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The effects of cannabidiol on psychosocial stress, situational anxiety and nausea in a virtual reality environment: A protocol for a randomised clinical trial

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3 4	1	The effects of cannabidiol on psychosocial stress, situational anxiety and nausea in a
5 6	2	virtual reality environment: A protocol for a randomised clinical trial
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ABSTRACT

Introduction: The non-intoxicating plant-derived cannabinoid, cannabidiol (CBD), has demonstrated therapeutic potential in many clinical conditions, including epilepsy, anxiety and psychosis. Most successful clinical trials have utilised relatively high (\geq 300 mg) oral doses of CBD. Relatively few studies have investigated the efficacy of lower (<300 mg) oral doses, typical of those available in over-the-counter CBD products.

Methods: We present a protocol for a randomised, double-blind, placebo-controlled, parallel-group clinical trial investigating the effects of a low oral dose (150 mg) of CBD on acute psychosocial stress, situational anxiety, motion sickness and cybersickness in healthy individuals. Participants (n=74) will receive 150 mg of CBD or a matched placebo 90 minutes before completing three virtual reality (VR) challenges (tasks) designed to induce transient stress and motion sickness: (1) a 15-minute "Public Speaking" task; (2) a 5-minute "Walk the Plank" task (above a sheer drop); and (3) a 5-minute "Rollercoaster Ride" task. The primary outcomes will be self-reported stress and nausea measured on 100-mm visual analogue scales. Secondary outcomes will include salivary cortisol concentrations, skin conductance, heart rate, and vomiting episodes (if any). Statistical analyses will test the hypothesis that CBD reduces nausea and attenuates subjective, endocrine, and physiological responses to stress compared to placebo. This study will indicate whether low-dose oral CBD has positive effects in reducing acute psychosocial stress, situational anxiety, motion sickness and cybersickness.

Ethics and dissemination: The University of Sydney Human Research Ethics Committee has granted approval (2023/307, Version 1.5, 28th September 2023). Study findings will be disseminated in a peer-reviewed journal and at academic conferences.

Trial Registration Number: ACTRN12623000872639 (ANZCTR public trials registry, registered 15th August 2023).

Keywords: cannabidiol (CBD), nausea, anxiety, virtual reality.

1 2		
3 4	58	STRENGTHS AND LIMITATIONS OF THIS STUDY
5 6	59	
7	60	• This study will use a robust randomised, double-blind, placebo-controlled design to
9	61	investigate the effects of a low oral dose (150 mg) of cannabidiol.
10 11	62	• Virtual reality (VR) will be used to administer safe, realistic, and precisely reproducible
12 13	63	test paradigms that induce transient stress and nausea in healthy volunteers.
14 15	64	• This study will provide novel insights into the potential efficacy of low doses of CBD to
16 17	65	ameliorate stress and nausea, with possible relevance to clinical populations.
18	66	• The study only involves a single test session in a laboratory environment and may,
19 20	67	therefore, lack ecological validity.
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1. INTRODUCTION

> Cannabidiol (CBD) is a non-intoxicating constituent of the *Cannabis sativa* plant [1, 2]. It has a good safety and tolerability profile [3-7] and a diverse range of pharmacological targets, including the serotonin receptors (e.g., 5-HT1A), G protein-coupled receptors (e.g., GPR55 and GPR18) and transient receptor potential ion channels (e.g. TRPA1) [8-10]. CBD has demonstrated therapeutic potential in several clinical conditions [4, 5], including anticonvulsant effects in paediatric epilepsy [11-13], anxiolytic effects in anxiety disorders [14, 15], antipsychotic effects in schizophrenia [16, 17] and "anti-addiction" effects in substance use disorders [18, 19]. These clinical benefits are typically observed at relatively high oral doses of CBD (e.g., ~300-1500mg) [4, 5].

In regions such as North America and Europe, CBD is available as both a prescription drug and a 'nutraceutical product' [20]. These nutraceutical or "wellness" products are typically oral formulations (e.g., oils, capsules, gummies) that contain low doses of CBD (i.e., ≤150 mg/day) and are widely available in health food stores and pharmacies [20, 21]. In Australia, regulation of "low-dose CBD products" (containing $\leq 150 \text{ mg/day}$) was recently eased to allow patients without a prescription access to registered products in pharmacies. However, registration of such products requires approval by Australia's medicines regulator based on demonstrated efficacy and safety [22]. With no products having been registered in the \sim 3 years since these regulatory changes were enacted (December 2020) [22], questions about whether CBD can demonstrate efficacy at these lower doses have been raised.

Indeed, a recent review found little high-quality evidence to support the efficacy of CBD (in any conditions) at doses ≤ 200 mg. This review acknowledged, however, that such doses were under-studied [21]. Some promising results have been obtained with public speaking tasks designed to induce "psychosocial stress" in healthy volunteers when 300 mg CBD was administered [23, 24]. Therefore, further research investigating the anxiolytic effects of low to moderate oral doses of CBD is warranted. It should be noted that the oral bioavailability of CBD is limited (~13-19%) [25]; therefore, oral formulations containing constituents that enhance the oral bioavailability of CBD may allow greater efficacy at lower doses; such a formulation will be used in the current study.

⁵⁷ 118 Virtual reality (VR) technologies are increasingly being used to investigate ⁵⁹ 119 psychosocial stress and anxiety in laboratory studies [26, 27]. This approach allows for Page 5 of 38

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minimal resourcing relative to "real-world" studies, customisable and reproducible test paradigms and the accurate monitoring and recording of key outcomes [27, 28]. Furthermore, VR provides the advantage of simulating physiologically-provoking activities without real danger e.g., walking a plank over a sheer drop. However, the use of VR is often accompanied by motion sickness (a pattern of symptoms that arise from exposure to stimuli involving significant visual or physical motion) and cybersickness (a sub-type of motion sickness that arises specifically due to exposure to VR) [29-32]. Interestingly, CBD has shown anti-nausea and anti-emetic effects in preclinical studies involving laboratory animals [33-35] and in human studies when used in combination with Δ^9 -tetrahydrocannabinol to treat chemotherapy-induced nausea and vomiting [36]. Accordingly, the current study will investigate CBD's possible anti-nausea effects in participants by exposure to VR scenarios [27].

We have developed a series of three unique VR challenges for the current trial. The "Public Speaking" task was adapted from studies that explored the anxiolytic effects of CBD during public speaking challenges [23, 24, 37] and will allow us to determine the effects of CBD during social threat (i.e., psychosocial stress). The 5-minutes "Walk the Plank" task has been modified from previous VR studies requiring participants to walk along a narrow virtual plank above a precipitous drop, inducing physiological markers of acute anxiety [38-40] (i.e., "situational anxiety"). Finally, the "Rollercoaster Ride" task challenges participants to complete two rounds of a virtual rollercoaster ride and has been modelled from VR rollercoaster ride paradigms that have been reliably used to induce motion sickness and cybersickness in participants [30, 41, 42].

In summary, the current protocol describes a study that aims to investigate the effects of low-dose (150 mg) CBD versus placebo on virtual reality (VR)-induced acute psychosocial stress, situational anxiety, acute motion sickness and cybersickness in healthy individuals.

- 2. METHODS
- 2.1 Study design

This study is a randomised, double-blind, placebo-controlled, parallel-group, clinical trial comparing the efficacy of low-dose CBD (150 mg) versus placebo. The study is known as the CAPSTAN (Cannabidiol for Acute Psychosocial Stress and Nausea) clinical trial. A crossover

design was deemed unsuitable due to the high likelihood of trial-order effects (e.g., habituation to the VR scenarios) [30]. The trial sponsor is the University of Sydney, and the trial site is the Brain and Mind

Centre in Sydney, Australia. The study has been approved by the University of Sydney Human Research Ethics Committee (HREC; 2023/307, Version 1.5, 28th September 2023) and registered on the Australian New Zealand Clinical Trials Registry (ACTRN12623000872639, 15th August 2023). The study is financially supported by the Lambert Initiative for Cannabinoid Therapeutics, a philanthropically funded centre for cannabinoid research at the University of Sydney. Recruitment commenced on 9th October 2023 and is anticipated to conclude in mid-2024.

2.2 Participant Population

2.2.1 Inclusion Criteria

We aim to recruit 74 participants who will be: (a) healthy adults aged between 18 and 50 years; (b) proficient in English and able to provide informed consent; (c) residing in the Greater Sydney region of New South Wales, Australia; and (d) willing to follow the protocol requirements.

2.2.2 Exclusion Criteria

The following exclusion criteria will apply:

- a. Self-reported regular use (i.e., more than twice weekly) of:
 - i. Cannabinoid-containing products (e.g., cannabis or CBD)
- Psychotropic drugs (prescriptive or illicit) (e.g., cannabis, amphetamines, ii. cocaine, ecstasy (MDMA), LSD (acid), antidepressants, antiepileptics, opioids, benzodiazepines)
 - Medication that may affect the stress response (e.g., corticosteroids, betaiii. blockers)
 - b. Self-reported history of allergic reaction (e.g., urticaria or anaphylaxis) to cannabis or cannabinoid-containing products.

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1 2		
3 4	179	c. Self-reported history of liver disease, renal disease, epilepsy or heart disease
5	180	(excluding medically controlled high blood pressure <140/90mmHg).
7	181	d. Current (i.e., within the past 2 weeks) otologic (vestibular) disease.
8 9 10	182	e. A history of repeated episodes of syncope.
10 11	183	f. Pregnant, lactating, or trying to conceive.
12 13	184	g. Self-reported history of drug and/or alcohol dependence (or suspected drug and/or
14 15 16	185	alcohol dependence as determined by the trial physician).
16 17	186	h. A medically diagnosed anxiety disorder (e.g., social anxiety disorder) within the past
18	187	12 months.
20	188	i. Current suicidal ideation (i.e., a score >0 on Question 9 of the Patient Health
21 22	189	Questionnaire) or suspected suicidal ideation as determined by the trial physician.
23 24	190	j. Current depression, anxiety, and stress scores outside the 'healthy range' on the
25 26 27 28 29 30	191	Depression Anxiety Stress Scale-21 [43] (i.e., > moderate scores for depression (>20),
	192	anxiety (>14) and stress (>25)).
	193	k. An uncontrolled chronic medical condition (mental or physical).
30 31	194	I. Self-reported high vulnerability to cybersickness or motion sickness.
32 33	195	m. Frequent (i.e., more than weekly) use of VR technologies, which tends to produce
33 34 35 36	196	desensitisation towards cybersickness [30].
36 37	197	n. Self-reported intense fear of heights.
38 39	198	
40 41 42	199	2.2.3 Recruitment and Retention
43	200	Participants will be recruited via social media, word of mouth, printed or online
44 45	201	study advertisements and direct emails to individuals who have previously registered their
46 47	202	interest in participating in clinical trials with the Lambert Initiative for Cannabinoid
48 49	203	Therapeutics. Participation is voluntary, and participants can withdraw at any time.
50 51	204	Participants will be reimbursed with a \$200 gift voucher as compensation for time and
52 53	205	expenses incurred as a result of study participation.
55 54	206	
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207 2.3 Treatments

The treatments will be purchased from Avecho Biotechnology Limited (Clayton, Victoria), manufactured (Catalent Pharma Solutions, St. Petersburg, FL), as well as packaged and labelled (Central Pharmacy Logistics, Coburg North, VIC) at GMP-licenced facilities, stored at the Brain and Mind Centre (in a secure, temperature-controlled room), and dispensed by the trial coordinator (who is also a registered pharmacist) and another blinded investigator.

As this trial utilises a non-clinical (healthy) population, a placebo comparator is the most suitable and ethical choice. Accordingly, an acute dose of CBD (as opposed to chronic administration) will be utilised. Indeed, the treatment of many ailments utilises an *ad hoc* treatment regime.

2.3.1 Intervention

The investigational product (Avecho Biotechnology Limited, Victoria, Australia) is an oil-based, soft-gel capsule. Each gel capsule contains 75 mg of pure, synthetic (-)-CBD enantiomer and 75 mg of 'Tocopheryl Phosphate Mixture' (TPM®) in medium chain triglyceride (MCT) oil. TPM® is a proprietary blend of tocopherol phosphates that has been shown to increase the bioavailability of lipid-soluble substances [44, 45]. The capsules will not contain any other cannabinoids or cannabis constituents.

³⁷ 225

226 2.3.1a Safety

CBD is generally considered to have a good safety profile [3, 4, 21, 46, 47]. In previous studies, 150 mg CBD caused a very low frequency of mild adverse events that did not differ from placebo [21]. The current study's comprehensive screening and exclusion criteria aims to reduce the likelihood of adverse events.

48 231

- 50 232 2.3.1b Dose 51
 - 233 A dose of 150 mg of CBD (i.e., two soft-gel capsules) will be administered orally.
- ⁵⁵ 56 235 2.3.1c Control

57
58236The control is a matched placebo. The placebo is identical to the intervention but59
60237contains no CBD and will also be administered via oral ingestion.

2.3.2 Randomisation, Allocation Concealment and Blinding

Participants will be randomised to one of two possible treatments in a 1:1 ratio at the beginning of their test day. Specifically, they will be assigned a unique randomisation number that is linked to a treatment via a pre-populated randomisation schedule. The schedule will be generated in seven balanced blocks of 10 and one balanced block of four by an independent statistician using an online random number generator and stored in a password-protected system inaccessible to blinded study personnel (centralised computerised randomisation). The schedule will only be available to the statistician, an independent researcher and the company that will package and label the treatments (Central Pharmacy Logistics, Coburg North, Victoria).

Treatment allocation will be concealed using numbered containers (or 'sachets'). Each 'dose' will be packaged in a separate, opaque, aluminium sachet labelled with a unique randomisation number.

As this is a double-blind study, participants and the remainder of the research team will not be aware of the assigned treatment. In the event of an emergency, the principal investigator or trial physician may request the unblinding of a participant for medical care.

2.4 Eligibility Screening

A Study Flowchart is presented in Figure 1. Willing volunteers will consent to and complete a comprehensive online Screening Questionnaire in REDCap[™] (~20 minutes). The questionnaire will assess their eligibility to participate. Each volunteer who attempts the Screening Questionnaire will be assigned a unique screening number to anonymise their identifying information. The trial physician will review volunteers' responses and decide on their eligibility for the trial. They will document their decision by completing an Eligibility Declaration form and a prescription for the trial drug (valid only when the volunteer has been randomised).

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[INSERT FIGURE 1 HERE]

Figure 1. Study flowchart summarising the screening, enrolment and randomisation of participants in the CAPSTAN trial.

2.5 Enrolment

Eligible participants will be invited to complete a telehealth interview with the trial coordinator. Here, they will receive detailed information about the trial procedures and risks and be informed that their enrolment requires a negative urine drug and pregnancy screen at the start of the experimental procedures (i.e., the "Test Day"). The trial coordinator will invite the volunteer to ask questions and to discuss participation in the trial with the trial doctor, or to take additional time to consider their decision to participate. Once the trial coordinator is confident that the volunteer understands the requirements of the trial, they will request that the participant sign the informed consent form. The trial coordinator will then counter-sign the consent form, collect basic demographic information and book the participant for a Test Day.

- **2.6 Experimental Procedure**
- Each participant will complete one Test Day (~3 hours) at the Brain and Mind Centre at the University of Sydney (Table 1).

Time (minutes) from start	Approximate Duration	Activity
0	10 min	Introduction and pre-trial compliance checks
10	5 min	Randomisation
15	15 min	Pre-treatment measures
30	10 min	CBD or placebo administration and caloric beverag
40	50 min	Rest period 1
90	15 min	Virtual reality orientation
105	15 min	Baseline measures
120	15 min total (2 min) (3 min) (5 min) (5 min)	Public Speaking task: Instructions Speech preparation Speech delivery Arithmetic challenge
135	10 min	Rest period 2
145	5 min total (2 min) (3 min)	Walk the Plank task: Instructions Walk the Plank task
150	10 min	Rest period 3
160	5 min total (2 min) (3 min)	Rollercoaster Ride task: Instructions Rollercoaster ride task
165	10 min	Rest period 4
175	15 min	Study Close
190	-	End Of Test Day

2.6.1 Standardisation Procedures

Prior to each onsite Test Day, participants will be instructed to: (a) abstain from alcohol (\geq 24 h); (b) avoid greater than one standard serving of caffeine at least 2-hours before the Test Day; (c) ensure they are well hydrated; and (d) ensure that they are adequately fed by consuming a meal at least 2 hours before arrival to the Test Day. These factors aim to reduce the likelihood of malaise, gastrointestinal disturbances or heightened anxiety on the Test Day.

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2.6.2 Compliance Checks

Participants will complete a urinary drug screen (to identify any recent use of cannabis and other psychoactive substances such as cocaine, ecstasy (MDMA), amphetamines, benzodiazepines and opioids) and, if they are female, a urine pregnancy screen, on arrival at the study site. The trial coordinator will also confirm compliance with the standardisation procedures and if there have been any changes to the participant's health status or medication use since the last contact. Participants who meet these requirements will be randomised; those who do not may be invited to return at another time if suitable.

2.6.3 Experimental Procedures

Following randomisation, participants will be fitted with the Equivital EQ02+ LifeMonitor belt and the VR headset (detailed below). There will then be a 10-minute collection of pre-treatment measures (see Study Outcomes below). After this, the VR headset and Equivital EQ02+ LifeMonitor belt will be temporarily removed, the treatment administered, and the participant provided with a standardised caloric beverage (i.e., 500 mL "Up & Go Liquid Breakfast", Sanitarium, Berkeley Vale NSW, Australia) to consume. This beverage aims to potentiate the absorption of CBD in the gastrointestinal tract [6, 48-50] and provide participants with sustenance during the test session. Participants will be provided with a rest period of approximately 50 minutes, during which they will be left alone in a quiet reception area and encouraged to undertake some low-stress reading; this delay is aimed at allowing CBD plasma concentrations to approach a near-maximal level [48]. Following this, participants will be provided with instructions on the three VR tasks and the functionality of the VR hardware during a 15-minute "VR Orientation" session. The VR headset and Equivital EQ02+ LifeMonitor belt will then be re-fitted for a 10-minutes collection of the pre-task measures. The devices will remain fitted to participants until the end of the experimental procedure.

2.6.4 Virtual Reality Tasks

The three tasks developed for this clinical trial are the "Public Speaking" task (for psychosocial stress), the "Walk the Plank" task (for situational anxiety) and the "Rollercoaster

Ride" task (for motion sickness). Although these exact VR tasks have not been previously used
in clinical trials or laboratory studies, similar tasks have been reported in the broader scientific
literature [27, 30, 38-40, 51].

The 15-minute "Public Speaking" task was modelled on previous studies that found CBD to have anxiolytic effects during public speaking challenges [23, 24, 37] and the Trier Social Stress Test (TSST) [52]. The abovementioned public speaking tasks varied in their methodology and involved either "simulated" public speaking tasks whereby participants delivered a speech in front of a video camera or real-life tasks where participants delivered speeches to a live audience [23, 24, 37]. Conversely, the TSST is a structured stress paradigm involving a 10-minute speech preparation period followed by a 10-minute test period during which participants complete a 5-minute job application speech followed by 5 minutes of mental arithmetic [53]. The TSST reliably induces psychosocial stress (i.e., stress involving the perception of one's worth, competence, or status by others) and results in an acute and reliable cortisol response in most participants [53-55]. In one study, a VR adaption of the TSST elicited similar salivary cortisol and subjective stress responses to a real-life TSST, demonstrating that the two were equivalent [27]. The current study utilises a modified VR version of the TSST involving a panel of virtual judges who withhold all feedback or affirmation (Figure 2A).

The task involves a three-minute "speech preparation period" (i.e., "please mentally prepare a speech on what attributes and experience you have that makes you the ideal candidate for your dream role") and a 10-minute "test period" consisting of (a) five-minute speech delivery period (i.e., "please deliver your speech and aim to speak for the full five-minutes") and (b) a five-minute mental arithmetic challenge (i.e., "please calculate 2703 – 13. From the result, please subtract 13 again and state your answer out loud. Repeat this process a total of five times. At the end of this process, please recall all five of your answers aloud").

The five-minute "Walk the Plank" task requires participants to virtually walk across a narrow virtual plank between two skyscrapers. Participants will be advised that they have become stranded on the top of the building and are required to signal for help using the safety beacon placed at the opposite end of the plank. For this task, participants will walk up and down the length of the clinic room with their movement mapped to the virtual plank and guided by virtual boundaries, signifying a safe space (Figure 2B). VR studies utilising a similar

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366 challenge provided realistic experiences that induce physiological markers of stress that are
 367 consistent with acute anxiety (i.e., "situational anxiety") [38-40].

The five-minute "Rollercoaster Ride" task challenges participants to complete a virtual rollercoaster ride (**Figure 2C**). Participants will remain seated throughout this task and can indicate if they would like to stop the task early. Similar VR tasks have been shown to induce motion sickness in participants [30, 41, 42]. Motion sickness will be explored explicitly during the "Rollercoaster Ride" task, while cybersickness will be explored during all three VR scenarios.

375 [INSERT FIGURE 2A,2B AND 2C HERE]

Figure 2. (A) The panel of virtual judges from the "Public Speaking" task; (B) The roof of the building and plank from the "Walk the Plank" task; and (C) The view from the seat of the "Rollercoaster Ride" task.

2.6.5 Post Trial Procedures

After completing the final VR task, participants have a 10-minute recovery period. After this, they will be queried on any adverse events (AEs) experienced (i.e., "Have you experienced any unfavourable symptoms?"), What treatment do they think they received (i.e., CBD or placebo), and what are their confidence estimates (i.e., How sure are you of your guess on which treatment you received?"). All participants will be provided with the contact details of the research team to self-report any AEs over the next 24 hours. The trial coordinator or research assistant will record all adverse event reports using a REDCap[™] AE report form and communicate to the trial physician if required.

The occurrence of AEs will be discussed weekly with the trial physician. Furthermore, a blinded summary of AE reports will be emailed to the trial physician monthly, and the trial physician will indicate if the rate of AEs is unacceptably high. In the unlikely event of a severe adverse event (SAE), the trial physician and the principal investigator (PI) will be immediately notified, and all SAEs will be reported to the trial sponsor and the HREC within 72 hours.

1 2						
3 ∡	396	2.7 Data Collection				
5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20	397	A summary of the data collected during the CAPSTAN trial and time of collection is provided				
	398	in Figure 3				
	399					
	400	[INSERT FIGURE 3 HERE]				
	401					
	402	Figure 3. Data collected during the CAPSTAN trial "Test Day.				
	403	IPS = instructions for the "Public Speaking" task, SP = speech preparation, SD = speech delivery, AC =				
	404	arithmetic challenge, IWP = instructions for the "Walk the Plank" task, WPT = "Walk the Plank" task,				
	405	IRR = instructions for the "Rollercoaster Ride" task, RRT = "Rollercoaster Ride" task				
21 22	406					
22 23 24 25 26 27 28 29	407	2.7.1 Study Outcomes				
	408	The primary outcome measures include:				
	409	 Self-reported stress ratings on a VAS (<i>nervous 0-100</i>) 				
	410	 Self-reported nausea ratings on a VAS (nauseous 0-100) 				
30 31	411					
31 32 33 34 35 36 37 38 39 40	412	The secondary outcome measures include:				
	413	Salivary Cortisol				
	414	Heart rate				
	415	Skin Conductance				
	416	Vomiting or near-vomiting episodes				
41 42	417	 Self-reported anxiety ratings on VASs include: 				
43 44	418	○ (tense 0-100)				
45	419	○ (calm 0-100)				
40 47	420	○ (excited 0-100)				
48 49	421	○ (bored 0-100)				
50 51	422					
52 53	423	The exploratory (tertiary) outcome measures are:				
54 55	424	Salivary testosterone and progesterone				
55 56	425	• Eye-tracking data including:				
57 58	426	 The frequency and duration of eye-closing 				
59 60	427	\circ The frequency and duration of gaze at areas of interest				

2.7.2 Visual Analogue Scales (VASs)

VASs will be used to measure the two primary outcomes: self-reported stress (nervousness) and nausea. They will also be used to measure the secondary outcome of self-reported anxiety (as detailed below) (Figure 4). These measures will be recorded before drug administration (pre-treatment measurement), at baseline, prior to the delivery of instructions for each VR task, prior to the performance of the task and at completion of each VR task. All VASs will appear on the screen of the VR headset, and participants will use the VR hand controllers to click on the numerical value (0-100) that best describes their current state (Figure 4). Using such virtual scales allows seamless execution of self-report without disturbing the participant's sense of immersion within the virtual environment.

438 For a well-rounded exploration of CBD effects on anxiety, we have utilised VASs that
439 query participant's affect (i.e., the outward expression of an emotion) [56]. Here, we consider
440 1) the "valence" of an emotion (i.e., its positivity or negativity) and 2) the intensity of the
441 emotion (i.e., whether it is arousing or deactivating). This provides four self-reported anxiety
442 rating VASs, including:

- positively arousing (excited 0-100)
 - positively deactivating (calm 0-100)
- negatively arousing (tense 0-100)
 - negatively deactivating (bored 0-100)
- 448 [INSERT FIGURE 4 HERE]

Figure 4. Self-reported Visual Analogue Scales (VASs) as they appear on the virtual reality 451 headset. Values are provided by the participants by clicking on the scales using the hand 452 controllers.

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2.7.3 Salivary Cortisol, Testosterone and Progesterone

55455During the experimental procedure, oral fluid samples will be collected from56574565745658595945760Germany). These samples will be collected immediately before drug administration, before

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the first VR task, and after each VR task. Participants will be advised to open the Salivette[®]
tube, place the pad in their mouth for two minutes or until soaked with saliva, then return
the pad to the tube and firmly seal it. The samples will be centrifuged for 2 minutes at 1,000
x g and analysed simultaneously for cortisol (a secondary outcome) and testosterone and
progesterone (exploratory outcomes) using an in-house developed mass spectrometry (MS)
method [57, 58].

2.7.4 Heart Rate

Heart rate will be measured for 10 minutes immediately before drug administration (baseline measurement), for 10 minutes at baseline and continuously throughout all three VR tasks using the EQ02+ LifeMonitor and belt, as described in previous studies [59, 60] (Equivital Ltd, Cambridge, United Kingdom; https://www.adinstruments.com/partners/equivital). This is a wireless, medical-grade monitoring system that records a range of physiological measures (such as electrocardiogram, breathing rate, tri-axial acceleration, galvanic skin response, skin temperature) using a wearable vest and permits live data streaming and download using the LabChart software.

4 474

2.7.5 Skin Conductance

476 Skin conductance will be measured for 10 minutes immediately before drug
477 administration (baseline measurement), for 10 minutes at baseline and continuously
478 throughout all three VR tasks.

Skin conductance of the forehead will be measured using the Equivital GSR Sensor connected to the EQ02+ LifeMonitor and belt (as described above). Skin conductance of the fingers will be measured using MLT117F/10 GSR finger electrodes connected to a FE116 GSR Amp with a PLCF1 front-end interface used with PowerLab C software (ADInstruments, Oxford United Kingdom), a system used in previous studies [61, 62]. Research suggests that forehead skin conductance may correlate with motion sickness, while finger skin conductance correlates with acute stress [30, 63]. Therefore, both will be measured in the current study.

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2.7.6 Vomiting Episodes

488 The Test Day source document will record all vomiting episodes throughout the 489 experimental procedure.

2.7.6 Eye-tracking

Eye tracking data will be collected continuously throughout the VR tasks using the VR headset. These measures will provide highly precise, objective data by which to examine participant's compliance (frequency and duration of eye closing) and engagement and response (frequency and duration of gaze at areas of interest, that is, the panel of judges in the "Public Speaking" task or the plank in the "Walk the Plank" task) during the VR challenges [64]. Gazing at pre-defined points of interest (e.g., the judges in the "Public Speaking" task or the plank in the "Walk the Plank" task) is based on the "Eye-Mind Hypothesis" that describes the tendency for people to direct their gaze towards what they are thinking about [64-66]. Both eye closing and gaze away from points of interest may correlate to fear or avoidance behaviours [67].

503 2.9 Data Management

Participant information collected for this trial will be securely stored and treated as confidential. Participants' identifying information will be anonymised using unique codes: initially, a screening number and, later, a randomisation number. The key to these codes will be securely stored in password-protected files inaccessible from the internet. Clinical trial data will be collected and managed using the Research Electronic Data Capture (REDCap[™]) web-based system, a secure, online program supported by the University of Sydney; access is password-protected and will only be available to approved research staff. Hard copies of patient data will be securely stored in locked filing cabinets at the study site. Only the study investigators have access to the participant data. All trial data will be stored securely for at least 15 years. The findings of this clinical trial will be disseminated via conferences, publications, and media, as applicable. Participants will be informed of the results of the study at the conclusion of the trial. No participants will be identified in any report or publication of this study or its results.

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518 2.10 Data and Safety Monitoring

519 Data monitoring will occur monthly for all new participant entries logged into the 520 REDCap system; a designated team member will adhere to a standardised process of data 521 review, raising queries and locking forms once the review has been completed. Safety 522 monitoring of AEs will be managed according to sponsor and HREC requirements. As this is a 523 small, single-centre, low risk, clinical trial utilising an acute, low-dose CBD, an independent 524 data safety monitoring committee will not be formed. However, an independent 'Expert 525 Group' has been formed and will be consulted by the research team and HREC in the unlikely 526 instance of a severe adverse event. The Expert Group comprises three research physicians 527 with extensive experience with CBD clinical trials. The decision to terminate the trial lies with 528 the principal investigator based on safety data and recruitment targets.

530 2.11 Roles and Responsibilities

531 The study investigators have led the design of this study and are responsible for the 532 management and conduct of this clinical trial. The study investigators will conduct the analysis 533 and will make all publication-related decisions.

535 2.12 Statistical Methods

537 2.5.1 Sample Size Estimation

538 The target sample size was determined a priori using power calculation software 539 (G*Power Version 3.1.9.6, University of Kiel, Germany). In an earlier investigation, Linares et 540 al. (2019) found that 150 mg CBD decreased subjective ratings of anxiety on the Visual 541 Analogue Mood Scale (VAMS) during a simulated public speaking test, albeit non-significantly 542 (Placebo: 18.6±15.9 mm, n=15; CBD: 7.6±15.5 mm; n=15; Cohen's d=0.70) [23].

543 Using an equivalent effect size (Cohen's d=0.70), a power (1-ß) of 0.8 and a two-sided 544 α =0.05, we estimate that n=68 participants will be required to detect a significant effect of 545 CBD on anxiety. Clinical trials conducted by the Lambert Initiative for Cannabinoid 546 Therapeutics have indicated participant retention of $\geq 90\%$ [48, 68]. Therefore, the n=74 547 will be recruited to account for attrition.

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2.5.2 Statistical Analysis Plan

The primary and secondary outcomes and eye-openness will be analysed using generalized linear mixed models (GLMM), while eye gaze will be analysed using a mixed-effects multinomial logistic regression. Treatment, Time and the Treatment × Time interaction will be included as fixed effects, and the participant will be included as a random effect, with other covartiates included as appropriate to improve goodness of fit (e.g., Sex, Age, Time of day). To refine the models, we will use corrected Akaike Information Criterion [69]. We will calculate Δm between models and exclude models with $\Delta m > 2$ as having substantially less support [70]. No covariance structure will be specified (unstructured). To identify the best distribution and link for the GLMM models, the data type, residual plots, Shapiro-Wilk normality test, Levene's test for Homogeneity of Variance, and Pearson's dispersion test will be used. Type III Wald chi-square tests will be used to generate main effects p-values. A priori planned uncorrected pairwise comparisons will be performed to compare:

subjective ratings of stress on a stress VAS (nervous 0-100) across treatments at • (Timepoint t=125 (SD), Figure 3)

- • subjective ratings of stress on a stress VAS (nervous 0-100) across treatments at (Timepoint t=147 (WPT), Figure 3)
- • subjective ratings of nausea on a nausea VAS (nauseous 0-100) across treatments at (Timepoint t=165, Figure 3)
- subjective ratings of nausea on a nausea VAS (nauseous 0-100) across treatments at • (Timepoint t=175, Figure 3)
- as these are the primary outcome measures.

Dunn-Šidák corrected pairwise comparisons will be performed where additional significant main and interaction effects are present. Statistical significance will be accepted as p<0.05. The statistical analysis plan will be finalised before the last participant Test Day and will be available on request.

3. CONCLUSION

The focus of the current study is a non-clinical (i.e., "healthy") population confronted with acute stressors such as delivering a speech (i.e., psychosocial stress), being exposed to

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heights (i.e., situational anxiety) or challenging vestibular stimulation (i.e., motion sickness and cybersickness) using VR. This is deemed noteworthy considering the popularity of over-the-counter, low-dose CBD "nutraceutical" or "wellness" products in many regions [20] and the lack of clinical trials investigating the efficacy of such products. This study will provide important practical insights that may inform the optimal use of low-dose CBD products that are accessed without a prescription. Findings from this study will help illuminate the efficacy of low-dose CBD in the four indications of interest and may provide insights into clinical populations that could benefit from low-dose CBD treatment.

4. STATEMENTS AND DECLARATIONS

Ethics and dissemination: The study has been approved by the University of Sydney Human 589 Research Ethics Committee (HREC; 2023/307, Version 1.5, 28th September 2023). The 590 findings of this clinical trial will be disseminated via conferences, publications, and media, as 591 applicable. Participants will be informed of the study's results at the trial's conclusion. No 592 participants will be identified in any report or publication of this study or its results.

Author Contributions

I.S.M, D.M, H.M, M.B.P, N.S.L, R.F and Z.B were involved in the conception and design of the
 research project. Z.B drafted the manuscript, and all authors were involved in critically
 revising it. I.S.M is the principal investigator who has overall responsibility for the design,
 conduct and decision to submit for publication. M.B.P is the study statistician, N.S.L will
 provide medical oversight, H.M and R.F created the virtual reality challenges in collaboration
 with I.S.M and Z.B. Z.B is the trial coordinator responsible for collecting trial data. All authors
 have read and approved the final manuscript.

48 602

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 54 606

57 607 **Competing Interests**

Author I.S.M. acts as a consultant to Kinoxis Therapeutics and has received honoraria from
 Janssen. He has also served as an expert witness in various medicolegal cases involving

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4	610	cannabis and cannabinoids. I.S.M. hold patents on cannabinoid therapies
5 6	611	(PCT/AU2018/05089 and PCT/AU2019/050554) and has received consulting fees from the
7 8	612	Medicinal Cannabis Industry Australia (MCIA). D.M. has also received consulting fees from
9	613	MCIA. Z.B, H.M N.S.L, R.F and M.B.P have no disclosures to report.
10 11	614	
12 13	615	Patient and public involvement
14 15	616	Patients and/or the public were not involved in the design, or conduct, or reporting or
15 16 17	617	dissemination plans of this research.
17	618	
19 20	619	Patient consent for publication
21 22	620	Not applicable.
23 24	621	
25	622	Trial Sponsor
26 27	623	The University of Sydney, Sydney NSW Australia.
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Figure 2. (A) The panel of virtual judges from the "Public Speaking" task

492x318mm (72 x 72 DPI)



Figure 2. (B) The roof of the building and plank from the "Walk the Plank" task 1711x962mm (38 x 38 DPI)

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Figure 2. (C) The view from the seat of the "Rollercoaster Ride" task.

1711x962mm (38 x 38 DPI)



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451x369mm (96 x 96 DPI)

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ltem No	Description	Manuscript Page and Notes
Administrative in	formatio		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	Yes, ANZCTR public trials registry, ACTRN12623000872639. Registered 15 August 2023.
Protocol version	3	Date and version identifier	2, 6 and 25
Funding	4	Sources and types of financial, material, and other support	6, 25
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1,25
	5b	Name and contact information for the trial sponsor	6
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	25
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	23
Introduction			
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Page	34	of	38
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Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5	
	6b	Explanation for choice of comparators	8	
Objectives	7	Specific objectives or hypotheses	6	
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5-6	
Methods: Particip	oants, ir			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6	
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6-7	
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8	
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	NA, intervention is a single acute dose of active or placebo with no ongoing involvement of participants.	
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	NA, intervention is a single acute dose of active or placebo with no ongoing involvement of participants.	
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	12-13	
Guicomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	19	
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Participant timeline	13Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)14Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations15Strategies for achieving adequate participant enrolment to reach target sample size		10 (Figure1) 23 7	
Sample size				
Recruitment				
		enforment to reach target sample size		
Methods: Assignr	nent of	interventions (for controlled trials)		
Methods: Assignr Allocation:	nent of	interventions (for controlled trials)		
Methods: Assignr Allocation: Sequence generation	nent of	interventions (for controlled trials) Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9	
Methods: Assignr Allocation: Sequence generation Allocation concealment mechanism	nent of 16a 16b	interventions (for controlled trials) Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9 9	

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Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	9
Methods: Data c	ollection	n, management, and analysis	
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	22
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	7,17
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	22-23
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	23-24
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	23-24
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	23-24
Methods: Monito	oring		

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	23	
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA	
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	17	
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	22-23	
Ethics and dissen	ninatior			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	2, 6, 25	
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	6	
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11	
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA	
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	22	

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Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	25
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	22
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	17
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	22
	31b	Authorship eligibility guidelines and any intended use of professional writers	23
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	23
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	NA
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "<u>Attribution-NonCommercial-NoDerivs 3.0 Unported</u>" license.

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The effects of cannabidiol on psychosocial stress, situational anxiety and nausea in a virtual reality environment: A protocol for a single-centre randomised clinical trial

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Complete List of Authors:	Bawa, Zeeta; The University of Sydney Lambert Initiative for Cannabinoid Therapeutics; The University of Sydney Brain and Mind Centre McCartney, Danielle; The University of Sydney Lambert Initiative for Cannabinoid Therapeutics; The University of Sydney Brain and Mind Centre Bedoya-Pérez, Miguel; The University of Sydney Lambert Initiative for Cannabinoid Therapeutics, School of Psychology, The University of Sydney, Sydney, New South Wales, Australia; The University of Sydney Brain and Mind Centre Lau, Namson; The Boden Initiative, Charles Perkins Centre, The University of Sydney, NSW, Sydney, Australia Fox, Richard; Yellow Dog Man Studios s.r.o, Ostrava-jih-Zábřeh, Czechia MacDougall, Hamish; RPA Institute of Academic Surgery, Sydney Local Health District McGregor, Iain; The University of Sydney Lambert Initiative for Cannabinoid Therapeutics
Primary Subject Heading :	Pharmacology and therapeutics
Secondary Subject Heading:	General practice / Family practice
Keywords:	Stress, Psychological, Stress, Physiological, Clinical Trial

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27 ABSTRACT

 Introduction: The non-intoxicating plant-derived cannabinoid, *cannabidiol* (CBD), has demonstrated therapeutic potential in a number of clinical conditions. Most successful clinical trials have utilised relatively high (≥ 300 mg) oral doses of CBD. Relatively few studies have investigated the efficacy of lower (<300 mg) oral doses, typical of those available in over-thecounter CBD products.

Methods: We present a protocol for a randomised, double-blind, placebo-controlled, parallel-group clinical trial investigating the effects of a low oral dose (150 mg) of CBD on acute psychosocial stress, situational anxiety, motion sickness and cybersickness in healthy individuals. Participants (n=74) will receive 150 mg of CBD or a matched placebo 90 minutes before completing three virtual reality (VR) challenges (tasks) designed to induce transient stress and motion sickness: (1) a 15-minute "Public Speaking" task; (2) a 5-minute "Walk the Plank" task (above a sheer drop); and (3) a 5-minute "Rollercoaster Ride" task. The primary outcomes will be self-reported stress and nausea measured on 100-mm visual analogue scales. Secondary outcomes will include salivary cortisol concentrations, skin conductance, heart rate, and vomiting episodes (if any). Statistical analyses will test the hypothesis that CBD reduces nausea and attenuates subjective, endocrine, and physiological responses to stress compared to placebo. This study will indicate whether low-dose oral CBD has positive effects in reducing acute psychosocial stress, situational anxiety, motion sickness and cybersickness.

Ethics and dissemination: The University of Sydney Human Research Ethics Committee has 49 granted approval (2023/307, Version 1.6, 16th February 2024). Study findings will be 50 disseminated in a peer-reviewed journal and at academic conferences.

52 Trial Registration Number: ACTRN12623000872639 (ANZCTR public trials registry, registered
53 15th August 2023).

Keywords: cannabidiol (CBD), nausea, anxiety, virtual reality.

2 3	57	STRENGTHS AND LIMITATIONS OF THIS STUDY
4 5	58	
6 7	59	• This study will use a rigorous randomised double-blind placebo-controlled design to
8	60	investigate the effects of a low oral dose (150 mg) of cannabidiol
9 10	61	The date of expendicial provided (i.e. 150 mg) will be comparable to these swellable
11 12	01	• The dose of cannabidior provided (i.e., 150 mg) will be comparable to those available
13 14	62	over-the-counter in many countries.
15	63	 Virtual reality (VR) will be used to administer safe, realistic, and precisely reproducible
16 17	64	test paradigms that induce transient stress and nausea in volunteers.
18 19	65	 Blood samples will not be obtained to verify plasma cannabidiol concentrations as
20 21	66	venepuncture has the potential to induce extraneous stress.
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1. INTRODUCTION

Cannabidiol (CBD) is a non-intoxicating constituent of the *Cannabis sativa* plant [1, 2]. It has a good safety and tolerability profile [3-7] and a diverse range of pharmacological targets, including the serotonin receptors (e.g., 5-HT1A), G protein-coupled receptors (e.g., GPR55 and GPR18) and transient receptor potential ion channels (e.g. TRPA1) [8-10]. CBD has demonstrated therapeutic potential in several clinical conditions [4, 5], including anticonvulsant effects in paediatric epilepsy [11-13], anxiolytic effects in anxiety disorders [14, 15], antipsychotic effects in schizophrenia [16, 17] and "anti-addiction" effects in substance use disorders [18, 19]. These clinical benefits are typically observed at relatively high oral doses of CBD (e.g., ~300-1500mg) [4, 5].

In regions such as North America and Europe, CBD is available as both a prescription drug and a 'nutraceutical product' [20]. These nutraceutical or "wellness" products are typically oral formulations (e.g., oils, capsules, gummies) that contain low doses of CBD (i.e., ≤150 mg/day) and are widely available in health food stores and pharmacies [20, 21]. In Australia, regulation of "low-dose CBD products" (containing $\leq 150 \text{ mg/day}$) was recently eased to allow patients without a prescription access to registered products in pharmacies. However, registration of such products requires approval by Australia's medicines regulator based on demonstrated efficacy and safety [22]. With no products having been registered in the \sim 3 years since these regulatory changes were enacted (December 2020) [22], questions about whether CBD can demonstrate efficacy at these lower doses have been raised.

Indeed, a recent review found little high-quality evidence to support the efficacy of CBD (in any conditions) at doses ≤ 200 mg. This review acknowledged, however, that such doses were under-studied [21]. Some promising results have been obtained with public speaking tasks designed to induce "psychosocial stress" in healthy volunteers when 300 mg CBD was administered [23, 24]. Therefore, further research investigating the anxiolytic effects of low to moderate oral doses of CBD is warranted. It should be noted that the oral bioavailability of CBD is limited (~13-19%) but may be enhanced by certain lipid-rich formulations or by administration with fatty foods [6, 25]. The current study will utilise a proprietary blend of tocopherol phosphates (so called 'Tocopheryl Phosphate Mixture' (TPM®)), which has been shown to increase the bioavailability of lipid-soluble substances [26, 27].

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Virtual reality (VR) technologies are increasingly being used to investigate psychosocial stress and anxiety in laboratory studies [28, 29]. This approach allows for minimal resourcing relative to "real-world" studies, customisable and reproducible test paradigms and the accurate monitoring and recording of key outcomes [29, 30]. Furthermore, VR provides the advantage of simulating physiologically-provoking activities without real danger e.g., walking a plank over a sheer drop. However, the use of VR is often accompanied by motion sickness (a pattern of symptoms that arise from exposure to stimuli involving significant visual or physical motion) and cybersickness (a sub-type of motion sickness that arises specifically due to exposure to VR) [31-34]. CBD has shown anti-nausea and anti-emetic effects in preclinical studies involving laboratory animals [35-37]. Interestingly, two of these studies demonstrated that CBD administered intraperitoneally at low doses (2.5 - 10 mg/kg) but not higher doses (25 and 40 mg/kg) reduced toxin-induced vomiting in house musk shrews [35, 36]. CBD also reduced vomiting in human studies when used in combination with Δ^9 -tetrahydrocannabinol to treat chemotherapy-induced nausea and vomiting [38]. Accordingly, the current study will investigate CBD's possible anti-nausea effects in participants by exposure to VR scenarios [29].

We have developed a series of three unique VR challenges for the current trial. The "Public Speaking" task was adapted from studies that explored the anxiolytic effects of CBD during public speaking challenges [23, 24, 39] and will allow us to determine the effects of CBD during social threat (i.e., psychosocial stress). The 5-minutes "Walk the Plank" task has been modified from previous VR studies requiring participants to walk along a narrow virtual plank above a precipitous drop, inducing physiological markers of acute anxiety [40-42] (i.e., "situational anxiety"). Finally, the "Rollercoaster Ride" task challenges participants to complete two rounds of a virtual rollercoaster ride and has been modelled from VR rollercoaster ride paradigms that have been reliably used to induce motion sickness and cybersickness in participants [32, 43, 44].

In summary, the current protocol describes a study that aims to investigate the effects of low-dose (150 mg) CBD versus placebo on virtual reality (VR)-induced acute psychosocial stress, situational anxiety, acute motion sickness and cybersickness in healthy individuals.

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2. METHODS

2.1 Study design

This study is a randomised, double-blind, placebo-controlled, parallel-group, clinical trial comparing the efficacy of low-dose CBD (150 mg) versus placebo. The study is known as the CAPSTAN (Cannabidiol for Acute Psychosocial Stress and Nausea) clinical trial. A crossover design was deemed unsuitable due to the high likelihood of trial-order effects (e.g., habituation to the VR scenarios) [32].

The trial sponsor is the University of Sydney, and the trial site is the Brain and Mind Centre in Sydney, Australia. The study has been approved by the University of Sydney Human Research Ethics Committee (HREC; 2023/307, Version 1.6, 16th February 2024) and registered on the Australian New Zealand Clinical Trials Registry (ACTRN12623000872639, 15th August 2023). The study is financially supported by the Lambert Initiative for Cannabinoid Therapeutics, a philanthropically funded centre for cannabinoid research at the University of Sydney. Recruitment commenced on 9th October 2023 and is anticipated to conclude in mid-2024. ere.

2.2 Participant Population

2.2.1 Inclusion Criteria

We aim to recruit 74 participants who will be: (a) healthy adults aged between 18 and 50 years; (b) proficient in English and able to provide informed consent; (c) residing in the Greater Sydney region of New South Wales, Australia; and (d) willing to follow the protocol requirements.

2.2.2 Exclusion Criteria

- The following exclusion criteria will apply:
 - a. Self-reported regular use (i.e., more than twice weekly) of:
 - i. Cannabinoid-containing products (e.g., cannabis or CBD)

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	ii.	Psychotropic drugs (prescriptive or illicit) (e.g., cannabis, amphetamines,
		cocaine, ecstasy (MDMA), LSD (acid), antidepressants, antiepileptics, opioids,
		benzodiazepines)
	iii.	Medication that may affect the stress response (e.g., corticosteroids, beta-
		blockers)
b.	Self-re	eported history of allergic reaction (e.g., urticaria or anaphylaxis) to cannabis or
	canna	binoid-containing products.
c.	Self-re	eported history of liver disease, renal disease, epilepsy or heart disease
	(medi	cally controlled high blood pressure <140/90mmHg is acceptable).
d.	Curre	nt (i.e., within the past 2 weeks) otologic (vestibular) disease.
e.	A hist	ory of repeated episodes of syncope.
f.	Pregn	ant, lactating, or trying to conceive.
g.	Self-re	eported history of drug and/or alcohol dependence (or suspected drug and/or
	alcoho	ol dependence as determined by the trial physician).
h.	A med	dically diagnosed anxiety disorder (e.g., social anxiety disorder) within the past
	12 mc	onths.
i.	Curre	nt suicidal ideation (i.e., a score >0 on Question 9 of the Patient Health
	Quest	ionnaire) or suspected suicidal ideation as determined by the trial physician.
j.	Curre	nt depression, anxiety, and stress scores outside the 'healthy range' on the
	Depre	ession Anxiety Stress Scale-21 [45] (i.e., > moderate scores for depression (>20),
	anxiet	ry (>14) and stress (>25)).
k.	A chro	onic medical condition (mental or physical) that is uncontrolled i.e., has been
	either	newly diagnosed, or previously diagnosed and remains symptomatic.
I.	Self-re	eported high vulnerability to cybersickness or motion sickness.
m.	Frequ	ent (i.e., more than weekly) use of VR technologies, which tends to produce
	desen	sitisation towards cybersickness [32].
n.	Self-re	eported intense fear of heights.
2.3 F	ecruiti	ment and Retention
	Partic	ipants will be recruited via social media, word of mouth, printed or online
udy a	adverti	sements and direct emails to individuals who have previously registered their

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interest in participating in clinical trials with the Lambert Initiative for Cannabinoid

Therapeutics. Participation is voluntary, and participants can withdraw at any time.

Participants will be reimbursed with a \$200 gift voucher as compensation for time and

2.3 Treatments

The treatments will be purchased from Avecho Biotechnology Limited (Clayton, Victoria), manufactured (Catalent Pharma Solutions, St. Petersburg, FL), as well as packaged and labelled (Central Pharmacy Logistics, Coburg North, VIC) at GMP-licenced facilities, stored at the Brain and Mind Centre (in a secure, temperature-controlled room), and dispensed by the trial coordinator (who is also a registered pharmacist) and another blinded investigator.

expenses incurred as a result of study participation.

As this trial utilises a non-clinical (healthy) population, a placebo comparator is the most suitable and ethical choice. Accordingly, an acute dose of CBD (as opposed to chronic administration) will be utilised. Indeed, the treatment of many ailments utilises an *ad hoc* treatment regime.

2.3.1 Int

2.3.1 Intervention

The investigational product (Avecho Biotechnology Limited, Victoria, Australia) is an oil-based, soft-gel capsule. Each gel capsule contains 75 mg of pure, synthetic (-)-CBD enantiomer and 75 mg of TPM[®] in medium chain triglyceride (MCT) oil. The capsules do not contain any other cannabinoids or cannabis constituents.

228 2.3.1a Safety

CBD is generally considered to have a good safety profile [3, 4, 21, 46, 47]. In previous studies, 150 mg CBD caused a very low frequency of mild adverse events that did not differ from placebo [21]. The current study's comprehensive screening and exclusion criteria aims to reduce the likelihood of adverse events.

56 234 2.3.1b Dose

A dose of 150 mg of CBD (i.e., two soft-gel capsules) will be administered orally.
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2.3.1c Control

The control is a matched placebo. The placebo is identical to the intervention but contains no CBD and will also be administered via oral ingestion.

2.3.2 Randomisation, Allocation Concealment and Blinding

Participants will be randomised to one of two possible treatments in a 1:1 ratio at the beginning of their test day. Specifically, they will be assigned a unique randomisation number that is linked to a treatment via a pre-populated randomisation schedule. The schedule will be generated in seven balanced blocks of 10 and one balanced block of four by an independent statistician using an online random number generator and stored in a password-protected system inaccessible to blinded study personnel (centralised computerised randomisation). The schedule will only be available to the statistician, an independent researcher and the company that will package and label the treatments (Central Pharmacy Logistics, Coburg North, Victoria).

Treatment allocation will be concealed using numbered containers (or 'sachets'). Each 'dose' will be packaged in a separate, opaque, aluminium sachet labelled with a unique randomisation number.

As this is a double-blind study, participants and the remainder of the research team will not be aware of the assigned treatment. In the event of an emergency, the principal investigator or trial physician may request the unblinding of a participant for medical care.

2.4 Eligibility Screening

A Study Flowchart is presented in Figure 1. Willing volunteers will complete a comprehensive online Screening Questionnaire using the 'Research Electronic Data Capture' (REDCap[™]) web-based system (~20 minutes). Volunteers are required to complete a compulsory online declaration tick-box at the start of the questionnaire consenting to the use of the information they provide to evaluate their eligibility. The questionnaire will assess their eligibility to participate. Each volunteer who attempts the Screening Questionnaire will be assigned a unique screening number to anonymise their identifying information. The trial physician will review volunteers' responses and decide on their eligibility for the trial. They will document their decision by completing an Eligibility

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1 2 3 4 5 6 7	268 269	Declaration form and a prescription for the trial drug (valid only when the volunteer has been randomised).
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57 58 59 60		

270 [INSERT FIGURE 1 HERE]

Figure 1. Study flowchart summarising the screening, enrolment and randomisation of participants in the CAPSTAN trial.

¹² 13 275 **2.5 Enrolment**

Eligible participants will be invited to complete a telehealth interview with the trial coordinator. Here, they will receive detailed information about the trial procedures and risks and be informed that their enrolment requires a negative urine drug and pregnancy screen at the start of the experimental procedures (i.e., the "Test Day"). The trial coordinator will invite the volunteer to ask questions and to discuss participation in the trial with the trial doctor, or to take additional time to consider their decision to participate. Once the trial coordinator is confident that the volunteer understands the requirements of the trial, they will request that the participant sign the informed consent form (please see Supplementary file). The trial coordinator will then counter-sign the consent form, collect basic demographic information and book the participant for a Test Day.

- **2.6 Experimental Procedure**
- Each participant will complete one Test Day (~3 hours) at the Brain and Mind Centre at the University of Sydney (**Table 1**).

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Time (minutes) from start	Approximate Duration	Activity
0	10 min	Introduction and pre-trial compliance checks
10	5 min	Randomisation
15	15 min	Pre-treatment measures
30	10 min	CBD or placebo administration and caloric beverage
40	50 min	Rest period 1
90	15 min	Virtual reality orientation
105	15 min	Baseline measures
120	15 min total (2 min) (3 min) (5 min) (5 min)	Public Speaking task: Instructions Speech preparation Speech delivery Arithmetic challenge
135	10 min	Rest period 2
145	5 min total (2 min) (3 min)	Walk the Plank task: Instructions Walk the Plank task
150	10 min	Rest period 3
160	5 min total (2 min) (3 min)	Rollercoaster Ride task: Instructions Rollercoaster ride task

2.6.1 Standardisation Procedures

10 min

15 min

_

Prior to each onsite Test Day, participants will be instructed to: (a) abstain from alcohol (≥24 h); (b) avoid greater than one standard serving of caffeine at least 2-hours before the Test Day; (c) ensure they are well hydrated; and (d) ensure that they are adequately fed by consuming a meal at least 2 hours before arrival to the Test Day. These factors aim to reduce the likelihood of malaise, gastrointestinal disturbances or heightened anxiety on the Test Day.

Rest period 4

Study Close

End Of Test Day

 2.6.2 Compliance Checks

Participants will complete a urinary drug screen (to identify any recent use of cannabis and other psychoactive substances such as cocaine, ecstasy (MDMA), amphetamines, benzodiazepines and opioids) and, if they are female, a urine pregnancy screen, on arrival at the study site. The trial coordinator will also confirm compliance with the standardisation procedures and if there have been any changes to the participant's health status or medication use since the last contact. Participants who meet these requirements will be randomised; those who do not may be invited to return at another time if suitable.

¹⁸ 319 19 320

0 2.6.3 Experimental Procedures

Following randomisation, participants will be fitted with the Equivital EQ02+ LifeMonitor belt and the VR headset (detailed below). There will then be a 10-minute collection of pre-treatment measures (see Study Outcomes below). After this, the VR headset and Equivital EQ02+ LifeMonitor belt will be temporarily removed, the treatment administered, and the participant given a compulsory standardised caloric beverage to consume; specifically, 500 mL of "Up & Go Liquid Breakfast" (Sanitarium, Berkeley Vale NSW, Australia) containing approximately 1,640 kilojoules, 16.8g of protein, 8.6g of fat and 57g of carbohydrates. For consistency, all participants are required to consume this beverage in its entirety, which aims to potentiate the absorption of CBD in the gastrointestinal tract [6, 48-50] and provide participants with sustenance during the test session. Participants will be provided with a rest period of approximately 50 minutes, during which they will be left alone in a quiet reception area and encouraged to undertake some low-stress reading; this delay is aimed at allowing CBD plasma concentrations to approach a near-maximal level [48]. Following this, participants will be provided with instructions on the three VR tasks and the functionality of the VR hardware during a 15-minute "VR Orientation" session. The VR headset and Equivital EQ02+ LifeMonitor belt will then be re-fitted for a 10-minutes collection of the pre-task measures. The devices will remain fitted to participants until the end of the experimental procedure.

340 2.6.4 Virtual Reality Tasks

The three tasks developed for this clinical trial are the "Public Speaking" task (for psychosocial stress), the "Walk the Plank" task (for situational anxiety) and the "Rollercoaster Ride" task (for motion sickness). Although these exact VR tasks have not been previously used in clinical trials or laboratory studies, similar tasks have been reported in the broader scientific literature [29, 32, 40-42, 51].

The 15-minute "Public Speaking" task was modelled on previous studies that found CBD to have anxiolytic effects during public speaking challenges [23, 24, 39] and the Trier Social Stress Test (TSST) [52]. The abovementioned public speaking tasks varied in their methodology and involved either "simulated" public speaking tasks whereby participants delivered a speech in front of a video camera or real-life tasks where participants delivered speeches to a live audience [23, 24, 39]. Conversely, the TSST is a structured stress paradigm involving a 10-minute speech preparation period followed by a 10-minute test period during which participants complete a 5-minute job application speech followed by 5 minutes of mental arithmetic [53]. The TSST reliably induces psychosocial stress (i.e., stress involving the perception of one's worth, competence, or status by others) and results in an acute and reliable cortisol response in most participants [53-55]. In one study, a VR adaption of the TSST elicited similar salivary cortisol and subjective stress responses to a real-life TSST, demonstrating that the two were equivalent [29]. The current study utilises a modified VR version of the TSST involving a panel of virtual judges who withhold all feedback or affirmation (Figure 2A).

The task involves a three-minute "speech preparation period" (i.e., "please mentally prepare a speech on what attributes and experience you have that makes you the ideal candidate for your dream role") and a 10-minute "test period" consisting of (a) five-minute speech delivery period (i.e., "please deliver your speech and aim to speak for the full five-minutes") and (b) a five-minute mental arithmetic challenge (i.e., "please calculate 2703 – 13. From the result, please subtract 13 again and state your answer out loud. Repeat this process a total of five times. At the end of this process, please recall all five of your answers aloud").

55
56368The five-minute "Walk the Plank" task requires participants to virtually walk across a57
58369narrow virtual plank between two skyscrapers. Participants will be advised that they have59
60370become stranded on the top of the building and are required to signal for help using the safety

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beacon placed at the opposite end of the plank. For this task, participants will walk up and
down the length of the clinic room with their movement mapped to the virtual plank and
guided by virtual boundaries, signifying a safe space (Figure 2B). VR studies utilising a similar
challenge provided realistic experiences that induce physiological markers of stress that are
consistent with acute anxiety (i.e., "situational anxiety") [40-42].
The five-minute "Rollercoaster Ride" task challenges participants to complete a virtual
rollercoaster ride (Figure 2C). Participants will remain seated throughout this task and can
indicate if they would like to stop the task early. Similar VR tasks have been shown to induce
motion sickness in participants [32, 43, 44]. Motion sickness will be explored explicitly during
the "Rollercoaster Ride" task, while cybersickness will be explored during all three VR
scenarios.
[INSERT FIGURE 2A,2B AND 2C HERE]
Figure 2. (A) The panel of virtual judges from the "Public Speaking" task; (B) The roof of the building
and plank from the "Walk the Plank" task; and (C) The view from the seat of the "Rollercoaster Ride"
task.
2.6.5 Post Trial Procedures
After completing the final VR task, participants have a 10-minute recovery period.
After this, they will be queried on any adverse events (AEs) experienced (i.e., "Have you
experienced any unfavourable symptoms?"), What treatment do they think they received
(i.e., CBD or placebo), and what are their confidence estimates (i.e., How sure are you of your
guess on which treatment you received?"). All participants will be provided with the contact
details of the research team to self-report any AEs over the next 24 hours. The trial
coordinator or research assistant will record all adverse event reports using a REDCap [™] AE
report form and communicate to the trial physician if required.
The occurrence of AEs will be discussed weekly with the trial physician. Furthermore,
a blinded summary of AE reports will be emailed to the trial physician monthly, and the trial
physician will indicate if the rate of AEs is unacceptably high. In the unlikely event of a severe

2.6.5 Post Trial Procedures After completing the final After this, they will be gueried on experienced any unfavourable sym (i.e., CBD or placebo), and what are guess on which treatment you rece details of the research team to coordinator or research assistant w report form and communicate to th The occurrence of AEs will b a blinded summary of AE reports w physician will indicate if the rate of

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3 4	401	adverse event (SAE), the trial physician and the principal investigator (PI) will be immediately			
5	402	notified, and all SAEs will be reported to the trial sponsor and the HREC within 72 hours.			
6 7	403				
8 9	404	2.7 Data Collection			
10 11	405	A summary of the data collected during the CAPSTAN trial and time of collection is provided			
12 13	406	in Figure 3			
14 15	407				
16 17	408	[INSERT FIGURE 3 HERE]			
18	409				
20	410	Figure 3. Data collected during the CAPSTAN trial "Test Day.			
21 22	411	IPS = instructions for the "Public Speaking" task, SP = speech preparation, SD = speech delivery, AC =			
23 24	412	arithmetic challenge, IWP = instructions for the "Walk the Plank" task, WPT = "Walk the Plank" task,			
25	413	IRR = instructions for the "Rollercoaster Ride" task, RRT = "Rollercoaster Ride" task			
26 27	414				
28 29	415	2.7.1 Study Outcomes			
30 31	416	The primary outcome measures include:			
32 33 34	417	 Self-reported stress ratings on a VAS (<i>nervous 0-100</i>) 			
	418	 Self-reported nausea ratings on a VAS (nauseous 0-100) 			
35 36	419				
37 38	420	The secondary outcome measures include:			
39 40	421	Salivary Cortisol			
41 42	422	Heart rate			
43 44	423	Skin Conductance			
45 46	424	 Vomiting or near-vomiting episodes 			
47	425	 Self-reported anxiety ratings on VASs include: 			
48 49	426	o (tense 0-100)			
50 51	427	o (calm 0-100)			
52 53	428	○ (excited 0-100)			
54 55	429	o (bored 0-100)			
56 57	430				
58 50	431	The exploratory (tertiary) outcome measures are:			
60	432	Salivary testosterone and progesterone			

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3 4	433	Eye-tracking data including:				
5 6	434	 The frequency and duration of eye-closing 				
7	435	\circ The frequency and duration of gaze at areas of interest				
9	436					
10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34	437	2.7.2 Visual Analogue Scales (VASs)				
	438	VASs will be used to measure the two primary outcomes: self-reported stress				
	439	(nervousness) and nausea. They will also be used to measure the secondary outcome of self-				
	440	reported anxiety (as detailed below) (Figure 4). These measures will be recorded before drug				
	441	administration (pre-treatment measurement), at baseline, prior to the commencement of				
	442	each VR task, at the completion of each VR task and at the study close. VAS measures will also				
	443	be recorded prior to the performance of the speech during the "Public Speaking" task				
	444	(Timepoint "SD" Figure 3) and prior to the performance of the walk during the "Walk the				
	445	Plank" (Timepoint "WPT" Figure 3) task. These measures aim to capture "anticipator				
	446	anxiety" reported prior to anxiety-inducing tasks in previous studies [23, 24]. As nausea is the				
	447	main interest during the Rollercoaster Ride task, no VAS measures for anticipatory anxiety				
	448	will be taken for this task. All VASs will appear on the screen of the VR headset, and				
	449	participants will use the VR hand controllers to click on the numerical value (0-100) that best				
35 36	450	describes their current state (Figure 4). Using such virtual scales allows seamless execution of				
37 38	451	self-report without disturbing the participant's sense of immersion within the virtual				
39	452	environment.				
40 41	453	For a well-rounded exploration of CBD effects on anxiety, we have utilised VASs that				
42 43	454	query participant's affect (i.e., the outward expression of an emotion) [56]. Here, we consider				
44 45	455	1) the "valence" of an emotion (i.e., its positivity or negativity) and 2) the intensity of the				
46 47	456	emotion (i.e., whether it is arousing or deactivating). This provides four self-reported anxiety				
48 49	457	rating VASs, including:				
50	458	 positively arousing (excited 0-100) 				
52	459	 positively deactivating (calm 0-100) 				
53 54	460	 negatively arousing (tense 0-100) 				
55 56	461	 negatively deactivating (bored 0-100) 				
57 58	462					
59 60	463	[INSERT FIGURE 4 HERE]				

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3 4	464				
5	465	Figure 4. Self-reported Visual Analogue Scales (VASs) as they appear on the virtual reality			
7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30	466	headset. Values are provided by the participants by clicking on the scales using the hand			
	467	controllers.			
	468				
	469	2.7.3 Salivary Cortisol, Testosterone and Progesterone			
	470	During the experimental procedure, oral fluid samples will be collected from			
	471	participants five times using Salivette® collection tubes (Sarstedt AG and Co., Nümbrecht			
	472	Germany). These samples will be collected immediately before drug administration. before			
	473	the first VR task, and after each VR task. Participants will be advised to open the Salivette®			
	474	tube, place the pad in their mouth for two minutes or until soaked with saliva, then return			
	475	the pad to the tube and firmly seal it. The samples will be centrifuged for 2 minutes at 1,000			
	476	x g and analysed simultaneously for cortisol (a secondary outcome) and testosterone and			
	477	progesterone (exploratory outcomes) using an in-house developed mass spectrometry (MS)			
	478	method [57, 58].			
31 32	479				
33 34 35	480	2.7.4 Heart Rate			
36 37	481	Heart rate will be measured for 10 minutes immediately before drug administration			
37 38	482	(baseline measurement), for 10 minutes at baseline and continuously throughout all three VR			
40	483	tasks using the EQ02+ LifeMonitor and belt, as described in previous studies [59, 60] (Equivital			
41 42	484	Ltd. Cambridge. United Kingdom: https://www.adinstruments.com/partners/equivital). This			
43 44	485	is a wireless, medical-grade monitoring system that records a range of physiological measures			
45 46	486	(such as electrocardiogram breathing rate tri-axial acceleration galvanic skin response skin			
47	487	temperature) using a wearable vest and permits live data streaming and download using the			
48 49	188	LabChart coftware			
50 51	400				
52 53	409				
54 55	490	2.7.5 Skin Conductance			
55 56	491	Skin conductance will be measured for 10 minutes immediately before drug			
57 58	492	administration (baseline measurement), for 10 minutes at baseline and continuously			
59		. "			

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Skin conductance of the forehead will be measured using the Equivital GSR Sensor connected to the EQ02+ LifeMonitor and belt (as described above). Skin conductance of the fingers will be measured using MLT117F/10 GSR finger electrodes connected to a FE116 GSR Amp with a PLCF1 front-end interface used with PowerLab C software (ADInstruments, Oxford United Kingdom), a system used in previous studies [61, 62]. Research suggests that forehead skin conductance may correlate with motion sickness, while finger skin conductance correlates with acute stress [32, 63]. Therefore, both will be measured in the current study.

502 **2.7.6 Vomiting Episodes**

The Test Day source document will record all vomiting episodes throughout the experimental procedure.

6 2.7.6 Eye-tracking

507 Eye tracking data will be collected continuously throughout the VR tasks using the VR 508 headset. These measures will provide highly precise, objective data by which to examine 509 participant's compliance (frequency and duration of eye closing) and engagement and 510 response (frequency and duration of gaze at areas of interest, that is, the panel of judges in 511 the "Public Speaking" task or the plank in the "Walk the Plank" task) during the VR challenges 512 [64]. Gazing at pre-defined points of interest (e.g., the judges in the "Public Speaking" task or 513 the plank in the "Walk the Plank" task) is based on the "Eye-Mind Hypothesis" that describes 514 the tendency for people to direct their gaze towards what they are thinking about [64-66]. 515 Both eye closing and gaze away from points of interest may correlate to fear or avoidance 516 behaviours [67].

518 2.9 Data Management

519 Participant information collected for this trial will be securely stored and treated as 520 confidential. Participants' identifying information will be anonymised using unique codes: 521 initially, a screening number and, later, a randomisation number. The key to these codes will 522 be securely stored in password-protected files inaccessible from the internet. Clinical trial 523 data will be collected and managed using REDCap[™], a secure, online program supported by 524 the University of Sydney; access is password-protected and will only be available to approved **BMJ** Open

research staff. Hard copies of patient data will be securely stored in locked filing cabinets at the study site. Only the study investigators have access to the participant data. All trial data will be stored securely for at least 15 years. The findings of this clinical trial will be disseminated via conferences, publications, and media, as applicable. Participants will be informed of the results of the study at the conclusion of the trial. No participants will be identified in any report or publication of this study or its results.

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2.10 Data and Safety Monitoring

Data monitoring will occur monthly for all new participant entries logged into the REDCap system; a designated team member will adhere to a standardised process of data review, raising queries and locking forms once the review has been completed. Safety monitoring of AEs will be managed according to sponsor and HREC requirements. As this is a small, single-centre, low risk, clinical trial utilising an acute, low-dose CBD, an independent data safety monitoring committee will not be formed. However, an independent 'Expert Group' has been formed and will be consulted by the research team and HREC in the unlikely instance of a severe adverse event. The Expert Group comprises three research physicians with extensive experience with CBD clinical trials. The decision to terminate the trial lies with the principal investigator based on safety data and recruitment targets.

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 2.11 Roles and Responsibilities

545 The study investigators have led the design of this study and are responsible for the 546 management and conduct of this clinical trial. The study investigators will conduct the analysis 547 and will make all publication-related decisions.

- 48 549 **2.12 Statistical Methods**
- 50 550

2.5.1 Sample Size Estimation

53
54552The target sample size was determined *a priori* using power calculation software55
55553(G*Power Version 3.1.9.6, University of Kiel, Germany). In an earlier investigation, Linares *et*57
58554*al.* (2019) found that 150 mg CBD decreased subjective ratings of anxiety on the Visual

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Analogue Mood Scale (VAMS) during a simulated public speaking test, albeit non-significantly
(Placebo: 18.6±15.9 mm, n=15; CBD: 7.6±15.5 mm; n=15; Cohen's *d*=0.70) [23].

Using an equivalent effect size (Cohen's d=0.70), a power (1-ß) of 0.8 and a two-sided $\alpha=0.05$, we estimate that n=68 participants will be required to detect a significant effect of CBD on anxiety. Clinical trials conducted by the Lambert Initiative for Cannabinoid Therapeutics have indicated participant retention of $\ge 90\%$ [48, 68]. Therefore, the n=74 will be recruited to account for attrition.

563 2.5.2 Statistical Analysis Plan

564 The primary and secondary outcomes and eye-openness will be analysed using 565 generalized linear mixed models (GLMM), while eye gaze will be analysed using a mixed-566 effects multinomial logistic regression. Treatment, Time and the Treatment × Time interaction 567 will be included as fixed effects, and the participant will be included as a random effect, with 568 other covartiates included as appropriate to improve goodness of fit (e.g., Sex, Age, Time of day). To refine the models, we will use corrected Akaike Information Criterion [69]. We will 569 570 calculate Δm between models and exclude models with $\Delta m > 2$ as having substantially less 571 support [70]. No covariance structure will be specified (unstructured). To identify the best 572 distribution and link for the GLMM models, the data type, residual plots, Shapiro-Wilk 573 normality test, Levene's test for Homogeneity of Variance, and Pearson's dispersion test will 574 be used. Type III Wald chi-square tests will be used to generate main effects p-values. A priori 575 planned uncorrected pairwise comparisons will be performed to compare:

- subjective ratings of stress on a stress VAS (*nervous 0-100*) across treatments at
 (Timepoint t=125 (SD), Figure 3)
- subjective ratings of stress on a stress VAS (*nervous 0-100*) across treatments at
 (Timepoint t=147 (WPT), Figure 3)
- subjective ratings of nausea on a nausea VAS (*nauseous 0-100*) across treatments at
 (Timepoint t=165, Figure 3)
 - subjective ratings of nausea on a nausea VAS (*nauseous 0-100*) across treatments at
 (Timepoint t=175, Figure 3)
- 584 as these are the primary outcome measures.

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585 Dunn-Šidák corrected pairwise comparisons will be performed where additional 586 significant main and interaction effects are present. Statistical significance will be accepted as 587 p<0.05. The statistical analysis plan will be finalised before the last participant Test Day and 588 will be available on request.

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3. STATEMENTS AND DECLARATIONS

Ethics and dissemination: The study has been approved by the University of Sydney Human 592 Research Ethics Committee (HREC; 2023/307, Version 1.6, 16th February 2024). The findings 593 of this clinical trial will be disseminated via conferences, publications, and media, as 594 applicable. Participants will be informed of the study's results at the trial's conclusion. No 595 participants will be identified in any report or publication of this study or its results.

27 597 Author Contributions

I.S.M, D.M, H.M, M.B.P, N.S.L, R.F and Z.B were involved in the conception and design of the research project. Z.B drafted the manuscript, and all authors were involved in critically revising it. I.S.M is the principal investigator who has overall responsibility for the design, conduct and decision to submit for publication. M.B.P is the study statistician, N.S.L will provide medical oversight, H.M and R.F created the virtual reality challenges in collaboration with I.S.M and Z.B. Z.B is the trial coordinator responsible for collecting trial data. All authors have read and approved the final manuscript.

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44606Funding Statement

This work was supported by The Lambert Initiative for Cannabinoid Therapeutics, a
 philanthropically funded centre for medicinal cannabis research at The University of Sydney.
 609

51 610 **Competing Interests**

Author I.S.M. acts as a consultant to Kinoxis Therapeutics and has received honoraria from Janssen. He has also served as an expert witness in various medicolegal cases involving cannabis and cannabinoids. I.S.M. hold patents on cannabinoid therapies (PCT/AU2018/05089 and PCT/AU2019/050554) and has received consulting fees from the

2		
3 4	615	Medicinal Cannabis Industry Australia (MCIA). D.M. has also received consulting fees from
5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 22	616	MCIA. Z.B, H.M N.S.L, R.F and M.B.P have no disclosures to report.
	617	
	618	Patient and public involvement
	619	Patients and/or the public were not involved in the design, or conduct, or reporting or
	620	dissemination plans of this research.
	621	
	622	Patient consent for publication
	623	Not applicable.
	624	
	625	Trial Sponsor
	626	The University of Sydney, Sydney NSW Australia.
	627	
	628	Data Availability Statements
	629	The deidentified participant data are available from Professor Iain McGregor
	630	(iain.mcgregor@sydney.edu.au) upon reasonable request.
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The Cannabidiol for Acute Psychosocial Stress and Nausea (CAPSTAN) Trial ENROLMENT CONSENT FORM (HREC Approval No.: 2023/307)

- 1. I have read and understood the Participant Information Sheet and agree to take part in the CAPSTAN trial.
- 2. I have had the project, so far as it affects me, and the potential risks and burdens fully explained to my satisfaction by the research team. I have had the opportunity to ask any questions I may have about the project and my participation. My consent is given freely.
- 3. I have no history of allergy or other adverse reactions to the drug, cannabidiol.
- 4. Although I understand the purpose of the research project is to improve the quality of health/medical care, it has also been explained to me that my involvement may not be of any benefit to me.
- 5. I realise my participation in this study is voluntary and that I have the right to withdraw from the study at any stage without prejudice. I also understand that the research team has the right to terminate the study at any stage before completion, without jeopardising my medical care, if they believe this is in my best interests, for non-compliance with study procedures or for other legitimate reasons. If I decide to withdraw from the study, I agree that information collected about me up to the point when I withdraw may continue to be processed.
- 6. I understand that all information will remain confidential and while the information gained during the study may be published in journal articles, conferences, presentations etc, I will not be identified in any way. I agree to my non-identifiable information being used for future research purposes limited to the work of the University of Sydney.
- 7. My information will only be used for the purposes of this research, and it will only be disclosed according to the consent provided, except where disclosure is required by law.
- 8. I understand that access may be required to my medical records for the purpose of this study as well as for quality assurance, auditing and in the event of a serious adverse event and I consent to this access.
- 9. I am aware that I should keep a copy of this Consent Form, when completed, and a copy of the Patient Information Sheet.

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- 10. I agree to have my General Practitioner informed of my participation in this study if required for my medical care and that he/she may divulge details of my past medical history, as he/she sees relevant, to the Investigator.
- 11. I am aware that I should keep a copy of the completed Consent Form and the attached Participant Information Sheet.
- 12. I am 18 years of age or over.

This consent form relates to Participant Information Statement Version 1.6_1 December 2023

Participant to com	olete:	
I consent to partici participate in the C	pate in the CASTAN trial screening proce ASTAN trial.	edure and if eligible, I consent to
Name:	Signature:	Date:
I have described the	e nature of the research to she/he understood the explanation.	print name of participant
Name:	Signature:	Date:

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ltem No	Description	Manuscript Page and Notes
Administrative ir	nformati	on	
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	Yes, ANZCTR public trials registry, ACTRN12623000872639. Registered 15 August 2023.
Protocol version	3	Date and version identifier	2, 6 and 25
Funding	4	Sources and types of financial, material, and other support	6, 25
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1,25
	5b	Name and contact information for the trial sponsor	6
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	25
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	23
Introduction			

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
	6b	Explanation for choice of comparators	8
Objectives	7	Specific objectives or hypotheses	6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5-6
Methods: Particip	oants, in	terventions, and outcomes	
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6-7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	NA, intervention is a single acute dose of active or placebo with no ongoing involvement of participants.
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	NA, intervention is a single acute dose of active or placebo with no ongoing involvement of participants.
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	12-13

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Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	19
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	10 (Figure1)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	23
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7
Methods: Assignn	nent of	interventions (for controlled trials)	
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9

Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	9
Methods: Data c	ollection	n, management, and analysis	
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	22
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	7,17
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	22-23
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	23-24
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	23-24
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to	23-24
		handle missing data (eg, multiple imputation)	

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Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	23
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	17
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	22-23
Ethics and disser	ninatio	n	
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	2, 6, 25
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	6
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	22

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Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	25
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	22
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	17
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	22
	31b	Authorship eligibility guidelines and any intended use of professional writers	23
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	23
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	NA
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "<u>Attribution-NonCommercial-NoDerivs 3.0 Unported</u>" license.

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The effects of cannabidiol on psychosocial stress, situational anxiety and nausea in a virtual reality environment: A protocol for a single-centre randomised clinical trial

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27 ABSTRACT

 Introduction: The non-intoxicating plant-derived cannabinoid, *cannabidiol* (CBD), has demonstrated therapeutic potential in a number of clinical conditions. Most successful clinical trials have utilised relatively high (≥ 300 mg) oral doses of CBD. Relatively few studies have investigated the efficacy of lower (<300 mg) oral doses, typical of those available in over-thecounter CBD products.

Methods: We present a protocol for a randomised, double-blind, placebo-controlled, parallel-group clinical trial investigating the effects of a low oral dose (150 mg) of CBD on acute psychosocial stress, situational anxiety, motion sickness and cybersickness in healthy individuals. Participants (n=74) will receive 150 mg of CBD or a matched placebo 90 minutes before completing three virtual reality (VR) challenges (tasks) designed to induce transient stress and motion sickness: (1) a 15-minute "Public Speaking" task; (2) a 5-minute "Walk the Plank" task (above a sheer drop); and (3) a 5-minute "Rollercoaster Ride" task. The primary outcomes will be self-reported stress and nausea measured on 100-mm visual analogue scales. Secondary outcomes will include salivary cortisol concentrations, skin conductance, heart rate, and vomiting episodes (if any). Statistical analyses will test the hypothesis that CBD reduces nausea and attenuates subjective, endocrine, and physiological responses to stress compared to placebo. This study will indicate whether low-dose oral CBD has positive effects in reducing acute psychosocial stress, situational anxiety, motion sickness and cybersickness.

Ethics and dissemination: The University of Sydney Human Research Ethics Committee has 49 granted approval (2023/307, Version 1.6, 16th February 2024). Study findings will be 50 disseminated in a peer-reviewed journal and at academic conferences.

52 Trial Registration Number: ACTRN12623000872639 (ANZCTR public trials registry, registered
53 15th August 2023).

Keywords: cannabidiol (CBD), nausea, anxiety, virtual reality.

2 3	57	STRENGTHS AND LIMITATIONS OF THIS STUDY
4 5	58	
6 7	59	• This study will use a rigorous randomised double-blind placebo-controlled design to
8	60	investigate the effects of a low oral dose (150 mg) of cannabidiol
9 10	61	The date of expendicial provided (i.e. 150 mg) will be comparable to these swellable
11 12	01	• The dose of cannabidior provided (i.e., 150 mg) will be comparable to those available
13 14	62	over-the-counter in many countries.
15	63	 Virtual reality (VR) will be used to administer safe, realistic, and precisely reproducible
16 17	64	test paradigms that induce transient stress and nausea in volunteers.
18 19	65	 Blood samples will not be obtained to verify plasma cannabidiol concentrations as
20 21	66	venepuncture has the potential to induce extraneous stress.
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1. INTRODUCTION

Cannabidiol (CBD) is a non-intoxicating constituent of the *Cannabis sativa* plant [1, 2]. It has a good safety and tolerability profile [3-7] and a diverse range of pharmacological targets, including the serotonin receptors (e.g., 5-HT1A), G protein-coupled receptors (e.g., GPR55 and GPR18) and transient receptor potential ion channels (e.g. TRPA1) [8-10]. CBD has demonstrated therapeutic potential in several clinical conditions [4, 5], including anticonvulsant effects in paediatric epilepsy [11-13], anxiolytic effects in anxiety disorders [14, 15], antipsychotic effects in schizophrenia [16, 17] and "anti-addiction" effects in substance use disorders [18, 19]. These clinical benefits are typically observed at relatively high oral doses of CBD (e.g., ~300-1500mg) [4, 5].

In regions such as North America and Europe, CBD is available as both a prescription drug and a 'nutraceutical product' [20]. These nutraceutical or "wellness" products are typically oral formulations (e.g., oils, capsules, gummies) that contain low doses of CBD (i.e., ≤150 mg/day) and are widely available in health food stores and pharmacies [20, 21]. In Australia, regulation of "low-dose CBD products" (containing $\leq 150 \text{ mg/day}$) was recently eased to allow patients without a prescription access to registered products in pharmacies. However, registration of such products requires approval by Australia's medicines regulator based on demonstrated efficacy and safety [22]. With no products having been registered in the \sim 3 years since these regulatory changes were enacted (December 2020) [22], questions about whether CBD can demonstrate efficacy at these lower doses have been raised.

Indeed, a recent review found little high-quality evidence to support the efficacy of CBD (in any conditions) at doses ≤ 200 mg. This review acknowledged, however, that such doses were under-studied [21]. Some promising results have been obtained with public speaking tasks designed to induce "psychosocial stress" in healthy volunteers when 300 mg CBD was administered [23, 24]. Therefore, further research investigating the anxiolytic effects of low to moderate oral doses of CBD is warranted. It should be noted that the oral bioavailability of CBD is limited (~13-19%) but may be enhanced by certain lipid-rich formulations or by administration with fatty foods [6, 25]. The current study will utilise a proprietary blend of tocopherol phosphates (so called 'Tocopheryl Phosphate Mixture' (TPM®)), which has been shown to increase the bioavailability of lipid-soluble substances [26, 27].

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Virtual reality (VR) technologies are increasingly being used to investigate psychosocial stress and anxiety in laboratory studies [28, 29]. This approach allows for minimal resourcing relative to "real-world" studies, customisable and reproducible test paradigms and the accurate monitoring and recording of key outcomes [29, 30]. Furthermore, VR provides the advantage of simulating physiologically-provoking activities without real danger e.g., walking a plank over a sheer drop. However, the use of VR is often accompanied by motion sickness (a pattern of symptoms that arise from exposure to stimuli involving significant visual or physical motion) and cybersickness (a sub-type of motion sickness that arises specifically due to exposure to VR) [31-34]. CBD has shown anti-nausea and anti-emetic effects in preclinical studies involving laboratory animals [35-37]. Interestingly, two of these studies demonstrated that CBD administered intraperitoneally at low doses (2.5 - 10 mg/kg) but not higher doses (25 and 40 mg/kg) reduced toxin-induced vomiting in house musk shrews [35, 36]. CBD also reduced vomiting in human studies when used in combination with Δ^9 -tetrahydrocannabinol to treat chemotherapy-induced nausea and vomiting [38]. Accordingly, the current study will investigate CBD's possible anti-nausea effects in participants by exposure to VR scenarios [29].

We have developed a series of three unique VR challenges for the current trial. The "Public Speaking" task was adapted from studies that explored the anxiolytic effects of CBD during public speaking challenges [23, 24, 39] and will allow us to determine the effects of CBD during social threat (i.e., psychosocial stress). The 5-minutes "Walk the Plank" task has been modified from previous VR studies requiring participants to walk along a narrow virtual plank above a precipitous drop, inducing physiological markers of acute anxiety [40-42] (i.e., "situational anxiety"). Finally, the "Rollercoaster Ride" task challenges participants to complete two rounds of a virtual rollercoaster ride and has been modelled from VR rollercoaster ride paradigms that have been reliably used to induce motion sickness and cybersickness in participants [32, 43, 44].

In summary, the current protocol describes a study that aims to investigate the effects of low-dose (150 mg) CBD versus placebo on virtual reality (VR)-induced acute psychosocial stress, situational anxiety, acute motion sickness and cybersickness in healthy individuals.

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2. METHODS

2.1 Study design

This study is a randomised, double-blind, placebo-controlled, parallel-group, clinical trial comparing the efficacy of low-dose CBD (150 mg) versus placebo. The study is known as the CAPSTAN (Cannabidiol for Acute Psychosocial Stress and Nausea) clinical trial. A crossover design was deemed unsuitable due to the high likelihood of trial-order effects (e.g., habituation to the VR scenarios) [32].

The trial sponsor is the University of Sydney, and the trial site is the Brain and Mind Centre in Sydney, Australia. The study has been approved by the University of Sydney Human Research Ethics Committee (HREC; 2023/307, Version 1.6, 16th February 2024) and registered on the Australian New Zealand Clinical Trials Registry (ACTRN12623000872639, 15th August 2023). The study is financially supported by the Lambert Initiative for Cannabinoid Therapeutics, a philanthropically funded centre for cannabinoid research at the University of Sydney. Recruitment commenced on 9th October 2023 and is anticipated to conclude in mid-2024. ere.

2.2 Participant Population

2.2.1 Inclusion Criteria

We aim to recruit 74 participants who will be: (a) healthy adults aged between 18 and 50 years; (b) proficient in English and able to provide informed consent; (c) residing in the Greater Sydney region of New South Wales, Australia; and (d) willing to follow the protocol requirements.

2.2.2 Exclusion Criteria

- The following exclusion criteria will apply:
 - a. Self-reported regular use (i.e., more than twice weekly) in the past two weeks of:
 - i. Cannabinoid-containing products (e.g., cannabis or CBD)

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	ii.	Psychotropic drugs (prescriptive or illicit) (e.g., cannabis, amphetamines,
		cocaine, ecstasy (MDMA), LSD (acid), antidepressants, antiepileptics, opioids,
		benzodiazepines)
	iii.	Medication that may affect the stress response (e.g., corticosteroids, beta-
		blockers)
b.	Self-re	eported history of allergic reaction (e.g., urticaria or anaphylaxis) to cannabis or
	canna	binoid-containing products.
c.	Self-re	eported history of liver disease, renal disease, epilepsy or heart disease
	(medi	cally controlled high blood pressure <140/90mmHg is acceptable).
d.	Curre	nt (i.e., within the past 2 weeks) otologic (vestibular) disease.
e.	A hist	ory of repeated episodes of syncope.
f.	Pregn	ant, lactating, or trying to conceive.
g.	Self-re	eported history of drug and/or alcohol dependence (or suspected drug and/or
	alcoho	ol dependence as determined by the trial physician).
h.	A med	dically diagnosed anxiety disorder (e.g., social anxiety disorder) within the past
	12 mc	onths.
i.	Curre	nt suicidal ideation (i.e., a score >0 on Question 9 of the Patient Health
	Quest	ionnaire) or suspected suicidal ideation as determined by the trial physician.
j.	Curre	nt depression, anxiety, and stress scores outside the 'healthy range' on the
	Depre	ession Anxiety Stress Scale-21 [45] (i.e., > moderate scores for depression (>20),
	anxiet	ry (>14) and stress (>25)).
k.	A chro	onic medical condition (mental or physical) that is uncontrolled i.e., has been
	either	newly diagnosed, or previously diagnosed and remains symptomatic.
I.	Self-re	eported high vulnerability to cybersickness or motion sickness.
m.	Frequ	ent (i.e., more than weekly) use of VR technologies, which tends to produce
	desen	sitisation towards cybersickness [32].
n.	Self-re	eported intense fear of heights.
2.3 F	ecruiti	ment and Retention
	Partic	ipants will be recruited via social media, word of mouth, printed or online
udy a	adverti	sements and direct emails to individuals who have previously registered their

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interest in participating in clinical trials with the Lambert Initiative for Cannabinoid

Therapeutics. Participation is voluntary, and participants can withdraw at any time.

Participants will be reimbursed with a \$200 gift voucher as compensation for time and

2.3 Treatments

The treatments will be purchased from Avecho Biotechnology Limited (Clayton, Victoria), manufactured (Catalent Pharma Solutions, St. Petersburg, FL), as well as packaged and labelled (Central Pharmacy Logistics, Coburg North, VIC) at GMP-licenced facilities, stored at the Brain and Mind Centre (in a secure, temperature-controlled room), and dispensed by the trial coordinator (who is also a registered pharmacist) and another blinded investigator.

expenses incurred as a result of study participation.

As this trial utilises a non-clinical (healthy) population, a placebo comparator is the most suitable and ethical choice. Accordingly, an acute dose of CBD (as opposed to chronic administration) will be utilised. Indeed, the treatment of many ailments utilises an *ad hoc* treatment regime.

2.3.1 Int

2.3.1 Intervention

The investigational product (Avecho Biotechnology Limited, Victoria, Australia) is an oil-based, soft-gel capsule. Each gel capsule contains 75 mg of pure, synthetic (-)-CBD enantiomer and 75 mg of TPM[®] in medium chain triglyceride (MCT) oil. The capsules do not contain any other cannabinoids or cannabis constituents.

228 2.3.1a Safety

CBD is generally considered to have a good safety profile [3, 4, 21, 46, 47]. In previous studies, 150 mg CBD caused a very low frequency of mild adverse events that did not differ from placebo [21]. The current study's comprehensive screening and exclusion criteria aims to reduce the likelihood of adverse events.

56 234 2.3.1b Dose

A dose of 150 mg of CBD (i.e., two soft-gel capsules) will be administered orally.
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2.3.1c Control

The control is a matched placebo. The placebo is identical to the intervention but contains no CBD and will also be administered via oral ingestion.

2.3.2 Randomisation, Allocation Concealment and Blinding

Participants will be randomised to one of two possible treatments in a 1:1 ratio at the beginning of their test day. Specifically, they will be assigned a unique randomisation number that is linked to a treatment via a pre-populated randomisation schedule. The schedule will be generated in seven balanced blocks of 10 and one balanced block of four by an independent statistician using an online random number generator and stored in a password-protected system inaccessible to blinded study personnel (centralised computerised randomisation). The schedule will only be available to the statistician, an independent researcher and the company that will package and label the treatments (Central Pharmacy Logistics, Coburg North, Victoria).

Treatment allocation will be concealed using numbered containers (or 'sachets'). Each 'dose' will be packaged in a separate, opaque, aluminium sachet labelled with a unique randomisation number.

As this is a double-blind study, participants and the remainder of the research team will not be aware of the assigned treatment. In the event of an emergency, the principal investigator or trial physician may request the unblinding of a participant for medical care.

2.4 Eligibility Screening

A Study Flowchart is presented in Figure 1. Willing volunteers will complete a comprehensive online Screening Questionnaire using the 'Research Electronic Data Capture' (REDCap[™]) web-based system (~20 minutes). Volunteers are required to complete a compulsory online declaration tick-box at the start of the questionnaire consenting to the use of the information they provide to evaluate their eligibility. The questionnaire will assess their eligibility to participate. Each volunteer who attempts the Screening Questionnaire will be assigned a unique screening number to anonymise their identifying information. The trial physician will review volunteers' responses and decide on their eligibility for the trial. They will document their decision by completing an Eligibility

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1 2 3 4 5 6 7	268 269	Declaration form and a prescription for the trial drug (valid only when the volunteer has been randomised).
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15 16 17 18 19 20 21		
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36 37 38 39 40 41 42		
43 44 45 46 47 48 49		
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270 [INSERT FIGURE 1 HERE]

Figure 1. Study flowchart summarising the screening, enrolment and randomisation of participants in the CAPSTAN trial.

¹² 13 275 **2.5 Enrolment**

Eligible participants will be invited to complete a telehealth interview with the trial coordinator. Here, they will receive detailed information about the trial procedures and risks and be informed that their enrolment requires a negative urine drug and pregnancy screen at the start of the experimental procedures (i.e., the "Test Day"). The trial coordinator will invite the volunteer to ask questions and to discuss participation in the trial with the trial doctor, or to take additional time to consider their decision to participate. Once the trial coordinator is confident that the volunteer understands the requirements of the trial, they will request that the participant sign the informed consent form (please see Supplementary file). The trial coordinator will then counter-sign the consent form, collect basic demographic information and book the participant for a Test Day.

- **2.6 Experimental Procedure**
- Each participant will complete one Test Day (~3 hours) at the Brain and Mind Centre at the University of Sydney (**Table 1**).

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Time (minutes) from start	Approximate Duration	Activity
0	10 min	Introduction and pre-trial compliance checks
10	5 min	Randomisation
15	15 min	Pre-treatment measures
30	10 min	CBD or placebo administration and caloric beverage
40	50 min	Rest period 1
90	15 min	Virtual reality orientation
105	15 min	Baseline measures
120	15 min total (2 min) (3 min) (5 min) (5 min)	Public Speaking task: Instructions Speech preparation Speech delivery Arithmetic challenge
135	10 min	Rest period 2
145	5 min total (2 min) (3 min)	Walk the Plank task: Instructions Walk the Plank task
150	10 min	Rest period 3
160	5 min total (2 min) (3 min)	Rollercoaster Ride task: Instructions Rollercoaster ride task

2.6.1 Standardisation Procedures

10 min

15 min

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Prior to each onsite Test Day, participants will be instructed to: (a) abstain from alcohol (≥24 h); (b) avoid greater than one standard serving of caffeine at least 2-hours before the Test Day; (c) ensure they are well hydrated; and (d) ensure that they are adequately fed by consuming a meal at least 2 hours before arrival to the Test Day. These factors aim to reduce the likelihood of malaise, gastrointestinal disturbances or heightened anxiety on the Test Day.

Rest period 4

Study Close

End Of Test Day

 2.6.2 Compliance Checks

Participants will complete a urinary drug screen (to identify any recent use of cannabis and other psychoactive substances such as cocaine, ecstasy (MDMA), amphetamines, benzodiazepines and opioids) and, if they are female, a urine pregnancy screen, on arrival at the study site. The trial coordinator will also confirm compliance with the standardisation procedures and if there have been any changes to the participant's health status or medication use since the last contact. Participants who meet these requirements will be randomised; those who do not may be invited to return at another time if suitable.

¹⁸ 319 19 320

0 2.6.3 Experimental Procedures

Following randomisation, participants will be fitted with the Equivital EQ02+ LifeMonitor belt and the VR headset (detailed below). There will then be a 10-minute collection of pre-treatment measures (see Study Outcomes below). After this, the VR headset and Equivital EQ02+ LifeMonitor belt will be temporarily removed, the treatment administered, and the participant given a compulsory standardised caloric beverage to consume; specifically, 500 mL of "Up & Go Liquid Breakfast" (Sanitarium, Berkeley Vale NSW, Australia) containing approximately 1,640 kilojoules, 16.8g of protein, 8.6g of fat and 57g of carbohydrates. For consistency, all participants are required to consume this beverage in its entirety, which aims to potentiate the absorption of CBD in the gastrointestinal tract [6, 48-50] and provide participants with sustenance during the test session. Participants will be provided with a rest period of approximately 50 minutes, during which they will be left alone in a quiet reception area and encouraged to undertake some low-stress reading; this delay is aimed at allowing CBD plasma concentrations to approach a near-maximal level [48]. Following this, participants will be provided with instructions on the three VR tasks and the functionality of the VR hardware during a 15-minute "VR Orientation" session. The VR headset and Equivital EQ02+ LifeMonitor belt will then be re-fitted for a 10-minutes collection of the pre-task measures. The devices will remain fitted to participants until the end of the experimental procedure.

2.6.4 Virtual Reality Tasks

The three tasks developed for this clinical trial are the "Public Speaking" task (for psychosocial stress), the "Walk the Plank" task (for situational anxiety) and the "Rollercoaster Ride" task (for motion sickness). Although these exact VR tasks have not been previously used in clinical trials or laboratory studies, similar tasks have been reported in the broader scientific literature [29, 32, 40-42, 51].

The 15-minute "Public Speaking" task was modelled on previous studies that found CBD to have anxiolytic effects during public speaking challenges [23, 24, 39] and the Trier Social Stress Test (TSST) [52]. The abovementioned public speaking tasks varied in their methodology and involved either "simulated" public speaking tasks whereby participants delivered a speech in front of a video camera or real-life tasks where participants delivered speeches to a live audience [23, 24, 39]. Conversely, the TSST is a structured stress paradigm involving a 10-minute speech preparation period followed by a 10-minute test period during which participants complete a 5-minute job application speech followed by 5 minutes of mental arithmetic [53]. The TSST reliably induces psychosocial stress (i.e., stress involving the perception of one's worth, competence, or status by others) and results in an acute and reliable cortisol response in most participants [53-55]. In one study, a VR adaption of the TSST elicited similar salivary cortisol and subjective stress responses to a real-life TSST, demonstrating that the two were equivalent [29]. The current study utilises a modified VR version of the TSST involving a panel of virtual judges who withhold all feedback or affirmation (Figure 2A).

The task involves a three-minute "speech preparation period" (i.e., "please mentally prepare a speech on what attributes and experience you have that makes you the ideal candidate for your dream role") and a 10-minute "test period" consisting of (a) five-minute speech delivery period (i.e., "please deliver your speech and aim to speak for the full five-minutes") and (b) a five-minute mental arithmetic challenge (i.e., "please calculate 2703 – 13. From the result, please subtract 13 again and state your answer out loud. Repeat this process a total of five times. At the end of this process, please recall all five of your answers aloud").

55
56368The five-minute "Walk the Plank" task requires participants to virtually walk across a57
58369narrow virtual plank between two skyscrapers. Participants will be advised that they have59
60370become stranded on the top of the building and are required to signal for help using the safety

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beacon placed at the opposite end of the plank. For this task, participants will walk up and
down the length of the clinic room with their movement mapped to the virtual plank and
guided by virtual boundaries, signifying a safe space (Figure 2B). VR studies utilising a similar
challenge provided realistic experiences that induce physiological markers of stress that are
consistent with acute anxiety (i.e., "situational anxiety") [40-42].
The five-minute "Rollercoaster Ride" task challenges participants to complete a virtual
rollercoaster ride (Figure 2C). Participants will remain seated throughout this task and can
indicate if they would like to stop the task early. Similar VR tasks have been shown to induce
motion sickness in participants [32, 43, 44]. Motion sickness will be explored explicitly during
the "Rollercoaster Ride" task, while cybersickness will be explored during all three VR
scenarios.
[INSERT FIGURE 2A,2B AND 2C HERE]
Figure 2. (A) The panel of virtual judges from the "Public Speaking" task; (B) The roof of the building
and plank from the "Walk the Plank" task; and (C) The view from the seat of the "Rollercoaster Ride"
task.
2.6.5 Post Trial Procedures
After completing the final VR task, participants have a 10-minute recovery period.
After this, they will be queried on any adverse events (AEs) experienced (i.e., "Have you
experienced any unfavourable symptoms?"), What treatment do they think they received
(i.e., CBD or placebo), and what are their confidence estimates (i.e., How sure are you of your
guess on which treatment you received?"). All participants will be provided with the contact
details of the research team to self-report any AEs over the next 24 hours. The trial
coordinator or research assistant will record all adverse event reports using a REDCap [™] AE
report form and communicate to the trial physician if required.
The occurrence of AEs will be discussed weekly with the trial physician. Furthermore,
a blinded summary of AE reports will be emailed to the trial physician monthly, and the trial
physician will indicate if the rate of AEs is unacceptably high. In the unlikely event of a severe

2.6.5 Post Trial Procedures After completing the final After this, they will be gueried on experienced any unfavourable sym (i.e., CBD or placebo), and what are guess on which treatment you rece details of the research team to coordinator or research assistant w report form and communicate to th The occurrence of AEs will b a blinded summary of AE reports w physician will indicate if the rate of

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3 4	401	adverse event (SAE), the trial physician and the principal investigator (PI) will be immediately				
5	402	notified, and all SAEs will be reported to the trial sponsor and the HREC within 72 hours.				
6 7	403					
8 9	404	2.7 Data Collection				
10 11	405	A summary of the data collected during the CAPSTAN trial and time of collection is provided				
12 13	406	in Figure 3				
14 15	407					
16 17	408	[INSERT FIGURE 3 HERE]				
18	409					
20	410	Figure 3. Data collected during the CAPSTAN trial "Test Day.				
21 22	411	IPS = instructions for the "Public Speaking" task, SP = speech preparation, SD = speech delivery, AC =				
23 24	412	arithmetic challenge, IWP = instructions for the "Walk the Plank" task, WPT = "Walk the Plank" task,				
25	413	IRR = instructions for the "Rollercoaster Ride" task, RRT = "Rollercoaster Ride" task				
26 27	414					
28 29	415	2.7.1 Study Outcomes				
30 31	416	The primary outcome measures include:				
32	417	 Self-reported stress ratings on a VAS (<i>nervous 0-100</i>) 				
33 34 25	418	 Self-reported nausea ratings on a VAS (nauseous 0-100) 				
35 36	419					
37 38	420	The secondary outcome measures include:				
39 40	421	Salivary Cortisol				
41 42	422	Heart rate				
43 44	423	Skin Conductance				
45 46	424	 Vomiting or near-vomiting episodes 				
40 47 48 49 50 51 52 53 54 55 56 57 58 58	425	 Self-reported anxiety ratings on VASs include: 				
	426	o (tense 0-100)				
	427	o (calm 0-100)				
	428	○ (excited 0-100)				
	429	o (bored 0-100)				
	430					
	431	The exploratory (tertiary) outcome measures are:				
60	432	Salivary testosterone and progesterone				

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2					
3 4 5 6	433	Eye-tracking data including:			
	434	 The frequency and duration of eye-closing 			
7	435	\circ $$ The frequency and duration of gaze at areas of interest			
9	436				
10 11 12 13 14	437	2.7.2 Visual Analogue Scales (VASs)			
	438	VASs will be used to measure the two primary outcomes: self-reported stress			
15 16	439	(nervousness) and nausea. They will also be used to measure the secondary outcome of self-			
17 18	440	reported anxiety (as detailed below) (Figure 4). These measures will be recorded before drug			
19	441	administration (pre-treatment measurement), at baseline, prior to the commencement of			
20 21	442	each VR task, at the completion of each VR task and at the study close. VAS measures will also			
22 23	443	be recorded prior to the performance of the speech during the "Public Speaking" task			
24 25	444	(Timepoint "SD" Figure 3) and prior to the performance of the walk during the "Walk the			
26 27	445	Plank" (Timepoint "WPT" Figure 3) task. These measures aim to capture "anticipatory			
28	446	anxiety" reported prior to anxiety-inducing tasks in previous studies [23, 24]. As nausea is the			
30	447	main interest during the Rollercoaster Ride task, no VAS measures for anticipatory anxiety			
31 32	448	will be taken for this task. All VASs will appear on the screen of the VR headset, and			
33 34	449	participants will use the VR hand controllers to click on the numerical value (0-100) that best			
35 36	450	describes their current state (Figure 4). Using such virtual scales allows seamless execution of			
37 38	451	self-report without disturbing the participant's sense of immersion within the virtual			
39	452	environment.			
40 41	453	For a well-rounded exploration of CBD effects on anxiety, we have utilised VASs that			
42 43	454	query participant's affect (i.e., the outward expression of an emotion) [56]. Here, we consider			
44 45	455	1) the "valence" of an emotion (i.e., its positivity or negativity) and 2) the intensity of the			
46 47 48	456	emotion (i.e., whether it is arousing or deactivating). This provides four self-reported anxiety			
	457	rating VASs, including:			
50	458	 positively arousing (excited 0-100) 			
51 52 53 54 55 56	459	 positively deactivating (calm 0-100) 			
	460	 negatively arousing (tense 0-100) 			
	461	 negatively deactivating (bored 0-100) 			
57 58	462				
59 60	463	[INSERT FIGURE 4 HERE]			

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2					
3 4	464				
5 6 7 8 9 10 11 12 13	465	Figure 4. Self-reported Visual Analogue Scales (VASs) as they appear on the virtual reality			
	466	headset. Values are provided by the participants by clicking on the scales using the hand			
	467	controllers.			
	468				
	469	2.7.3 Salivary Cortisol, Testosterone and Progesterone			
15 16	470	During the experimental procedure, oral fluid samples will be collected from			
17	471	participants five times using Salivette® collection tubes (Sarstedt AG and Co., Nümbrecht			
18 19 20 21	472	Germany). These samples will be collected immediately before drug administration, before			
	473	the first VR task, and after each VR task. Participants will be advised to open the Salivette®			
22 23	474	tube, place the pad in their mouth for two minutes or until soaked with saliva, then return			
24 25	475	the pad to the tube and firmly seal it. The samples will be centrifuged for 2 minutes at 1,000			
26 27	476	x g and analysed simultaneously for cortisol (a secondary outcome) and testosterone and			
27 28 29 30	477	progesterone (exploratory outcomes) using an in-house developed mass spectrometry (MS)			
	478	method [57, 58].			
31 32	479				
33 34 35	480	2.7.4 Heart Rate			
36 37	481	Heart rate will be measured for 10 minutes immediately before drug administration			
37 38 39 40	482	(baseline measurement), for 10 minutes at baseline and continuously throughout all three VR			
	483	tasks using the EQ02+ LifeMonitor and belt, as described in previous studies [59, 60] (Equivital			
41 42	484	Ltd. Cambridge. United Kingdom: https://www.adinstruments.com/partners/equivital). This			
43 44	485	is a wireless, medical-grade monitoring system that records a range of physiological measures			
45 46	486	(such as electrocardiogram breathing rate tri-axial acceleration galvanic skin response skin			
47	487	temperature) using a wearable vest and permits live data streaming and download using the			
48 49	188	LabChart coftware			
50 51	400				
52 53	409				
54 55	490	2.7.5 Skin Conductance			
55 56	491	Skin conductance will be measured for 10 minutes immediately before drug			
57 58	492	administration (baseline measurement), for 10 minutes at baseline and continuously			
59		. "			

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Skin conductance of the forehead will be measured using the Equivital GSR Sensor connected to the EQ02+ LifeMonitor and belt (as described above). Skin conductance of the fingers will be measured using MLT117F/10 GSR finger electrodes connected to a FE116 GSR Amp with a PLCF1 front-end interface used with PowerLab C software (ADInstruments, Oxford United Kingdom), a system used in previous studies [61, 62]. Research suggests that forehead skin conductance may correlate with motion sickness, while finger skin conductance correlates with acute stress [32, 63]. Therefore, both will be measured in the current study.

502 **2.7.6 Vomiting Episodes**

The Test Day source document will record all vomiting episodes throughout the experimental procedure.

6 2.7.6 Eye-tracking

507 Eye tracking data will be collected continuously throughout the VR tasks using the VR 508 headset. These measures will provide highly precise, objective data by which to examine 509 participant's compliance (frequency and duration of eye closing) and engagement and 510 response (frequency and duration of gaze at areas of interest, that is, the panel of judges in 511 the "Public Speaking" task or the plank in the "Walk the Plank" task) during the VR challenges 512 [64]. Gazing at pre-defined points of interest (e.g., the judges in the "Public Speaking" task or 513 the plank in the "Walk the Plank" task) is based on the "Eye-Mind Hypothesis" that describes 514 the tendency for people to direct their gaze towards what they are thinking about [64-66]. 515 Both eye closing and gaze away from points of interest may correlate to fear or avoidance 516 behaviours [67].

518 2.9 Data Management

519 Participant information collected for this trial will be securely stored and treated as 520 confidential. Participants' identifying information will be anonymised using unique codes: 521 initially, a screening number and, later, a randomisation number. The key to these codes will 522 be securely stored in password-protected files inaccessible from the internet. Clinical trial 523 data will be collected and managed using REDCap[™], a secure, online program supported by 524 the University of Sydney; access is password-protected and will only be available to approved **BMJ** Open

research staff. Hard copies of patient data will be securely stored in locked filing cabinets at the study site. Only the study investigators have access to the participant data. All trial data will be stored securely for at least 15 years. The findings of this clinical trial will be disseminated via conferences, publications, and media, as applicable. Participants will be informed of the results of the study at the conclusion of the trial. No participants will be identified in any report or publication of this study or its results.

14 531

2.10 Data and Safety Monitoring

Data monitoring will occur monthly for all new participant entries logged into the REDCap system; a designated team member will adhere to a standardised process of data review, raising queries and locking forms once the review has been completed. Safety monitoring of AEs will be managed according to sponsor and HREC requirements. As this is a small, single-centre, low risk, clinical trial utilising an acute, low-dose CBD, an independent data safety monitoring committee will not be formed. However, an independent 'Expert Group' has been formed and will be consulted by the research team and HREC in the unlikely instance of a severe adverse event. The Expert Group comprises three research physicians with extensive experience with CBD clinical trials. The decision to terminate the trial lies with the principal investigator based on safety data and recruitment targets.

³⁶ 37 543

 2.11 Roles and Responsibilities

545 The study investigators have led the design of this study and are responsible for the 546 management and conduct of this clinical trial. The study investigators will conduct the analysis 547 and will make all publication-related decisions.

- 48 549 **2.12 Statistical Methods**
- 50 550

2.5.1 Sample Size Estimation

53
54552The target sample size was determined *a priori* using power calculation software55
55553(G*Power Version 3.1.9.6, University of Kiel, Germany). In an earlier investigation, Linares *et*57
58554*al.* (2019) found that 150 mg CBD decreased subjective ratings of anxiety on the Visual

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Analogue Mood Scale (VAMS) during a simulated public speaking test, albeit non-significantly
(Placebo: 18.6±15.9 mm, n=15; CBD: 7.6±15.5 mm; n=15; Cohen's *d*=0.70) [23].

Using an equivalent effect size (Cohen's d=0.70), a power (1-ß) of 0.8 and a two-sided α =0.05, we estimate that n=68 participants will be required to detect a significant effect of CBD on anxiety. Clinical trials conducted by the Lambert Initiative for Cannabinoid Therapeutics have indicated participant retention of ≥90% [48, 68]. Therefore, the n=74 will be recruited to account for attrition.

563 2.5.2 Statistical Analysis Plan

564 The primary and secondary outcomes and eye-openness will be analysed using 565 generalized linear mixed models (GLMM), while eye gaze will be analysed using a mixed-566 effects multinomial logistic regression. Treatment, Time and the Treatment × Time interaction 567 will be included as fixed effects, and the participant will be included as a random effect, with 568 other covartiates included as appropriate to improve goodness of fit (e.g., Sex, Age, Time of day). To refine the models, we will use corrected Akaike Information Criterion [69]. We will 569 570 calculate Δm between models and exclude models with $\Delta m > 2$ as having substantially less 571 support [70]. No covariance structure will be specified (unstructured). To identify the best 572 distribution and link for the GLMM models, the data type, residual plots, Shapiro-Wilk 573 normality test, Levene's test for Homogeneity of Variance, and Pearson's dispersion test will 574 be used. Type III Wald chi-square tests will be used to generate main effects p-values. A priori 575 planned uncorrected pairwise comparisons will be performed to compare:

- subjective ratings of stress on a stress VAS (*nervous 0-100*) across treatments at
 (Timepoint t=125 (SD), Figure 3)
- subjective ratings of stress on a stress VAS (*nervous 0-100*) across treatments at
 (Timepoint t=147 (WPT), Figure 3)
- subjective ratings of nausea on a nausea VAS (*nauseous 0-100*) across treatments at
 (Timepoint t=165, Figure 3)
 - subjective ratings of nausea on a nausea VAS (*nauseous 0-100*) across treatments at
 (Timepoint t=175, Figure 3)
- 584 as these are the primary outcome measures.

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585 Dunn-Šidák corrected pairwise comparisons will be performed where additional 586 significant main and interaction effects are present. Statistical significance will be accepted as 587 p<0.05. The statistical analysis plan will be finalised before the last participant Test Day and 588 will be available on request.

11 589

13 590 **3.**

3. STATEMENTS AND DECLARATIONS

Ethics and dissemination: The study has been approved by the University of Sydney Human 592 Research Ethics Committee (HREC; 2023/307, Version 1.6, 16th February 2024). The findings 593 of this clinical trial will be disseminated via conferences, publications, and media, as 594 applicable. Participants will be informed of the study's results at the trial's conclusion. No 595 participants will be identified in any report or publication of this study or its results.

27 597 Author Contributions

I.S.M, D.M, H.M, M.B.P, N.S.L, R.F and Z.B were involved in the conception and design of the research project. Z.B drafted the manuscript, and all authors were involved in critically revising it. I.S.M is the principal investigator who has overall responsibility for the design, conduct and decision to submit for publication. M.B.P is the study statistician, N.S.L will provide medical oversight, H.M and R.F created the virtual reality challenges in collaboration with I.S.M and Z.B. Z.B is the trial coordinator responsible for collecting trial data. All authors have read and approved the final manuscript.

41 605

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44606Funding Statement

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 philanthropically funded centre for medicinal cannabis research at The University of Sydney.
 609

51 610 **Competing Interests**

Author I.S.M. acts as a consultant to Kinoxis Therapeutics and has received honoraria from Janssen. He has also served as an expert witness in various medicolegal cases involving cannabis and cannabinoids. I.S.M. hold patents on cannabinoid therapies (PCT/AU2018/05089 and PCT/AU2019/050554) and has received consulting fees from the

2		
3 4	615	Medicinal Cannabis Industry Australia (MCIA). D.M. has also received consulting fees from
5 6	616	MCIA. Z.B, H.M N.S.L, R.F and M.B.P have no disclosures to report.
7	617	
8 9	618	Patient and public involvement
10 11 12 13 14 5 6 7 8 9 0 12 23 24 25 22 22 22 22 22 22 22 22 22 22 22 22	619	Patients and/or the public were not involved in the design, or conduct, or reporting or
	620	dissemination plans of this research.
	621	
	622	Patient consent for publication
	623	Not applicable.
	624	
	625	Trial Sponsor
	626	The University of Sydney, Sydney NSW Australia.
	627	
	628	Data Availability Statements
	629	The deidentified participant data are available from Professor lain McGregor
	630	(iain.mcgregor@sydney.edu.au) upon reasonable request.
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The Cannabidiol for Acute Psychosocial Stress and Nausea (CAPSTAN) Trial ENROLMENT CONSENT FORM (HREC Approval No.: 2023/307)

- 1. I have read and understood the Participant Information Sheet and agree to take part in the CAPSTAN trial.
- 2. I have had the project, so far as it affects me, and the potential risks and burdens fully explained to my satisfaction by the research team. I have had the opportunity to ask any questions I may have about the project and my participation. My consent is given freely.
- 3. I have no history of allergy or other adverse reactions to the drug, cannabidiol.
- 4. Although I understand the purpose of the research project is to improve the quality of health/medical care, it has also been explained to me that my involvement may not be of any benefit to me.
- 5. I realise my participation in this study is voluntary and that I have the right to withdraw from the study at any stage without prejudice. I also understand that the research team has the right to terminate the study at any stage before completion, without jeopardising my medical care, if they believe this is in my best interests, for non-compliance with study procedures or for other legitimate reasons. If I decide to withdraw from the study, I agree that information collected about me up to the point when I withdraw may continue to be processed.
- 6. I understand that all information will remain confidential and while the information gained during the study may be published in journal articles, conferences, presentations etc, I will not be identified in any way. I agree to my non-identifiable information being used for future research purposes limited to the work of the University of Sydney.
- 7. My information will only be used for the purposes of this research, and it will only be disclosed according to the consent provided, except where disclosure is required by law.
- 8. I understand that access may be required to my medical records for the purpose of this study as well as for quality assurance, auditing and in the event of a serious adverse event and I consent to this access.
- 9. I am aware that I should keep a copy of this Consent Form, when completed, and a copy of the Patient Information Sheet.

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- 10. I agree to have my General Practitioner informed of my participation in this study if required for my medical care and that he/she may divulge details of my past medical history, as he/she sees relevant, to the Investigator.
- 11. I am aware that I should keep a copy of the completed Consent Form and the attached Participant Information Sheet.
- 12. I am 18 years of age or over.

This consent form relates to Participant Information Statement Version 1.6_1 December 2023

Participant to comp	lete:	
I consent to particip participate in the CA	ate in the CASTAN trial screening proc ASTAN trial.	cedure and if eligible, I consent to
Name:	Signature:	Date:
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I have described the and in my opinion, s	nature of the research to he/he understood the explanation.	print name of participant
Name:	Signature:	Date:
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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ltem No	Description	Manuscript Page and Notes
Administrative in	nformati	on	
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	Yes, ANZCTR public trials registry, ACTRN12623000872639. Registered 15 August 2023.
Protocol version	3	Date and version identifier	2, 6 and 25
Funding	4	Sources and types of financial, material, and other support	6, 25
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1,25
	5b	Name and contact information for the trial sponsor	6
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	25
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	23
Introduction			

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
	6b	Explanation for choice of comparators	8
Objectives	7	Specific objectives or hypotheses	6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5-6
Methods: Particip	oants, in	terventions, and outcomes	
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6-7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	NA, intervention is a single acute dose of active or placebo with no ongoing involvement of participants.
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	NA, intervention is a single acute dose of active or placebo with no ongoing involvement of participants.
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	12-13

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Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	19
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	10 (Figure1)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	23
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7
Methods: Assignn	nent of	interventions (for controlled trials)	
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9

Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	9
Methods: Data c	ollection	n, management, and analysis	
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	22
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	7,17
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	22-23
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	23-24
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	23-24
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to	23-24
		handle missing data (eg, multiple imputation)	

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Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	23
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	17
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	22-23
Ethics and disser	ninatio	n	
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	2, 6, 25
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	6
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	22

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Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	25
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	22
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	17
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	22
	31b	Authorship eligibility guidelines and any intended use of professional writers	23
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	23
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	NA
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "<u>Attribution-NonCommercial-NoDerivs 3.0 Unported</u>" license.