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Synopsis

Cannabidiol as a treatment for patients who are clinically at high risk of developing psychosis: learnings from the CANTOP-RCT

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Abstract

Background: There are no licensed pharmacological treatments for people who are at clinical high risk of developing psychosis. Although psychological interventions are well tolerated, they do not appear to reduce the risk of later transition to psychosis. Clinically high-risk people commonly experience low-grade anxiety and psychotic symptoms. Cannabidiol is a non-intoxicating substance present in cannabis that shows promise in terms of its antipsychotic and antianxiety potential. However, no fully powered randomised clinical trial has investigated the efficacy of cannabidiol as a treatment in people with clinical high risk. Further, the mechanisms that may underlie its beneficial effects remain unclear.

Objectives: To conduct a double-blind, placebo-controlled randomised controlled trial to investigate the efficacy of cannabidiol as a treatment for psychotic and anxiety symptoms in people at clinical high risk, its safety and tolerability, and the neurochemical and neurophysiological basis of its effects.

Design: We proposed to conduct a parallel-arm, multisite, double-blind randomised control trial to evaluate the efficacy and tolerability of cannabidiol when added to treatment as usual, compared to treatment as usual plus placebo, in 300 clinically high-risk patients (n = 150 per treatment arm).

In a subsample of participants (total N = 100; n = 50 per treatment arm), we proposed to use magnetic resonance spectroscopy to measure hippocampal glutamate levels, functional magnetic resonance imaging to measure brain activation (while patients performed verbal memory and emotional processing tasks), and arterial spin labelling to measure blood flow to investigate the neurochemical and neurophysiological basis of the effects of cannabidiol (mechanism substudy).

Setting: Multicentre study involving early intervention services within the United Kingdom.

Participants: Three hundred patients aged 18–35 years (N = 300; n = 150 per treatment arm) diagnosed with a clinical high-risk state for psychosis and attenuated psychotic symptoms for the randomised controlled trial. A subsample of participants (total N = 100; n = 50 per treatment arm) for the mechanism substudy.

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Intervention: Participants were to receive a single daily dose of 600 mg cannabidiol or placebo to be taken orally for 6 months.
Main outcome measure: Severity of psychotic symptoms at 6 months using the Comprehensive Assessment of At-Risk Mental States.
In the mechanism substudy, we aimed to compare their effects following 28 days treatment on hippocampal glutamate levels, and on brain activation while performing verbal memory and emotional processing tasks, as well as resting regional cerebral blood flow in the medial temporal cortex and basal ganglia.
Results: Funding for the research commenced in September 2018, when we entered a planned 6-month study set-up phase. The trial was not able to be delivered in a timely manner due to uncertainty over the drug supply, leading to eventual closure of the study in March 2022.
Conclusions: Here we summarise the events that led to this decision, reflect on the contributing factors and suggest potential learning points to help other researchers avoid such outcomes in future.
Study limitations and future work: The CANTOP-RCT did not start owing to challenges in securing supply of the study drug, and therefore addressing this issue is essential for any future definitive study to investigate the efficacy of cannabidiol as a treatment for clinical high-risk patients with attenuated psychotic symptoms.
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Background

Health need

According to the Global Burden of Disease Study 2010,[1] schizophrenia and other forms of psychoses affecting young people rank as some of the most disabling of all non-fatal human disorders. They place an enormous burden in terms of suffering to humankind, with the total societal cost in England alone estimated at around £11.8B per year (http://eprints.lse.ac.uk/47406/). In the UK, this equates to an average annual societal cost of £60,000 and cost to the public sector of £36,000 for each individual who develops the illness. Despite the efficacy of antipsychotic treatment in providing relief from symptoms following the onset of psychosis,[2] psychotic disorders are typically characterised by relapse, with between 40% and 63% of patients with first episode psychosis experiencing a relapse within the first few years following onset of illness.[3] Hence, worldwide, there has been increasing focus over the last couple of decades on early detection and treatment of psychoses because of growing recognition that much of the disability associated with psychosis develops long before the onset of frank psychosis, which is very difficult to reverse even if the first psychotic episode is successfully treated.

Estimates, now dated, suggest that in England, 15,763 people present annually with early symptoms of psychosis before the onset of fully fledged disorder.[4] Many of these individuals are at clinical high risk (CHR) of developing psychosis, and about one-third of them will develop the disorder within 3 years. Economic modelling indicates that if clinical intervention at this stage produced even a modest (15%) reduction in the transition rate to psychosis, this would result in annual savings of about £47.6 million.[4] However, as it is not possible currently to accurately predict whether an individual with a CHR state will later develop psychosis, clinical interventions such as antipsychotic medications have to be applied to the entire at-risk population to reduce the risk of transition, raising ethical concerns about the long-term effects of such treatment.

Against this background, following the publication of the policy paper *Achieving Better Access to Mental Health Services by 2020*[5] by the UK Department of Health, the NHS has been at the forefront of implementing specialised mental health services for people at high risk of psychosis. However, although young people are now being engaged by NHS services in the high-risk phase, at present there are still no proven means of reducing the risk of progression to a full-blown psychosis. The absence of effective treatments for this group therefore represents an important unmet clinical need.

What are the currently available solutions?

The main interventions that have been tried have been drawn from the treatment of schizophrenia, and comprise antipsychotic medications and psychological interventions – in particular, cognitive–behavioural therapy (CBT).

Cognitive–behavioural therapy

In the UK, it is recommended that CHR patients should be offered CBT (with or without family therapy), and CBT is often perceived as popular and well tolerated. However, evidence (including meta-analyses) from randomised controlled trials (RCTs) (total $N = 672$; sample range 51–288; total events = 69) indicates that CBT may not

reduce the risk of transition to psychosis[6–9] and may not be widely acceptable.[10] In particular, although early evidence suggested that CBT had beneficial effects, a later multisite RCT carried out in the UK did not show an effect on transition to psychosis.[11] Similarly, there was no effect on symptoms at 6 months, although an improvement was seen after 12 months. In line with previous meta-analyses,[12,13] a large RCT recently found that CBT offered no benefit over clinical management and placebo in terms of preventing transition or reducing symptoms.[14] Further, access to psychological treatments including CBT remains a challenge in the UK[15] and internationally,[16] even for people with established psychotic disorder.

Pharmacological interventions

Other existing competing solutions to the unmet treatment need in CHR patients mainly involve the use of antipsychotic medications that are normally used for treating established psychosis, as well as novel pharmacological treatments. Guidelines from the UK's National Institute for Health and Care Excellence (NICE) suggest that antipsychotics should not be used for CHR patients.[17] Available meta-analytic evidence suggests that antipsychotics have, at best, a modest effect[8,9] and are poorly tolerated. Tolerability is a particular issue in CHR patients, as many of them will never go on to develop a psychotic disorder. The main novel pharmacological treatment that has been evaluated is fish oil (ω-3 polyunsaturated fatty acids). Unfortunately, the promising results from an initial study were not borne out in a larger (n = 304) multicentre RCT.[18]

Summary of efficacy evidence

Network meta-analytic approaches examining the efficacy of currently available treatments for CHR patients suggest that none of the available treatments (psychological or pharmacological) show efficacy in terms of preventing transition to psychosis at 6 or 12 months, nor are there significant differences between treatments in terms of efficacy or acceptability.[12,13]

There is thus a clinical need for interventions that are effective in treating symptoms and alleviating distress in CHR individuals, and that have the potential to reduce the risk of psychosis. Ideally, interventions in this population should be acceptable, well tolerated[19] and deliverable by NHS services that have limited clinical resources. None of the treatments that are currently available or have been recently evaluated addresses this clinical need.

Cannabidiol as a potential novel treatment

While drugs targeting the dopaminergic and glutamatergic neurotransmitter systems have typically been investigated as treatments for psychosis,[20,21] there is growing attention on the endocannabinoid system as a potential therapeutic target.[22–24] The CB1 receptor, the main central cannabinoid receptor,[25] is ubiquitous and modulates the function of several neurotransmitters, including dopamine and glutamate.[26] Converging evidence from epidemiological studies suggests that regular use of cannabis is a significant risk factor for the development and relapse of psychotic disorders such as schizophrenia[27–29] in a dose-responsive manner,[27,29] as well as severity of symptoms (and risk of transition to full-blown psychosis) in those at risk.[30,31] Independent of this evidence, studies have also reported alterations in the endocannabinoid system in people with psychosis.[22,32–38]

Delta-9-tetrahydrocannabinol (THC), the major intoxicating and psychoactive ingredient in cannabis, has psychotomimetic effects, which are mediated through a partial agonist effect at the CB1 receptor.[26] In contrast, cannabidiol (CBD), the other major constituent of cannabis extract, does not cause intoxication, and has a range of effects including an inverse agonist/antagonist effect at CB1 receptors,[26] and may oppose the neural and behavioural effects of THC.[39] In healthy individuals, THC-induced psychotic and anxiety symptoms have been related to its effects on activation in the striatum during verbal memory[40] and salience processing[41,42] and in the amygdala during emotional (fear) processing tasks. In the same individuals, CBD had the opposite effect to THC on both striatal and amygdala activation.[40,42] Furthermore, pretreatment with CBD has been shown to block the subsequent induction of psychotic symptoms by THC.[40] Consistent with these findings, independent evidence has emerged of antipsychotic and anxiolytic properties of CBD in patients with mental health disorders (reviewed by Leweke *et al.*[24]). CBD has been found to be non-inferior to antipsychotic medication in a 4-week clinical trial in acute schizophrenia,[43] and improved psychotic symptoms in a 6-week trial in patients with chronic schizophrenia.[44] CBD also has been shown to reduce anxiety symptoms in those with social phobia[45] and following public speaking,[46] in line with its antiaversive effects in preclinical models of anxiety.[47] Finally, studies in preclinical models of cognitive impairment have demonstrated that CBD can promote hippocampal neurogenesis[48] and rescue memory function,[49] which is consistent with human data showing that it attenuates the cognitive impairments associated with THC use.[50,51]

Cannabidiol as potential treatment in the clinical high-risk state

One of the prevailing hypotheses of the key pathophysiological abnormalities which drive the onset of

psychosis suggests that altered inhibitory feedback from Gamma-Aminobutyric acid (GABA)ergic interneurons leads to disinhibition of hippocampal glutamatergic pyramidal cells,[52] which in turn drive a hyperdopaminergic state through projections to the subcortical dopamine system, resulting in the positive symptoms of psychosis.[52] This preclinical model is supported by a body of evidence indicating that transition to psychosis is associated with increased resting hippocampal blood flow,[53] altered hippocampal glutamate levels,[54–56] a reduction in hippocampal volume[57] and elevated striatal dopamine function.[58] This is consistent with the most robust findings from neurobiological research on psychosis suggesting an elevation of presynaptic dopamine function in the striatum and midbrain,[59–61] and neuroanatomical and neurophysiological alterations in the hippocampus and adjacent medial temporal lobe structures.[62,63] Collectively, these findings suggest that the onset of psychosis in CHR patients is critically dependent on alterations in the medial temporal cortex and the striatum.

Emerging evidence from a number of neuroimaging studies suggests that the effects of CBD may be mediated by modulation of brain function in psychosis-linked regions. For example, CBD has been shown to modulate hippocampal glutamate levels;[64] brain activation in response to motivational salience processing;[65] and mediotemporal and prefrontal dysfunction, and mediotemporal–striatal functional connectivity in patients with established psychosis, alongside trend-level reductions in psychotic symptoms.[66] Consistent with this, studies in CHR patients suggest that a single dose of CBD may modulate alterations in regional brain function during verbal memory[67] and fear-processing,[68] such that activation in CBD-treated patients was intermediate between healthy controls and placebo-treated CHR patients. Moreover, the effects of CBD occurred in the same brain regions that were significantly altered in CHR patients under placebo, suggesting that CBD may partially normalise aberrant brain function in regions specifically altered in CHR patients. Similar effects of CBD on brain activation during salience processing,[69] cortisol responses following social stress,[70] hippocampal perfusion[71] and hippocampal glutamate levels[72] have also been observed in these individuals.

These as well as previous studies have also generated extensive evidence regarding the safety of CBD following acute and longer-term dosing in humans.[45,73] The absence of significant adverse effects associated with CBD[24,45] is a critical advantage in relation to the treatment of CHR individuals – young people who, although highly vulnerable to later illness, do not have a full-blown disorder. However, aside from a proof-of-concept study,[74,75] CBD has not yet been tested in this patient group.

Rationale for the CANTOP-RCT study

While these previous findings strongly suggested that CBD may engage the key neurobiological treatment targets for patients at CHR, no studies have yet tested the clinical efficacy of CBD in a well-powered RCT. Generating such evidence remains the natural next step for evaluation of CBD as a potential treatment for symptoms or the prevention of transition to psychosis in CHR populations. To address this gap in knowledge, the National Institute for Health and Care Research (NIHR) funded the first large-scale RCT of CBD for CHR patients in 2018 (CANTOP-RCT) through its Efficacy and Mechanism Evaluation funding scheme. This project was a randomised, double-blind, placebo-controlled, Phase IIb trial to evaluate the efficacy and tolerability of 6-month treatment with 600 mg/day CBD or placebo in 300 CHR patients in a multisite study across the UK. In addition, a neuroimaging substudy aimed to examine the neural bases and predictors of therapeutic effects of CBD over time. However, despite the immense potential and clinical significance of this work, the study was moved to early closure in March 2022. In this article, we describe the events that led to this decision, reflect on the contributing factors and suggest potential learning points to help other researchers avoid such outcomes in future.

Aims and objectives

Our overarching aim was to address a major unmet clinical need in CHR patients as summarised above. To address this, we proposed to conduct a double-blind, placebo-controlled RCT to investigate the efficacy of CBD added to treatment as usual (TAU), to evaluate:

i. its ability to alleviate psychotic and anxiety symptoms in CHR patients
ii. its safety and tolerability
iii. the neurochemical and neurophysiological basis of its effects.

Methods

The trial was registered at the International Standard Randomised Controlled Trial Number (ISRCTN) registry (ISRCTN10334895) and was assigned a European Clinical trials database number (2018-004434-16). The full protocol is available here (https://fundingawards.nihr.ac.uk/award/16/126/53).

We proposed a randomised, placebo-controlled trial of CBD versus placebo to reduce attenuated psychotic symptoms (APS) in CHR patients. Participants were to

TABLE 1 Planned project timeline

Milestones	Months
Study set-up including ethical and MHRA approval	1–6
Recruitment	7–42
Completion of internal pilot	19
Follow-up	8–48
Analysis	51–53
Dissemination (including manuscripts)	54–57
Submission of final report to NIHR	57

be randomised to either TAU + placebo or TAU + CBD. Randomisation was planned to be double-blind (with both patients and researchers involved in the assessment of outcomes and the statistician blinded to the allocation) and stratified by site. Please see *Table 1* for the initial planned project timeline.

Study population

Heterogeneity in clinical high-risk patients

Clinical high-risk patients are those considered to be at high risk of development of psychotic disorder. This is a heterogeneous group, and CHR diagnosis has been operationalised using standardised and internationally recognised criteria supported by a clinical tool, the Comprehensive Assessment of At-Risk Mental States (CAARMS).[76] CAARMS identifies three subgroups: (1) those with APS, (2) those with 'brief limited intermittent psychotic symptoms', and (3) a vulnerability subgroup. Because the proposed study was primarily designed to assess the effect of CBD on the symptoms of the CHR state, we planned to focus on the CHR-APS subgroup of patients and exclude the other two groups at the screening stage. CHR-APS patients comprise the great majority (at least 80%) of CHR patients treated by NHS early intervention services.[77] Patients belonging to the other subgroups have either minimal or only transient psychotic symptoms, and are often signposted to other mental health services or to primary care, as early intervention services typically prioritise care for those CHR patients who are most symptomatic. A final consideration was that there is increasing evidence that the three CHR subgroups have distinct clinical outcomes and may be biologically heterogeneous.[11,18,78,79]

We proposed to recruit 300 (N = 300; n = 150 per arm) CHR-APS patients satisfying the following criteria into the study.

Inclusion criteria

- Individuals (aged 18–35 years) diagnosed with a CHR state for psychosis, APS subgroup (CHR-APS), as defined using CAARMS criteria.[76]
- Able to understand and communicate in English.
- Able to give informed consent.

Exclusion criteria

- History of a previous psychotic or manic episode lasting 7 days or longer.
- At screening, active suicidal ideation indicating significant current risk or past history of serious suicide attempt in the opinion of the principal investigator and chief investigator.
- Neurological disorders (e.g. epilepsy) or severe intercurrent illness.
- Current treatment with psychotropic medication or previous treatment with antipsychotic medication for more than 7 days.
- Poor premorbid/pre-existing functioning, as assessed with the National Adult Reading Test,[80] defined as an IQ < 70.
- Female patients who were pregnant, lactating or not using contraception.
- Taking part in another RCT.

Withdrawal criteria

In accordance with the Declaration of Helsinki, subjects could voluntarily withdraw from the study at any time without needing to give a reason. Subjects were also proposed to be withdrawn from the RCT if it affected their ongoing care, if they experienced a serious adverse drug reaction to treatment (such as an allergic response or vomiting) or if they were unable to tolerate any of the experimental procedures. It was planned that CHR patients who experienced progression to a first episode of psychosis would exit from the study and be deemed as treatment failure. In line with established practice, and as used in previous clinical trials in CHR patients,[11,18] transition to psychosis was operationally defined using the CAARMS.[76]

Mechanism substudy

For practical reasons, it was proposed that only patients living in or within easy commuting distance of London would be recruited into the mechanism substudy. Conducting the neuroimaging assessments at a single centre was planned to avoid the potentially confounding effects of scanning at different sites. We planned to recruit 100 (n = 100) CHR patients from the main trial (50 from each of the CBD and placebo treatment arms) into the mechanism substudy, if they satisfied the additional standard safety criteria for magnetic resonance imaging (MRI).

Setting

The study was proposed as a multicentre study primarily involving five research-led early intervention services within the UK, led by researchers based at King's College London (KCL)/South London and Maudsley (SLaM) NHS Foundation Trust; Universities of Manchester, Birmingham and Newcastle; and at Cambridgeshire and Peterborough NHS Foundation Trust/University of Cambridge.

Each of these five recruitment hubs was to serve as the research site for patients recruited at that centre, as well as from early intervention services in the surrounding geographical area. It was planned that the recruitment hubs would be linked with a total of 25 additional early intervention teams/services with whom the investigators from the hubs already had close collaborative links, for the purpose of this study. Recruitment from early intervention services was going to be facilitated using support from Mental Health Research Networks.

Internal pilot

An internal pilot was proposed within the first year of opening the study to recruitment. This was proposed to assess the viability of continuing the study based on ability to identify, consent and randomise a certain number of CHR-APS patients into the study by that time point.

Planned interventions

It was proposed that participants would receive either:

i. a single daily dose of CBD for 6 months in addition to TAU (experimental intervention), or
ii. a single daily dose of placebo for 6 months in addition to TAU (control intervention).

Both CBD and placebo were to be formulated as matched capsules. The proposed dose of CBD was 600 mg/day, a safe dose[45] that we had employed in our proof-of-concept study in CHR patients.

Treatment as usual was proposed to correspond to the package of clinical care that is typically provided to CHR patients in NHS early intervention services. This includes 'case management', which involves psychoeducation; support; symptom monitoring; help with social, vocational and housing issues; signposting to appropriate local services; and, when necessary, crisis management (e.g. referral to a crisis team or psychiatric liaison at Accident and Emergency departments).

Outcome measures

All the outcome measures for the clinical trial were proposed to be compared between CBD and placebo groups at end of treatment (6 months), adjusting for baseline.

Primary clinical outcome

1. Severity of psychotic symptoms as measured using the CAARMS.[76]

Secondary clinical outcomes

1. Distress associated with psychotic symptoms as measured using the CAARMS.[76]
2. Severity of anxiety symptoms assessed using the Hospital Anxiety and Depression Scale.[20]
3. Level of global functioning assessed using the Social and Role Functioning Scale.[81]
4. Clinical remission, defined as no longer meeting the criteria for a diagnosis of CHR-APS.
5. Total CAARMS score.

Secondary mechanism substudy outcomes

These outcomes were proposed to be measured at baseline and after 4 weeks of treatment:

1. within-subject change in left hippocampal glutamate levels measured using ^{1}H magnetic resonance spectroscopy (^{1}H-MRS)
2. within-subject change in activation [indexed using the blood oxygen level-dependent (BOLD) signal] in the medial temporal cortex and basal ganglia during a verbal memory task, and during an emotional (fear) processing task
3. within-subject change in resting-state medial temporal lobe and basal ganglia perfusion, as indexed using arterial spin labelling (ASL).

Safety outcomes

1. Incidence of adverse effects during the study period, assessed using reported adverse events.

Psychotic symptom severity assessed by CAARMS was operationalised as in the study by Morrison *et al.*[11] by summing the scores of product of the global rating and frequency scores of the four CAARMS psychotic symptom subscales.[76]

Clinical remission was defined on the basis of the CAARMS criteria[76] as in previous studies.[82] Remission requires a score of < 3 on the 'unusual thought content', 'non-bizarre ideas' and 'perceptual abnormalities' subscales and < 4 on the 'disorganised speech' subscale, and a frequency scale score of < 3 over the past month.

Mechanism substudy data

Neuroimaging [^{1}H-MRS, functional magnetic resonance imaging (fMRI) and ASL] data were proposed to be acquired using well-established protocols (described below) on a 3-T MRI scanner at the Centre for Neuroimaging Sciences, KCL, with each scanning session lasting about 1 hour.

Functional magnetic resonance imaging

Functional MRI data were going to be acquired while participants performed a verbal memory task and an emotional processing task. Both paradigms have been used in previous fMRI studies of the effects of CBD,[40,41] including in our previous studies[67,68] in CHR patients.

1. Verbal memory task:[67] In this task, during an encoding condition, subjects are shown word pairs and asked to say ('yes' or 'no') whether the words 'go together'. In a subsequent retrieval condition, they are shown one from each pair and asked to say the word that it was previously paired with. Stimuli are presented every 5 seconds in alternating blocks of eight pairs, and verbal responses are recorded online.
2. Emotional (fear) processing task:[68] In this task, subjects are presented with a series of 10 different facial identities, each expressing either a 50% (mildly fearful) or 100% (prototypically fearful) intensity of fear, or a neutral expression. They are asked to indicate the gender of each face by pressing one of two buttons. A total of 30 different facial stimuli are presented twice each for 2 seconds, with the order of facial identities and expression type pseudo-randomised such that the same identity or facial expression type is not presented successively.

Magnetic resonance spectroscopy

Hippocampal glutamate levels were proposed to be measured from a spectroscopic voxel placed over the left hippocampus (2 cm^3) using ^{1}H-MRS spectra [point-RESolved spectroscopy (PRESS); echo time (TE) = 30 ms; repetition time = 3000 ms; 96 averages] as previously employed at our centre including in our previous studies with CBD,[64,72] employing the standard GE probe (proton brain examination) sequence, which uses a standardised chemically selective water suppression routine.

Arterial spin labelling

Resting cerebral blood flow (rCBF) was going to be measured using pseudo-continuous ASL scans acquired with a 3D fast spin echo spiral multishot readout, following a post-labelling delay of 1.5 seconds using a sequence that we have employed before in this age group,[53] including in conjunction with CBD administration.[83] The spiral acquisition uses a short (4 ms) TE, and eight spiral arms (interleaves) with 512 points in each arm.

Structural magnetic resonance imaging

For image registration, we planned to acquire both a high-resolution T2-weighted fast spin echo image and a high-resolution T1-weighted spoiled gradient recalled image.

Assessment and follow-up

The proposed schedule of the assessments for each visit is included in the full protocol.

Proposed sample size

We aimed to recruit 300 CHR-APS patients (n = 150 per treatment arm) into the RCT and 100 CHR patients drawn from the main clinical trial (n = 50 each from the CBD and placebo treatment arms) into the mechanism substudy.

Justification of effect size

Primary outcome power

The study was powered for the primary outcome. For a novel intervention for CHR patients to be clinically meaningful, we assumed that its effect size (on symptoms) should be comparable to or greater than that of CBT, the treatment currently recommended for this group in the NICE guidelines.[17] The effect size for change in the severity of psychotic symptoms after 12 months of CBT in the trial by Morrison *et al.*[11] was 0.39 (estimated as standardised mean difference).

Sample size calculation

We estimated that to have 80% power to detect a difference between CBD and placebo on symptom severity at 6 months with an effect size of 0.4, using a two-sided t-test at p = 0.05, would require a sample size of n = 100 per treatment arm. There was a dropout rate of 32% (based on those lost to follow-up or withdrawn from study at 6-month follow-up) reported by Morrison *et al.*[11] After inflating the sample size by this, we aimed to recruit 300 participants for a minimum of 80% power.

Statistical analysis

Clinical efficacy measures

It was planned that statistical analyses would be carried out following a statistical analysis plan approved by the Trial Steering Committee (TSC) before any partially blinded data were summarised. No interim analyses were planned.

We expected to carry out analyses following the intention-to-treat (ITT) principle. Using the ITT population, we aimed to analyse the primary outcome adjusting for baseline severity, site (stratification factor) and other key covariate information (e.g. age, gender) as reported in the statistical analysis plan, using mixed-effects linear models including a random effect to account for the longitudinal data. We planned to analyse continuous outcome variables such as symptom severity and distress adjusting for baseline severity, site (stratification factor) and other key covariate information (e.g. age, gender) as reported in the statistical analysis plan, using mixed-effects linear models including a random effect to account for repeated measures on the same participant.

Dichotomous outcomes (e.g. proportion in clinical remission) were to be analysed using logistic regression and adjusted for baseline scores and site. Any time-to-event outcomes were to be presented with a Kaplan–Meier plot and analyses described with a median time to event, and a log rank test. Additionally, secondary analyses were to be carried out following a model building process, fitting a multivariable model for each.

We anticipated very few participants withdrawing consent and expected those withdrawn to be missing at random. Since linear mixed-effects modelling adjusts unbalanced designs to account for patients missing time point information, as long as each patient had one post-baseline outcome measure, they were to be included in each analysis. However, we planned to explore patterns of missing data to investigate any evidence against missingness at random. If there was evidence against missingness at random, we aimed to consider the impact on the analysis, with potential consideration of imputation methods.

We also planned to carry out a complementary secondary analysis of the primary outcome, using the per-protocol population, excluding the set of patients that were coded as protocol violators.

We planned to carry out all statistical programming using Stata® (version 15, or later; StataCorp LP, College Station, TX, USA).

Imaging data analysis

For the mechanism (neuroimaging) substudy outcomes [which focused on changes from pre-treatment (scan 1) estimate to 28-day follow-up post-treatment estimate (scan 2)], we aimed to analyse only those with complete data for each of the outcomes.

In line with our hypotheses, for the purposes of our statistical analyses with the fMRI and ASL data, we aimed to focus on two hypothesised regions of interest (ROIs), based on previous literature: one for the 'medial temporal cortex' (to include bilateral medial temporal cortices including hippocampi and parahippocampal gyri) and another for the 'basal ganglia' (to include caudate, putamen and pallidum bilaterally) combined in separate study-specific masks.

Functional magnetic resonance imaging analysis

Functional MRI data from the verbal memory and emotional (fear) processing tasks were to be preprocessed using standard approaches and then analysed employing a non-parametric approach (XBAM version 4.1) that we have employed before in the analysis of data from these fMRI activation tasks.[40,41,67,68] For each fMRI paradigm, it was planned to examine whether the within-subject change in BOLD signal (at 28 days relative to baseline) within prespecified ROIs differed between the two treatment conditions by examining the interaction between time (baseline and 28 days) and treatment (CBD vs. placebo) using a repeated-measures non-parametric analysis of covariance (ANCOVA).

Pseudo-continuous arterial spin labelling analysis

Resting cerebral blood flow images were to be processed using FMRIB Software Library (FSL) software applications (www.fmrib.ox.ac.uk). Statistical analyses of rCBF data were to be performed using the 'randomise' program implemented within FSL, which uses a non-parametric permutation-based approach to infer statistical significance against a null data set generated by random permutation using approaches that we have employed before.[53,83] We aimed to examine whether the within-subject change in rCBF (at 28 days relative to baseline) within prespecified ROIs differed between the two treatment conditions by examining the interaction between time (baseline and 28 days) and treatment (CBD vs. placebo) using a repeated-measures non-parametric ANCOVA.

^{1}H Magnetic resonance spectroscopy quantification and analysis

It was planned that all acquired spectra would be analysed in accordance with a previously described analysis protocol[84] using LCModel version 6.3-0A.[85] A standard basis set of 16 metabolites (L-alanine, aspartate, creatine, phosphocreatine, GABA, glucose, glutamine, glutamate, glycerophosphocholine, glycine, myo-inositol, L-lactate, N-acetylaspartate, N-acetylaspartylglutamate, phosphocholine and taurine), acquired using a MRI

scanner of the same field strength (3 T), same PRESS localisation sequence and 30 ms TE, was planned. Complete details of the basis set model metabolites and concentrations are documented in the LCModel manual (http://s-provencher.com/lcm-manual.shtml). As per accepted practice, we planned to exclude poorly fitted metabolite peaks (Cramér–Rao minimum variance bounds of > 20% as reported by LCModel) from further analysis. We also planned to employ previously documented approaches[64,72] to correct the values of the water-scaled measure of glutamate for cerebrospinal fluid content of the ROI. We aimed to examine whether the within-subject change in hippocampal glutamate level (at 28 days relative to baseline) differed between the two treatment conditions by examining the interaction between time (baseline and 28 days) and treatment (CBD vs. placebo) in a repeated-measures ANCOVA.

Ethical and regulatory arrangements

The study was planned to be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of good clinical practice and in accordance with all applicable regulatory requirements, including but not limited to the Research Governance Framework and the Medicines for Human Use (Clinical Trial) Regulations 2004, as amended in 2006 and any subsequent amendments.

It was planned that the trial would commence after ethical approval was obtained from the appropriate Research Ethics Committee in the UK and clinical trial authorisation was obtained from the Medicines and Healthcare products Regulatory Agency (MHRA), UK.

Research governance

King's College London and the SLaM NHS Foundation Trust were proposed to be the joint sponsors of the research and their King's Health Partners Clinical Trials Office was responsible for monitoring, audit and pharmacovigilance on behalf of the sponsors.

A TSC was appointed and chaired by an experienced researcher in the area with members selected according to NIHR guidelines. An independent Data Monitoring Committee was constituted to act in an advisory capacity to meet regularly to review accumulating data, monitor patient safety and outcome and make recommendations to the TSC.

Results

Study set-up

The study went live from September 2018. Within the first 6 months, the following tasks were completed: (1) collaborating agreement with all parties was finalised following review by each party and was awaiting final sign-off; (2) draft contracts with the main NHS study sites had been drafted and were awaiting finalisation and sign-off once collaboration agreements were signed off; (3) local material transfer agreements for transfer of blood samples for cannabinoid assay as well as vendor identification and draft contracts for investigations had been finalised; (4) appointment of trial co-ordinator; (5) local processes for risk assessment and confirmation of study sponsorship for the purpose of ethics application and clinical trial authorisation applications; (6) sponsor review of ethics and regulatory (MHRA) submissions under way with plans to submit for both ethical approval and MHRA approval (clinical trial authorisation application) simultaneously; and (7) creation of study database under way with most aspects finalised. This process included obtaining permissions for clinical rating instruments/scales either through appropriate payment or through written confirmation when free, and had been completed for most rating instruments/scales.

By this stage, the clinical trial authorisation application form was complete as well as associated documentation (investigator brochure and investigational medicinal product dossier) based on information from the identified drug supply partner at that stage. We were awaiting completion of review and final sign-off from the study sponsor before submitting both ethics and clinical trial authorisation applications.

Drug supply challenges

Although the study was on course in terms of the initial milestones, progress stalled as a result of uncertainty over drug supply. At the time of funding application, CBD active pharmaceutical ingredient was offered as an in-kind contribution from the drug supply partner. However, multiple changes in company ownership led to limited progression in terms of finalisation of the drug supply. As drug supply details could not be finalised, this meant that applications for ethical and regulatory approval could not be finalised and submitted, delaying the start of the clinical trial. Subsequent and similar discussions with other providers (13 potential suppliers) did not result in other in-kind offers due to limitations on intellectual property (IP) grounds (in keeping with NIHR Terms and Conditions and government funding regulations on state aid). Hence, KCL sought to meet with NIHR towards the end of 2020 to obtain advice regarding what was allowed within the terms and conditions of NIHR. At that time, there was a potential supply partner interested in supplying formulated study drug for free that wanted some clarity on IP issues to understand the potential path for them to licensing/commercialisation following completion of the

study. Following this meeting, with the encouragement of NIHR, efforts were made to determine the viability of commercially procuring CBD active pharmaceutical ingredient. It was clear throughout the discussions that any such procurement would incur additional cost and would need the agreement of the MRC/NIHR EME Programme Director and the Department of Health and Social Care through a contract variation request. Preliminary quotes were obtained from different suppliers for commercial procurement of the study drug and were shared with NIHR. Subsequently, a study drug supplier for the trial was identified by KCL through a competitive tendering process, and a contract variation request was submitted as per discussions with NIHR.

National Institute for Health and Care Research decision

The study was subjected to an escalated review due to the increased costs and a relevant ongoing study being identified. During this review, it was decided that the study should be closed as it no longer offered value for money, and because another multicentre, three-arm, 12-week, placebo-controlled RCT of two doses of CBD (600 or 1000 mg/day) for the treatment of positive psychotic symptoms in people with an ultra-high risk for psychosis[86] was now planned to start in another country. The decision to close down the study was communicated in March 2022.

Discussion

Challenges and reflections on the research process

Several unfortunate circumstances contributed to early closure, one of which was the arrival of the COVID-19 pandemic early in 2020. More proximally, the main issue contributing to the project closure was related to challenges in securing drug supply. Medical-grade CBD is a particularly challenging drug to obtain for large-scale studies, in part because CBD as a natural substance is not patentable. Although we had commitment from a company to supply CBD (in-kind) when the grant was awarded, ownership of the company changed hands several times during the trial set-up and preparation period. Over time, no meaningful progression towards a supply agreement was achieved with the new owners. Subsequently, through discussions with 17 potential suppliers, it became apparent that all companies, large or small, needed a clear compelling commercial exit strategy beyond the proposed trial (CANTOP-RCT) in case the trial results were positive. This seemed to be challenging given that CBD itself (a natural substance) is not patentable. This meant that despite the need for significant investment from a company to manufacture and supply CBD for use in research, even if the trial findings were positive, there was no credible way for them to protect and commercialise the IP. As such, from a business perspective, there was no viable exit or commercialisation strategy and thus no incentive for companies to engage in such an arrangement. While a new formulation using CBD may be patentable, potential interested partners wanted upfront commitment regarding emerging IP beyond what was possible for the sponsors (KCL and SLaM) to agree to, in order to ensure compliance with the standard NIHR research agreement. The terms and conditions of the standard research agreement are rightly there to protect the outcomes of publicly funded research such that their material results benefit society and stay within the public realm. However, in the rather unique situation that we found ourselves in, the terms and conditions may have posed particular challenges in finding an agreeable industrial partner. A potential solution to this issue would be for a specific mechanism to be embedded into grants to enable additional financial support to ensure drug supply, specifically for studies such as this where the drug substance itself is not patentable. This would mean an agreed and approved mechanism exists such that supply of a study drug based on a drug substance that may not itself be patentable may be secured at commercial rates, with the emerging IP remaining with the academic and/or NHS sponsor. Another possible solution would be to reconsider and rationalise the terms and conditions of the standard NIHR research agreement to accommodate commercial viability when there is no reasonable alternative, in situations such as the present case.

Following discussions with NIHR, we eventually found a route to securing drug supply through commercial procurement, but the additional costs meant that agreement was needed from the funders and government departments. Although we complied with requests and recommendations throughout this process, and the study sponsors carried out a competitive tendering process to identify a drug supply partner, after submitting these plans we were informed that our study should be subject to an escalated review due to the increased costs and a relevant ongoing study being identified. During this re-review, it was decided that the study should be closed as it no longer offered value for money, and because another study of CBD[86] was now planned to start in another country. The COVID-19 pandemic undoubtedly added significant stress

to the various decision-making systems and individuals involved, but the delays in these processes and procedures, including sending funded grants back out for escalated review, seemed not timely, particularly as the study related to initiation of a trial for patient benefit, where there is a clear need for novel effective interventions. It is likely that without the added crisis that was the COVID-19 pandemic, these processes may have been more efficient.

The future is bright

In sharing our experiences, we hope that our reflections can help researchers in similar situations, or those who are embarking on a new grant or at the development stage, to think about these issues and look ahead to consider what potential mitigations might help to avert a negative outcome in their own studies. We also hope that these experiences may help focus minds on systemic changes that may help deliver studies of novel interventions for mental health patients.

Finally, despite the disappointing outcome, there are several notable positive reflections to be made. During the decision-making timeline, we received communications from a number of clinicians and at least five additional NHS Trusts who were interested in, and committed in principle to, becoming sites in our RCT. This demonstrated that clinicians, researchers and indeed patients themselves have a very real interest in cannabinoid-based medicines for the treatment of neuropsychiatric conditions. This is also borne out by our experience with other ongoing/recently completed trials using CBD in other indications[87] (EudraCT No: 2019-003623-37; EudraCT No: 2019-002106-52). As such, although this study of CBD for CHR patients did not go ahead, the momentum for fully investigating the potential of these compounds should continue. The UK is particularly well placed to lead the way in this regard – there is already a critical mass of scientists and clinicians with decades' worth of experience in working with these molecules. Despite the UK's particular research strength in cannabinoid-based medicines, this momentum needs nurturing if we are to ensure that this continues, tackles the most pressing questions addressing critical unmet clinical needs, and makes meaningful strides and contributions towards the future landscape of improved interventions.

Patient and public involvement

A participant from our previous proof-of-concept study using CBD had been involved at the funding application stage and had agreed to be involved as part of the patient advisory group. However, no direct trial-related activities including planned patient and public involvement activities took place due to the uncertainties associated with drug supply.

Equality, diversity and inclusion

The proposed trial involved a condition affecting a diverse group of individuals. Although the trial did not start, the plan was to recruit participants regardless of their gender or ethnicity from NHS sites spread across large parts of the UK.

Conclusions

The CANTOP-RCT trial could not be delivered in a timely manner due to uncertainty over drug supply, leading to eventual closure of the study in March 2022. The present report summarises events that led to this decision, reflecting on the contributing factors and potential learning points.

Additional information

CRediT contribution statement

Sagnik Bhattacharyya (https://orcid.org/0000-0002-8688-8025): Conceptualisation, Funding acquisition, Writing – original draft, Writing – reviewing and editing.

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Patient data statement

No patient data were collected as participant recruitment did not start.

Data-sharing statement

Although a data management plan was included in the trial protocol, no data were acquired as part of this study.

Ethics statement

Although the investigators had planned to apply for both ethical approval and MHRA approval (clinical trial authorisation application), this did not go ahead as supply of study drug was not secured.

Information governance statement

As described in the protocol, the study investigators planned to handle all personal information in accordance with applicable regulations. However, no personal data were collected as the trial did not start.

Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/YNFH9826.

Primary conflicts of interest: Sagnik Bhattacharyya has participated in advisory boards for or received research funding from EmpowerPharm/SanteCannabis. All of these honoraria/funding were received as contributions towards research support through King's College London, and not personally.

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Ben Carter serves as a member of the HTA General Committee (1 November 2022–31 July 2026).

Paolo Fusar-Poli has received funding from NIMH, USA (Psychosis risk Outcomes Network) and consulting fees/honoraria from Lundbeck, Angelini, Menarini, Sunovion, Boehringer Ingelheim, Proxymm Science, and Otsuka outside the current study. Matthew Broome receives royalties from Cambridge University Press, Oxford University Press, and Elsevier for books published, has received consulting fees from Niche Consulting/NHS England, and is a visiting consultant for Priory Health. Stuart Watson is funded partly (5% FTE) by NIHR funding to Newcastle University. Jesus Perez has received an honorarium from Otsuka. Alison Yung has received an honorarium for lecture and expenses for travel and stay from the Royal Australian New Zealand College of Psychiatrists. She also has unpaid positions with the International Early Psychosis Association (President, 2023–current); Psychosis Australia (board member, 2019–2024); and Kathryn-Browne Yung scholarship fund (director and board member).

No other relevant conflicts of interest reported for any of the other authors.

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This synopsis was published based on current knowledge at the time and date of publication. NIHR is committed to being inclusive and will continually monitor best practice and guidance in relation to terminology and language to ensure that we remain relevant to our stakeholders.

Trial registration

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This synopsis provided an overview of the research award CANnabidiol as a Treatment fOr Psychosis clinical high-risk state- a Randomised Clinical Trial (CANTOP-RCT). For more information about this research please view the award page (www.fundingawards.nihr.ac.uk/award/16/126/53).

About this synopsis

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ensure the accuracy of the authors' article and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this article.

List of abbreviations

ANCOVA	analysis of covariance
APS	attenuated psychotic symptoms
ASL	arterial spin labelling
BOLD	blood oxygen level-dependent
CAARMS	Comprehensive Assessment of At-Risk Mental States
CBD	cannabidiol
CBT	cognitive–behavioural therapy
CHR	clinical high risk
FMRI	functional magnetic resonance imaging
IP	intellectual property
ISRCTN	International Standard Randomised Controlled Trial Number
ITT	intention to treat
KCL	King's College London
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	magnetic resonance imaging
MRS	magnetic resonance spectroscopy
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
PRESS	Point RESolved Spectroscopy
rCBF	resting cerebral blood flow
RCT	randomised controlled trial
ROI	region of interest
SLAM	South London and Maudsley NHS Foundation Trust
TAU	treatment as usual
TE	echo time
THC	delta-9-tetrahydrocannabinol
TSC	Trial Steering Committee

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