopiclone. In a clinical trial, there was clear evidence for a transitory pharmacodynamic interaction between Circadin and zolpidem one hour following co-dosing. Concomitant administration resulted in increased impairment of attention, memory and co-ordination compared to zolpidem alone. Thioridazine and imipramine - Circadin has been co-administered in studies with thioridazine and imipramine, active substances which affect the central nervous system. No clinically significant pharmacokinetic interactions were found in each case. However, Circadin co-administration resulted in increased feelings of tranquility and difficulty in performing tasks compared to imipramine alone, and increased feelings of “muzzy-headedness” compared to thioridazine alone. Effect on laboratory tests: No information is available on the effect of melatonin on laboratory tests.

10. Declarations And Signatures

Applicant / Principal Researchers (including students where permitted)

Project Title (in full):	Randomised double-blind placebo-controlled phase III trial of oral melatonin for the prevention of delirium in hospital in people with advanced cancer
HREC to which this application is made:	
HREC Reference number:	

I/we certify that:

- All information is truthful and as complete as possible.
- I/we have had access to and read the National Statement on Ethical Conduct in Research InvolvingHumans.
- The research will be conducted in accordance with the National Statement.
- The research will be conducted in accordance with the ethical and research arrangements of the organisations involved.

- The research will be conducted in accordance with the ethical and research arrangements of the organisations involved.
- I/we have consulted any relevant legislation and regulations, and the research will be conducted in accordance with these.
- I/we will immediately report to the HREC anything which might warrant review of the ethical approval of the proposal (NS 2.37), including:
- serious or unexpected adverse effects on participants;
- proposed changes in the protocol; and
- unforseen events that might affect continued ethical acceptability of the project.
- I/we will inform the HREC, giving reasons, if the research project is discontinued before the expected date of completion (NS 2.38);
- I/we will not continue the research if ethical approval is withdrawn and will comply with any special conditions required by the HREC (NS. 2.45);
- I/we will adhere to the conditions of approval stipulated by the HREC and will cooperate with HREC monitoring requirements. At a minimum annual progress reports and a final report will be provided to the HREC.

Applicant / Chief Researcher(s) / Principal Researcher(s)

Professor Meera Agar Faculty of Health, SWSLHD Palliative Care Department	..... Signature	...../ ...../ ..... Date
A/Prof Gideon Caplan Post-acute Services, Prince of Wales Hospital	..... Signature	...../ ...../ ..... Date
A/Prof Peter Lawlor University of Ottawa, Canada	..... Signature	...../ ...../ ..... Date
A/Prof Delwyn Bartlett Woolcock institute of Medical Research & The University of Sydney	..... Signature	...../ ...../ ..... Date
Prof David Currow Flinders University	..... Signature	...../ ...../ ..... Date
Dr Jane Nikles University of Queensland	..... Signature	...../ ...../ ..... Date
Prof Jane Phillips University of Technology	..... Signature	...../ ...../ ..... Date
A/Prof Lawrence Lam University of Technology	..... Signature	...../ ...../ ..... Date
Ms Nikki McCaffrey Flinders University	..... Signature	...../ ...../ ..... Date
Prof Wes Ely Vanderbilt University	..... Signature	...../ ...../ ..... Date

Associate Researchers

Dr Tim Luckett University of Technology	..... Signature	...../ ...../ ..... Date
Ms Bev Noble Improving palliative care through clinical trials - NSW Palliative Care Clinical Trials group	..... Signature	...../ ...../ ..... Date

Dr AnnMarie Hosie University of Technology	..... Signature	...../ ...../ ..... Date
A/Prof Brian Le The Royal Melbourne Hospital	..... Signature	...../ ...../ ..... Date
A/Prof Jennifer Philip St Vincents Hospital	..... Signature	...../ ...../ ..... Date
Ms Meg Brassil Palliative Care Clinical Studies Collaborative	..... Signature	...../ ...../ ..... Date
A/Prof Peter Martin Barwon Health	..... Signature	...../ ...../ ..... Date
Prof Richard Chye St Vincents Hospital, Sydney	..... Signature	...../ ...../ ..... Date
A/Prof Shirley Bush University of Ottawa	..... Signature	...../ ...../ ..... Date
Dr Andrew Teodorczuk Newcastle University	..... Signature	...../ ...../ ..... Date
Dr Peter Allcroft Repatriation General Hospital	..... Signature	...../ ...../ ..... Date

Supervisor(s) of student(s)

Project Title (in full):	Randomised double-blind placebo-controlled phase III trial of oral melatonin for the prevention of delirium in hospital in people with advanced cancer
HREC to which this application is made:	
HREC Reference number:	

I/we certify that:

- I/we will provide appropriate supervision to the student to ensure that the project is undertaken in accordance with the undertakings above;
- I/we will ensure that training is provided necessary to enable the project to be undertaken skilfully and ethically.

Heads of departments/schools/research organisation

Project Title (in full):	Randomised double-blind placebo-controlled phase III trial of oral melatonin for the prevention of delirium in hospital in people with

advanced cancer

HREC to which this application is made:

HREC Reference number:

I/we certify that:

- I/we are familiar with this project and endorse its undertaking;
- the resources required to undertake this project are available;
- the researchers have the skill and expertise to undertake this project appropriately or will undergo appropriate training as specified in this application.

....
Title First Name Surname

....
Position Organisation Name

..../ ...../ .....
Signature Date

11. Attachments

List of Attachments

Core Attachments	**Attachments which may be required/appropriate**
Recruitment/invitation	Copy of advertisement, letter of invitation etc
Participant Information	Copy or script for participant Copy or script for parent, legal guardian or person responsible as appropriate
Consent Form	Copy for participant For parent, legal guardian or person responsible as appropriate For, optional components of the project eg. genetic sub study
Peer review	Copy of peer review report or grant submission outcome
HREC approvals	Copy of outcome of other HREC reviews

Attachments specific to project or participant group	**Attachments which may be required/appropriate**
People whose primary language is other than	English translation of participant information/consent forms

English (LOTE)	
People highly dependent on medical care	Information/consent form for legal guardian or person responsible
Aboriginal and/or Torres Strait Islander peoples	Evidence of support / permission of elders and/or other appropriate bodies

Participant information elements

Core Elements
Provision of information to participants about the following topics should be considered for all research projects.

Core Elements	**Issues to consider in participant information**
About the project	Full title and / or short title of the project Plain language description of the project Purpose / aim of the project and research methods as appropriate Demands, risks, inconveniences, discomforts of participation in the project Outcomes and benefits of the project Project start, finish, duration
About the investigators / organisation	Researchers conducting the project (including whether student researchers are involved) Organisations which are involved / responsible Organistions which have given approvals Relationship between researchers and particpants and organisations
Participant description	How and why participants are chosen How participants are recruited How many participants are to be recruited
Participant experience	What will happen to the particant, what will they have to do, what will they experience? Benefits to individual, community, and contribution to knowledge Risks to individual, community Consequences of participation
Participant options	Alternatives to participation Whether participation may be for part of project or only for whole of project Whether any of the following will be provided: counselling, post research follow-up, or post research access to services, equipment or goods
Participants rights and responsibilities	That participation is voluntary That participants can withdraw, how to withdraw and what consequences may follow Expectations on participants, consequences of non-compliance with the protocol How to seek more information How to raise a concern or make a complaint
Handling of information	How information will be accessed, collected, used, stored, and to whom data will be disclosed Can participants withdraw their information, how, when Confidentiality of information Ownership of information Subsequent use of information Storage and disposal of information
Unlawful conduct	Whether researcher has any obligations to report unlawful conduct of participant

Financial issues	How the project is funded Declaration of any duality of interests Compensation entitlements Costs to participants Payments, reimbursements to participants Commercial application of results
Results	What will particpants be told, when and by whom Will individual results be provided What are the consequences of being told or not being told the results of research How will results be reported / published Ownership of intellectual property and commercial benefits
Cessation	Circumstances under which the participation of an individual might cease Circumstances under which the project might be terminated

Research Specific Elements

Provision of information to participants about the following topics should be considered as may be relevant to the research project.

Specific to project or participant group	**Additional issues to consider in participant information**
Aboriginal and/or Torres Strait Islander peoples	Describe consultation process to date and involvement of leaderswhether ATSI status will be recorded