INFORMATION TO PARTICIPANTS INVOLVED IN RESEARCH: PROJECT TWENTY21 AUSTRALIA

You are invited to participate

You are invited to participate in a research project entitled **Project Twenty21 Australia: A Prospective, Real-World Observational Cohort Study to Investigate the Efficacy of Medicinal Cannabis.**

This study is being conducted by Dr Sylvia Victor PhD (Chief Commercial Officer at Releaf Group Ltd and Adjunct Professor Torrens University), Professor Justin Beilby, MBBS, PhD (Torrens University) and a team of Australian clinicians and academics in Australia and the UK and US.

Ethics Approval

This research project has been approved by the National Institute of Integrative Medicine Human Research Ethics Committee on 20 December 2021. The HREC Approval no. is 0097E_2021.

Project explanation and objectives

Project Twenty21 Australia is a collaboration between Releaf Training and Education Pty Ltd, an Australian company trading as the Australasian College of Cannabinoid Medicine (ACCM) which is conducting research into medicinal cannabis), and Drug Science Org in the UK. Project Twenty21 is already underway in the UK (see https://www.drugscience.org.uk/). Project Twenty21 Australia is the Australian arm of this project, where data will be collected in an Australian population in four out of the seven clinical conditions being investigated in the UK. These four clinical conditions are: chronic pain, anxiety, post-traumatic stress disorder (PTSD) and multiple sclerosis (MS).

If you are a patient who is about to or has just consulted a Releaf Clinic clinician (doctor or nurse practitioner) about medicinal cannabis and is eligible for its prescription, and you have one of the following conditions: anxiety, chronic pain, PTSD and MS, you are invited to participate in this study.

This study is an observational study in which participants will be followed for up to a total of 6 months. Outcome measures which measure change in symptoms are predominantly questionnaires, which you will complete at three timepoints (beginning of study, then every three months for up to 6 months depending on how long you are prescribed medicinal cannabis for your condition). Data on safety and tolerability of medicinal cannabis will also be collected. Medicinal cannabis products prescribed by the study clinicians for study participants will be chosen from a Project Formulary containing a range of cannabis oils and flower from five companies in Australia.

Aims and Objectives

Overall, *Project Twenty21 Australia* aims to investigate whether medicinal cannabis (as a whole) is efficacious in alleviating symptoms associated with chronic pain, anxiety, post-traumatic stress disorder (PTSD) and symptoms of multiple sclerosis (MS). It also aims to investigate whether particular sub-categories of medicinal cannabis oil (high CBD, balanced CBD/THC and high THC) and cannabis flower (THC-dominant) are efficacious in alleviating symptoms associated with these conditions. It will achieve these aims by aggregating data from questionnaires from all participants and analysing this as a whole as well as conducting statistical analysis of results in relation to subcategories of oils and flower products prescribed from the Project Formulary.

Who can participate in this study?

This study is open to patients who are about to consult or have just consulted a clinician at Releaf Clinics about having medicinal cannabis prescribed, are not currently using medicinal cannabis or using it recreationally AND have at least one of the following diagnosed conditions below and meet the inclusion criteria (set out below):

- Anxiety
- Post-traumatic stress disorder (PTSD)
- Chronic pain
- Multiple sclerosis (MS)

Inclusion Criteria

1. Patients, females and males, aged 18 years and over with a diagnosis which falls under one of the following five study categories: chronic pain, anxiety, PTSD, and multiple sclerosis and who are prescribed medicinal cannabis as per standard clinical practice by a clinician at Releaf Clinics.
2. In the professional opinion of the treating clinician, the patient is eligible to be prescribed medicinal cannabis in Australia.
3. Ability to fully understand the potential side effects associated with medicinal cannabis, and the fact that driving with any amount of THC in your system is an offence under Australian driving laws in all states and territories.
4. Ability to fully understand the requirements of participation in the study.
5. Provide written informed consent to participate in the study and are willing to comply with the study procedures.
6. Agree to be prescribed medicinal cannabis products from the Project Formulary.

Exclusion Criteria

1. Patients currently using recreational cannabis (where use is chronic and more than three days per week for the past 2 months) or currently using medicinal cannabis for medical reasons.
2. Evidence of clinically relevant haematological, gastrointestinal, hepatic, renal, endocrine, pulmonary, neurologic or psychiatric disorder which in the opinion of the medical practitioner should preclude them from participating in the study.
3. Known allergy to medicinal cannabis, CBD or any of the components of the medicinal cannabis products in the Project Formulary.
4. Pregnancy or active breast feeding.
5. Clinically significant abnormalities in baseline laboratory test results including liver function and kidney function: Creatinine > 1.5 times upper limit of normal; ALT, AST or ALP > 2 times upper limit of normal.
6. Taking warfarin or any other blood thinning medication (which may interact adversely with CBD).
7. Have participated in a clinical trial or receipt of an experimental therapy within 30 days prior to inclusion.
8. Unwilling or unable to provide written informed consent.

What will I be asked to do? How will this project be conducted?

Recruitment

Information about the clinical study will be made available on the Releaf Clinics website (and also the website of the ACCM, the Australasian College of Cannabinoid Medicine). Posters will be displayed in the waiting rooms of participating Releaf Clinics. Study participants may be recruited to the study in two main ways. 1) When booking an initial medicinal cannabis consultation online with a Releaf clinician, or via phone, potential participants will be advised of the study and 4 conditions being investigated, and asked if they would be interested in being contacted about the study by the Study Coordinator, prior to their clinician appointment. If they answer yes, the Study Coordinator will then contact the potential participant prior to their initial clinician appointment and explain the study. The Study Coordinator will go through the Inclusion and Exclusion criteria to see if the potential participant meets these. The patient will be emailed the Participant Information form and the Informed Consent form to fill in electronically. The Study Coordinator will inform the Releaf Clinician that the patient has consented to be part of

the study prior to their appointment. 2) The second means of recruitment is that a Releaf clinician involved in the study may ask a patient during her/his medicinal cannabis consultation if she/he is interested in being part of the study, and will explain the study and answer any questions she/he may have about the study. The doctor will advise the Study Coordinator of the patient's interest in participating. The patient will then be given an electronic copy of the Participant Information form and asked to sign an Informed Consent form electronically (which attests to the fact that she/he has agreed to participate in the study and understands the nature of what is required) and is then is enrolled in the study.

Initial Consultation
At the initial consultation, a normal consultation for medicinal cannabis occurs, where the suitability of medicinal cannabis is ascertained and potential side effects also discussed. Some general data is collected including age, gender, smoking status (for smokers, no. of cigarettes/day), previous history of cannabis use and whether you drink alcohol or not (if yes, no. of standard drinks per week). Weight and height are measured and body-mass index calculated.

You will be given a pathology slip to have a blood test (which includes a full blood examination plus liver and kidney function tests) completed which you need to do before you start using medicinal cannabis. You will be prescribed medicinal cannabis by your clinician under the two main cannabis prescribing schemes. The clinician will choose from several different types of cannabis products from the Project Formulary, which contains medicinal cannabis products from the five companies supporting this study (these include cannabis flower, cannabis oils and cannabis tablets). Your medicinal cannabis prescription can take up to a week to be filled, depending on the prescribing pathway the clinician uses. The prescription will be dispensed via Releaf dispensaries. You pay for your cannabis medicine, the same as any other patient, however you will receive a small discount on any cannabis medicines prescribed from the Project Formulary for the time you are in the study. Medicinal cannabis prescriptions are not covered under the Pharmaceutical Benefits Scheme.

Follow-Up Visits and Questionnaires
You will attend regular follow-up visits with your Releaf clinician every three months after your initial consultation for up to 6 months as part of the study. Please note that your clinician is likely to suggest additional appointments that are unrelated to the study, as part of routine medical care, in particular within the first 1-2 months of being prescribed cannabis for the first time (this is to assess how well medicinal cannabis is working for you, and in order to fine tune the type of cannabis medicine and dosage). The study follow-up visits can be face-to-face consultation or telehealth consultations, depending on your preference and circumstances.

The following questionnaires will be conducted at each of the thee time-points during the study (baseline/beginning of study and at months 3, and 6:

- a health-related quality of life questionnaire;
- a sleep questionnaire;
- a depression/mood questionnaire;
- a condition-specific questionnaire (there are two condition-specific questionnaires for those with MS)

You will also be asked to complete two general questionnaires which measures overall (global) impression of change and a Cannabis-Based Medicine questionnaire and a medicinal cannabis symptom diary at months 3 and 6*.

You are required to fill in these questionnaires before or within 2-3 days of your initial visit- this gives baseline information. The questionnaires will be emailed to you.

You will also be emailed the questionnaires prior to each of your clinician study follow-up visits at 3 and6* after your initial visit. A second reminder email is also sent automatically. You are asked to complete these questionnaires 2-3 days prior to your clinician appointment so that the clinician can review these.

* Note that as this is an observational study, in some cases participants may not be prescribed medicinal cannabis for 6 months (for example, in the case where a condition resolves and the medication is no longer necessary). In such cases, therefore, study participation would be less than 6 months.

Other measurements during the study
In addition to having these measurements at your initial consultation, your height and weight will be measured again at the 6 month appointment (and body-mass index calculated) and you will also be given a pathology slip to have blood tests (full blood exam, liver and kidney function tests) done at 6 months.

What will I gain from participating?

By participating in this study, you may learn about how medicinal cannabis is impacting on your health through participating and completing the study questionnaires. You will also be contributing to knowledge within the field of medicinal cannabis.

Costs Associated with Participating in the Study: Cannabis medicines prescribed from the Project Formulary for study participants will be available at a discounted price for the time that you are part of the study. As this study is an observational, real-world study, participants cover the cost of their initial consultation with the Releaf clinician as they would normally (Medicare rebates may be available for face-to-face consultations but are not available for all doctors). Patients also cover the costs of any subsequent follow-up visits with their Releaf Clinic doctor that are part of their normal care and are not associated with the study. However, the 3, and 6month follow-up study visits (that is, those visits that are part of the observational study) may be bulk-billed under Medicare where eligible. Generally face-to-face consultations are eligible for Medicare rebates, however there are particular conditions attached to eligibility for Medicare rebates and telehealth consultations set by the government, and these can change from time to time. Note that Medicare rebates are not available for all doctors. Information regarding consultations fees and Medicare rebates for face-to-face and telehealth consultations at Releaf Clinics is available through the clinic reception.

How will the information I give be used?

The results will be de-identified (names removed) and collated (combined with data from other participants) with statistical analysis performed to see primarily if medicinal cannabis or specific subcategories of cannabis medicines are efficacious (effective) in alleviating the conditions investigated in this study, and whether they are safe and tolerable. Data from the Project Twenty21 Australia project (de-identified) will also be combined with data collected in the United Kingdom and statistical analyses conducted on this combined data. Finally, there are five companies supporting this study. A summary of the (de-identified and collated) results for company products will be provided to each company and for those companies who request it, the de-identified raw data will also be provided (which includes the results of the questionnaires, but without any participant names associated) so that they may conduct more in-depth statistical analysis on their cannabis products. The results of this study (Australian data), the results found from combining the Australia-UK data, and the results for specific categories of cannabis products for individual supporting companies will be written up for submission in peer-reviewed medical journals and may also be presented at medical conferences.

What are the potential risks of participating in this project?

There are no additional risks of participating in the study above those risks that are associated with the use of medicinal cannabis that have been or will be discussed with your doctor. According to the Australian government's Therapeutic Goods Administration (TGA), known side effects of medicinal cannabis, both CBD and THC, include fatigue, sedation, vertigo, nausea, vomiting, fever, decreased or increased appetite, dry mouth and diarrhoea. THC and products containing high amounts of THC have also been associated with convulsions, feeling high, feeling dissatisfied, depression, confusion, hallucinations, paranoid delusions, psychosis, and cognitive distortion (having thoughts that are not true) (for more information please see: https://www.tga.gov.au/publication/guidance-use-medicinal-cannabis-australia-patient-information). Note that it is illegal to drive in any state/territory in Australia with

any amount of THC in the body and having a prescription for medicinal cannabis is not a legal defence. The TGA also advises that patients should not operate heavy machinery while being treated with medicinal cannabis. You therefore should not drive or operate heavy machinery whilst taking THC-containing medicines. There is also a risk of cannabis dependence in a minority of patients with medicines containing THC, and withdrawal symptoms associated with stopping cannabis medicines containing THC.

You remain under the care of your medical practitioner or nurse practitioner in relation to your prescription of medicinal cannabis. This study simply tracks and measures a range of patient outcomes in a formal sense. However, you should be aware that driving with any amount of tetrahydrocannabinol (THC, the one potentially intoxicating component of cannabis) in your body is an offence under driving laws in all states and territories of Australia at this time. This will be discussed with your clinician at your consultation.

Withdrawing from study

Note that you may withdraw from the study at any time. Withdrawing from the study will not in any way impact on your medical care at Releaf Clinics.

Exclusion from study

It is sometimes necessary to try more than one cannabis product before the right product is found for you. As long as you are prescribed at least one product from the Project Formulary, you are eligible to remain in the study. However, please note that if all of your prescribed medicinal cannabis medicines fall outside the Project Formulary at any point, for any reason, this will exclude you from the study. Also note that some people may be excluded from participating in the study on the initial blood/pathology screening, as part of the Exclusion Criteria.

Privacy and confidentiality

Only the study investigators have access to the study data. All data collected for statistical analysis will be de-identified (this means your name is removed) and aggregated (combined with the data of other participants). Your participation in this study therefore remains confidential.

Each participant's name is coded, and the code is what is associated with the study data including the questionnaires, not the participant's name. The Study Coordinators will have access to the code which is assigned to each participant. De-identified, coded data (including completed questionnaires) is what will be collated and analysed by the statistician and electronic copies of the de-identified, coded data will be password protected and stored on a secure site within the Project Twenty21 database. Electronic copies of informed consent forms will be password protected and stored on a secure site within the Project Twenty21 database, separate from completed questionnaires.

Any other information collected during your regular consultation with your medical practitioner or nurse practitioner forms part of your medical record, the confidentiality and privacy of which is regulated under various state and territory regulations (in Victoria, this is the Health Records Act 2001).

Who is conducting the study and who should I contact if I have any questions about participating?

The following people are involved in the conduct of the study:

Chief Investigators: Dr Sylvia Victor PhD Email sylvia@releafgroupltd.com
Professor Justin Beilby PhD, Email: justin.beilby@torrens.edu.au, phone 0403 017 457

Associate Investigators (Clinical, Australia):
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Associate Investigators (Academic, UK, US)
Ms Alkyoni Athanasiou-Fragkouli (Project Twenty21 Study Coordinator UK)
Professor Michael Lynsky (epidemiologist and statistician, UK)

Professor David Nutt (psychiatrist, UK)
Professor Mike Barnes (neurologist, UK)
Dr Philip Blair (MD, US)

Study Coordinator: Ms Michelle Frans, registered nurse, **Phone:** 03 9988 0878
Email: michelle@releafgroupltd.com

FOR ALL QUESTIONS IN RELATION TO THE STUDY: please contact the **Study Coordinator** Ms Michelle Frans, registered nurse, Email: michelle@releafgroupltd.com, phone 03 9988 0878

Queries or complaints

If you have any queries or complaints about the way you have been treated or your rights as a participant, you may contact the NIIM Human Research Ethics Committee Secretary, at hrec@niimm.com.au