Does cannabidiol reduce severe behavioural problems in children with intellectual disability? Study protocol for a pilot single-site phase I/II randomised placebo controlled trial

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ABSTRACT

Introduction Severe behavioural problems (SBPs) are a common contributor to morbidity and reduced quality of life in children with intellectual disability (ID). Current medication treatment for SBP is associated with a high risk of side effects. Innovative and safe interventions are urgently needed. Anecdotal reports and preliminary research suggest that medicinal cannabis may be effective in managing SBP in children with developmental disabilities. In particular, cannabidiol (CBD) may be a plausible and safe alternative to current medications. Families who are in urgent need of solutions are seeking cannabis for their ID children with SBP. However, there is no evidence from randomised controlled trials to support the use of CBD for SBP. This pilot study aims to investigate the feasibility of conducting a randomised placebo-controlled trial of CBD to improve SBP in children with ID.

Methods and analysis This is a single-site, double-blind, parallel-group, randomised, placebo-controlled pilot study of 10 participants comparing 98% CBD oil with placebo in reducing SBP in children aged 8–16 years with ID. Eligible participants will be randomised 1:1 to receive either CBD 20 mg/kg/day or placebo for 8 weeks. Data will be collected regarding the feasibility and acceptability of all study components, including recruitment, drop-out rate, study visit attendance, protocol adherence and the time burden of parent questionnaires. Safety outcomes and adverse events will be recorded. All data will be reported using descriptive statistics. These data will inform the design of a full scale randomised controlled trial to evaluate the efficacy of CBD in this patient group.

Ethics and dissemination This protocol has received ethics approval from the Royal Children’s Hospital ethics committee (Human Research Ethics Committee no. 38236). Results will be disseminated through peer-reviewed journals, professional networks, conferences and social media.

Trial registration number ACTRN12618001852246

INTRODUCTION

Intellectual disability with severe behaviour problems and associated burden

Two per cent of children and adolescents have an intellectual disability (ID),1 and approximately half of these individuals have mental health problems,2 including many with challenging behaviours. These commonly include aggression, self-injury, agitation, mood changes, screaming and banging objects. We use the term severe behavioural problems (SBP) to describe this clinical phenotype.

SBPs in children with ID are a major contributor to morbidity, functional impairments, missed opportunities for learning and reduced quality of life. SBP also places an enormous burden on families and carers,3 as well as health, education and disability sectors. Parents and siblings of youth with SBP often live in fear of them and are at increased risk of mental health problems.4 Expensive long-term residential placement is often the only option.5 ID is estimated to cost $A15 billion annually in Australia.6 Much of this cost, including personal expenses, service use, government expenditure and opportunity cost for families, relates to SBP impacting on the health and care needs of these patients.7 Patients with ID and SBP cause challenging demands for hospitals to
manage, with implications for staff training, ward design and safety of both staff and patients.

Problems with current treatment of SBP in youth with ID

Challenging behaviours are extremely difficult to treat in children with ID and SBP. Psychological interventions are often ineffective in patients with ID, leaving environmental modification and medication as the main strategies available. Psychotropic medications are prescribed by Australian paediatricians for almost 50% of youth with ID. The medications—antipsychotics, psychostimulants and antidepressants—carry a high risk of side effects for children and adolescents in general; however, patients with developmental disabilities are at particularly high risk, and less able to report side effects. For example, adults with ID exposed to antipsychotic drugs have a higher incidence of treatment-emergent movement disorders compared with patients without ID. Another common side effect of antipsychotics, weight gain, affects health in a patient group already at increased risk of chronic illness, and is a risk factor for avoidable death. Weight gain also brings practical problems in youth with ID, who are often dependent on carers for everyday activities such as dressing, bathing and toileting, as well as compounding the management of aggressive behaviour.

Current pharmacotherapy in children with ID and SBP is characterised by concerning practices, including polypharmacy and frequent changes to medication regimens; adding drugs to treat side effects, such as use of metformin to control weight gain caused by antipsychotic medication and long-term use of drugs ‘off-label’, for example, atypical antipsychotics. Innovative and safer interventions are urgently needed for children with ID and SBP.

Medicinal cannabis

The potential for medicinal cannabis products to treat a range of medical and psychiatric conditions is becoming increasingly understood. There has recently been great interest in the potential therapeutic role of cannabinoids. The primary psychoactive compound in the cannabis plant is Δ⁹-tetrahydrocannabinol (Δ⁹-THC), which can cause serious side effects such as paranoia and hallucinations. In contrast cannabidiol (CBD), another cannabis extract, does not have intoxicating properties and may provide benefits with minimal adverse psychological effects.

CBD pharmacology and safety

CBD has been delivered orally in an oil-based capsule or sublingual spray in human trials, in variable ratios with Δ⁹-THC. The onset and duration of activity depends on the preparation and route of administration. The plasma half-life of CBD following oral administration is approximately 60 hours after two times per day dosing for 7 days in healthy adults. It is highly lipophilic and accumulates in fat. CBD is metabolised by cytochrome P450 enzymes 3A and 2C in the liver.

Both animal and human studies have indicated that CBD does not affect physiological parameters or psychological functions. Studies in healthy adults have shown CBD to be well tolerated across a wide dose range, with no significant adverse effects on vital signs, cognition or mood in oral doses of up to 1500 mg per day. In children with epilepsy up to 50 mg/kg/day of CBD has been prescribed. Reported tolerance in trials has been generally good, with the most common adverse effects, somnolence, diarrhoea and decreased appetite, occurring in a minority of exposed patients.

Indications for CBD

Medical cannabis is being advocated for an increasing range of indications. In children, the main indication for CBD is drug-resistant epilepsy, with supportive evidence emerging for its effectiveness as an adjuvant treatment to conventional antiepileptic medications for some specific epileptic syndromes. In 2018, Epidiolex, a pure CBD oral solution manufactured by GW Pharmaceuticals, received approval from the US Food and Drug Administration for patients with Lennox-Gastaut syndrome and Dravet syndrome. It is possible that reported improvements in ‘overall condition’ of children given CBD in epilepsy trials were due to more settled behaviour, although this has not specifically been reported.

Biological plausibility of CBD to treat SBP in youth

Neural mechanisms by which CBD may influence mood and behaviour are only partially established, but include alterations in neurotransmission and calcium homeostasis, antioxidant activity and anti-inflammatory effects. Thus, the endocannabinoid system is a novel target for pharmacological treatments of behavioural problems. Alterations in endocannabinoid signalling have been found in mice carrying a mutation related to autism, and in a mouse model of Fragile-X syndrome, so this system appears to play an important role in neurodevelopment and behaviour. While THC has strong affinity for both cannabinoid receptors receptors (CB1 and CB2), CBD appears to exert its effects on the endocannabinoid system through indirect actions, and may also have activity on other neurotransmitter systems. Thus, CBD has biologically plausible potential therapeutic benefits for human behaviour, and there is emerging evidence of benefit from CBD in adult mental health disorders.

A recent review described the anticonvulsive, anxiolytic, antipsychotic, anti-inflammatory and neuroprotective properties of CBD, and suggested CBD may be a candidate for the treatment of autism spectrum disorder (ASD). However, the lack of data showing efficacy and safety in this population was noted.

Evidence for cannabis products in treating SBP in youth

The use of medicinal cannabis to treat children and adolescents with behavioural problems has been discussed in the mainstream media (Ellison K. Medical Marijuana: No Longer Just for Adults. New York Times, 21 November
methods and analysis
study objective

The primary objective of this pilot study is to evaluate all elements of the study design (recruitment strategy, tolerability of the study medication, study duration, study procedures and outcome measures) to assess if they are acceptable and feasible for the conduct of a full-scale RCT of CBD to reduce SBP in children with ID. The secondary objective is to collect preliminary data on the safety of oral administration of CBD in children aged 8–16 years with ID and SBP, by assessing adverse event signals. An exploratory aim of this study is to assess for a signal of behavioural change in participants treated with CBD, through completion of a parent-reported behavioural questionnaire pretreatment and post-treatment.

patient and public involvement

Two clinician stakeholder forums have been held with groups of paediatricians and child and adolescent psychiatrists who manage children with ID. There was a strong and consistent expression of the need for evidence regarding the efficacy and safety of CBD in these patients, and a belief, based on the common experience of parents inquiring in consultations, that parents would be interested in participating in a trial.

Prior to development of this protocol, we conducted brief, semistructured telephone interviews with eight parents of children with ID and SBPs, in which they were asked whether they would be willing to enrol their child in an 8-week placebo-controlled trial of CBD. Responses were uniformly enthusiastic, with all parents indicating a willingness to participate if such a trial was conducted.

In this pilot study, parents will complete a brief questionnaire poststudy completion regarding their experience participating in the study research. Parents will be asked to rate their experience with recruitment, study visits, drug tolerability and questionnaires using Likert scales. They will also be invited to provide suggestions for improvements to the study design. This information will inform the design of the definitive trial.

Questionnaires to be piloted in this study include child-specific outcomes, as well as those assessing parent/carer quality of life and mental health.

Following completion of the study, participating families will be sent a summary of the study findings. Dissemination of findings will include distribution through community resources, including those accessed by carers such as support groups, and the Murdoch Children’s Research Institute (MCRI) Facebook page.

trial design

This is a single-site, double-blind, parallel-group, randomised, placebo-controlled pilot study of 10 participants comparing 98% CBD oil with placebo in reducing SBP in children aged 8–16 years with ID. Eligible participants will be randomised 1:1 to receive either CBD or placebo.

Investigational product

This study will use 98% CBD in grapeseed oil provided by Tilray, Canada as a 100 mg/mL CBD oral solution, and a placebo grapeseed oil matched for smell, taste and appearance.

Participants

Inclusion criteria

Each patient must meet all of the following criteria to be enrolled in this study:

1. Aged 8–16 years.
2. Diagnostic and Statistical Manual of Mental Disorders (DSM–5) diagnosis of ID.
Table 1  Completed and ongoing studies reporting behavioural outcomes of youth treated with medicinal cannabis products

| Published studies |
|-------------------|-----------------|-----------------|-----------------|
| Sample size | Population | Study design | Product used | Findings |
| 1 | Child with ID+SBP | Case report | Dronabinol (∆9-THC) | Improvements in hyperactivity, irritability and speech<sup>38</sup> |
| 10 | Adolescents with ID+SBP | Open-label case series | Dronabinol (∆9-THC) | Reductions in self-injurious behaviour in 7 out of 10 participants<sup>39</sup> |
| 75 | Children with epilepsy (heterogeneous sample) | Retrospective chart review | ‘Oral cannabis’ | Improvements in behaviour<sup>40</sup> |
| 19 | Children with epilepsy: | Facebook survey | ‘CBD-enriched cannabis’ | Improvements in mood, sleep and self-stimulation<sup>41</sup> |
| 53 | Children with ASD | Open-label, symptoms graded as improvement, no change, worsening | CBD:∆9-THC 20:1 | Improvements in self-injury, rage-attacks, hyperactivity, sleep and anxiety<sup>42</sup>. Adverse events were mildQ |
| 60 | Children with ASD+SBP | Retrospective open label | ‘CBD-rich cannabis’ | ‘Much improved’ or ‘very much improved’ behaviour in 61% of patients<sup>43</sup>. Only one serious adverse event was noted, a transient psychotic event, which was considered to be related to an increase in ∆9-THC. |
| 188 | Children with ASD | Prospective open label | ‘CBD-enriched cannabis’ (mostly 30% CBD and 1.5% ∆9-THC) | Significant or moderate improvements in anxiety, agitation and rage attacks for 79.8% of 119 participants assessed after 1 month. The most common side effect was restlessness |

Ongoing registered trials

| Sample size | Population | Study design | Product used | ClinicalTrials.gov Identifier |
|-------------|------------|--------------|--------------|-------------------------------|
| 150 | Youth with ASD+SBP | Double-blind, cross-over RCT | Cannabis oil with a 20:1 ratio of CBD to ∆9-THC | NCT02956226 |
| 100 | Children with ASD+SBP | Double-blind RCT | Cannabidivarin (CBDV; a homolog of CBD) | NCT03202303 |
| 26 | Youth with Prader-Willi Syndrome +SBP | Double-blind RCT | CBDV | NCT03848481 |
| 204 | Children with Fragile X Syndrome | Double-blind RCT | Synthetic CBD | NCT03614663 |

ASD, autism spectrum disorder; CBD, cannabidiol; ID, intellectual disability; RCT, randomised controlled trial; SBP, severe behavioural problem; ∆9-THC, ∆9-tetrahydrocannabinol.

a. Full scale IQ <70 on standardised cognitive assessment on verified records of testing performed within 2 years of enrolment. In the event that records of prior testing are unavailable or the assessment was more than 2 years prior, IQ will be estimated using the Wechsler Abbreviated Scale of Intelligence-II (WASI-II).

b. Deficit in adaptive function (basis for severity rating of ID in DSM-5) in at least one activity of life: Vineland Adaptive Behaviour Scales completed by the parent or carer; derives scores in Communication, Daily Living Skills and Socialisation domains and a Global Adaptive score.

3. SBP: defined as:

a. Scores of 18 or higher on the Aberrant Behaviour Checklist-Irritability subscale (ABC-I).<sup>31</sup>

b. Moderate or higher on the Clinical Global Impressions-Severity scale.
4. Consistent pattern of frequent SBP symptoms for >3 months (parent interview).
5. No changes in either medication or other interventions in the 4 weeks prior to randomisation.
6. Has the ability to comply with the protocol requirements, in the opinion of the investigator.

Exclusion criteria
1. Non-English-speaking parents.
2. Psychosis, bipolar disorder, major depressive disorder, obsessive compulsive disorder.
3. Taking antiepileptic medications which interact with CBD (eg, clobazam, topiramate, zonisamide).
4. Current medicinal cannabis use or use within the 3 months prior to enrolment.

Procedure
Recruitment procedure
Participants will be recruited from the Royal Children’s Hospital’s (RCH) Paediatric Clinics and Child and Adolescent Mental Health Service, as well as paediatric private practices in Victoria. The study will be advertised to clinicians in relevant departments and private clinics with a request to consider whether they have eligible patients. Paediatricians and psychiatrists will send standard-study-designed letters, signed by the doctor, to potentially eligible families that briefly outline the study and invite interested parents to contact the study coordinator for further information. Potential participants will then attend a screening visit to determine eligibility. The researchers will obtain written informed consent from parents at the screening assessment (refer to online supplementary material 1 for a sample consent form).

Randomisation, allocation concealment and double-blind conditions
A randomisation schedule will be generated by an independent statistician at the Clinical Epidemiology and Biostatistics Unit at the MCRI.

The randomisation schedule will be provided to the trials pharmacist at the RCH. Treatment allocation will be conducted by the pharmacy and will be blinded to all members of the study team and participants. Study medication codes will only be available once all data collected have been entered into the study database for every participant and the database has been finalised. In the event of a medical emergency, a pharmacist will be available to break the blind.

Study procedures
This study will be conducted at RCH, Melbourne. Study visits and assessments will be conducted as per table 2. To maximise protocol adherence and minimise treatment dropouts, a dedicated study coordinator will be available to respond to parent queries or concerns between study visits.

Further description of the assessments included in table 2 are as follows:

WASI-II. The WASI-II is a general intelligence, or IQ test designed to assess specific and overall cognitive capabilities and is individually administered to children, adolescents and adults (ages 6–89). This will be administered to children who have not had an IQ test in the 2 years prior to screening.

Vineland-3. Vineland Adaptive Behaviour Scales V.3 will be completed by interview with the parent or carer of children who have not had an IQ test in the 2 years prior to screening. This instrument derives scores in Communication, Daily Living Skills and Socialisation domains, and a Global Adaptive score.

Autism-Tics attention deficit/hyperactivity disorder (ADHD) and Comorbidities (A-TAC). A-TAC inventory is a comprehensive screening interview for ASD, attention deficit/hyperactivity disorder (ADHD), tic disorders, developmental coordination disorder, learning disorders and other childhood mental disorders. Modules screening for Motor skills, ADHD, Tics, Compulsions, Mood, Anxiety and Oppositional defiance will be administered with the participants’ parent or carer by a study doctor.

Social Communication Questionnaire (SCQ). The ‘current’ version of the SCQ will be used to screen for ASD symptoms. This will be administered online with the outcome measures.

ABC-I. The ABC-I is an informant-rated questionnaire assessing severity of behavioural symptoms commonly seen in youth with ID that includes five subscales: Irritability, Social Withdrawal, Stereotypic Behaviour, Hyperactivity/Non-compliance and Inappropriate Speech. The Irritability subscale (ABC-I), which covers symptoms such as agitation, aggression, meltdowns and self-harm, will be used to determine eligibility.

Parent survey and Medical history. Demographic details will be collected from parents, along with details of the child’s medical history, previous medications, allied health service utilisation and any non-pharmacological behaviour management strategies that have been tried.

Concomitant medications. At each visit, the investigators will ask about changes in participants’ medications.

Physical examination. Physical examination including vital signs (temperature, heart rate, respiratory rate and blood pressure) and height and weight measurement will be conducted by a study doctor.

Haematology and Biochemistry. Blood will be collected by finger prick and tested for full blood count, electrolytes, creatinine, liver function tests and lipase. Participants with clinically significant abnormalities will be excluded from participating at the judgement of the investigators. Any abnormal results will be communicated to the families immediately, and to the paediatrician at the conclusion of the study (or immediately if considered clinically significant).

Study drug administration. Investigational product will be administered orally at a starting dose of 5 mg/kg/day in two divided doses. The dose will be increased in increments of 5 mg/kg every 3 days for 9 days up to
Table 2  Schedule of study visit procedures and assessments

|                | Baseline/ start of up titration | Double-blind evaluation |
|----------------|---------------------------------|-------------------------|
|                | Screening                        | Start of maintenance  | Maintenance mid-point | Start of down-titration | End of down-titration | End of study (phone call) |
| Day            | −14 to −1                        | Day 9–13               | Day 36–40*            | Day 66–70               | Day 74*               | Day 104                  |
| WASI-II        | X                               |                         |                       |                         |                      |                          |
| Vineland-3     | X                               |                         |                       |                         |                      |                          |
| A-TAC          | X                               |                         |                       |                         |                      |                          |
| SCQ            | X                               |                         |                       |                         |                      |                          |
| Parent survey  | X                               |                         |                       |                         |                      |                          |
| Medical history| X                               |                         |                       |                         |                      |                          |
| Concomitant medications | X       | X                      | X                    | X                      |                      |                          |
| Physical examination (including vital signs) | X       | X                      | X                    | X                      |                      |                          |
| Weight measurement | X       | X                      | X                    | X                      |                      |                          |
| Height measurement | X     |                         |                       |                       |                      |                          |
| Haematology    | X                               |                         |                       |                       |                      |                          |
| Biochemistry   | X                               |                         |                       |                       |                      |                          |
| Randomisation  | X                               |                         |                       |                       |                      |                          |
| Dispense study medication | X       | X                      | X                    | X                      |                      |                          |
| Study drug administration | X                | X                      | X                    | X                      |                      |                          |
| Dispense diary cards | X           |                         |                       |                       |                      |                          |
| Collect diary cards | X           |                         |                       |                       |                      |                          |
| Evaluation measures | X              |                         |                       |                       |                      |                          |
| Safety outcome measure (MOSES) | X          | X                      |                       |                       |                      |                          |
| Adverse events | X                               | X                      | X                    | X                      | X                    |                          |
| Compliance check | X                 | X                      | X                    | X                      | X                    |                          |
| Pilot evaluation questionnaire | X          |                         |                       |                       |                      |                          |

*Maintenance midpoint and end of down-titration visits require only the parent or carer to attend to return study medication.

ABC-1, Aberrant Behaviour Checklist-Irritability subscale; A-TAC, Autism Tics ADHD and Comorbidities; MOSES, Monitoring of Side Effects Scale; SCQ, Social Communication Questionnaire; WASI-II, Wechsler Abbreviated Scale of Intelligence-II.

the maintenance dose of 20mg/kg/day (up titration phase). This dose was chosen to be consistent with a recent Dravet syndrome trial,21 and because good human pharmacokinetic data are available for 20mg/kg.36 A ceiling dose of 1000mg/day will be administered to all participants weighing 50kg or greater. Participants will continue to receive investigational product at the maintenance dose for 8 weeks (maintenance phase). The treatment duration was chosen because the RCT of CBD in Dravet syndrome reported that ‘the difference in favour of CBD was seen in the first month of the maintenance period’.21 This was corroborated by personal correspondence with both researchers and clinicians experienced in prescribing CBD for youth with ASD. The 8-week maintenance period, therefore, will allow 4 weeks for treatment effects to emerge, followed by an additional 4 weeks, which corresponds with the period over which parents are required to reflect when completing the behavioural outcome questionnaire. On completion of the maintenance phase, the dose will be decreased in increments
of 5 mg/kg for 9 days at which time administration will cease.

Diary cards. Diary cards will be provided to parents to record each administration of study medication, including administration time, dosage and any noteworthy comments such as incomplete administration of medication or possible side effects.

Evaluation measures. Parent-report questionnaires will be trialled for feasibility, burden and acceptability for this population, with a view to include these as outcome measures in a future full-scale randomised clinical trial of CBD to reduce SBP in children with ID. These will be administered online through Research Electronic Data Capture (REDCap). See Table 3 for further details of these questionnaires.

Safety Outcome Measure. Safety outcomes will be collected using the Monitoring of Side Effects Scale (MOSES), which will be completed by the parent or carer with the assistance of a study doctor. The MOSES is an 83-item measure that includes known side effects of psychotropic medications.

Assessment of adverse events. Adverse events will be evaluated at baseline (to exclude pre-existing problems) and throughout the study. Adverse events will be documented from physical examination findings, clinically significant lab results and diary cards. Documentation for all adverse events will include the specific event/condition, the dates and times of occurrence, the event severity, duration, likely relationship to CBD, action taken and date of resolution. In the event any participant (or their parent/carer) reports an intolerability to study medication, or there is a clinical or laboratory observation suggesting an intolerability to study medication, dose modification or cessation may be initiated in consultation with the Study Management Group.

In the event, any clinical observation suggests a severe intolerability of an individual participant to the study medication, study medication discontinuation will be considered. Any adverse event still ongoing at the time of study medication discontinuation will be monitored until it has returned to baseline status, stabilised, or, in the opinion of the Investigator and the Study Management Group agree that follow-up is no longer required.

Serious adverse events will be reported to the research governance office within 72 hours of becoming aware of the event and in accordance with local governance authorisation.

Compliance check. Parents will be instructed to return all medication bottles, empty or otherwise, for weighing by pharmacy staff to measure compliance. Compliance between 80% and 120% will be considered acceptable.

Pilot evaluation questionnaire. At the conclusion of the study, parents will complete a questionnaire specifically designed for this study to assess parent acceptability of study procedures (recruitment approach, number of study visits, questionnaire completion and blood tests) and medication tolerability. Refer to the online supplementary material 2 for a copy of this questionnaire.

### Data collection and analysis

Data will be collected regarding the feasibility and acceptability of all study components, including recruitment, withdrawal rate, study visit attendance, protocol adherence and the time burden of parent questionnaires.

Data will be entered directly into an online database (REDCap) at the time of collection and cross-checked for

| Table 3 Evaluation measures |
|-----------------------------|
| **Construct**               | **Measurement**                        | **Source**     |
| SBP                         | Summary score from the ABC-1 (15 items) | Parent report  |
| Behaviour                   | Other subscales of the ABC (4 outcomes) | Parent report  |
| Overall clinical impression | Clinical Global Impressions (2-item clinician-rated summary measures of (a) severity of psychopathology and (b) improvement) | Clinician-rating |
| Participation               | Child and Adolescent Scale of Participation (20 items). Participation in home, school and community activities | Parent report  |
| Quality of life             | Child Health Utility 9D (9 items). Preference-weighted measure used to calculate quality adjusted life years for children. | Parent report  |
| Sleep                       | Sleep Disturbance Scale for Children (26 items) | Parent report  |
| Parent quality of life      | Assessment of Quality of Life 8D (35 items). Health-related instrument used to calculate quality adjusted life years for parents. | Parent report  |
| Family quality of life      | Beach Centre Family Quality of Life (25 items). Family interaction, parenting, emotional and material well-being, disability-related support | Parent report  |
| Parent mental health        | Depression Anxiety Stress Scale –21 (21 items). Report of symptoms over the past week. | Parent report  |
| Parenting stress            | Autism Parenting Stress Index (13 items). Measures three categories of stress drivers: core social disability, difficult behaviour, physical issues | Parent report  |

ABC-1, Aberrant Behaviour Checklist-Irritability subscale; SBP, severe behavioural problems.
completion by the study coordinator. Only de-identified data will be entered into REDCap. Identifiable data (such as contact details) will be held in a separate, confidential, secure document accessible only to the investigators.

As this is a pilot study, all data will be reported using descriptive statistics. The recruitment rate will be presented as the percentage of eligible participants enrolled, and the reasons for not participating will be summarised. Study visit attendance and protocol adherence, medication compliance, study withdrawals, treatment discontinuations and protocol violations will be summarised by treatment arm. The acceptability of study visits and procedures, and tolerability of the study medication will be presented as mean scores with ranges and SD.

MOSES assessed safety outcomes and adverse events will also be summarised.

Scores from the evaluation measures listed in table 3 will be summarised as means and SD by treatment group.

ETHICS AND DISSEMINATION

Study-specific unique identifiers will be used to identify trial subjects. Data will be deidentified and associated with study specific identification numbers. Data will be captured and stored directly in REDCap, Vanderbilt University, a secure, web-based application for building and managing online databases and surveys. REDCap is hosted on MCRI infrastructure. Data will be kept for at least 15 years after the completion of the trial in accordance with the requirements of the Therapeutic Goods Administration or until the 25th birthday of the youngest participant, whichever is the later date (Victorian Health Records Act 2001).

Research data for this project will be presented at conferences and published in peer-reviewed journals. Aggregated data only will be reported in publications and presentations, with individual identifying information removed. We will endeavour to make these research data/resources as widely available as possible, while safeguarding the privacy of participants, protecting confidential and proprietary data, and third-party intellectual property.

DISCUSSION

This pilot study aims to investigate the feasibility of conducting a double-blind RCT of CBD to reduce SBP in children with ID. This study is not sufficiently powered to evaluate the efficacy of CBD in this population, however, the findings of this pilot study will inform the design of a fully powered RCT of CBD for reducing SBP in ID. The secondary aim of collecting preliminary safety data of CBD in this population, and the exploratory aim of examining for a signal of behavioural change in those treated with CBD, may also be informative for future study design. The planned RCT will address an identified evidence-practice gap in the use of CBD to meet an important need for services, the community and families, the safe and effective treatment of SBP in children and adolescents with ID. If safe and effective the transition into medical practice will require dissemination of research findings, education and training of prescribers, and support material solutions such as evidence-based clinical practice guidelines.

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