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Cannabidiol to reduce Severe Behavioural Problems in children with Intellectual Disability: Protocol for a pilot randomised controlled trial

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Abstract

Introduction

Severe Behavioural Problems (SBP) 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 medical 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% cannabidiol oil (CBD) with placebo in reducing SBP in children aged 8 – 16 years with ID. Eligible participants will be randomised 1:1 to receive either CBD 20mg/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

Australian New Zealand Clinical Trials Registry prospective registration: ACTRN12618001852246

ARTICLE SUMMARY

Strengths and limitations of this study

- This is the first study to investigate CBD for SBP in children with ID and will contribute to the literature more broadly on the use of cannabinoids in children.
- Randomised, placebo-controlled study using online completion of outcome measures.
- This pilot study will inform the design of a full-scale randomised controlled trial of CBD for this indication, and will inform other CBD trials in children.
- The study is not powered to provide meaningful efficacy outcomes.

INTRODUCTION

Intellectual Disability with Severe Behaviour Problems and associated burden

Two percent 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.

SBP 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 $15 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,(8) leaving environmental modification and medication as the main strategies available. Psychotropic medications are prescribed by Australian paediatricians for almost 50% of youth with ID.(9) The medications – anti-psychotics, psychostimulants and anti-depressants – carry a high risk of side-effects for children and adolescents in general, however patients with developmental disabilities are at particularly high risk,(10) 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.(11) Another common side-effect of antipsychotics, weight gain, affects health in a patient group already at increased risk of chronic illness,(12) and is a risk factor for avoidable death.(13) 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;(10) adding drugs to treat side effects, such as use of metformin to control weight gain caused by antipsychotic medication;(14) and long-term use of drugs "off-label" e.g. atypical antipsychotics. Innovative and safer interventions are urgently needed for children with ID and SBP.

Medical Cannabis

The potential for cannabis products to treat a range of medical and psychiatric conditions is becoming increasingly understood.(15) There has recently been great interest in the potential therapeutic role of cannabinoids. The primary psychoactive compound in the cannabis plant is Δ^9-tetrahydrocannabinol (THC), which can cause serious side effects such as paranoia and hallucinations.(16) 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 sub-lingual spray in human trials, in variable ratios with Δ^9-THC. The onset and duration of activity depends on the preparation and route of administration. The plasma half-life of cannabidiol following oral administration is approximately 60 hours after twice-daily dosing for 7 days in healthy adults.(17) It is highly lipophilic and accumulates in fat. CBD is metabolized 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.(18) 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.(19) In children with epilepsy up to 50 mg/kg/day of CBD has been prescribed.(20) 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.(21)

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 some supportive evidence emerging for its effectiveness as an adjuvant treatment to conventional antiepileptic medications for some specific epileptic syndromes.(21) 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.(22)

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, anti-oxidant activity, and anti-inflammatory effects.(23) 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,(24) and in a mouse model of Fragile-X syndrome,(25) so this system appears to play an important role in neurodevelopment and behaviour.(26) 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.(27) 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).(28) 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 medical 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, Nov 21 2009), and parents have described "the transformative power of medical cannabis" for their children with ID + SBP (e.g. Mothers Advocating Medical Marijuana for Autism). Anecdotally some parents have reported giving non-medicinal cannabis products to their children to help with their behaviour, and increasingly Australian parents of children with developmental disabilities and/or

mental health disorders are asking their paediatricians if medical cannabis would be a useful treatment and whether they can assist them in obtaining it for their child.(22) Research to date suggests that CBD has substantially less side-effects than anti-psychotic medications,(21) however there is currently insufficient evidence to inform its use in treating SBP. The American Academy of Pediatrics and the Royal Australasian College of Physicians (29) have highlighted the need for further research into the therapeutic uses of cannabinoids in youth.

A handful of reports in the literature suggest there may be a legitimate role for medical cannabis to treat SBP in youth with developmental disabilities (Table 1). Although promising, these uncontrolled reports provide only weak evidence in support of benefit.

Table 1. Completed and ongoing studies reporting behavioural outcomes of youth treated with medical cannabis products

Published studies				
Sample size	Population	Study design	Product used	Findings
1	Child with ID + SBP	Case report	Dronabinol (THC)	Improvements in hyperactivity, irritability and speech (30)
10	Adolescents with ID + SBP	Open-label case series	Dronabinol (THC)	Reductions in self-injurious behaviour in 7 out of 10 participants (31)
75	Children with epilepsy	Retrospective chart review	"Oral cannabis extracts"	Improvements in behaviour (32)
19	Children with epilepsy	Facebook survey	"CBD-enriched cannabis"	Improvements in mood, sleep and self-stimulation (33)
53	Children with ASD	Open-label, symptoms graded as improvement, no change, worsening	CBD:THC 20:1	Improvements in self-injury, rage-attacks, hyperactivity, sleep and anxiety.(34) Adverse events were mild
60	Children with	Retrospective	"CBD-rich	"Much improved" or "very much

	ASD + SBP	open-label	cannabis"	improved" behaviour in 61% of patients.(35) Only one serious adverse event was noted, a transient psychotic event, which was considered to be related to an increase in THC.
188	Children with ASD	Prospective open-label	"CBD-enriched cannabis" (mostly 30% CBD and 1.5% THC)	Significant or moderate improvements in anxiety, agitation and rage attacks for 79.8% of 119 participants assessed after 1 month.(36) 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 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

There are currently four registered trials of medical cannabis products use for behavioural problems in youth (also summarised in Table 1). In contrast to these, our study will include all children with ID and SBP, regardless of aetiology, and irrespective whether they have been diagnosed with ASD. Whereas one currently registered trial uses a THC containing product, our study will use CBD alone, thus

avoiding the potential risks associated with THC. Two registered studies describe randomised controlled trials (RCT) comparing cannabidivarin (a homolog of CBD) to placebo. CBD has a more established safety profile, is more commonly known and sought by consumers, and more readily available commercially. Given the larger number of pharmaceutical companies manufacturing CBD, it would be expected that CBD is also more competitively priced – an important consideration for both research funding bodies and patients.

This pilot study will assess the feasibility of conducting a large scale, randomised, double blind, placebo-controlled study of oral CBD in children with ID and SBP. We will also collect preliminary data on the safety and tolerance of CBD in children with ID and SBP.

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.

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, semi-structured telephone interviews with 8 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 post-study completion regarding their experience participating in the research study. 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 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 randomized 1:1 to receive either CBD or placebo.

Investigational medical 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.

a. Full scale IQ < 70 on standardised cognitive assessment on verified records of testing performed within two 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 Behavior Scales completed by interview with the parent or carer; derives scores in Communication, Daily Living Skills and Socialization domains, and a Global Adaptive score.

3. SBP: Defined as:

   a. Scores of 18 or higher on the Aberrant Behavior Checklist-Irritability subscale (ABC-I) (37) and

   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 anti-epileptic medications which interact with CBD (e.g. clobazam, topiramate, zonisamide)

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.

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 Murdoch Children's Research Institute (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.

Table 2. Schedule of study visit procedures and assessments

	Screening	Baseline/ Start of Up-titration	Double-blind evaluation				End of Study (Phone Call)
			Start of Maintenance	Maintenance Mid-point	Start of Down-titration	End of Down-titration	
Day	-14 to -1	1	Day 9-13	Day 36-40[1]	Day 66-70	Day 74[1]	Day 104
WASI-II	X						
Vineland-3	X						
A-TAC	X						
SCQ	X						
ABC-I	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		X		X		
Biochemistry	X		X		X		
Randomisation		X					
Dispense study medication		X	X	X	X		
Study drug administration		X----------				----------X	
Dispense diary cards		X	X		X	X	
Collect diary cards			X		X	X	X
Evaluation measures		X			X		
Safety outcome measure (MOSES)		X	X		X		
Adverse events		X	X		X	X	X
Compliance check			X	X	X	X	
Pilot evaluation questionnaire							X

[1] Maintenance Mid-point and End of Down-titration visits require only the parent or carer to attend to return study medication

WASI-II= Wechsler Abbreviated Scale of Intelligence-II; A-TAC=Autism- Tics ADHD and Comorbidities; SCQ= Social Communication Questionnaire; MOSES= Monitoring of Side Effects Scale

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

WASI-II. The WASI-II(38) 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 two years prior to screening.

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

A-TAC. Autism-Tics ADHD and Comorbidities (A-TAC)(39 ,40) inventory is a comprehensive screening interview for ASD, attention deficit/hyperactivity disorder (ADHD), tic disorders (TD), developmental coordination disorder (DCD), learning disorders (LD) and other childhood mental disorders. Modules screening for Motor skills, ADHD, Tics, Compulsions, Mood, Anxiety & Oppositional defiance will be administered with the participants' parent or carer by a study doctor.

SCQ. The "current" version of the Social Communication Questionnaire (SCQ)(41) will be used to screen for ASD symptoms. This will be administered online with the outcome measures.

ABC-I. The Aberrant Behaviour Checklist (ABC) (37) is an informant-rated questionnaire assessing severity of behavioural symptoms commonly seen in youth with ID that includes five subscales: Irritability, Social Withdrawal, Stereotypic Behavior, Hyperactivity/Noncompliance 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 (sodium and potassium), creatinine, liver function tests (ALT, ALP, total bilirubin, albumin, GGT and total protein) and lipase. Participants with clinically significant abnormalities will be excluded from participating at the judgment 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 the maintenance dose of 20 mg/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.(42) 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). On completion of the maintenance phase the dose will be decreased in increments of 5mg/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 randomized clinical trial of CBD to reduce SBP in children with ID. These will be administered online through 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),(43) 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 suggest 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 80-120% 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 *Supplementary Material* for a copy of this questionnaire.

Table 3. Evaluation measures

Construct	Measurement	Source
SBP	Summary score from the ABC-I (37) (15 items)	Parent report
Behaviour	Other subscales of the ABC (37) (4 outcomes)	Parent report
Overall clinical impression	Clinical Global Impressions (43): 2-item clinician-rated summary measures of a) severity of psychopathology and b) improvement	Clinician-rating
Participation	Child & Adolescent Scale of Participation (44) (20 items). Participation in home, school, and community activities	Parent report
Quality of life	Child Health Utility 9D (45 ,46) (9 items). Preference-weighted measure used to calculate quality adjusted life years for children.	Parent report
Sleep	Sleep Disturbance Scale for Children (47)(26 items)	Parent report
Parent quality of life	Assessment of Quality of Life 8D (48)(35 items). Health-related instrument used to calculate quality adjusted life	Parent report

	years for parents.	
Family quality of life	Beach Center Family Quality of Life (49)(25 items). Family interaction, parenting, emotional and material wellbeing, disability-related support	Parent report
Parent mental health	Depression Anxiety Stress Scale -21(50) (21 items). Report of symptoms over the past week.	Parent report
Parenting stress	Autism Parenting Stress Index (51)(13 items). Measures three categories of stress drivers: core social disability, difficult behaviour, physical issues	Parent report

SBP= Severe Behavioural Problems

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 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 standard deviations.

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 standard deviations by treatment group.

ETHICS AND DISSEMINATION

This project has ethics approval from the Human Research Ethics Committee of the Royal Children's Hospital, Melbourne (38236). Study-specific unique identifiers will to be used to identify trial subjects. Data will be de-identified and associated with study specific ID numbers. Data will be captured and stored directly in Research Electronic Data Capture (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. The findings of this study will inform the design of a fully-powered RCT of CBD for reducing SBP in ID. The RCT will address an identified evidence-practice gap in the use of cannabidiol 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.

Author contributions

- All authors made substantial contributions to the design of this study and the writing of the protocol
- All authors made substantial contributions to drafting the work and revising it critically for intellectual content;
- All authors approved the final version submitted;
- All authors agree to be accountable for the accuracy or integrity of the work

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Competing interests statement

The authors declare no competing interests.

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SUPPLEMENTARY MATERIAL 1: Pilot evaluation questionnaire

CBD Pilot: Evaluation

We would like to ask you some questions about the study.

For each question please indicate your response on the 5-point scale provided.

What did you think about the **way we approached you** for your child to participate in this study?

☐ Very poor ☐ Poor ☐ Satisfactory ☐ Very good ☐ Excellent

How did your **child tolerate the medication** s/he took in this study?

☐ Very poor ☐ Poor ☐ Satisfactory ☐ Very good ☐ Excellent

What did you think about the **number of visits** to the hospital required for this study?

☐ Far too many/ Not acceptable ☐ Too many ☐ Acceptable

What did you think about completing the **questionnaires** (how many questions and how hard to complete)?

☐ Unacceptable ☐ Difficult ☐ Acceptable ☐ Good / fine

What did you think about the following parts of the study visits?

Psychology assessment

☐	☐	☐	☐	☐
Not applicable	Unacceptable	Difficult	Acceptable	Good / fine

Blood tests

☐	☐	☐	☐
Unacceptable	Difficult	Acceptable	Good / fine

Your thoughts on the study *(tick one box per line)*

What is your overall opinion of the quality of the study?

☐	☐	☐	☐	☐
Very poor	Poor	Satisfactory	Very good	Excellent

My child found the study…

☐	☐	☐	☐
Very difficult	Difficult	Satisfactory	Easy

What did you find **best** about the study?_____

_____

_____

_____

_____

_____

_____

What did you find **worst** about the study?_____

_____

_____

_____

_____

How could we improve things?_____

_____

_____

_____

_____

Would you recommend this study to other families with children with similar problems?

☐ Yes ☐ No

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
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	
Protocol version	3	Date and version identifier	
Funding	4	Sources and types of financial, material, and other support	19
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	1
	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	19
	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)	N/A

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	4-9
	6b	Explanation for choice of comparators	N/A – pilot study
Objectives	7	Specific objectives or hypotheses	9
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)	10
Methods: Participants, interventions, 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	12
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)	10-11
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10
	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)	15-16
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	12,15-16
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	11
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	17
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)	12-13

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	10 (note: this is a pilot study, nil power calculations)
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	____11-12___
Methods: Assignment 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	____12_____
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	____12_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	____12_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	____12_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	____12_____
Methods: Data collection, 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	____17_____

	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	___12_____
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	___17_____
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	___17_____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	___N/A_____
	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)	___N/A_____
Methods: Monitoring			
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	__Pilot study____
	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	_____
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	___15-16____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_____
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	_____18_____

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)	N/A
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	12
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
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	17-18
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	19
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	18
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	N/A
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	10,18
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	
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	

*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 "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Cannabidiol to reduce Severe Behavioural Problems in children with Intellectual Disability: Protocol for a pilot randomised controlled trial

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Cannabidiol to reduce Severe Behavioural Problems in children with Intellectual Disability: Protocol for a pilot randomised controlled trial

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Key words: Cannabidiol, Severe Behavioural Problems, Children, Intellectual Disability

Word count: 3,693 words

Abstract

Introduction

Severe Behavioural Problems (SBP) 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 medical 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 20mg/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

Australian New Zealand Clinical Trials Registry prospective registration: ACTRN12618001852246

ARTICLE SUMMARY

Strengths and limitations of this study

- This is the first study to investigate CBD for SBP in children with ID and will contribute to the literature more broadly on the use of cannabinoids in children.
- Randomised, placebo-controlled study using online completion of outcome measures.
- This pilot study will inform the design of a full-scale randomised controlled trial of CBD for this indication, and will inform other CBD trials in children.
- The study is not powered to provide meaningful efficacy outcomes.

INTRODUCTION

Intellectual Disability with Severe Behaviour Problems and associated burden

Two percent 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.

SBP 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 $15 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,(8) leaving environmental modification and medication as the main strategies available. Psychotropic medications are prescribed by Australian paediatricians for almost 50% of youth with ID.(9) The medications – anti-psychotics, psychostimulants and anti-depressants – carry a high risk of side-effects for children and adolescents in general, however patients with developmental disabilities are at particularly high risk,(10) 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.(11) Another common side-effect of antipsychotics, weight gain, affects health in a patient group already at increased risk of chronic illness(12), and is a risk factor for avoidable death(13). 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;(10) adding drugs to treat side effects, such as use of metformin to control weight gain caused by antipsychotic medication;(14) and long-term use of drugs "off-label" e.g. atypical antipsychotics. Innovative and safer interventions are urgently needed for children with ID and SBP.

Medical Cannabis

The potential for cannabis products to treat a range of medical and psychiatric conditions is becoming increasingly understood.(15) There has recently been great interest in the potential therapeutic role of cannabinoids. The primary psychoactive compound in the cannabis plant is Δ^9-tetrahydrocannabinol (Δ9-THC), which can cause serious side effects such as paranoia and hallucinations.(16) 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 sub-lingual spray in human trials, in variable ratios with Δ^9-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 twice-daily dosing for 7 days in healthy adults.(17) It is highly lipophilic and accumulates in fat.(18) CBD is metabolized 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.(19) 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.(18) In children with epilepsy up to 50 mg/kg/day of CBD has been prescribed.(20) 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.(21)

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.(21) 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-Gastaux or Dravet syndromes.(22) 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.(23)

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, anti-oxidant activity, and anti-inflammatory effects.(24) 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, (25) and in a mouse model of Fragile-X syndrome, (26) so this system appears to play an important role in neurodevelopment and behaviour.(27) 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.(28) 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).(29) 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 medical 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, Nov 21 2009), and parents have described "the transformative power of medical cannabis" for their children with ID + SBP (e.g. Mothers Advocating Medical Marijuana for Autism). Anecdotally some parents have reported giving non-prescribed unregulated cannabis products to their children to help with their behaviour, and increasingly Australian parents of children with developmental disabilities and/or mental health disorders are asking their paediatricians if medical cannabis would be a useful treatment and whether they can assist them in obtaining it for their child.(23) Research to date suggests that CBD has substantially less side-effects than anti-psychotic medications,(21) however there is currently insufficient evidence to inform its use in treating SBP. The American Academy of Pediatrics and the Royal Australasian College of Physicians (30) have highlighted the need for further research into the therapeutic uses of cannabinoids in youth.

A handful of reports in the literature suggest there may be a legitimate role for medical cannabis to treat SBP in youth with developmental disabilities (Table 1). Although promising, these uncontrolled reports provide only weak evidence in support of benefit.

Table 1. Completed and ongoing studies reporting behavioural outcomes of youth treated with medical cannabis products

Published studies				
Sample size	Population	Study design	Product used	Findings
1	Child with ID + SBP	Case report	Dronabinol (Δ9-THC)	Improvements in hyperactivity, irritability and speech (31)
10	Adolescents with ID + SBP	Open-label case series	Dronabinol (Δ9-THC)	Reductions in self-injurious behaviour in 7 out of 10 participants (32)
75	Children with epilepsy (heterogeneous sample)	Retrospective chart review	"Oral cannabis extracts"	Improvements in behaviour (33)

19	Children with epilepsy: Dravet syndrome (n=13), Doose syndrome (n=4), Lennox-Gastaut syndrome (n=1) and idiopathic epilepsy (n=1)	Facebook survey	"CBD-enriched cannabis"	Improvements in mood, sleep and self-stimulation (34)
53	Children with ASD	Open-label, symptoms graded as improvement, no change, worsening	CBD:Δ9-THC 20:1	Improvements in self-injury, rage-attacks, hyperactivity, sleep and anxiety.(35) Adverse events were mild
60	Children with ASD + SBP	Retrospective open-label	"CBD-rich cannabis"	"Much improved" or "very much improved" behaviour in 61% of patients.(36) Only one serious adverse event was noted, a transient psychotic event, which was considered to be related to an increase in Δ9-THC.
188	Children with ASD	Prospective open-label	"CBD-enriched cannabis" (mostly 30% CBD and 1.5% Δ9-THC)	Significant or moderate improvements in anxiety, agitation and rage attacks for 79.8% of 119 participants assessed after 1 month.(37) The most common side-effect was restlessness
Ongoing registered trials				
Sample	Population	Study design	Product used	ClinicalTrials.gov Identifier

size				
150	Youth with ASD + SBP	Double-blind, cross-over RCT	Cannabis oil with a 20:1 ratio of CBD to Δ9-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

There are currently four registered trials of medical cannabis products use for behavioural problems in youth (also summarised in Table 1). In contrast to these, our study will include all children with ID and SBP, regardless of aetiology, and irrespective whether they have been diagnosed with ASD. Whereas one currently registered trial uses a Δ9-THC containing product, our study will use CBD alone, thus avoiding the potential risks associated with Δ9-THC. Two registered studies describe randomised controlled trials (RCT) comparing cannabidivarin (a homolog of CBD) to placebo. CBD has a more established safety profile, is more commonly known and sought by consumers, and more readily available commercially. Given the larger number of pharmaceutical companies manufacturing CBD, it would be expected that CBD is also more competitively priced – an important consideration for both research funding bodies and patients.

This pilot study will assess the feasibility of conducting a large scale, randomised, double blind, placebo-controlled study of oral CBD in children with ID and SBP. We will also collect preliminary data on the safety and tolerance of CBD in children with ID and SBP.

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 pre- 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, semi-structured telephone interviews with 8 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 post-study completion regarding their experience participating in the research study. 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 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 medical 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.
    a. Full scale IQ < 70 on standardised cognitive assessment on verified records of testing performed within two 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 Behavior Scales completed by interview with the parent or carer; derives scores in Communication, Daily Living Skills and Socialization domains, and a Global Adaptive score.
3. SBP: Defined as:

a. Scores of 18 or higher on the Aberrant Behavior Checklist-Irritability subscale (ABC-I) (38) and

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 anti-epileptic medications which interact with CBD (e.g. clobazam, topiramate, zonisamide)
4. Current medical 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.

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 Murdoch Children's Research Institute (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.

Table 2. Schedule of study visit procedures and assessments

			Double-blind evaluation				
	Screening	Baseline/ Start of Up-titration	Start of Maintenance	Maintenance Mid-point	Start of Down-titration	End of Down-titration	End of Study (Phone Call)
Day	-14 to -1	1	Day 9-13	Day 36-40[1]	Day 66-70	Day 74[1]	Day 104
WASI-II	X						
Vineland-3	X						
A-TAC	X						
SCQ	X						
ABC-I	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		X		X		
Biochemistry	X		X		X		

Randomisation		X					
Dispense study medication		X	X	X	X		
Study drug administration		X----------X					
Dispense diary cards		X	X		X	X	
Collect diary cards			X		X	X	X
Evaluation measures		X			X		
Safety outcome measure (MOSES)		X	X		X		
Adverse events		X	X		X	X	X
Compliance check			X	X	X	X	
Pilot evaluation questionnaire							X

[1] Maintenance Mid-point and End of Down-titration visits require only the parent or carer to attend to return study medication
WASI-II= Wechsler Abbreviated Scale of Intelligence-II; A-TAC=Autism- Tics ADHD and Comorbidities; SCQ= Social Communication Questionnaire; MOSES= Monitoring of Side Effects Scale

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

WASI-II. The WASI-II(39) 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 two years prior to screening.

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

A-TAC. Autism-Tics ADHD and Comorbidities (A-TAC)(40 ,41) inventory is a comprehensive screening interview for ASD, attention deficit/hyperactivity disorder (ADHD), tic disorders (TD), developmental coordination disorder (DCD), learning disorders (LD) and other childhood mental disorders. Modules screening for Motor skills, ADHD, Tics, Compulsions, Mood, Anxiety & Oppositional defiance will be administered with the participants' parent or carer by a study doctor.

SCQ. The "current" version of the Social Communication Questionnaire (SCQ)(42) will be used to screen for ASD symptoms. This will be administered online with the outcome measures.

ABC-I. The Aberrant Behaviour Checklist (ABC) (38) is an informant-rated questionnaire assessing severity of behavioural symptoms commonly seen in youth with ID that includes five subscales: Irritability, Social Withdrawal, Stereotypic Behavior, Hyperactivity/Noncompliance 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 (sodium and potassium), creatinine, liver function tests (ALT, ALP, total bilirubin, albumin, GGT and total protein) and lipase. Participants with clinically significant abnormalities will be excluded from participating at the judgment 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 the maintenance dose of 20 mg/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.(43) 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). On completion of the maintenance phase the dose will be decreased in increments of 5mg/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 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),(44) 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 suggest 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 80-120% 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 *Supplementary Material* for a copy of this questionnaire.

Table 3. Evaluation measures

Construct	Measurement	Source
SBP	Summary score from the ABC-I (38) (15 items)	Parent report
Behaviour	Other subscales of the ABC (38) (4 outcomes)	Parent report
Overall clinical impression	Clinical Global Impressions (44): 2-item clinician-rated summary measures of a) severity of psychopathology and b) improvement	Clinician-rating
Participation	Child & Adolescent Scale of Participation (45) (20 items). Participation in home, school, and community activities	Parent report
Quality of life	Child Health Utility 9D (46 ,47) (9 items). Preference-weighted measure used to calculate quality adjusted life years for children.	Parent report
Sleep	Sleep Disturbance Scale for Children (48)(26 items)	Parent report
Parent quality of life	Assessment of Quality of Life 8D (49)(35 items). Health-related instrument used to calculate quality adjusted life years for parents.	Parent report
Family quality of life	Beach Center Family Quality of Life (50)(25 items). Family interaction, parenting, emotional and material wellbeing, disability-related support	Parent report
Parent mental health	Depression Anxiety Stress Scale -21(51) (21 items). Report of symptoms over the past week.	Parent report
Parenting stress	Autism Parenting Stress Index (52)(13 items). Measures three categories of stress drivers: core social disability, difficult behaviour, physical issues	Parent report

SBP= Severe Behavioural Problems

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 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 standard deviations.

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 standard deviations by treatment group.

ETHICS AND DISSEMINATION

This project has ethics approval from the Human Research Ethics Committee of the Royal Children's Hospital, Melbourne (38236). Study-specific unique identifiers will to be used to identify trial subjects. Data will be de-identified and associated with study specific identification numbers. Data will be captured and stored directly in Research Electronic Data Capture (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.

Author contributions

- All authors (DE, KT, JMP, JLF, NC, MM, CP, KJL, KW) made substantial contributions to the design of this study and the writing of the protocol
- All authors (DE, KT, JMP, JLF, NC, MM, CP, KJL, KW) made substantial contributions to drafting the work and revising it critically for intellectual content;
- All authors (DE, KT, JMP, JLF, NC, MM, CP, KJL, KW) approved the final version submitted;
- All authors (DE, KT, JMP, JLF, NC, MM, CP, KJL, KW) agree to be accountable for the accuracy or integrity of the work

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Competing interests statement

The authors declare no competing interests.

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SUPPLEMENTARY MATERIAL 1: Pilot evaluation questionnaire

CBD Pilot: Evaluation

We would like to ask you some questions about the study.

For each question please indicate your response on the 5-point scale provided.

What did you think about the **way we approached you** for your child to participate in this study?

☐ Very poor ☐ Poor ☐ Satisfactory ☐ Very good ☐ Excellent

How did your **child tolerate the medication** s/he took in this study?

☐ Very poor ☐ Poor ☐ Satisfactory ☐ Very good ☐ Excellent

What did you think about the **number of visits** to the hospital required for this study?

☐ Far too many/ Not acceptable ☐ Too many ☐ Acceptable

What did you think about completing the **questionnaires** (how many questions and how hard to complete)?

☐ Unacceptable ☐ Difficult ☐ Acceptable ☐ Good / fine

What did you think about the following parts of the study visits?

Psychology assessment

☐	☐	☐	☐	☐
Not applicable	Unacceptable	Difficult	Acceptable	Good / fine

Blood tests

☐	☐	☐	☐
Unacceptable	Difficult	Acceptable	Good / fine

Your thoughts on the study *(tick one box per line)*

What is your overall opinion of the quality of the study?

☐	☐	☐	☐	☐
Very poor	Poor	Satisfactory	Very good	Excellent

My child found the study…

☐	☐	☐	☐
Very difficult	Difficult	Satisfactory	Easy

What did you find **best** about the study?_____

_____

_____

_____

_____

_____

_____

What did you find **worst** about the study?_____

_____

_____

_____

_____

How could we improve things?_____

_____

_____

_____

_____

Would you recommend this study to other families with children with similar problems?

☐ Yes ☐ No

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
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	
Protocol version	3	Date and version identifier	
Funding	4	Sources and types of financial, material, and other support	19
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	1
	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	19
	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)	N/A

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	4-9
	6b	Explanation for choice of comparators	N/A – pilot study
Objectives	7	Specific objectives or hypotheses	9
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)	10
Methods: Participants, interventions, 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	12
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)	10-11
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10
	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)	15-16
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	12,15-16
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	11
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	17
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)	12-13

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	10 (note: this is a pilot study, nil power calculations)
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	____11-12___
Methods: Assignment 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	____12_____
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	____12_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	____12_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	____12_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	____12_____
Methods: Data collection, 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	____17_____

	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	___12_____
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	___17_____
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	___17_____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	___N/A_____
	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)	___N/A_____
Methods: Monitoring			
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	__Pilot study____
	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	_____
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	___15-16____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_____
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	_____18_____

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)	N/A
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	12
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
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	17-18
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	19
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	18
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	N/A
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	10,18
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	
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	

*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.

BMJ Open

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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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 (SBP) 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 medical 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 20mg/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

Australian New Zealand Clinical Trials Registry prospective registration: ACTRN12618001852246

ARTICLE SUMMARY

Strengths and limitations of this study

- This is the first study to investigate CBD for SBP in children with ID and will contribute to the literature more broadly on the use of cannabinoids in children.
- Randomised, placebo-controlled study using online completion of outcome measures.
- This pilot study will inform the design of a full-scale randomised controlled trial of CBD for this indication, and will inform other CBD trials in children.
- The study is not powered to provide meaningful efficacy outcomes.

INTRODUCTION

Intellectual Disability with Severe Behaviour Problems and associated burden

Two percent 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.

SBP 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 $15 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,(8) leaving environmental modification and medication as the main strategies available. Psychotropic medications are prescribed by Australian paediatricians for almost 50% of youth with ID.(9) The medications – anti-psychotics, psychostimulants and anti-depressants – carry a high risk of side-effects for children and adolescents in general, however patients with developmental disabilities are at particularly high risk,(10) 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.(11) Another common side-effect of antipsychotics, weight gain, affects health in a patient group already at increased risk of chronic illness(12), and is a risk factor for avoidable death(13). 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;(10) adding drugs to treat side effects, such as use of metformin to control weight gain caused by antipsychotic medication;(14) and long-term use of drugs "off-label" e.g. atypical antipsychotics. Innovative and safer interventions are urgently needed for children with ID and SBP.

Medical Cannabis

The potential for cannabis products to treat a range of medical and psychiatric conditions is becoming increasingly understood.(15) There has recently been great interest in the potential therapeutic role of cannabinoids. The primary psychoactive compound in the cannabis plant is Δ^9-tetrahydrocannabinol (Δ9-THC), which can cause serious side effects such as paranoia and hallucinations.(16) 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 sub-lingual spray in human trials, in variable ratios with Δ^9-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 twice-daily dosing for 7 days in healthy adults.(17) It is highly lipophilic and accumulates in fat.(18) CBD is metabolized 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.(19) 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.(18) In children with epilepsy up to 50 mg/kg/day of CBD has been prescribed.(20) 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.(21)

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.(21) 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-Gastaux or Dravet syndromes.(22) 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.(23)

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, anti-oxidant activity, and anti-inflammatory effects.(24) 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, (25) and in a mouse model of Fragile-X syndrome, (26) so this system appears to play an important role in neurodevelopment and behaviour.(27) 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.(28) 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).(29) 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 medical 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, Nov 21 2009), and parents have described "the transformative power of medical cannabis" for their children with ID + SBP (e.g. Mothers Advocating Medical Marijuana for Autism). Anecdotally some parents have reported giving non-prescribed unregulated cannabis products to their children to help with their behaviour, and increasingly Australian parents of children with developmental disabilities and/or mental health disorders are asking their paediatricians if medical cannabis would be a useful treatment and whether they can assist them in obtaining it for their child.(23) Research to date suggests that CBD has substantially less side-effects than anti-psychotic medications,(21) however there is currently insufficient evidence to inform its use in treating SBP. The American Academy of Pediatrics and the Royal Australasian College of Physicians (30) have highlighted the need for further research into the therapeutic uses of cannabinoids in youth.

A handful of reports in the literature suggest there may be a legitimate role for medical cannabis to treat SBP in youth with developmental disabilities (Table 1). Although promising, these uncontrolled reports provide only weak evidence in support of benefit.

Table 1. Completed and ongoing studies reporting behavioural outcomes of youth treated with medical cannabis products

Published studies				
Sample size	Population	Study design	Product used	Findings
1	Child with ID + SBP	Case report	Dronabinol (Δ9-THC)	Improvements in hyperactivity, irritability and speech (31)
10	Adolescents with ID + SBP	Open-label case series	Dronabinol (Δ9-THC)	Reductions in self-injurious behaviour in 7 out of 10 participants (32)
75	Children with epilepsy (heterogeneous sample)	Retrospective chart review	"Oral cannabis extracts"	Improvements in behaviour (33)

19	Children with epilepsy: Dravet syndrome (n=13), Doose syndrome (n=4), Lennox-Gastaut syndrome (n=1) and idiopathic epilepsy (n=1)	Facebook survey	"CBD-enriched cannabis"	Improvements in mood, sleep and self-stimulation (34)
53	Children with ASD	Open-label, symptoms graded as improvement, no change, worsening	CBD:Δ9-THC 20:1	Improvements in self-injury, rage-attacks, hyperactivity, sleep and anxiety.(35) Adverse events were mild
60	Children with ASD + SBP	Retrospective open-label	"CBD-rich cannabis"	"Much improved" or "very much improved" behaviour in 61% of patients.(36) Only one serious adverse event was noted, a transient psychotic event, which was considered to be related to an increase in Δ9-THC.
188	Children with ASD	Prospective open-label	"CBD-enriched cannabis" (mostly 30% CBD and 1.5% Δ9-THC)	Significant or moderate improvements in anxiety, agitation and rage attacks for 79.8% of 119 participants assessed after 1 month.(37) The most common side-effect was restlessness
Ongoing registered trials				
Sample	Population	Study design	Product used	ClinicalTrials.gov Identifier

size				
150	Youth with ASD + SBP	Double-blind, cross-over RCT	Cannabis oil with a 20:1 ratio of CBD to Δ9-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

There are currently four registered trials of medical cannabis products use for behavioural problems in youth (also summarised in Table 1). In contrast to these, our study will include all children with ID and SBP, regardless of aetiology, and irrespective whether they have been diagnosed with ASD. Whereas one currently registered trial uses a Δ9-THC containing product, our study will use CBD alone, thus avoiding the potential risks associated with Δ9-THC. Two registered studies describe randomised controlled trials (RCT) comparing cannabidivarin (a homolog of CBD) to placebo. CBD has a more established safety profile, is more commonly known and sought by consumers, and more readily available commercially. Given the larger number of pharmaceutical companies manufacturing CBD, it would be expected that CBD is also more competitively priced – an important consideration for both research funding bodies and patients.

This pilot study will assess the feasibility of conducting a large scale, randomised, double blind, placebo-controlled study of oral CBD in children with ID and SBP. We will also collect preliminary data on the safety and tolerance of CBD in children with ID and SBP.

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 pre- 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, semi-structured telephone interviews with 8 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 post-study completion regarding their experience participating in the research study. 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 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 medical 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.
    a. Full scale IQ < 70 on standardised cognitive assessment on verified records of testing performed within two 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 Behavior Scales completed by interview with the parent or carer; derives scores in Communication, Daily Living Skills and Socialization domains, and a Global Adaptive score.
3. SBP: Defined as:

a. Scores of 18 or higher on the Aberrant Behavior Checklist-Irritability subscale (ABC-I) (38) and

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 anti-epileptic medications which interact with CBD (e.g. clobazam, topiramate, zonisamide)
4. Current medical 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 *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 Murdoch Children's Research Institute (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.

Table 2. Schedule of study visit procedures and assessments

			Double-blind evaluation				
	Screening	Baseline/ Start of Up-titration	Start of Maintenance	Maintenance Mid-point	Start of Down-titration	End of Down-titration	End of Study (Phone Call)
Day	-14 to -1	1	Day 9-13	Day 36-40[1]	Day 66-70	Day 74[1]	Day 104
WASI-II	X						
Vineland-3	X						
A-TAC	X						
SCQ	X						
ABC-I	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		X		X		
Biochemistry	X		X		X		

Randomisation		X					
Dispense study medication		X	X	X	X		
Study drug administration		X----------					-X
Dispense diary cards		X	X		X	X	
Collect diary cards			X		X	X	X
Evaluation measures		X			X		
Safety outcome measure (MOSES)		X	X		X		
Adverse events		X	X		X	X	X
Compliance check			X	X	X	X	
Pilot evaluation questionnaire							X

[1] Maintenance Mid-point and End of Down-titration visits require only the parent or carer to attend to return study medication
WASI-II= Wechsler Abbreviated Scale of Intelligence-II; A-TAC=Autism- Tics ADHD and Comorbidities; SCQ= Social Communication Questionnaire; MOSES= Monitoring of Side Effects Scale

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

WASI-II. The WASI-II(39) 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 two years prior to screening.

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

A-TAC. Autism-Tics ADHD and Comorbidities (A-TAC)(40 ,41) inventory is a comprehensive screening interview for ASD, attention deficit/hyperactivity disorder (ADHD), tic disorders (TD), developmental coordination disorder (DCD), learning disorders (LD) and other childhood mental disorders. Modules screening for Motor skills, ADHD, Tics, Compulsions, Mood, Anxiety & Oppositional defiance will be administered with the participants' parent or carer by a study doctor.

SCQ. The "current" version of the Social Communication Questionnaire (SCQ)(42) will be used to screen for ASD symptoms. This will be administered online with the outcome measures.

ABC-I. The Aberrant Behaviour Checklist (ABC) (38) is an informant-rated questionnaire assessing severity of behavioural symptoms commonly seen in youth with ID that includes five subscales: Irritability, Social Withdrawal, Stereotypic Behavior, Hyperactivity/Noncompliance 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 (sodium and potassium), creatinine, liver function tests (ALT, ALP, total bilirubin, albumin, GGT and total protein) and lipase. Participants with clinically significant abnormalities will be excluded from participating at the judgment 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 the maintenance dose of 20 mg/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.(43) 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 favor of cannabidiol 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 5mg/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 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),(44) 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 suggest 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 80-120% 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 *Supplementary Material 2* for a copy of this questionnaire.

Table 3. Evaluation measures

Construct	Measurement	Source
SBP	Summary score from the ABC-I (38) (15 items)	Parent report
Behaviour	Other subscales of the ABC (38) (4 outcomes)	Parent report
Overall clinical impression	Clinical Global Impressions (44): 2-item clinician-rated summary measures of a) severity of psychopathology and b) improvement	Clinician-rating
Participation	Child & Adolescent Scale of Participation (45) (20 items). Participation in home, school, and community activities	Parent report
Quality of life	Child Health Utility 9D (46 ,47) (9 items). Preference-weighted measure used to calculate quality adjusted life years for children.	Parent report
Sleep	Sleep Disturbance Scale for Children (48)(26 items)	Parent report
Parent quality of life	Assessment of Quality of Life 8D (49)(35 items). Health-related instrument used to calculate quality adjusted life	Parent report

	years for parents.	
Family quality of life	Beach Center Family Quality of Life (50)(25 items). Family interaction, parenting, emotional and material wellbeing, disability-related support	Parent report
Parent mental health	Depression Anxiety Stress Scale -21(51) (21 items). Report of symptoms over the past week.	Parent report
Parenting stress	Autism Parenting Stress Index (52)(13 items). Measures three categories of stress drivers: core social disability, difficult behaviour, physical issues	Parent report

SBP= Severe Behavioural Problems

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 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 standard deviations.

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 standard deviations by treatment group.

ETHICS AND DISSEMINATION

This project has ethics approval from the Human Research Ethics Committee of the Royal Children's Hospital, Melbourne (38236). Study-specific unique identifiers will to be used to identify trial subjects. Data will be de-identified and associated with study specific identification numbers. Data will be captured and stored directly in Research Electronic Data Capture (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.

Author contributions

- All authors (DE, KT, JMP, JLF, NC, MM, CP, KJL, KW) made substantial contributions to the design of this study and the writing of the protocol
- All authors (DE, KT, JMP, JLF, NC, MM, CP, KJL, KW) made substantial contributions to drafting the work and revising it critically for intellectual content;
- All authors (DE, KT, JMP, JLF, NC, MM, CP, KJL, KW) approved the final version submitted;
- All authors (DE, KT, JMP, JLF, NC, MM, CP, KJL, KW) agree to be accountable for the accuracy or integrity of the work

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Competing interests statement

The authors declare no competing interests.

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Information statement and consent form

HREC Project Number: 38236

Short Name of Project: Pilot study of CBD in children with ID

Full Name of Project: Pilot study of cannabidiol (CBD) in children with Intellectual Disability (ID) and Severe Behavioural Problems (SBP)

Principal Researcher: Associate Professor Daryl Efron, Consultant Paediatrician, The Royal Children's Hospital

Version Number: 2.0 **Version Date:** 31 October 2018

Thank you for taking the time to read this **Participant Information Statement and Consent Form**. We would like to invite your child to take part in a research project that is explained in this form.

This form is 10 pages long. Please make sure you have all the pages.

What is an Information Statement and Consent Form?

An Information and Consent Form tells you about the research project. It explains exactly what the research project will involve. This information is to help you decide whether or not you would like your child to take part in the research. Please read it carefully.

Before you decide if you want your child to take part or not, you can ask us any questions you have about the project. You may want to talk about the project with your family, friends or a health care worker.

Taking part in the research project is up to you

It is your choice whether or not your child takes part in the research project. You do not have to agree if you do not want to. If you decide you do not want to take part, it will not affect the treatment and care your child gets at The Royal Children's Hospital or from their paediatrician.

Signing the form

If you want your child to take part in the research, please sign the consent form at the end of this document. By signing the form you are telling us that you:

- understand what you have read
- have had a chance to ask questions and received satisfactory answers
- consent to your child taking part in the project.

We will give you a copy of this form to keep.

What is the research project about?

Our research project is a *pilot study*. A pilot study helps us to prepare for a bigger study. In a pilot study, we look at how the study works, as well as how a study treatment affects people.

Children with ***Intellectual Disability*** (ID) can also have ***Severe Behavioural Problems*** (SBP). SBP can have an effect on their families and carers, and can also affect their health care, education and the management of their disability.

At the moment, dealing with SBP is difficult. There are drugs that can be used to treat SBP, but these are not always effective. These drugs can also cause serious side-effects.

Parents and doctors are interested in using **medical cannabis** as a treatment for SBP in children with ID. However, there is not enough evidence to know if cannabis works for these patients.

In this study, we are testing a treatment called CBD100 (cannabidiol). CBD100 is a legal cannabis extract, which does not appear to have the same intoxication, addiction, or withdrawal effects seen in THC-containing cannabis. It may be helpful in improving behaviour, and may also have fewer side effects than existing medications. We hope to find out if CBD100 works and if it is safe. We aim to recruit 10 children with ID and SBP to take part in this pilot study.

Because this is a pilot study, we are also collecting information to help us understand how we can run a bigger trial. The information we collect may help us to do a large trial to show whether CBD100 is safe and helpful for reducing SBP in children with ID.

1. Who is running the project?

This project is being led by Associate Professor Daryl Efron. The project plan was written by staff of the Murdoch Children's Research Institute, including A/Prof Efron.

The company Tilray are supplying the study drug.

This project will be run at the Royal Children's Hospital, Melbourne (RCH). The research team for this project includes doctors and researchers at the RCH.

2. Why is my child being asked to take part?

We are asking your child to take part in the project because they:

- are aged between 8 and 16 years

  and

- have ID

  and

- have SBP.

3. What does my child need to do in this project?

Your child will be in this study for 17 weeks. Your child will need to visit the hospital on five occasions.

The study is in three parts:

- Screening period: Up to 14 days
- Treatment period: 74 days (9 days up titration, 8 weeks maintenance, 9 days down titration)
- Post-treatment follow up: 30 days

a) Screening

We first need to check that your child is suitable for this study. To do this, we will need to do some tests and procedures.
These tests and procedures are:

Test/Procedure	**What will happen?**
Medical history	We will ask you some questions about your child's medical history including about their ID and SBP, and other illnesses they may have had. We will ask you about medications your child may have taken in the past to help manage their SBP, and any medication they are currently taking for any reason.
Physical examination	We will examine your child to check their overall health. We will measure their temperature, heart rate, breathing rate and blood pressure, and also their height and weight.
Parent/carer survey	We will ask you to complete a questionnaire about your child and their disability, and how this affects their life. We will also ask you some questions about your family and what supports you have for your child.
Blood collection	We will collect some blood by pricking your child's finger. We may need to put a needle into a vein in your child's arm to collect blood. We will test your child's blood to see if there are any health concerns for your child that could be a problem if they took CBD.
ID assessment	We will do an assessment of your child's level of intelligence using an IQ test. Your child will need to do things like answer questions, look at pictures, and work with blocks.

b) Baseline

If your child is eligible for the study, then they will be invited back to the hospital for a baseline visit. This could be up to two weeks after the screening visit. At the baseline visit we will collect information about your child before we give them the study drug.

At this visit we will do the following procedures:

Test/Procedure	**What will happen?**
Physical examination	We will examine your child to check their overall health. We will measure their temperature, heart rate breathing rate and blood pressure, and also measure their height and weight.
Medication check	We will ask you about any medications your child is taking.
Side effect monitoring	We will ask you to complete a questionnaire about possible side effects of CBD100 as a baseline, so we can compare with when they are taking the medication.

c) Randomisation

We will put your child into one of two groups:

- Group 1. *Treatment group*. In this group your child will be given CBD100
- Group 2. *No treatment group*. In this group your child will be given placebo drug. A placebo is a medication with no active ingredients. It looks like the real thing but is not.

This will be done by chance, like tossing a coin, so your child has an equal chance of being in either group.

We can't choose which group your child is put in, and neither can you or your child. For the duration of the study neither you nor any of the researchers will know what group your child is in.

d) Treatment

We will give your child their first dose of study drug at the hospital on the same day as the baseline visit. Your child will need to stay at the hospital for an hour after we give them the study drug to make sure they are OK.

We will give you a supply of the study drug to take home with you, and also diary cards to complete to record your child's doses of study drug and symptoms. At each visit, you will need to return all unused study drug, as well as completed diary cards and empty drug bottles.

Over the first nine days we will increase your child's dose of study drug every three days. Then the dose will remain the same from days 10 to 66, after which the dose will be reduced over the next 9 days and then stopped.

At day 10 and day 66, your child will need to return to the hospital for an examination.

On Day 38, you will need to attend the hospital to collect another supply of the study drug. Your child does not need to attend this visit. They will also not need to attend the visit on Day 74.

The procedures that will be done at each visit are shown in the table below.

	Screening	Baseline/ Day 1	Day 10	Day 38	Day 66	Day 74	End of study phone call (Day 104)
		First dose, increased for 9 days	Stable dose	Mid-way	Dose decreased for 9 days	End of treatment	
Medical history	X						
Physical examination	X				X		
Comorbidity assessment	X						
Behaviour assessment	X						
Parent/carer survey	X						
Blood collection	X		X		X		
ID assessment	X						
Medication check	X	X	X		X		X
Side effect monitoring		X	X		X	X	X
Provide supply of study drug		X	X	X	X		
Provide diary		X	X		X	X	
Collect diary			X		X	X	X
Visit length (hours)	2-3 hours	1 ½ hours	1 hour	½ hour	1 hour	½ hour	

e) Post-treatment Follow Up

30 days after your child's last dose of study drug, we will call you at an arranged time for an end of study check.

f) Questionnaires

At various times throughout the study you will be asked to complete questionnaires that provide us with important information about your family wellbeing, your child, and any physical symptoms your child may experience during the study. These questionnaires will be sent via email as a secure web-link, and can be completed on your home computer or tablet. The questionnaires will be sent to you on Days 1, 10, 66 and 104.

g) Study samples

This study involves the collection of blood samples. These will be used to make sure there are no side-effects, and also for research purposes.

We will test these samples at the Royal Children's Hospital Laboratory Service. The samples will be destroyed once the laboratory tests have been done.

h) Other treatment

It is important to tell us about any treatments or medicines your child may be taking. This includes prescription medicines, over-the-counter medicines, vitamins or herbal medicines. If there are any changes to these while they are in this study, you must let us know.

During the study, your child may not be able to take some or all of the medicines or treatments they usually take for their condition. We will tell you which treatments or medicines need to be stopped while your child is in the study.

i) Informing your child's GP

You should tell your child's GP that your child is taking part in this research study.

j) Reimbursement

Your child will not be paid to take part in this research project. We will give you parking vouchers when you come to the hospital for research study visits.

k) After the study

If you are interested, we can only inform you whether your child was given the study drug or placebo after all the results of this research study have been finalised. The study drug is available through the Special Access Scheme with approval on a case-by-case basis due to exceptional clinical circumstances. This product is not currently subsidised, meaning that families must fund the cost themselves. If you wish to apply for approval for cannabidiol through this scheme, you could discuss this with your child's paediatrician.

l) Alternatives to participation

Your child does not have to be in this study. There are alternative treatments for your child, including the standard treatment for SBP. This treatment includes anti-psychotic and other psychotropic medications

4. Can my child stop taking part in the project?

Your child can stop taking part in the project at any time. You just need to tell us so. You do not need to tell us the reason why. If your child leaves the project we will use any information already collected unless you tell us not to.

We may also stop the study for a variety of reasons. We may need to take your child off the study treatment for the following reasons, such as if:

- we believe that it is in their best interest
- they have side effects from the treatment that are considered too severe
- your child becomes pregnant

- your child does not follow instructions or come to planned study visits
- the sponsor stops the study unexpectedly.

If your child leaves the study early, we will need to reduce their dose of study drug slowly. We will explain how to do this. It is important that you do not just stop giving your child the study drug without talking to us.

New information may become available that might affect your decision to let your child stay in the study. If we learn any new information, we will talk to you about it.

5. What are the possible benefits for my child and other people in the future?

We cannot guarantee that your child will get any benefits from this project. However, the study drug may help with your child's SBP.

Information from this study will be used to plan a larger study of CBD100 (or a similar product).

6. What are the possible risks, side-effects, discomforts and/or inconveniences?

Medical treatments often have side effects. Your child may have none, some or all of the side effects listed below. These side effects may be mild, moderate or severe. We will also be looking out for side effects.

There may be side effects that we do not expect or know about. Please tell us immediately if your child gets any new or unusual symptoms. If a severe side effect or reaction occurs, we may need to stop your child's treatment.

Many side effects go away shortly after treatment ends. However, sometimes they can be long lasting or permanent.

If your child experiences any symptoms listed below, or if you notice something different about their body, please call us straightaway. We will assess whether these symptoms are related to the study drug.

CBD100

We don't know completely what side effects children with ID may have from taking CBD100, or how likely it is that they will have side effects.

In other studies of CBD100, researchers have seen the following side effects:

- drowsiness, or sleeping for increased lengths of time
- change in appetite
- diarrhoea
- nausea and vomiting
- change in liver function on blood tests

Blood tests

There are no major risks associated with a blood test. It is possible your child may feel some pain or discomfort during the test. We can use a numbing cream before the needle to reduce this. There may be a little bruising, swelling or bleeding where the needle enters the skin. Some people can feel light-headed when blood is taken.

Reproductive risks

Because of the age-range of participants in this study, it is possible that your child may have started or gone through puberty. The following information is important if your child is able to become pregnant or father a baby:

- The effects of the study drug on an unborn or newborn baby are not known.
- If your child is pregnant, she cannot take part in this study.
- If your child becomes pregnant during the project, we need to be told immediately.

Compensation for Injury

By signing the consent form, you are not giving up any legal rights to seek to obtain compensation for injury.

7. What will be done to make sure my child's information is confidential?

In this study we will collect and use personal and health information about your child for research purposes. Any identifying information that we collect about your child will be treated as confidential. It will be used only in this project, unless we say otherwise. We can disclose the information only with your permission, except as required by law.

All information will be stored securely in the Australian Paediatric Pharmacology Research Unit (APPRU) at The Royal Children's Hospital.

The information will be re-identifiable. This means that we will remove your child's name and give the information a special code number. Only we can match your child's name to their code number, if it is necessary to do so.

As the participants in this project are under 18 years old, we will keep their information at least until the youngest participant turns 25 years old. Alternatively, we will keep their information for at least 15 years after the study has closed – whichever date is latest.

You have the right to access and correct the information we collect and store about your child. This is in accordance with relevant Australian and/or Victorian privacy and other relevant laws. Please contact us if you would like to access this information.

The Royal Children's Hospital and Murdoch Children's Research Institute are research partners. This means that the two organisations share research information with each other.

The following people may access information collected as part of this research project:

- the research team involved with this project
- The Royal Children's Hospital Human Research Ethics Committee.

These groups may need to inspect and/or copy your child's research records for data analysis. They may also want to check that study procedures are followed correctly. Your child's name and personal details will not be released unless required by law.

Some of the information collected as part of this research may be important for your child's medical treatment and health. The following information will be placed in your child's hospital medical record and/or sent to your child's doctor to help the people who care for them:

- your child's participation in this study

We will tell your child's pediatrician if there are any abnormal test results that they need to know about.

At the end of the study, we may present the results at conferences. We may also publish the results in medical journals. This will be done in such a way that your child cannot be identified.

8. Will we be informed of the results when the research project is finished?

We will send you a summary of the overall project results. The summary will be of the whole group of research study participants, not your child's individual results.

9. Who should I contact for more information?

If you would like more information about the project, or in the case of an emergency, please contact:

Name: Associate Professor Daryl Efron

Contact telephone: 03 9345 4563

Email: Daryl.Efron@rch.org.au

You can contact the Director of Research Ethics & Governance at The Royal Children's Hospital Melbourne if you:

- have any concerns or complaints about the project
- are worried about your child's rights as a research participant
- would like to speak to someone independent of the project.

The Director can be contacted on (03) 9345 5044.

CONSENT FORM

HREC Project Number: 36236

Short Name of Project: Pilot study of CBD in children with ID

Version Number: 2.0 **Version Date:** October 31 2018

- I have read this information statement and I understand its contents.
- I understand what my child and I have to do to be involved in this project.
- I understand the risks my child could face because of their involvement in this project.
- I voluntarily consent for my child to take part in this research project.
- I have had an opportunity to ask questions about the project and I am satisfied with the answers I have received.
- I understand that this project has been approved by The Royal Children's Hospital Melbourne Human Research Ethics Committee. I understand that the project and any updates will be carried out in line with the National Statement on Ethical Conduct in Human Research (2007).
- I understand I will receive a copy of this Information Statement and Consent Form.

Child's Name

Parent/Guardian Name	Parent/Guardian Signature	Date
Name of Witness to Parent/Guardian's Signature	Witness Signature	Date

Declaration by researcher: I have explained the project to the parent/guardian who has signed above. I believe that they understand the purpose, extent and possible risks of their child's involvement in this project.

Research Team Member Name	Research Team Member Signature	Date

Note: All parties signing the consent form must date their own signature.

SUPPLEMENTARY MATERIAL 2: Pilot evaluation questionnaire

CBD Pilot: Evaluation

We would like to ask you some questions about the study.

For each question please indicate your response on the 5-point scale provided.

What did you think about the **way we approached you** for your child to participate in this study?

☐ Very poor ☐ Poor ☐ Satisfactory ☐ Very good ☐ Excellent

How did your **child tolerate the medication** s/he took in this study?

☐ Very poor ☐ Poor ☐ Satisfactory ☐ Very good ☐ Excellent

What did you think about the **number of visits** to the hospital required for this study?

☐ Far too many/ Not acceptable ☐ Too many ☐ Acceptable

What did you think about completing the **questionnaires** (how many questions and how hard to complete)?

☐ Unacceptable ☐ Difficult ☐ Acceptable ☐ Good / fine

What did you think about the following parts of the study visits?

Psychology assessment

☐ Not applicable ☐ Unacceptable ☐ Difficult ☐ Acceptable ☐ Good / fine

Blood tests

☐ Unacceptable ☐ Difficult ☐ Acceptable ☐ Good / fine

Your thoughts on the study *(tick one box per line)*

What is your overall opinion of the quality of the study?

☐ Very poor ☐ Poor ☐ Satisfactory ☐ Very good ☐ Excellent

My child found the study…

☐ Very difficult ☐ Difficult ☐ Satisfactory ☐ Easy

What did you find **best** about the study? _____

_____

_____

_____

What did you find **worst** about the study?

How could we improve things?

Would you recommend this study to other families with children with similar problems?

☐ Yes ☐ No

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
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	
Protocol version	3	Date and version identifier	
Funding	4	Sources and types of financial, material, and other support	19
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	1
	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	19
	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)	N/A

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	4-9
	6b	Explanation for choice of comparators	N/A – pilot study
Objectives	7	Specific objectives or hypotheses	9
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)	10
Methods: Participants, interventions, 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	12
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)	10-11
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10
	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)	15-16
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	12,15-16
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	11
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	17
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)	12-13

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	10 (note: this is a pilot study, nil power calculations)
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	____11-12___
Methods: Assignment 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	____12_____
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	____12_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	____12_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	____12_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	____12_____
Methods: Data collection, 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	____17_____

	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	___12_____
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	___17_____
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	___17_____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	___N/A_____
	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)	___N/A_____
Methods: Monitoring			
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	__Pilot study____
	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	_____
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	___15-16____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_____
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	_____18_____

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)	N/A
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	12
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
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	17-18
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	19
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	18
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	N/A
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	10,18
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	
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	

*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 "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.