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Application Report

Application Details	
Grant Opportunity:	2024 MRFF Alcohol and Other Drugs
Application ID:	2044364
Application Title:	A Phase II study of medicinal cannabis products in the treatment of chronic pain in patients with opioid dependence
Chief Investigator A:	Prof Nicholas Lintzeris
Eligible Organisation:	University of Sydney
Grant Duration:	2 years
Stream:	Stream 4
Sub-Stream:	Topic A

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Contents

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Participating Institutions

Participating Institutions		
Participating Institution	**Department**	**Research Effort (%)**
South Eastern Sydney Local Health District	Drug and Alcohol Services	30
South Eastern Sydney Local Health District	Pain Department, Prince of Wales Hospital	30
NSW Users and AIDS Association	N/A	5
Bordeaux Segalen University	Sleep Addiction and Neuropsychiatry Laboratory (SANPSY)	5
University of Sydney	Addiction Medicine, Faculty Medicine and Health	30

Is this application using services provided by a research facility? No
If yes, see separate attachment for details

Does this research proposal include an Aboriginal and/or Torres Strait Islander health research or capacity building component?

Priority Populations

Does your application specifically focus on the health of a priority population/s as identified in the Assessment Criteria and Glossary in the grant opportunity guidelines?

- People with rare or currently untreatable diseases/conditions

Synopsis

Synopsis

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Medicinal cannabis (MC) is being increasingly used for the treatment of chronic pain, most notably tetrahydrocannabinol (THC), cannabidiol (CBD) or combination THC-CBD products. Despite the limited evidence regarding safety and efficacy for chronic pain, there is strong consumer demand for MC, with hundreds of thousands of Australians prescribed MC for pain management.

Prior clinical trials of MC for chronic pain have excluded people with opioid dependence, limiting our understanding of whether and how MC should be used in people with both conditions. This Phase 2 study examines the safety and efficacy of three medicinal cannabis products in people with concurrent chronic low back pain and dependence to prescription opioids, providing the evidence that will inform future and more definitive Phase 3 trials.

The study employs a double-blinded randomised cross-over within-subject design with N=30 participants, in which each participant is exposed (in random order) to four x two-week periods of treatment with oral doses of placebo, THC (20mg/day), CBD (400mg/day), THC+CBD (20mg+400mg), with a one-week washout period between each drug exposure. The trial examines the impact of each MC medication upon the outcomes: pain (primary endpoint), mood, anxiety, cravings, substance use, sleep, adverse events and consumer experience.

The project will use Ecological Momentary Assessment (EMA) methods - a data collection approach that captures experience in real time and in real-world settings, alongside conventional data collection approaches, to enhance our understanding of interactions between pain, cravings, mood and medication use, which in turn can inform the design of future pharmacological and non-pharmacological treatment interventions.

The project brings together Australian and international specialists in addiction and pain medicine, consumer representatives, and researchers with expertise in medicinal cannabis interventions and EMA methods in these patient populations.

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Research Team

Research Team			
Role	**Investigator**	**Primary Institution**	**Will CI be based in Australia?**
CIA	Prof Nicholas Lintzeris	University of Sydney	Yes

Role	Investigator	Primary Institution
CI	Prof Apo Demirkol	South Eastern Sydney Local Health District
CI	Prof Marc Auriacombe	University of Bordeaux
CI	Dr Jonathan Penm	University of Sydney
CI	Dr Mary Ellen Harrod	NSW Users and AIDS Association
CI	Prof Maurice Dematteis	CHU Grenoble Alpes
CI	Assoc Prof Kok-Eng Khor	Prince of Wales Hospital
CI	Dr Llewellyn Mills	University of Sydney
CI	Dr Fuschia Serre	University of Bordeaux
CI	Mr Justin Sinclair	Australian Natural Therapeutics Group
CI	Dr Anjali Bhardwaj	
CI	Mr Arshman Sahid	University of Sydney
CI	Dr Mark Hardy	South Western Sydney Local Health District

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Associate Investigators		
Name	**Primary Institution**	**Position**
Dr Laila Parvaresh	South Eastern Sydney Local Health District	Addiction Medicine Specialist, SESLHD
Ms Louisa Jansen	South Eastern Sydney Local Health District	Consumer Worker, NUAA
Ms Sophie Maiolo	South Eastern Sydney Local Health District	Consumer Worker, Drug and Alcohol Services, SESLHD
Dr Robert Page		Addiction Medicine Specialist, Drug and Alcohol Services
Dr Victoria Hayes	South Eastern Sydney Local Health District	Addiction Medicine Specialist, Drug and Alcohol Services
Anna Schiff	NSW Users and AIDS Association	Director Operations, NUAA

Partner Organisation(s)

Partner Organisation(s)

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Partner Organisation Details

Partner Name: South Eastern Sydney Local Health District
Annual Report URL:
https://www.seslhd.health.nsw.gov.au/sites/default/files/groups/Media_and_Communications/Our%20Year%20In%20Review%20Documents/OurYearinReview2023Finalweb_spreads.pdf

Partner Organisation Details

Partner Name: NSW Users and AIDS Association
Annual Report URL:
https://static1.squarespace.com/static/61bc083a85af43143a2eb69a/t/656593494e1d0824da4510fb/1701155680700/NUAA+Annual+Report+2022+-+23.pdf

Partner Organisation Details

Partner Name: University of Bordeaux
Annual Report URL: https://www.u-bordeaux.fr/universite/organisation-et-fonctionnement/documents-reglementaires-administratifs-institutionnels/bilans-sociaux

Partner Organisation Details

Partner Name: University of Grenoble
Annual Report URL: https://www.univ-grenoble-alpes.fr/universite/ambition-et-strategie/les-documents-strategiques/rapport-d-activites-2020-2021-1271367.kjsp

Partner Organisation Details

Partner Name: South Western Sydney Local Health District
Annual Report URL: https://www.swslhd.health.nsw.gov.au/pdfs/2023_Review.pdf

Partner Organisation Details

Partner Name: Painaustralia
Annual Report URL: https://www.painaustralia.org.au/static/uploads/files/painaustralia-annual-report-2022.pdf

Partner Organisation Details

Partner Name: Australian Natural Therapeutics Group
Annual Report URL:

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Total Budget Summary

Total Budget Summary					
Summary of Total 'Salary' per year					
Year 1 ($)	**Year 2 ($)**	**Year 3 ($)**	**Year 4 ($)**	**Year 5 ($)**	**Total Salary ($)**
$283,386	$275,365				$558,751
Summary of total 'Other Research Costs' (ORC) per year					
Year 1 ($)	**Year 2 ($)**	**Year 3 ($)**	**Year 4 ($)**	**Year 5 ($)**	**Total ORC ($)**
$181,439	$119,819				$301,258
Summary of total 'Equipment' per year					
Year 1 ($)	**Year 2 ($)**	**Year 3 ($)**	**Year 4 ($)**	**Year 5 ($)**	**Total Equipment ($)**
$	$				$
Total Requested Budget					
Year 1 ($)	**Year 2 ($)**	**Year 3 ($)**	**Year 4 ($)**	**Year 5 ($)**	**Total Budget ($)**
$464,825	$395,184				$860,009

Salary Request Summary

Salary Request Summary						
Position Function	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total**
Clinical Trial Lead (CTL) PSP5	$107,941	$107,941				**$215,882**
	100%	100%				
Clinical Trial Research Nurse PSP4	$75,191	$50,127				**$125,318**
	75%	50%				
Ecological Momentary Assessment (EMA) IT Engineer PSP4	$40,102	$42,107				**$82,208**
	40%	42%				
Specialist in EMA Protocol PSP4	$20,051	$15,038				**$35,089**
	20%	15%				
Trial Statistician PSP4	$	$40,102				**$40,102**
	%	40%				
Clinical Data Manager PSP4	$40,102	$20,051				**$60,152**
	40%	20%				
	$283,386	**$275,365**				**$558,751**

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Salary Request

Salary Request	
Position Function	**Justification**
Clinical Trial Lead (CTL) PSP5	An experienced, postdoctoral CTL is responsible for the comprehensive management of the trial, overseeing all phases from planning to execution, ensuring that the trial stays on schedule and on budget. Duties will include the planning, set-up and organisation of the study, including the coordination of ethics and other research governance, setting up and managing CTSAs and CTRAs with study partners, CTN applications, progress reports to funders, sponsors, HREC and relevant pharmaceutical companies; coordination of the Project Steering Committee over the duration of the project, oversee completion (in consultation with CIs) of the study protocol, operating procedures (e.g. pharmacy manual, database manual, DSMB manual etc.) study CRFs and develop and maintain the study database; monitor participant recruitment, data collection and cleaning. The CTL will liaise and coordinate the Data Management and Consumer Advisory Group; assist in data analysis, write up and dissemination activities.
Clinical Trial Research Nurse PSP4	An experienced clinical trial research nurse (Clinical Nurse Consultant level - equivalent to PSP4) is required at 1 FTE for 15 months: 3 months prior to site initiation to establish the clinical research procedures (SOPs including pathology and pharmacy procedures), study promotion and establishing recruitment pathways with relevant local services; and 12 months of participant recruitment, implementation of study interventions and data collection. The Research Nurse will co-ordinate participant recruitment (screening and assessment, enrolment, coordination with the SMO, participant and their GP), participant education (regarding medication use and use of EMA technologies), collection and handling of biospecimens (urine, bloods) and ECGs, participant follow-up and liaison with SMO, conduct participant research interviews (4 interviews per participant with 30 participants), data entry and cleaning, assist close out of site.
Ecological Momentary Assessment (EMA) IT Engineer PSP4	The EMA IT engineer is crucial for ensuring the effective design, implementation, and management of technology solutions to support real-time data collection in natural settings. They will ensure that the EMA system is compatible with the device selected to be used for this study optimizing user engagement and data quality. They will implement protocols for data validation and quality assurance, critical for ensuring the accuracy of real-time data collected and establish robust security measures to protect sensitive participant data, ensuring compliance with data protection regulations. They will provide ongoing support to the Clinical Trial team and troubleshoot any technical issues ensuring smooth operation of the EMA toolkit. They will facilitate the integration of EMA systems into the EDC system ensuring cohesive data management and develop analytical tools to assist the statistician to interpret data collected through EMA, providing insights into behavioral patterns and trends.
Specialist in EMA Protocol PSP4	A specialist in EMA design with clinical research background and ability to implement the study protocol is required to ensure accurate data collection systems for the project. The University of Bordeaux has considerable expertise in the use of EMA in the field of addiction research and will assist the researchers in Sydney to establish EMA research methods tailored to this project, including adaptation of the EMA smartphone app for use in this current project. This includes contribution to the project's design and protocol development, development of the smartphone app, engineering support (adaptation of existing EMA programs, development and testing of the app, database management and app maintenance) and data analysis support over the course of the 2 year project.

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Trial Statistician PSP4	An experienced post-graduate trial statistician is crucial for ensuring the scientific rigor and validity of the study. The statistician is responsible for creating a detailed Statistical Analysis Plan (SAP) that outlines the analysis methods and procedures, providing a clear roadmap for data analysis. The statistician will deal with complex data structures allowing for modifications based on interim results. The trial statistician will sit on the DSMB, Data Management and Project Steering Committees, providing high level statistical analysis required for data and patient safety. They will assist in data cleaning and undertake the statistical analysis of study data, prepare results for publication and dissemination to the research team, regulatory bodies and scientific conferences.
Clinical Data Manager PSP4	The Clinical Data Manager (CDM) is essential for ensuring the integrity and reliability of the trial data. The CDM ensures that data collected from various sources is accurate, complete, and consistent and implement validation checks to identify and resolve discrepancies or errors in data entry. The CDM will work closely with the Clinical Trial Lead, trial statistician, trial nurse and EMA IT engineer to ensure the data needs are met for accurate analysis. The CDM will develop and oversee the Electronic Data Capture (EDC) system ensuring it is capturing the required data efficiently. CDM will prepare datasets for statistical analysis, ensuring they are clean and structured according to the analysis plan. A qualified and experienced CDM can reduce the costs associated with data correction and reanalysis at a later date and ensures efficient data management processes accelerating trial results. The position is required at 0.4FTE during year 1 and for 6 months in Year 2

Other Research Costs Summary

Other Research Costs Summary						
Item	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total**
Investigtional Product (IP)	$95,250	$57,150				**$152,400**
Clinical Trial Pharmacy	$11,200	$13,700				**$24,900**
Pathology: liver function and other blood tests	$5,620	$1,780				**$7,400**
Electrocardiogram (ECG)	$4,400	$2,200				**$6,600**
Participant reimbursement	$14,400	$14,400				**$28,800**
Consumer Advisory Group (CAG)	$15,000	$2,560				**$17,560**
Trial recruitment strategies	$4,000	$3,000				**$7,000**
DSMB	$3,250	$3,250				**$6,500**
Software Licensing & Server Hosting	$3,249	$3,249				**$6,498**
Smartphone costs	$6,000	$0				**$6,000**
Point of Care Urine Tests	$1,070	$530				**$1,600**
Study Medical Officer	$18,000	$18,000				**$36,000**
	$181,439	**$119,819**				**$301,258**

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Other Research Costs

Other Research Costs	
Item	**Justification**
Investigtional Product (IP)	Acquire investigational medication product (IP) for up to 30 participants across 4 study arms: CBD approx. 336,000mg, THC approx. 16,800mg and sufficient placebo to dose 420 days of medication. Costs include a GMP compounding pharmacy to formulate the IP into soft gel capsules and undertake 6-month product stability testing. Packaging of capsules into blister packs and outer box packaging. Development and printing of GMP compliant labelling of IP to meet regulatory requirements.
Clinical Trial Pharmacy	Expenses based on Clinical Trial Drug Fees of the NSW Hospital Pharmacy Departments: (i) Establishment & administration fee, (ii) pharmacy services, (iii) dispensing fee of S8 special requirement medication, (iv) storage fees (S8 IP), (v) document amendment fee, (vi) completion fee, (vii) drug destruction fee = $24,900.
Pathology: liver function and other blood tests	Blood samples collected at baseline for eligibility assessment (liver function tests, full blood count, urea electrolytes) in an estimated 60 participants (to recruit 30). Each set of bloods estimated to cost $90 for collection and analysis of samples by a NSW Health approved pathology service. Cost of samples = 60 x $90 per participant = $5,400, with anticipated 66.7% ($3620) in year 1 and 33.3% ($1780) in Year 2. Establishment of trial pathology procedures =$2,000 (Yr 1) for total cost $7,400
Electrocardiogram (ECG)	ECG conducted at baseline for safety assessment. ~60 participants (to recruit 30 at baseline) = ~60 ECGs. Cost of conducting an ECG = $110 per participant. Total cost = 60 x $110 = $6,600, with anticipated 66.7% in Year 1 and 33.3% in Year 2.
Participant reimbursement	Reimbursement of participant's time, expenses and inconvenience in attending research interviews and EMA data collection. Each research interview (1 hour plus travel) reimbursed at $80 (DACRIN rates) x 5 interviews per participant (baseline and Day 14 of each of the 4 medication conditions)=$400 each. EMA Qs via smartphone at $5/timepoint x 4 per day = $20 per day x 7 days per condition = $140 per condition x 4 conditions = $560pp. Total $960 pp x 30 participants = $28800 spread over 2 years
Consumer Advisory Group (CAG)	Consultation with consumer organisations NUAA and Painaustralia, including establishment and coordination of the CAG, appointment and reimbursement of a lead consumer representative to co-ordinate consumer consultation and for reimbursement of consumer pilot testing of EMA and research interview procedures, estimated at a total of $15,000; plus reimbursement of CAG members ($40 per hour reimbursement, a total of 8 hours across study (4 x 2 hour meetings) per CAG member x 8 members = $2,560)
Trial recruitment strategies	Recruitment strategies will include social media (e.g. facebook, Instagram, Google Ads etc.), trial recruitment platforms and other advertising costs, such as printing and mailouts. All recruitment strategies to be submitted and approved by HREC committee. Costs based on tight recruitment time frames and from previous studies using social media for recruitment by this research group.
DSMB	Costs associated with establishing and maintating the Independent Data & Safety Monitoring Board (DSMB). These include payment of independent statistician and clinical experts, and any associated expenses (catering, travel). Allow $3,250 per meeting x 2 meetings.
Software Licensing & Server Hosting	Costs associated with purchasing the EMA licence and hosting it on the secure server.
Smartphone costs	Smartphones are essential for EMA data collection. Android smartphones (with data plans) will be loaded with the EMA App and provided to study participants for their use during the 11-week trial (and to be returned to research team to be used by subsequent participants). 15 smartphones and data plans will be purchased, estimated at $400 each ($total 6,000).

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Other Research Costs	
Item	**Justification**
Point of Care Urine Tests	Point of care (PoC) urine tests will be used during screening for eligibility and will include urine drug test and pregnancy tests (beta-hCG) in women. We estimate 60 participants will be screened for eligibility (all tested for urine drug screen), of which 40% (24) will be women (requiring beta-hCG). Each PoC urine test costs $20, with 84 tests = $1,600. Anticipate 67% testing Year 1 and 33% testing in Year 2.
Study Medical Officer	Research related (not routine clinical care) SMO activities include eligibility assessment x 60 participants (to recruit 30) at 1 hr per assessment = 60 hrs; plus 2 hrs SMO activity per participant enrolled (4 x 30 min reviews - one per medication condition for safety assessments) = 60 hrs for a total of 120 hrs over the course of the study (approximately 50% year 1, 50% year 2). Funded at $300 per hr (NSW Health Staff Specialist rate including on-costs) = $36,000 total ($18,000 per annum).

Equipment Request Summary

Equipment Request Summary						
Item	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total**
	$	**$**				**$**

Equipment Request

Equipment Request	
Item	**Justification**