Prof Iain McGregor
Director of Lambert Initiative for Cannabinoid Therapeutics
A/Prof Sarah Maguire
Director of InsideOut Institute for Eating Disorders
Sarah-Catherine Rodan
CAFTAN Clinical Trial Coordinator
Dr Karen Spielman
CAFTAN Trial Doctor

Lambert Initiative for Cannabinoid Therapeutics
Brain and Mind Centre, NSW 2050
InsideOut Institute for Eating Disorders
Charles Perkins Centre, NSW 2006
Camperdown, University of Sydney
Australia
Email: sarah-catherine.rodan@sydney.edu.au
Telephone: 0403224986

Cannabidiol as an Adjunct for the Treatment of Anorexia Nervosa (CAFTAN): An Open Label Pilot Trial with Extension in Young People

Therapist Information Sheet

(1) What is the purpose of this research?

This study aims to determine the safety and effectiveness of a new pharmacological treatment, cannabidiol (CBD) – the non-intoxicating component of the cannabis plant – in reducing anxiety and improving treatment outcomes in young people with anorexia nervosa who are about to commence Maudsley Family-Based Treatment (MFBT) in the community.

Anorexia nervosa is frequently co-morbid with anxiety disorders and marked by high levels of anxiety in general, particularly in the early stages of treatment where refeeding and weight gain are required. We hypothesize that by targeting the anxiety with this medication we may be able to make therapy easier to deliver, better tolerated by the young person, easier for parents and carers to manage and, ultimately, improve recovery rates.

High anxiety around food, weight, shape are central features for all young people with anorexia nervosa. Treatment, including MFBT, can be associated with heightened anxiety, due to the need for refeeding and frequently substantial weight gain, required for recovery. Fear of weight gain in the early stages of treatment can lead to resistance to weight gain, rendering the task of refeeding more difficult, as parents are required to support their young person to undertake the challenging job of restoring weight, alongside managing their increased anxiety and distress. Increased distress has been shown to impact treatment and its effectiveness. Therefore, an intervention aimed at targeting this anxiety **may make treatment easier to deliver, reducing the stress on families and improving response to MFBT, subsequently improving weight gain and remission rates from the eating disorder.**

The new treatment, cannabidiol (CBD), is a non-intoxicating compound known as a 'cannabinoid' extracted from the cannabis plant. The cannabis plant contains hundreds of different cannabinoids with the two most studied being cannabidiol (CBD) and delta-9-tetrahydrocannabinol (THC). Unlike THC, CBD is non-intoxicating and will not get your child 'high' or 'stoned'. CBD will be administered in the form of a capsule.

The safety of CBD has been extensively researched and safety has been widely demonstrated. CBD products are currently available under prescription in Australia. CBD products are currently prescribed to patients in Australia under the TGA Special Access Scheme pathways for a variety of conditions such as anxiety, chronic pain (including cancer pain and symptoms), epilepsy, and insomnia. CBD has a favourable safety profile with nil risk of addiction, dependence, or tolerance. The most common side effects are nausea, diarrhea, fatigue, and headaches, and are typically mild-to-moderate in severity, tolerable, and self-limiting.

We cannot guarantee that the young person will receive benefit from this trial. However, recent evidence showed that 12-week treatment with 800 mg/day of CBD (same dose as in the present study) resulted in significant reductions in anxiety in young persons aged 12-25 years with treatment-resistant anxiety (Berger et al., 2022). Two-thirds of participants had a >33% reduction and 40% of participants had a >50% reduction in anxiety by end of Week 12. This provides strong incentive to explore the effectiveness of CBD in young people with anorexia nervosa for whom anxiety is both a major feature of illness and a factor impacting the success of treatment.

We anticipate that this study will contribute to important research on the effects of CBD in anorexia nervosa, and may assist in improving pharmacological treatments for eating disorders in the future.

(2) Who is conducting this research?

The research is being sponsored by the University of Sydney and conducted by the Lambert Initiative for Cannabinoid Therapeutics and the InsideOut Institute for Eating Disorders. The results of this research will be used by the study investigator, Sarah-Catherine Rodan, as part of a doctorate (PhD) degree.

For a full list of investigators listed on this research study, please see Appendix B at the end of this letter for their details and contact information.

(3) What does my participation in this research involve?

If you agree to participate in this study, you will be asked to sign the *Therapist Consent Form*. As part of the trial, you will be asked to:

- Follow the MFBT manual and have weekly sessions booked with the participant for the first 12 weeks,

- Keep a record of the participant's weight at each session and to share this information with the research team on a weekly basis,
- Use the **same weight scales** for the full duration of the study,
- Advise the participant's medical practitioner and research team if rapid weight loss occurs (please see guidelines below),
- Complete a brief multiple-choice form, *Therapy Fidelity Form* (5 min to complete), each month reporting on therapy sessions. At the end of MFBT, or in the case of disengagement/withdrawal, you will receive an invitation to complete a brief survey (5 min to complete).

We are very interested in your perception of how CBD may have worked (or not worked) for your client. This brief survey will ask whether CBD was tolerated by your client throughout MFBT and any adjustments they made to the process or regimen. In the case of disengagement, the MFBT clinician will be asked their perspective on the reason for the family's disengagement.

By consenting to participate as a Therapist in the study, you are also agreeing that you will abide by professional registration, ethical guidelines (APS Code of Ethics and relevant ethical guidelines), child protection legislation, mandatory reporting, and legal requirements and obligations, including:

- Make and keep adequate clinical records of client contact,
- Monitor and respond to risk concerns, as per the Clinical Governance Policy (Please see Appendix A for risk management procedures).

(4) Do I have to be in the study? Can I withdraw from the study once I/we've started?

Participating in this research study is completely voluntary and you do not have to take part. However, if you elect not to participate in the trial, the young people you are treating will not be eligible to participate in the study. Your decision whether to participate will not affect your current or future relationship with the researchers or anyone else at The University of Sydney, The Lambert Initiative for Cannabinoid Therapeutics or The InsideOut Institute for Eating Disorders.

When completing the online survey for your client(s), you can withdraw your responses any time before you have submitted the survey.

(5) Are there any benefits associated with being in the study?

The main anticipated benefit to participating in this study is the ability to enhance and ease the delivery of an evidence-based outpatient treatment (MFBT) for anorexia nervosa in young people, with a new promising intervention, CBD, intended to reduce client anxiety and therefore family distress during treatment.

(6) Are there any risks or costs associated with being in the study?

Aside from giving up your time, we do not expect that there will be any risks or costs associated with taking part in this research study. It is possible participants may elect not to participate in the

study. This should not impact your capacity to provide treatment as usual.

(7) Can I tell other people about the study?

Yes, you are welcome to tell other people about the research study.

(8) What if I would like further information about the study?

Once you have read this information, the trial coordinator, Sarah-Catherine Rodan, will be available to discuss further and answer any questions you may have. You may contact Sarah via email (sarah-catherine.rodan@sydney.edu.au), or phone 0403224986.

(9) Will I be told the results of the study?

Yes, it is anticipated that the results of this research study will be published in academic journals and be presented at local and international scientific conferences. Results may also be communicated to the wider community through public talks, social media networks and print media as well as via the Lambert Initiative and InsideOut Institute website. In any publication and/or presentation, information will be provided in such a way that neither you, nor your clients will be able to be identified.

(10) CBD investigational drug

The parent/guardian will be responsible for administering CBD to their child/young person. The young person will begin CBD dosing at the commencement of their routine MFBT. CBD will be administered every day for 12 weeks throughout MFBT.

CBD capsules will be administered orally. Dosing will commence at 200 mg/day (1 capsule) and will increase by 200 mg (1 capsule) per week to a maximum dose of 800 mg/day (4 capsules) at the start of week 4. Participants will have an option to enrol in an extension arm (an additional 3 months) to continue on a dose of 800 mg/day until the end of MFBT, if deemed appropriate by immediate care team and research team.

Dosing will start at:

- Week 1: 200 mg/day (1 capsule at night)
- Week 2: 400 mg/day (1 capsule in the morning + 1 capsule at night).
- Week 3: 600mg/day (1 capsule in the morning + 2 capsules at night).
- Week 4-Week 12: 800mg/day (2 capsules in the morning + 2 capsules at night).

- Extension arm: Week 12-Week 24: 800mg/day (2 capsules in the morning + 2 capsules at night).

Dose tolerability and efficacy will be assessed by trial doctor and the maximum dose of 800 mg/day **may be adjusted to a lower dose if necessary.** Liver function tests will also be monitored weekly by the young person's medical practitioner and prior to each dose increase.

A sample of the participant's urine will be collected on a monthly basis to ensure study medication adherence throughout the trial.

Access to CBD is exclusively through participation in this trial. The young person will not be granted further access to CBD after this trial has been concluded. CBD is non-intoxicating and has nil potential for addition or dependence. Participants should not experience any adverse events or withdrawl symptoms after ceasing CBD treatment.

(10. 1) CBD is an investigational drug, is it safe? Are there any risks for the young person taking the investigational product?

Overall, CBD is generally well-tolerated and has a good safety profile. It is non-intoxicating and has nil potential for addiction, dependence, or tolerance. The most common side effects include changes to liver function (raised liver enzymes) which may be accompanied by symptoms such as nausea, vomiting and/or diarrhea, fever or feeling unwell, unusual tiredness or sleepiness.

Other side effects observed in a recent 12-week trial of 800mg/day CBD treatment in young people with treatment-resistant anxiety (Berger et al., 2022) included fatigue, hot flushes/cold chills, low mood, somnolence, insomnia, changes in appetite, headache, and gastrointestinal upset. Side effects were mild-to-moderate in severity, and all were transient (resolved).

Medical treatments often cause side effects. The young person may have none, some or all of the effects listed above, and they may be mild, moderate or (very rarely) severe.

Elevated liver serum enzymes are common in anorexia nervosa, due to malnutrition and/ or re-feeding. While elevated liver function enzymes have not been reported in trials investigating CBD outside of paediatric epilepsy in young persons, this has been reported in healthy adults. To closely monitor liver function, the participant's medical practitioner will **conduct blood tests weekly for the first month** and then **monthly for the rest of the study duration**. Liver function tests will be reviewed by the participants medical practitioner and trial doctor prior to each CBD dose titration.

The effects of CBD on the liver can be exacerbated by the use of other medications (specifically, with antiepileptic medications). This is known as a 'drug-drug interaction'. Should any signs of potential drug-drug interactions develop, the trial doctor and medical practitioner will review the participant's treatment plan and may discontinue the drug intervention but continue with MFBT.

(10.2) Trial doctor

The trial doctor will provide prescription for the supply of CBD for the young person. The investigational product will be dispensed monthly to the family's home. The young person will meet with the trial doctor online (via telehealth) at intervals specified necessary by the trial doctor, in addition to routine medical review, as above, with their medical practitioner. Should the young person experience any adverse events during the course of this trial they will be instructed to inform the clinical trial coordinator or trial doctor. Parents/guardian will be provided with a medication card with the trial doctor's and clinical trial coordinator's contact details.

(11) Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the HREC of the Sydney Local Health District.

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

(12) What if I have a complaint or any concerns about the study?

Research involving Humans in Australia is reviewed by an independent Human Research Ethics Committee (HREC). The ethical aspects of this study have been approved by the HREC of the Sydney Local Health District – RPAH Zone (Protocol No. X21-0440). As part of this process, we have agreed to carry out the study according to the National Statement on Ethical Conduct in Human Research (2007). If you have any complaints about the ethical nature of this research project, please contact the Sydney Local Health District using the details outlined below. Please quote the study title and protocol number.

- **Telephone:** (02) 9515 7035
- **Email:** SLHD-RPAEthics@health.nsw.gov.au

This participant information sheet is for you to keep

Appendix A
Risk Management

Monitoring Medical Signs

If the young person reports symptoms of possible medical instability, they must see their medical practitioner immediately. If the young person cannot see their medical practitioner, they are *advised to* present to their nearest Emergency Department for an assessment. Possible symptoms could include:

- Feeling like fainting or passing out when going from sitting to standing
- Constipation
- Nausea
- Shakiness
- Headaches
- Weakness

If the young person describes or the family reports the young person experiencing any of the following symptoms, they are *required to* present to their nearest Emergency Department or call 000 immediately:

- Shortness of breath
- Chest pains
- Rapid or low heart rate
- Fainting
- Dizziness
- Loss of consciousness
- Confusion
- Weakness
- Oedema/ swollen ankles
- Palpitations
- Vomiting of blood
- Abdominal distension
- Abdominal pain
- Muscle pain
- Tingling around mouth and/or fingers and toes

Monitoring Liver Function

Elevated liver serum enzymes are common in anorexia nervosa, due to malnutrition and/ or re-feeding. While elevated liver function enzymes have not been reported in trials investigating CBD outside of paediatric epilepsy in young persons, it has been reported in healthy adults. Liver serum enzymes will be monitored by the participants medical practitioner, **weekly** for the **first month** of the trial and then **monthly for the duration of the study**.

Weight Loss Management Plan

Given the risks associated with weight loss, the following weight loss management strategy will be used for all participants.

As is for routine MFBT, the weight and BMI will be measured at each session by the MFBT clinician. Weight will be taken as per the treatment manual, at the same time of day and on the same scales,

with the young person wearing light clothing and after the bladder has been voided. The research team will communicate with you if the patient has rapid weight loss at any point during the trial.

If your patient is attending MFBT via telehealth, there will need to be the opportunity either for parents to weigh or for medical practitioner to take over this role. The clinician will work this out with the family, so each family can be engaged around what will work.

Response to Rapid Weight Loss:
If there is evidence of rapid or consistent weight loss*, the following actions are put in place:

- The study coordinator is alerted by the community clinician, and,
- The participant's medical practitioner is notified via email, and the participant is recommended to see medical practitioner for medical assessment
- The participant will be discontinued from the trial if there is any observable deterioration in participant's medical or psychiatric parameters as noted by medical practitioner, therapist or above indicators. In this instance, the discontinuation protocol would be activated. The therapist and/or study coordinator would advise the participant, their family, and their medical practitioner verbally and in writing that they were discontinued from the study.

*Rapid weight loss is indexed by >1kg a week for 2 weeks. Note that this is definition is different to the *NSW Eating Disorders Toolkit* (2018). This ensures that the Inside Out Institute site holds a lower risk threshold.

If you observe or if the young person, family or GP report any of the following at any time (see list in **Figure 1**), please ensure the patient attends their local hospital for an urgent assessment:

Indications for Hospitalisation

A hospital admission may be indicated for any of the following criteria:

- Heart Rate <50 bpm,
- Cardia arrhythmia including a prolonged QTc interval (>450 msec)
- Postural tachycardia >20bpm increase heart rate
- Blood pressure <80/40 mm/Hg or postural drop >30 mm/Hg
- Temperature < 35.5°C
- Low serum potassium ≤3.0 mmol/L
- BSL <3.0mmol/L
- Other significant electrolyte imbalances
- BMI ≤ 14
- Rapid or consistent weight loss (e.g., > 1kg each week for six or more weeks)
- Acute dehydration or patient has ceased fluid intake
- Intensive community-based treatment has proven ineffective
- Comorbid or pre-existing psychiatric conditions that require hospitalisation
- Suicidality with an active intent and plan
- Other special considerations such as diabetes or pregnancy

Figure 1. Indications for hospitalisation according to the NSW Eating Disorders Toolkit (2018)

It is not anticipated that there should be any serious side effects from this treatment. However, if you become concerned regarding the participant's medical stability throughout the trial or consider him/her to be unsafe to participate in the trial, please notify us and refer the participant for additional care appropriately according to the *National Eating Disorder Collaboration's Professional Resource for General Practitioners*.

Additionally, if you are unsure about how to detect and respond to high-risk symptoms or behaviours, please refer to the guide created by the Victorian Centre of Excellence in Eating Disorders (CEED) titled, 'Physical Risk in Suspected Eating Disorders Mental Health Clinician Response Guide'.

Psychiatric Risk Management

1. Psychiatric Risk of Harm Assessment

Given that many people with anorexia nervosa also experience heightened levels of distress, self-harm and suicide, should a participant, their family, GP or trial doctor report the presence of risk of harm to self, the below risk framework will be used.

Further, the therapist will rate the level of risk of harm to self or others at each session. Again, if indicated, the therapist will use the below framework to document risk status, and this is included as an attachment to the relevant clinical note:

Risk:	• Indicated – complete below • Not indicated	
Domain	**Self-Injury**	**Suicide**
Context • Stressors • Planned or impulsive • Triggers		
Intention (thoughts) • Passive thoughts • Active thoughts • Consider frequency, level of distress and persistence of thoughts		
Plans • Decision (method, timing)		

• Details (of harm or suicide plan) • Preparations (any preparations completed for suicide) • Time profile (how long had plan, timeline)		
Willingness • Desire for help • Acceptance of care		
Protective • Current supports • Safety planning • Resistance (previous resistance to not enacting plan)		
Current safety • Is harm imminent? • Are they help eliciting? • Access to dangerous items?		
Overall risk rating		
Action Plan *Include notification of support people, safety planning, provision of crisis numbers, referral to relevant services etc.*		

2. Risk of Harm Action Plan

- *High risk*: Those individuals who report immediate risk, in that they are unable to guarantee their safety for at least 24 hours, or who the researcher has reason to believe is at imminent risk, are referred for urgent assessment by a mental health crisis team or are referred immediately to emergency services. The GP is also notified via email and phone that a high level of risk of harm was identified, detailing what actions were taken.

- *Low risk*: For all individuals who are at low risk a safety plan will be developed utilising the Beyond Now Safety Plan template (app or web version). This plan identifies at least three

people or services the person agrees to contact if symptoms return or worsen. All individuals are provided with the contact details for LifeLine and a 24-hour Suicide Call Back Service as part of the feedback. The safety plan is then sent to the individual, their family (in the case of young people) and their GP.

Child Protection

As registered health professionals, the therapist will be required to abide by the Child Protection and Mandatory Reporting obligations of the jurisdiction with which the young person resides.

Appendix B
List of Investigators

Principal Investigator (Trial Oversight)

Name:	Professor Iain McGregor PhD
Address:	Brain and Mind Centre, 94 Mallet Street, Camperdown NSW 2050
Telephone:	+61 2 9351 3571
Email:	iain.mcgregor@sydney.edu.au

Principal Clinical Investigator (Medical/Supervision of Trial doctor)

Name:	Professor Janice Russell
Address:	RPAH, Marie Bashir Centre, 67-73 Missenden Rd, Camperdown NSW 2050
Telephone:	+61 2 9515 1430
Email:	janice.russell@sydney.edu.au

Co-Investigator (Trial doctor/GP specialist)

Name:	Dr. Karen Spielman
Address:	InsideOut Institute for Eating Disorders, Charles Perkin Centre (D17), Camperdown NSW 2006
Email:	Karen.spielman@sydney.edu.au

Co-investigator (Trial Oversight)

Name:	A/Prof Sarah Maguire PhD
Address:	InsideOut Institute for Eating Disorders, Charles Perkin Centre (D17), Camperdown NSW 2006
Telephone:	+61 2 86271910
Email:	sarah.maguire@sydney.edu.au

Co-investigator (Clinical trial coordinator/PhD Student)

Name:	Ms Sarah-Catherine Rodan
Address:	Brain and Mind Centre, 94 Mallet Street, Camperdown NSW 2050
Telephone:	+61 4 77222500
Email:	sarah-catherine.rodan@sydney.edu.au

Co-investigator (Trial management)

Name:	Dr. Jane Miskovich-Wheatley
Address:	InsideOut Institute for Eating Disorders, Charles Perkin Centre (D17), Camperdown NSW 2006
Telephone:	+61 4 1336668
Email:	Jane.miskovic-wheatley@sydney.edu.au