PROTOCOL FULL TITLE: ***CAN*nabidiol as a *T*reatment f*O*r *P*sychosis clinical high-risk state- a *R*andomised *C*ontrolled Clinical *T*rial (CANTOP-RCT) (EME Project: 16/126/53)**

Protocol Short Title/Acronym

CANTOP-RCT

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Trial Registration

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1 Study Synopsis

Title of clinical trial	***CAN*nabidiol as a *T*reatment f*O*r *P*sychosis clinical high-risk state- a *R*andomised *C*ontrolled Clinical *T*rial (CANTOP-RCT)**
Protocol Short Title/Acronym	**CANTOP-RCT**
Trial Phase if not mentioned in title	Phase IIB
Sponsor name	King's College London & South London & Maudsley NHS Foundation Trust
Chief Investigator	Dr Sagnik Bhattacharyya
Eudract number	2018-004434-16
REC number	IRAS Project ID: 241991
Medical condition or disease under investigation	Psychosis – Clinical high risk
Purpose of clinical trial	To evaluate the efficacy of cannabidiol (CBD) added to treatment as usual, in people at clinical high-risk (CHR) of developing psychosis to: (i) alleviate psychotic and anxiety symptoms in CHR patients (ii) establish its safety and tolerability (iii) and understand the neurochemical and neurophysiological basis of its effects
Feasibility objective (s)	To test whether we can: a. Screen 410 eligible patients b. Consent a minimum of 20% of the eligible patients c. Randomise a minimum of 60 patients d. Complete 70% patient (who have reached follow-up) six-month follow-up
Primary objective	To test: When added to treatment as usual in CHR patients, whether treatment with CBD improves psychotic symptoms.

Secondary objective (s)	To test: When added to treatment as usual in CHR patients, whether treatment with CBD: a. Improves psychotic symptoms to the extent that patients no longer satisfy the diagnostic criteria for the CHR state b. Relieves the distress associated with psychotic symptoms c. Improves anxiety symptoms d. Improve social and role functioning
Safety objective	To test: whether treatment with CBD for 6 months is well tolerated, with minimal side-effects
Trial Design	Pragmatic, randomised, placebo-controlled trial (RCT) of CBD versus placebo to reduce attenuated psychotic symptoms in CHR patients. Participants will be randomised to either 'Treatment as usual' (TAU) + Placebo; or TAU + Cannabidiol. This will be a blinded (patients, assessors, chief investigator and statistician blinded to the allocation).
Endpoints	**Feasibility endpoints** 1) Number of eligible patients screened 2) Percentage of eligible patients consented 3) Number of patients randomised 4) Percentage of randomised patients who have completed six-month follow-up ***All the study endpoints for the randomised clinical trial will be compared between the CBD and the placebo groups at study end-point (visit 3/ day 182), adjusting for the baseline.*** **Primary endpoint** Severity of psychotic symptoms as measured using the CAARMS. **Secondary endpoints** **Secondary clinical outcomes:** 1) Distress associated with psychotic symptoms as measured using the Comprehensive Assessment of At-Risk Mental States rating scale (CAARMS) 2) Severity of anxiety symptoms assessed using the Hospital Anxiety and Depression Scale (HADS) and in the level of global functioning (assessed using the social and role functioning scale) 3) Clinical remission, as defined as no longer meeting the criteria for a diagnosis of clinical high-risk of psychosis -attenuated psychotic symptoms (CHR-APS) 4) Total CAARMS score 5) Change (study endpoint minus baseline) in the

	severity of psychotic symptoms as measured using the CAARMS between the CBD and placebo groups **Safety endpoints** Incidence of adverse effects during the study period, assessed using the UKU side-effect rating scale
Sample Size	Three hundred (Total N=300; n= 150 per treatment arm) CHR-APS patients
Summary of eligibility criteria	**Inclusion criteria:** - Individuals (18-35 years) diagnosed with a clinical high-risk state (CHR) for psychosis, 'attenuated psychotic symptoms' sub-group (CHR-APS), as defined using CAARMS criteria [1]. - To be able to understand and communicate in English, - To be able to give informed consent. **Exclusion criteria:** - Lifetime 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 - Lifetime neurological disorders (eg., epilepsy, excluding febrile convulsions) or severe intercurrent physical illness, - Current treatment with psychotropic medication - Lifetime treatment with antipsychotic medication for more than 7 days -Poor premorbid/ preexisting functioning, as assessed with the National Adult Reading Test, translated in an IQ<70 - Female patients who are pregnant, lactating or not using an accepatable effective form of contraception, if they are at risk of falling pregnant - Taking part in another RCT
IMP, dosage and route of administration	Cannabidiol (CBD) given in capsule form to be taken orally. The CBD capsule will contain 600 mg of cannabidiol.
Comparator product(s)	Matched placebo capsules will be given to be taken orally for the placebo treatment arm.
Maximum duration of treatment of a Subject	182 days
Version and date of protocol	Version 1.0, 10th January 2019
Protocol Development (amendments, version date)	Not applicable

CANTOP Trial Office

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2 Glossary of Terms

Abbreviation	Definition
AE	Adverse Event
API	Active Pharmaceutical Ingredient
APS	Attenuated Psychotic Symptoms
AR	Adverse Reaction
AUDIT	Alcohol Use Disorders Identification Test
BLIPS	Brief Limited Intermittent Psychotic Symptoms'
CAARMS	Comprehensive Assessment of At-Risk Mental States rating scale
CANTOP	Cannabidiol as a treatment for psychosis clinical high-risk state
CB1	Cannabinoid receptor type 1
CBD	Cannabidiol
CBT	Cognitive Behavioural Therapy
CEQ	Cannabis Experience Questionnaire
CI	Chief Investigator
CHR	Clinical High Risk
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
ECG	Electrocardiogram
EI	Early Intervention
fMRI	functional Magnetic Resonance Imaging
FTND	Fagerstrom Test for Nicotine Dependence
GABA	Gamma-Aminobutyric Acid
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GP	General Practitioner
HADS	Hospital Anxiety and Depression Scale
HES	Hospital Episode Statistics
IB	Investigator's Brochure
IME	Important Medical Events
IMP	Investigational Medicinal Product
IQ	Intelligence Quotient
IRAS	Integrated Research Approval System
ISF	Investigator Site File
ITT	Intention-To-Treat
KCTU	King's Clinical Trial Unit
KHP-CTO	King's Health Partners Clinical Trials Office
MHRA	Medicines and Healthcare products Regulatory Agency
MRC	Medical Research Council
NART	National Adult Reading Test
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
RCT	Randomised Clinical Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction

SDS	Severity of Dependence Scales
SDW	Source Data Worksheet
SOPs	Standard Operating Procedures
SUSAR	Suspected Unexpected Serious Adverse Reaction
THC	Tetrahydrocannabinol
TAU	Treatment as Usual
TMG	Trial Management Group
TSC	Trial Steering Committee
UKU	The UKU Side Effects Rating Scale for the Registration of Unwanted Effects of Psychotropics

CONTENTS

3 Background & Rationale

3.1 Existing research

3.1.1 Health Need:

According to the Global burden of disease study 2010 [2], schizophrenia and other forms of psychoses affecting young people rank as one 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 £11.8 billion per year (http://eprints.lse.ac.uk/47406/). 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[3], psychotic disorders are typically characterized by relapse, with between 40-63% of patients with first episode psychosis experiencing a relapse within the first few years following onset of illness [4]. 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 suggest that in England, 15,763 people present with early symptoms of psychosis before the onset of full-fledged disorder [5]. 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 modeling 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 [5]. However, as it is not possible currently to accurately predict whether an individual CHR subject 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 on ‘Achieving Better Access to Mental health Services by 2020’ [6] by the Department of Health, UK, 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 is still no proven means of reducing the risk of progression to a full-blown psychosis. The absence of effective treatments for this group represents a major unmet clinical need.

3.1.2 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 such as cognitive behavioural therapy (CBT).

CBT: At present the NICE guideline recommends that CHR patients should be offered CBT (with or without family therapy) and CBT is often perceived as popular and well-tolerated. However, increasing evidence (including meta-analyses) from randomised controlled trials (RCTs) (total N=672; sample range 51-288; total events= 69) indicates that CBT does not reduce the risk of transition to psychosis [7-10] and that it is not widely

acceptable [11]. Although early evidence suggested that CBT had beneficial effects, the largest multi-site RCT carried out to date (which was MRC-funded) did not show an effect on transition to psychosis [12]. Similarly, there was no effect on symptoms at 6 months, although an improvement was seen after 12 months. A further consideration is that CBT is often not available to CHR patients in the NHS as many early intervention (EI) teams lack the specialized staff required to provide it. Thus, in most EI services in the NHS, CBT is not offered to CHR patients, either because of the lack of a robust evidence base, or because of limited capacity to provide it.

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. NICE guidelines suggest that antipsychotics should not be used for CHR patients [13]. Available meta-analytic evidence suggests that antipsychotics have, at best, a modest effect [9,10] and are poorly tolerated. Tolerability is a particular issue in CHR patients, as many of these individuals 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; ω-3 PUFAs). Unfortunately, the promising results from a small initial study were not borne out in a larger (n=304) multi-centre RCT [14].

Summary of efficacy evidence: Using network meta-analytic approaches [15], we have examined the efficacy of all currently available treatments for CHR patients. These results 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.

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 [16], 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.

3.1.3 The Endocannabinoid system as a therapeutic target and Cannabidiol:
While drugs that target the dopaminergic [17,18] and glutamatergic [17-22] neurotransmitter systems have been extensively investigated as treatments for psychosis, there is increasing attention on the endocannbinoid system as a therapeutic target [23]. The CB1 receptor, the main central cannabinoid receptor [24] is ubiquitous and modulates the function of several neurotransmitters, including dopamine and glutamate [25]. A growing body of epidemiological studies have linked regular use of cannabis as a significant risk factor for the development of schizophrenia [26]. There is also evidence that psychosis is associated with alterations in the endocannabinoid system, independent of exposure to cannabis [23,27-30].

The CB1 receptor is the main molecular target for delta-9-tetrahydrocannabinol (THC), the major psychoactive ingredient in cannabis. THC is responsible for the psychotogenic effects of cannabis, and is a partial agonist at the CB1 receptor [25]. On the other hand, Cannabidiol (CBD), the second major constituent of cannabis is a non-psychoactive

compound that may have an inverse agonist/antagonist effect at CB1 receptors, in addition to a range of other possible mechanisms of action [25]. Interest in the therapeutic potential of CBD stemmed from evidence that it has broadly opposite effects to that of THC, at both the neural and the behavioural level. Thus, we have shown that THC-induced psychotic and anxiety symptoms in healthy individuals are related to its effects on activation in the striatum during verbal memory [31] and salience processing [32,33] and in the amygdala during emotional (fear) processing tasks. In the same subjects, CBD had the opposite effect to THC on both striatal and amygdala activation [31,33]. Furthermore, we have also shown that pre-treatment with CBD blocks the subsequent induction of psychotic symptoms by THC [31]. These results are consistent with independent evidence that CBD has antipsychotic and anxiolytic properties in patients with mental health disorders (reviewed in [34]). Thus, CBD has been found to be non-inferior to antipsychotic medication in a 4-week clinical trial in acute schizophrenia [35], and improved psychotic symptoms in a 6-week trial in patients with chronic schizophrenia [36]. CBD also reduces anxiety symptoms in social phobia [37] and following public speaking [38], in line with its anti-aversive effects in preclinical models of anxiety [39]. Finally, studies in preclinical models of cognitive impairment have demonstrated that CBD can promote hippocampal neurogenesis [40] and rescue memory function [41], which is consistent with human data showing that it attenuates the cognitive impairments associated with THC use [42,43].

These studies have also generated extensive evidence regarding the safety of CBD following acute and longer-term dosing in humans [37]. The absence of significant adverse effects associated with CBD [34,37], 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 our proof-of-concept study (details below), CBD has not yet been tested in this patient group.

While there is good evidence that CBD can have beneficial effects on psychotic and anxiety symptoms, how these effects are mediated in the brain remains unclear. However, data on its mechanism of action has emerged from recently completed work by the applicants, including a proof-of-concept study funded by MRC (detailed below).

3.1.4 Key pathophysiological abnormalities in CHR state: The most robust findings from neurobiological research on psychosis comprise an elevation of presynaptic dopamine function in the striatum and midbrain [18,44,45], and neuroanatomical and neurophysiological alterations in the hippocampus and adjacent medial temporal lobe structures [46,47]. Current understanding of the key pathophysiological abnormalities that drive the onset of psychosis suggest that altered inhibitory feedback from GABAergic interneurons leads to disinhibition of hippocampal glutamatergic pyramidal cells [48]. It is thought that overactive hippocampal glutamatergic pyramidal neurons then drive a hyperdopaminergic state through projections to the subcortical dopamine system, which in turn leads to the positive symptoms of psychosis [48]. This preclinical model is supported by a body of evidence from a series of neuroimaging studies in CHR patients. These indicate that transition to psychosis is associated with increased resting hippocampal blood flow [49], increased hippocampal glutamate levels [50] (Bossong et al. in preparation), a reduction in hippocampal volume [51] and elevated striatal dopamine function [17]. 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. Thus, the modification of neurobiological abnormalities in these two regions represents a potentially useful biomarker for the evaluation of interventions for patients

in the CHR state.

3.1.5 Safety and feasibility: We have completed a series of studies informing on safety and feasibility of CBD treatment [52,53] as well as go/ no-go decisions regarding a large-scale efficacy trial with CBD. We investigated the effects of both acute (single dose) and short-term (21 days) treatment with CBD on regional brain activation (measured using functional magnetic resonance imaging; fMRI) and on psychotic and anxiety symptoms in 33 CHR patients, using a placebo-controlled, double-blind, parallel-arm design (CBD arm-16; placebo arm-17). Based on these studies, CBD seems to be a safe and satisfactory treatment and is likely to be used in the future as a treatment for psychosis. Also, implementation of CBD treatment in clinical settings appears to be relatively easy and practical, and we do not anticipate financial or organizational difficulties in integrating or expanding such treatment in routine clinical practice. Moreover, with reference to its efficacy, CBD shows promise of being successful with the patient population as results demonstrate that short-term (3-week) treatment with CBD can reduce total CAARMS score and distress associated with psychosis symptoms[52] in CHR patients and that both acute[53] as well as 3-week treatment[52] can partially normalise dysfunction in the medial temporal cortex and striatum, key brain regions implicated in psychosis.

3.2. Risks and benefits

3.2.1 Benefits

The present study would help to establish the safety and efficacy of CBD as a treatment that helps alleviate symptoms in CHR patients presenting to NHS services. Currently there are no treatments that are effective, easily available, accessible and safe as well as acceptable to CHR patients. Hence, establishing the efficacy and safety of CBD will meet an important unmet need and alleviate suffering in CHR patients and their families. Furthermore, although the trial we have proposed is not designed to test if CBD can also prevent psychosis, it represents the critical next step towards the evaluation of its effectiveness as a preventative intervention. The latter would entail a treatment period of at least 12 months and establishing the short-term safety and efficacy of CBD in the CHR population will provide strong grounds for such a trial. The proposed research is thus fundamental to the development of treatments to prevent the onset of psychosis, which could substantially reduce both NHS and societal health costs. About a third of CHR patients will develop psychosis within 3 years of presenting to NHS services. Economic modeling suggests that if clinical intervention at this stage led to even a modest (15%) reduction in the transition rate, this would translate into annual savings of £47.6 million [5].

Because we are planning to evaluate a treatment for young people who are at high risk of psychosis, but do not have a psychotic disorder, it is critical that the intervention has minimal adverse effects, particularly as many of this group will not go on to develop a mental health disorder. Similarly, these individuals are usually unwilling to accept treatments that are poorly tolerated. Compared with conventional psychiatric medications, CBD has a distinct advantage as a treatment for this group, as it has minimal side effects and is very well tolerated. A further advantage is that it has beneficial effects on both psychotic and anxiety symptoms, the predominant symptoms in CHR patients presenting to NHS services.

3.2.2 Risks

A wealth of evidence also exists regarding the safety of CBD following both acute and longer-term dosing in humans. Doses up to 1500mg a day are well-tolerated, with no reported effects on physiological parameters such as heart rate, blood pressure or body temperature, no effect on gastrointestinal tract, psychomotor or psychological function other than mild sedation [37]. Orally administered CBD is subject to significant first pass metabolism following absorption with primary oxidation to an alcohol and a carboxylic acid, substantial excretion in faeces, then urine [54], and an elimination half-life estimated at 2 to 5 days [55]. The 600 mg dose that we propose to use has previously been used in several acute and short-term studies, with minimal side effects [56]. In our proof-of-concept studies in CHR patients, CBD was tolerated as well as placebo, save for slightly more frequent reports of mild sedation. Published data from clinical trials in patients with acute psychosis [35], epilepsy [57] and neurodegenerative disease [58], a case series for bipolar disorder (acute manic episode) [59] and a survey of paediatric epilepsy [60] indicate that CBD is much safer and better tolerated than antipsychotic medications.

3.3. Rationale for current study:

The rationale for the present study is to address a major unmet clinical need in CHR patients, the absence of an effective treatment for this group. We therefore plan to conduct a multi-site, double-blind, placebo-controlled RCT to evaluate the efficacy of CBD added to treatment as usual, to evaluate:

(iv) Its ability to alleviate psychotic and anxiety symptoms in CHR patients
(v) Its safety and tolerability
(vi) The neurochemical and neurophysiological basis of its effects

4 Trial Objectives and Design

4.1. Trial Objectives

To evaluate:
1. The viability of identifying, consenting and randomising patients with clinical high-risk of psychosis -attenuated psychotic symptoms (CHR-APS) patients into an RCT with CBD.
2. CBD as treatment for providing relief from symptoms of an 'at-risk mental state' for psychosis in patients presenting with clinical high risk for psychosis (CHR).

3. To establish whether it is tolerated well by CHR patients over a sustained period of treatment.

Related to this, we aim to understand the neurochemical and neurophysiological mechanisms through which CBD exerts its beneficial effects in CHR patients (please, see Appendix "Protocol for the mechanistic sub-study").

Objective 1, Feasibility questions:
Over the first 12 months from first patient recruited we will assess whether:
1. 410 eligible patients have been screened?
2. A minimum of 20% of the eligible patients have consented?
3. A minimum of 60 patients have been randomised?
4. At least 70% of patients (who have reached follow-up) have completed six-month follow-up?

Objective 2, Research Questions:
Our primary research question is:

1. When added to treatment as usual in CHR patients, does treatment with CBD:
a. Improve psychotic symptoms?

Our secondary clinical research questions are:

2. When added to treatment as usual in CHR patients, does treatment with CBD:
b. Improve psychotic symptoms to the extent that patients no longer satisfy the diagnostic criteria for the CHR state?
c. Relieve the distress associated with psychotic symptoms?
d. Improve anxiety symptoms?
e. Improve social and role functioning?

Objective 3, Safety questions
1. Is treatment with CBD for 6 months well tolerated, with minimal side-effects?

4.1.1 Feasibility endpoints

1) Number of eligible patients screened
2) Percentage of eligible patients consented
3) Number of patients randomised
4) Proportion to patients that complete the six-month follow-up

All the study endpoints for the clinical trial will be compared between CBD and the placebo groups at study end-point (visit 3/ day 182), adjusting for the baseline.

4.1.2 Primary endpoints

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

4.1.3 Secondary endpoints

Secondary clinical outcomes:

1) Distress associated with psychotic symptoms as measured using the CAARMS [1]
2) Severity of anxiety symptoms assessed using the Hospital Anxiety and Depression Scale (HADS) [61] and in the level of global functioning (assessed using the social and role functioning scale) [62]
3) Clinical remission, as defined as no longer meeting the criteria for a diagnosis of CHR-APS
4) Total CAARMS score
5) Change (study endpoint minus baseline) in the severity of psychotic symptoms as measured using the CAARMS between the CBD and placebo groups

4.1.4 Safety endpoints

Incidence of adverse effects during the study period, assessed using the UKU side-effect rating scale [63]

4.2 Trial Design

The viability of running the study will be evaluated with an internal pilot that will assess the ability of the study to identify, consent, randomise and follow up CHR-APS patients in the study.

We proposed a pragmatic, parrallel group, multicentre, blinded (participants, outcome assessor, chief investigator and statistician) randomised, placebo-controlled trial (RCT) of CBD versus placebo to reduce attenuated psychotic symptoms in CHR patients. Participants will be randomised to either 'Treatment as usual' (TAU) + Placebo; or TAU + Cannabidiol. We plan to recruit 300 patients, and randomisation will be in a 1:1 ratio. The allocation sequence will be generated by King's Clinical Trial Unit (KCTU) webbased system and concealed from all investigators.

4.3 Trial Flowchart

Outcome	Screening	0	1	2	3	4
Week No.	**-1 to -3**	**1**	**4 (±3day)**	**13 (±7days)**	**26 (±14days)**	**30 (±7days)**
Informed Consent	**X**					
Socio-demographic Information	**X**					
Medical History	**X**					
Physical examination (Vital Signs, ECG)	**X**	**X**			**X**	
Urine Drug Abuse Screen		**X**	**X**			

AUDIT, FTND, CEQ, SDS	**X**				**X**	
TFLB		**X**	**X**		**X**	
Cannabinoid levels in blood to confirm use of or abstinence from cannabis		**X**	**X**	**X**	**X**	
Pregnancy Test	**X**	**X**	**X**	**X**	**X**	
Screening Blood Sampling- Clinical laboratory (Haematology & Biochemistry)	**X**				**X**	
Concomitant Medication	**X**	**X**	**X**	**X**	**X**	
Study Exclusion criteria check	**X**	**X**				
NART	**X**					
Adverse Events		**X**	**X**	**X**	**X**	**X**
Randomisation		**X**				
Study Medication Dispensing		**X**	**X**	**X**		
Study Medication Compliance (pill count)			**X**	**X**	**X**	
Compliance Blood Sampling (Cannabidiol levels)		**X**	**X**	**X**	**X**	
Comprehensive Assessment of At-Risk Mental State	**X**	**X**	**X**	**X**	**X**	
Hospital Anxiety Depression Scale		**X**	**X**	**X**	**X**	
Global Functioning (Social and Role scales)		**X**			**X**	
UKU Side Effect Rating Scale		**X**	**X**	**X**	**X**	

5 Participants

5.1 Selection of Participants

The proposed study will be a multi-centre study involving research-led early intervention services in the UK.

All centres will recruit patients into the internal pilot, that will progress to the RCT. Patients will be identified from early intervention (EI) teams linked to the recruitment hubs. Those participants recruited to the internal pilot will be included in the RCT. Patients who express an interest in the study and are identfied as having CHR-APS by their clinical teams will be approached by study researchers and given a patient information sheet. Those who agree to take part in the study will be invited for a screening visit.

Heterogeneity in CHR: CHR patients are not a homogenous group and include three sub-groups of patients operationalised using standardized and internationally recognized criteria ('Comprehensive Assessment of At-Risk Mental States'; CAARMS) [1] into: (i) those with 'attenuated psychotic symptoms' (APS), (ii) those with 'brief limited intermittent psychotic symptoms' (BLIPS) and (iii) a Vulnerability subgroup. *Because the present study is primarily designed to assess the effect of CBD on the symptoms of CHR state, we will focus on the CHR-APS sub-group of patients and exclude the other two groups at the screening stage.* This comprises the great majority (at least 80%) of CHR patients treated by NHS early intervention services [64]. Patients belonging to the other sub-groups 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 CHR patients who are most symptomatic. A final consideration is that there is increasing evidence that the three CHR subgroups have distinct clinical outcomes, and may be biologically heterogenous [12,14 65,66].

5.2 Inclusion Criteria

- Individuals (18-35 years) diagnosed with a clinical high-risk state (CHR) for psychosis, 'attenuated psychotic symptoms' sub-group (CHR-APS), as defined using CAARMS criteria [1],
- To be able to understand and communicate in English,
- To be able to give informed consent.

5.3 Exclusion Criteria

- Lifetime 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
- Lifetime neurological disorders (eg., epilepsy, excluding febrile convulsions) or severe intercurrent physical illness,
- Current treatment with psychotropic medication
- Lifetime treatment with antipsychotic medication for more than 7 days
- Poor premorbid/ preexisting functioning, as assessed with the National Adult Reading Test [67], translated in an IQ<70

- Female patients who are pregnant, lactating or not using an accepatable effective form contraception if they are at risk of falling pregnant
-Taking part in another RCT

6 Interventions

6.1 Trial Medication

6.1.1 Investigational medicinal product

Cannabidiol (CBD; 600 mg/day) or matching placebo given in capsule form to be taken orally once a day around meal time.

Stephenson CBD Centre Ltd will supply the CBD and matching placebo capsules manufactured under good manufacturing practice conditions with appropriate certification.

Stephenson CBD Centre Ltd.

Address: 8, The Mount, Weybridge, Surrey, KT13 9LT, United Kingdom

Email: michael@stephensonpost.com

The information presented on the labels for the CBD will comply with applicable national and local regulations.

6.1.2 Placebo

In order to guarantee masking, the placebo will be matched by color and size, not labelled, and consist of identical looking capsules manufactured and packaged by the same supplier in compliance with good manufacturing practice.

6.1.3 Dosing Regimen

For both the internal pilot and the RCT, the trial medication (CBD 600mg/day in capsule or matching placebo capsules) is to be taken once a day, after the first meal of the day, for a maximum of 182 days.

6.2 IMP Risks

IMP Risks, including safety data and overdose, are as documented in the Investigator brochure as well as in the Background & Rationale ‘3.2.2 Risks’ subparagraph.

6.3 Drug Accountability

Only a study specific prescription can be used for dispensing/supplying study products. Only qualified physicians clearly given this role on the study delegation log can prescribe for the study, and only people designated again by the PI can collect medication (unless prior agreement that participants can collect themselves in which case ID is required). Only CBD supplied for this study can be dispensed against the study specific prescription. Full accountability records (recording the batch, expiry date and people

dispensing or checking the prescription) will be completed. All prescriptions for both the CBD and Placebo will be dispensed and checked. All drug returns and empty packaging handed back to the pharmacy are recorded (quantity and date of return) and are held in a separate quarantine/drugs retuned area. Once medication has left the pharmacy it cannot under any circumstances be re-dispensed. Nothing is destroyed without the authorization from the PI and KHP-CTO CRA (destruction will be authorized on an ongoing basis).

6.4 Supply of study medication (IMP/Placebo) to local pharmacy

This will be operated by the manufacturer who will supervise the entire pharmaceutical supply chain, including study medication final form (packaging), quality (product release), and logistics (distribution). Distribution to each study site will happen prior to the site initiation.

6.5 Storage of study medication (IMP/Placebo)

The study medication must be stored at room temperature (<30deg C) and not kept in a refrigerator. It will be stored in compliance with local regulations. At all study sites, it will be stored away from other CBD products clearly marked for this study with the PI and EudraCT number on the outer box. It will be stored in a secure area with temperature monitoring and control. In the event of a temperature deviation, pharmacy will report this immediately to the sponsor and not issue medications until cleared by the qualified person.

6.6 Removal of study medication outside of expiry date/ at trial conclusion and destruction

The expiry date will always be reported on the study medication. Study medication outside of the expiry date will not be dispensed and will be destroyed, subject to authorization, on an ongoing basis.

6.7 Withdrawal of Subjects

6.7.1 Withdrawal from study

Category of withdrawal I: As per the Declaration of Helsinki, all participants will have the right to withdraw from the study at any time without giving any reason without any prejudice to their future medical care and will be informed as such before consent. If a participant chooses to withdraw from the study, we will discuss the possibility of withdrawing from the study intervention (treatment) only and to continue their follow-up as closely as possible to the follow-up schedule defined in the protocol. They would be encouraged to not leave the study, even if they no longer wished to take the study medications. However, if a participant expresses the wish to be completely withdrawn from the study, then this view will be respected and implemented by the study team. Although not obliged to give a reason for discontinuation, a reasonable effort will be

made to establish this reason. Data already collected will be kept and included in the final analysis.

6.7.2 Withdrawal from study intervention

Category of withdrawal II: Participants may be withdrawn by the investigator for various reasons including but not limited to the following: protocol violations, inter-current illness, AEs, SAE's, SUSAR's, administrative reasons or other reasons or participation in the RCT affecting their ongoing care. Participants may also be withdrawn by the investigator in case of emergence or worsening of depression, suicidal thoughts or behaviour, or any unusual changes in mood or behaviour, suggesting serious risk to the patient. Patients will be followed up with the same schedule of research assessments as those who continue in the study, till they complete the 6-month follow-up period or till they progress to frank psychosis (whichever is earlier);
Category of withdrawal III: In case of CHR patients experiencing progression to a first episode of psychosis (frank psychosis), they will exit from the study intervention, be deemed as treatment failure, and will only be assessed for safety outcomes after confirming progression to psychosis. In line with established practice, and as used in previous clinical trials in CHR patients [12,14] transition to psychosis will be operationally defined using CAARMS [1]. We will carry out complete follow-up of patients who develop frank psychosis during the follow-up period.

Participants who stop treatment early will not be replaced. As an excessive rate of withdrawals can render the study un-interpretable, attempts will be made avoid unnecessary withdrawal of patients.

6.8 Subject Compliance

Compliance with CBD treatment will be assessed using pill-counts at visits 2, 3 and 4. Patients will be defined as complying in the presence of a pill count greater than 50% the expected number taken.

Furthermore, before the end of the study we will document a secondary measure of compliance by carrying out assay of CBD levels in blood at visits 1-4 in both arms of the study.

Patients who are defined as non-complying with the medication will be coded as protocol deviators.

6.9 Concomitant Medication

Based on participants' clinical history, concomitant requirement of psychotropic medication is an exclusion criterion for the study. Patients requiring continued treatment with psychotropic medications other than antipsychotic, antidepressant or mood-stabilizer medications during the treatment phase may be withdrawn from the study by the Chief Investigator. Very short-term treatment with rescue medications that have a sedative or calming effect (such as Benzodiazepines) during the study may be allowed. For management of concomitant therapies, please refer to the Investigators Brochure. There is a possibility of pharmacological interactions between CBD and other concomitantly administered drugs as mentioned in the investigator brochure. Throughout the study, investigators may prescribe any other concomitant medications or treatments deemed necessary to provide adequate supportive care. A complete listing of all concomitant medication received during the treatment phase will be recorded in the relevant SDW.

7 Visit assessments

For both the internal pilot and the RCT, the following visit assessments will be performed:

7.1 Screening Visit (Visit window -1): This will take place between one to three weeks prior to the baseline visit. At screening, informed consent will be obtained from those who wish to take part. Consenting patients will then be screened against the study inclusion and exclusion criteria using the CAARMS [1], and those satisfying the criteria will be recruited by employed or delegated investigators. Safety blood samples (for routine biochemistry and haematology) will be obtained and physical examination and vital signs recorded on all participants screened (i.e. including those who are screen failures/ not randomised for some reason). Also, blood samples for genotyping as well as for cannabinoid measurements will be obtained on all participants screened who consent to it. Consent will be sought to analyse screening data as well as regarding long-term follow up beyond the outcomes of the trial and also to link participants' data to routinely collected data sources such as HES and GP records.

7.2 Baseline Visit (Randomisation, on Day 0): Following satisfactory completion of screening, patients will be randomised to one of the treatment arms in a double-blind manner. Before randomisation baseline measures (CAARMS and HADS including alcohol and drug use (in particular cannabis) [68-70]), physical examination and blood samples for cannabinoid levels and for Cannabidiol will be acquired. The participant will be randomised and study drugs dispensed from the local hub pharmacy. Side effects will also be assessed, by using the UKU side-effect rating scale [63].

7.3 Month One Visit (Visit window 1, at approximately day 28): This visit will involve only clinical assessments, assessment of alcohol and drug use (in particular cannabis), blood sampling, monitoring of compliance, side effects, AEs, and dispensing of study drugs.

7.4 Month three Visit (Visit window 2, at approximately Day 91) and Month Six Visit (Visit window 3, at approximately Day 182): These visits will involve only clinical assessments, assessment of alcohol and drug use (in particular cannabis), blood sampling, monitoring of compliance and side effects as well as AEs. Study drugs will be dispensed as well on visit 3.

7.5 Month Seven Final safety visit (Visit window 4, at approximately Day 212): Only AEs will be recorded at this visit, via review of medical records.

7.6 Laboratory Tests

Clinical Laboratory measures: Bloods for Haematology (Full blood count and Haemoglobin) and Biochemistry (Urea & Electrolytes, liver function test, lipid profile). All blood tests will be carried out at each study site as per their standard procedure. Blood results will be printed and filed as source in the patient SDW.
Genotyping and cannabinoid measures: Blood samples for these measures will be carried out at each study site and shipped to the London site where they will be stored and analysed. Genomic and proteomic samples will be stored for use in future ethically approved research.

8 Outcomes

8.1 Assessment of Feasibility

At 12 months following start of the first patient recruited we will assess the feasibility of conducting the study through an internal pilot where we will assess the following outcomes:

- To have screened 410 eligible patients.
- To have consented a minimum of 20% of the eligible patients.
- To have randomised a minimum of 60 patients.
- To have completed six-month follow-up from at least 70% patients (who require follow-up).

We will proceed to the full study based on satisfying the following go/no go criteria:

- To have screened 410 eligible patients within 12 months of the start of patient recruitment.
- To have consented a minimum of 20% of the eligible patients within 12 months of the start of patient recruitment (e.g. at least 82 out of 410).
- To have randomised a minimum of 60 patients within 12 months of the start of patient recruitment. (By the Go/ No Go time-point, we anticipate 20 of the randomised patients to have completed the 6-month follow-up end-point).
- To have completed six-month follow-up of at least 70% of the randomised patients who are expected to have completed their 6-month follow-up within 12 months of the start of patient recruitment (e.g. 14 out of 20 randomised patients that are eligible for their follow-up and have reached Month 7).

8.2 Assessment of Efficacy

All the study endpoints for the clinical trial will be compared between the IMP and the placebo groups at study end-point (visit 3/ day 182), adjusting for the baseline.

8.2.1 Primary Efficacy Parameters

Our primary efficacy parameter will be measured using the Comprehensive Assessment of At-Risk Mental States' (CAARMS) [1] (Monthly Version 2006). This is a validated instrument to rule out or confirm criteria for acute psychosis, map a range of psychopathology and functioning factors over time in young people at ultra high-risk of psychosis, and determine if an individual meets the criteria for an 'At Risk Mental State'. We will be using the English version in this population. The assessment has 7 subscales that target different areas of psychopathology and functioning: 1. Positive symptoms, 2. Cognitive change attention/concentration, 3. Emotional disturbance, 4. Negative symptoms, 5. Behavioural change, 6. Motor/physical changes, and 7. General psychopathology. Each subscale item is scored against (i) Severity (from 0 – never, absent – to 6 – extreme/psychotic/psychotic and severe –. Most items are also scored against (ii) Frequency and duration (from 0 – absent – to 6 – continuous) and (iii) Pattern of symptoms (from 0 – no relation to substance use noted – to 2 – noted only in relation to substance use). Moreover, a few items are additionally scored against (iv) Level of distress (from 0 to 100). Finally, the CAARMS includes: 8. Inclusion criteria for Group 1 Vulnerability group, Group 2 Attenuated psychosis group (CHR-APS), and Group 3 BLIPS group; 9. Psychosis threshold criterion (based on symptom severity, frequency,

and duration); and 10. Study withdrawal threshold criterion (based on Aggression/Dangerous Behaviour and/or Suicidality/Self Harm subscale severity) (Appendix 1). Within this instrument, lower scores are indicative of improved state, and higher scores of worsened state.

Primary clinical outcome: Severity of psychotic symptoms as measured using the CAARMS subscale Positive symptoms [1]. This subscale includes 4 items: 1. Unusual thought content, 2. Non-bizarre ideas, 3. Perceptual abnormalities, 4. Disorganised speech. Each subscale item is scored against (i) Severity (from 0 – never, absent – to 6 –psychotic/psychotic and severe –, (ii) Frequency and duration (from 0 – absent – to 6 – continuous), (iii) Pattern of symptoms (from 0 – no relation to substance use noted – to 2 – noted only in relation to substance use), and (iv) Level of distress (from 0 to 100). Within this instrument, lower scores are indicative of improved state, and higher scores of worsened state.

8.2.2 Secondary Efficacy Parameters

Our secondary efficacy parameters will be measured using:

- The Comprehensive Assessment of At-Risk Mental States' (CAARMS) [1](Monthly Version 2006). This is a validated instrument to rule out or confirm criteria for acute psychosis, map a range of psychopathology and functioning factors over time in young people at ultra high-risk of psychosis, and determine if an individual meets the criteria for an 'At Risk Mental State'. We will be using the English version in this population.

- The Hospital Anxiety and Depression Scale (HADS), an English self-assessment scale developed and found to be a reliable instrument for detecting states of depression and anxiety in the setting of an hospital medical outpatient clinic. The anxiety and depressive subscales are also valid measures of severity of the emotional disorder [61]. Both the Anxiety and Depression scales range from 0 to 21, with 3 cut-offs: 0-7 = Normal; 8-10 = Borderline abnormal (borderline case); and 11-21 = Abnormal (case).

- The Social and Role Functioning scale [62], an English scale assessing participants' psychosocial functioning. Both the Social and Role scales range from 1 to 10, with 10 indicating superior functioning and 1 indicating extreme dysfunction. To increase reliability, both scales include focused and detailed anchor points for each rating interval. Each scale generates 3 scores: current functioning which is the lowest level of functioning in the past month, lowest and highest level of functioning reported over the past year.

Secondary clinical outcomes:
1) Distress associated with psychotic symptoms as measured using the CAARMS [1] subscale Positive symptoms – Level of distress score
2) Severity of anxiety symptoms assessed using the Hospital Anxiety and Depression Scale (HADS) [61] and level of psychosocial functioning assessed using the Social and Role Functioning scale[62]
3) Clinical remission, as defined as no longer meeting the criteria for a diagnosis of CHR-APS
4) Total CAARMS score assessing psychopathology and functioning across all 7 CAARMS subscales
5) Change (study endpoint minus baseline) in the severity of psychotic symptoms as measured using the CAARMS between the CBD and placebo groups

8.3 Procedures for Assessing Efficacy Parameters

Efficacy parameters will be assessed through clinical interview using standardized questionnaires/ rating instruments

8.3.1. Clinical Outcome assessment:

CAARMS psychotic symptom severity will be operationalised as in the study by Morrison and colleagues [12] by summing the scores of product of the global rating and frequency scores of the four items of the CAARMS subscale Positive symptoms[1]. CAARMS ratings will be carried out by a clinical researcher appropriately trained in administering CAARMS.
Distress associated with psychotic symptoms will be assessed by summing the Level of distress scores of the the four items of the CAARMS subscale Positive symptoms[1].
Anxiety symptoms will be assessed using the Hospital Anxiety and Depression Scale (HADS) [61] Anxiety scale score.
Level of global functioning will be assessed using the Social and Role Functioning scale current functioning score [62].

Clinical remission will be defined on the basis of the CAARMS criteria [1] as in previous studies [71]. Remission requires a score of < 3 on the 'unusual thought content', 'non-bizarre ideas' and 'perceptual abnormalities' subscales and < 4 on the 'disorganized speech' subscale and a frequency scale score of < 3 over the past month.

Total CAARMS score will be operationalised by summing the scores of product of the global rating and frequency scores of all the CAARMS subscales.

In case of missing data, we will get back to the relevant study site in order to complete it.

8.4 Assessment of Safety

8.4.1 Specification, Timing and Recording of Safety Parameters

At screening the main safety measures will involve checking for study inclusion/ exclusion criteria, physical examination/ medical history/ safety blood investigations to ensure the absence of relevant disease or conditions that are a contraindication to participation in the study procedure as relevant. These will be repeated at Visit 3 or at withdrawal. Urine pregnancy test will be carried out at each visit for female participants. In the event of a positive test, the patient will be withdrawn from the study and their GP and mental health team informed.These are summarised in detail per visit below.

Screening Visit (Visit window -1): Medical History, Physical Examination (Vital signs, ECG), Pregnancy test (as appropriate), Clinical laboratory (Haematology: Full blood count and Haemoglobin; and Biochemistry: Urea & Electrolytes, liver function test, lipid profile).

Baseline Visit (Randomisation, on Day 0): Physical Examination (Vital signs, ECG), Pregnancy test (as appropriate), UKU Side-effect rating scale.

Month One Visit (Visit Window 1, at approximately Day 28): Pregnancy test (as

appropriate), AEs, UKU Side-effect rating scale.

Month Three Visit (Visit window 2, at approximately Day 91): Pregnancy test (as appropriate), AEs, UKU Side-effect rating scale.

Month Six Visit (Visit window 3, at approxiamtely Day 182): Physical Examination (Vital signs, ECG), Pregnancy test (as appropriate), Clinical laboratory (Haematology: Full blood count and Haemoglobin; and Biochemistry: Urea & Electrolytes, liver function test, lipid profile), AEs, UKU Side-effect rating scale.

Month Seven Final safety visit (Visit window 4, at approaximately Day 212): AEs/SAEs. This is going to be the final study visit.

8.4.2 Procedures for Recording and Reporting Adverse Events

The Medicines for Human Use (Clinical Trials) Regulations 2004 and Amended Regulations 2006 gives the following definitions:

Adverse Event (AE): Any untoward medical occurrence in a subject to whom a medicinal product has been administered including occurrences which are not necessarily caused by or related to that product.

Adverse Reaction (AR): Any untoward and unintended response in a subject to an investigational medicinal product which is related to any dose administered to that subject.

Unexpected Adverse Reaction (UAR): An adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out in:

The Investigator's Brochure (IB) relating to the study.

Serious adverse Event (SAE), Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR): Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that

Results in death;
Is life-threatening;
Required hospitalisation or prolongation of existing hospitalisation;
Results in persistent or significant disability or incapacity;
Consists of a congenital anomaly or birth defect.

Important Medical Events (IME) & Pregnancy

Events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious.

Although not a serious adverse event, any unplanned pregnancy will also be reported via the SAE reporting system. Women who become pregnant within the study will be followed up with evaluation of the pregnancy, foetus and child.

Time period for collection of adverse events

AEs will be recorded from the randomisation visit to the final safety visit (day 212). Any AEs that are unresolved at the follow-up visit in the study will be followed up by the

investigator for as long as medically indicated, but without further recording in the SDW. The following information will be collected for each AE: 1) AE (verbatim); 2) the date and time when the AE started and stopped; 3) maximum intensity (see definitions of intensity below); 4) whether the AE is serious or not; 5) investigator causality rating against the Investigational Product (yes or no); 6) action taken with regard to Study intervention (IMP/Placebo); 7) AE caused patient's withdrawal from study (yes or no); 8) outcome.

In addition, the following variables will be collected for SAEs: 1) date AE met criteria for serious AE; 2) date Investigator became aware of serious AE; 3) Reason why AE is deemed serious; 4) date of hospitalisation; 5) date of discharge; 6) probable cause of death; 7) date of death; 8) autopsy performed; 9) causality assessment in relation to CBD; 10) causality in relation to any other medication if relevant; 11) description of AE.

Intensities will be reported for each AE under the following categories:
- mild (awareness of sign or symptom, but easily tolerated)
- moderate (discomfort sufficient to cause interference with normal activities)
- severe (incapacitating, with inability to perform normal activities)

Causality

The Investigator will assess causal relationship between Cannabidiol and each AE, and answer "yes" or "no" to the question "Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?" For SAEs, if felt necessary by the treating team, the patient's allocation to Cannabidiol or placebo will be decoded by contacting the 24 hours emergency unblinding service and the causal relationship will also be assessed for any other medications if relevant.

Detecting adverse events

Participants will be asked the open question "Have you had any health problems since you were last asked?" to evoke spontaneous reports of side-effects. Spontaneous and self-rated side-effects will be evaluated for intensity and seriousness. Deterioration in lab or examination safety measures will be recorded as AE if they are associated with symptoms or signs or if they are sufficiently marked to be clinically significant. Suicidal thoughts, acts or events are AEs that will be rated and recorded. All such events will be notified to the clinical team and carefully monitored by them. Worsening symptoms of the primary study condition will not be recorded as an AE. However, if hospitalization results from worsening of the primary study condition, the hospitalization will be reported as an SAE. Diagnoses will be recorded rather than symptoms, signs or lab parameters.

Reporting and follow-up of adverse events

All SAEs have to be reported, whether or not considered causally related to the trial medication. All SAEs will be recorded in the source data worksheet (SDW). If any SAE occurs in the course of the study, then investigators or other site personnel will inform the local Principal Investigator and clinician for that patient immediately; i.e. within one business day... All completed SAE forms will be filed appropriately in the Investigator Site File (ISF) and as required within the SDW Study Folder. The participant will be followed up by the medic until the event or reaction has reached an outcome. The participant's GP will be contacted by the PI or delegate, if it is medically indicated to do

so.

Reporting Responsibilities

King's College London and the South London & Maudsley NHS Foundation trust have delegated the delivery of the Sponsor's responsibility for Pharmacovigilance (as defined in Regulation 5 of the Medicines for Human Use (Clinical Trials) Regulations 2004 to the King's Health Partners Clinical Trials Office (KHP-CTO).

All SAEs, SARs and SUSARs (excepting those specified in this protocol as not requiring reporting) will be reported immediately (and certainly no later than 24hrs) by the Investigator to the KHP-CTO and CI for review in accordance with the current Pharmacovigilance Policy.

The KHP-CTO will report SUSARs to the regulatory authorities (MHRA, competent authorities of other EEA (European Economic Area) states in which the trial is taking place.

The Chief Investigator will report to the relevant ethics committee. Reporting timelines are as follows:

- SUSARs which are fatal or life-threatening must be reported no later than 7 days after the sponsor is first aware of the reaction. Any additional relevant information must be reported within a further 8 days.
- SUSARs that are not fatal or life-threatening must be reported within 15 days of the sponsor first becoming aware of the reaction.
- The Chief Investigator and KHP-CTO (on behalf of the co-sponsors), will submit a Development Safety Update Report (DSUR) relating to this trial IMP, to the MHRA and REC annually.

8.4.2.1 Adverse events

AEs will not be reported unless there is a reasonable suspicion of effect from the medical treatment. All AEs will be recorded on the SDW.

8.4.2.2 Anticipated Adverse events

In this population of CHR-APS, we anticipate:

1. AEs not related to the study intervention, not needing reporting:

- Worsening of psychotic symptoms, sleep disturbances, appetite disturbances, anxiety symptoms, mood symptoms, and suicidal ideation

- Transition to FEP

2. AEs potentially related to the study intervention, needing reporting:

- Hepatic Disorders (elevations of liver transaminases)

- Gastrointestinal Disorders (diarrhoea, gastroenteritis, abdominal pain, discomfort, weight decreased)

- Nervous System Disorders (somnolence, sedation, lethargy, fatigue, malaise, asthenia, drooling, salivary hypersecretion, gait disturbance)
- Infections (viral infections, pneumonia, fungal infections)
- Hypersensitivity Reactions (pruritus, erythema, rash, angioedema, hypoxia, respiratory failure)

8.4.3 Treatment Stopping Rules

The trial may be prematurely discontinued by the Sponsor, Chief Investigator or Regulatory Authority on the basis of new safety information or for other reasons given by the Data Monitoring & Ethics Committee / Trial Steering Committee, regulatory authority or ethics committee concerned.

If the trial is prematurely discontinued, active participants will be informed and no further participant data will be collected. The Competent Authority and Research Ethics Committee will be informed within 15 days of the early termination of the trial.

9 Participant timeline

With reference to the internal pilot as well as the RCT, the end of the trial will be defined as last patient last visit. Each individual subject will remain in the trial until the final visit, at month 7. This date will be 30 days after the study end-point (day 182). The total duration from first patient first visit to last patient last visit is anticipated to be 42 months.

10 Sample size

10.1. Proposed sample size:

1) Pilot study: 60 randomised within 12 months of the start of patient recruitment;

2) RCT: 300 hundred CHR-APS patients; n=150 per treatment arm

10.2. Sample size justification:

1) **Internal Pilot:** There was no powered sample size calculation for the internal pilot, the number is instead in line with suggested sample sizes for pilot and feasibility studies and is sufficient to estimate feasibility outcomes.

2) **Phase IIB RCT**

Justification of Effect Size (ES=0.4)

In our proof-of-concept studies, in which the effect size for 3 weeks of treatment with CBD (Mean change ±SD: 12.87±12.8) compared to placebo (Mean change ±SD: 7.64±12.6) on psychotic symptom severity was found with a standardised mean difference of 0.41.

The RCT has been powered for the primary outcome. For a novel intervention for CHR patients to be clinically meaningful, we have assumed that its effect-size should be comparable to, or greater than that of CBT, the treatment currently recommended for this group in the NICE guidelines [13]. The effect size for the change in the severity of psychotic symptoms after 12 months of CBT in the trial by Morrison et al [12] was 0.39 (estimated as standardized 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 drop-out rate of 32% reported by Morrison et al [12]. After inflating the sample size by this, we would need to recruit 300 participants for a minimum of 80% power.

10.2.2. Recruitment rate:

Out of 1980 eligible patients across all of our recruitment sites, we expect to screen a majority (around 85%) of those at each centre.

We anticipated a staggered recruitment of the sites as well as requiring three months to maximise recruitment at each site. However, by 1 year after opening our first site, we anticipated to experience our maximum consent and randsomisation rate across all sites.

At this time we anticipate a minimum of 20% (n=28, per quarter) of those screened will be randomised (See ‘Plan of Investigation and timetable’).

11 Assignment of interventions

11.1 Allocation

11.1.1 Sequence generation and Allocation concealment mechanism

The randomisation service will be provided by the bespoke online randomisation system managed by the King's Clinical Trials Unit (KCTU) such that randomisation information is concealed from the study researchers. Given the large sample size, the allocation sequence will be generated using a random permuted block design (block sizes of 4 to 12), stratified by site. The sequence will be held within a web-based system and concealed from the investigators including the chief investigator and trial statistician.

11.1.2 Implementation

The system is online and can be accessed 24 hours a day. Researchers within the study team log in, enter key information about the participant, and the randomisation allocation occurs instantly. Confirmation emails are generated automatically and sent to the Pharmacy personnel in the study team.

The Trial manager, under the direction of the study team, provide user access to the study sites, and withdraw access at the study conclusion.

11.2 Blinding

11.2.1 – Definitions

In line with KCTU Standard Operating Procedures (SOPs) on blinding.

Fully blinded: Not able to review any post Baseline outcome data coded as CBD/Placebo, or coded as A/B. All data should be presented aggregated across both allocation groups.

Partially blinded. Able to review data post Baseline outcome data as A/B

Unblinded: Able to review post Baseline outcome data as CBD/Placebo

11.2.2 Blinding of Personnel

Throughout the chief investigator, and senior statistician will be fully blind to treatment allocation and will only see pooled data for the duration of the trial. At the start of any TMG/TSC/DMC, the committee are to be reminded the CI and Senior statistician are fully blind and the need to present aggregate data to maintain this.

The Junior Statistician will be fully blind until the first version of the Statistical Analysis Plan (SAP) is approved by the TSC. The SAP should be detailed enough so that it presents a clear and structured plan for the primary outcome, required data manipulation, and analysis. It should be written consistent with the KCTU Statistics SOP on generating a SAP (ST-03 Statistical Analysis Plan). All changes to the SAP after approval by the TSC should be authored by a statistician who is fully blind, this would be expected to be the Trial statistician (Dr Ben Carter). Any amendments to the SAP will be approved by the TMG, and TSC.

After the first version of the SAP is approved by the TSC, the Junior statistician is

planned to become partially-blinded and access patient level data coded as A/B. They will present the closed DMC report to DMC members.

The trial manager is planned to be unblinded in order to expedite safety data from site PI to the Chair of the DMC. The Trial manager will not take part in any discussion that influences any decisions regarding early stopping of the trial.

11.3 Circumstances under which unblinding is permissible

11.3.1 Emergency Code Break

Twenty-four hr Emergency Code Break and Medical Information will be provided by ESMS Global Ltd through their 24-hour code-breaking service (along with emergency medical advice).

11.3.2 Serious health risk and unblinding

Each randomised subject will be provided with a card detailing code break telephone numbers and emergency contact details. Subjects will be requested to carry this card with them at all times whilst participating in the trial. While there is a wide margin of safety with regard to the dose of CBD used in this study, in case of overdose, study participants will be advised to attend the nearest A&E, carrying the emergency contact details card. They will be advised to notify the relevant study team as soon as possible. The contact details of the study team and ESMS Global Ltd (who will provide the emergency code-break service) will be on the emergency contact details card with advice for the treating physician to get in touch in case of overdose or other medical emergency that may require unblinding. In case of overdose, symptomatic and supportive treatment is advised. Evaluation will be also made whether to proceed with the withdrawal of the subject from the study/ study intervention as well as the unblinding.

In the circumstance unblinding is required, all care shall be taken to ensure that the study team are kept blinded. The unblinding procedure will be performed by the Clinical Trials Pharmacy (as named on the Delegation Log).

Details of any emergency unblinding shall be documented fully in the Sponsor file(s), Investigator file(s) and Site file(s). This includes but may not be limited to: 1) Date, 2) Subject details, 3) Reason for unblinding, 4) Name and role of the individual requesting the unblinding, 5) Name and role of the individual carrying out the unblinding. Details will NOT include the results of the unblinding and will also be included in the statistical report.

ESMS Global Ltd through their 24-hour code-breaking service phone number: +44(0)20 7113 7878

12 Methods

12.1 Data collection

Assessment and collection of baseline, outcome and other trial data will be performed as reported in Visit assessments. A detailed description of study instruments is also provided in 8.2 Assessment of Efficacy and 8.3 Procedures for Assessing Efficacy Parameters, they are also included within the Appendix, alongside their scoring algorithms, and coding of missing data.

Whenever possible, follow-up data will be collected independently of study intervention discontinuation. The only occasion in which follow-up data will not be collected is described in 6.6.1 Withdrawal from study Category of withdrawal I (if a participant expresses the wish to be completely withdrawn from the study).

12.2 Source Data

All source data will the held-on paper as a paper source data worksheet (SDW). These will be held locally under the care of the recruiting and consenting site PIs.

12.3 Data management

Data will be collected in paper source data worksheet (SDW) which will then be recorded on a web-based commercial data entry system (InferMed MACRO) hosted by King's Clinical Trials Unit (KCTU). The system is compliant with FDA 21 CFR part 11 and Good Clinical Practice (GCP). It is an appropriate system to use for medicinal trials falling under the Medicines for Human Use (Clinical Trials) Regulations 2004 and its subsequent amendments and has also been used for other complex intervention trials. The web-based system can usually be accessed 24 hours a day and will be accessible to study teams at different sites and allow data entry to run in parallel with patient recruitment and visits.

12.4 InferMed MACRO Database

The InferMed MACRO database will be developed by a KCTU database programmer. Prior to the KCTU developer being assigned, KCTU will be provided with the approved protocol by HRA. The database will be developed and follow a structured two stage process where the chief investigator and Senior statistician will generate and approve the sign off the data collection tools.

The database specification will be validated, and user acceptance tested and confirmed, prior to any patients being consented for this study, by the chief investigator and senior statistician.

Any changes to the specification of the database after the approval of the database will require documentation of the need to be changed, for example an updated protocol amendment from the Health Research Authority.

12.5 Data verification

At the start of the study, a structured data verification plan will be agreed and developed by the Junior statistician and approved by the TMG. The data verification checks will

include one-way tabulations of: baseline; and outcome data, range checks, as well as two-way tabulations of multiple item responses. Dates will also be checked for consistency across form completion times.

A data extract will be requested 6 to 8 weeks before a DMC report and unreliable data/ data queries will be raised and circulated by the Junior Statistician, to the Trial Manager to be resolved prior to the DMC report (where possible).

12.6 Central Statistical Monitoring

Part of the data verification plan will include typical central statistical monitoring. This will include, looking at the distribution of the following across the sites: AEs; patient severity level; withdrawal; and dates of Baseline; and outcomes [72].

12.7 Data Lock

At the conclusion of the trial: The study team will have resolved the data queries and request to remove user access from KCTU to ensure that the final dataset can not be changed.

12.7.1 Archiving

At the conclusion of the trial, the final MACRO database will be archived on paper in the Trial Master File, alongside all of the essential Trial documentation. This will include all analysis code to reconstruct each of the DMC reports, as well as the final statistical report.

12.8 Data Security and backup

There are systems in place to secure the data collection system against permanent loss and allow the recovery and restoration in the event of such a loss occurring.

12.9 Statistical methods

A Statistical Analysis Plan will be approved by the TSC within the first stages of the Study, and before any partially blinded data is summarised by either the Junior or Senior Statistician.

12.9.1 Baseline Data

Descriptive of baseline data for each study site will be provided in published reports.

12.9.2 Internal Pilot

No statistical analyses will be performed for the pilot study (feasibility data), proportions will be presented for each feasibility outcome.

12.9.3 Population under investigation

The analyses will follow an the intention-to-treat (ITT) principle. All participants will be analysed as part of the treatment arm they were allocated to unless a participant withdraws from the study and requests all previous data to be deleted. Or a patient is randomised and does not complete any post-baseline data.

12.9.4 Interim Analysis

No interim analysis is planned. The Data Monitoring & Ethics Committee will have

access to subgroup unblind safety data on an ongoing basis and will act in accordance with the Data Monitoring & Ethics Committee charter.

12.9.5 Analysis of Clinical Efficacy Measures

The statistical analysis will be carried out by the Junior Statistician and interpreted by the Trial Statistician, Dr Ben Carter, who is a Senior Lecturer in Biostatistics at King's College London and co-Investigator.

12.9.5.1 Analysis of the Primary outcome

Using the ITT population we will analyse the primary outcome adjusting for baseline severity, site (stratification factor) and other key covariate information (e.g. age, gender) as reported in the SAP, using mixed effect linear models including a random effect to account for the longititininal data.

12.9.5.2 Analysis of the Secondary outcomes

We will 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 SAP, using mixed effect linear models including a random effect to account for repeated measures on the same participant.

Dichotomous outcomes (e.g. proportion in clinical remission) will be analysed using logistic regression and adjusted for baseline scores and site.

Any time to event outcomes will be presented with a Kaplan Meier Plot and analyses described with a median time to event, and a log rank test.

Additionally secondary analyses will be carried out following a model building process, fitting a multivariable model for each.

12.9.6 Missing Data

We anticipate very few participants withdrawing consent and expect those withdrawn to be missing at random. Since linear mixed effect modelling adjusts unbalanced designs to account for patient missing timepoint information, as long as each patient has one post-baseline outcome measure, they would be included in each analysis. However, we will explore patterns of missing data to investigate any evidence against missing at random. If there is evidence against missing at random, we will consider the impact on the analysis and may introduce imputation methods.

12.9.7 Observation of the statistical modelling assumptions

We will assume that the observed empirical data meets the statistical assumption for the theoretical distributional assumption required for the model that are fitted. The residuals from the statistical models will be plotted to observe any instances where the assumptions may have failed.

12.9.8 Per protocol population and analysis

We will carry out a complimentary secondary analysis of the primary outcome, using the per protocol population, this will exclude the set of patients that are coded as protocol violators. These will be due to: non-compliance; non-completion of instruments within the time-windows; non-compliance with the protocol in any other way.

12.9.9 Subgroup analyses
The primary outcome will be split by the following subgroup: Time-window; sex; baseline severity; different levels of compliance; concomitant recreational cannabis use.

12.9.10 Sensitivity analysis
The primary outcome will be re-analysed to test our assumptions. Non-compliant will be considered protocol violators and excluded from analyses.

12.9.11 Patient completion compliance
Compliance will be determined as patient completion falling within the time windows provided in the Trial Flowchart.

12.9.12 Statistical Programming
All statistical programming will be using Stata (version 15, or later). All data manipulation will be carried out using the KCTU Statistics SOPs. In the generation of a statistical report., all syntax files will be held, alongside the data extract request, and data.

13 Quality Assurance

13.1 Monitoring

Monitoring of this trial will be to ensure compliance with Good Clinical Practice and scientific integrity will be managed and oversight retained, by the KHP-CTO Quality Team.

13.2 Notification of serious breaches of GCP and/or the protocol

In case of serious breaches of GCP and/or the protocol which compromise Safety or Physical; or mental integrity of the participants in the trial, or the scientific value of the trial, these will be reported in accordance with regulation 29A of the Medicine for Human Use (clinical Trials) Regulations (2004).

14 Trial Organisational Structure

14.1 Co-ordinating Team (CANTOP Clinical Trial Office)

The co-ordinating centre is based in The Department of Psychosis, Institute of Psychiatry, Psychology & Neuroscience, King's College London, and is chaired by the Chief investigator and co-ordinated by the Trial Manager (TM).

14.2 Trial Management Group (TMG)

The co-applicants, TM, and junior statistician consist of the TMG and meet monthly to determine how CANTOP is set up and conducted throughout the trial.

14.3 Trial Steering Committee

A ***Trial Steering Committee*** (TSC) will be appointed chaired by an experienced researcher in the area. Rest of the members will be selected according to guidelines from NIHR and will include a statistician and a patient or carer representative. Observers from the EME will be invited to attend all meetings and will be copied in on all committee papers. Meeting frequency will be agreed prior to study start but is likely to be at least annually, scheduled after DMC meetings. We will aim to minimise travel to meetings by using video conferencing.

14.5 Trial Data monitoring and Ethics Committee (DMC)

An independent ***Data Monitoring Committee (DMC)*** will be constituted to act in an advisory capacity to meet regularly to review accumulating data, monitor patient safety and make recommendations to the Trial Steering Committee. It will be chaired by an experienced clinician. The trial statistician will draft a Data Monitoring Committee Charter to ensure decisions on the way the committee functions are clearly documented and agreed prior to the start of patient recruitment. Meeting frequency will be agreed prior to study start but is likely to be at least annually. We will aim to minimise travel to meetings by using video conferencing.

15. Ethics

15.1 Ethics & Regulatory Approvals

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of GCP 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.

This protocol and related documents will be submitted for review to XXXXXX Research Ethics Committee (REC), and to the Medicines and Healthcare products Regulatory Agency (MHRA) for Clinical Trial Authorisation.

The Chief Investigator will submit a final report at conclusion of the trial to the KHP-CTO (on behalf of the Sponsor), the REC and the MHRA within the timelines defined in the Regulations.

In case of protocol amendments, these will be communicated to the Sponsor, R&D office and sites' PIs.

15.2 Consent

Prior to screening, the Early Intervention Consultant will refer the patients who have expressed interest into the study to the study research team.

At screening, investigators will introduce the trial to patients. Patients will also receive Patient information sheets (PIS).

Qualified physicians will discuss the trial with patients in light of the information provided in the information sheets and give appropriate time for the participants to understand the information provided. Qualified physicians will obtain written informed consent from patients willing to participate in the trial.

15.2.1. Biological Samples

A materials consent will be obtained to specifically address the collection of routine blood samples and genotyping. After collection at the study site, routine blood samples will be delivered by the study research team to the local laboratory for analysis. Blood samples for study drug and cannabis use levels as well as genotyping will be stored locally and then shipped to the London hub for analysis.

16 Confidentiality

All study-related information will be stored securely at the study sites. All participant information will be stored in locked file cabinets in areas with limited access. All laboratory specimens, reports, data collection, process, and administrative forms will be identified by a coded ID [identification] number only to maintain participant confidentiality. All records that contain names or other personal identifiers, such as locator forms and informed consent forms, will be stored separately from study records identified by code number. All local databases will be secured with password-protected access systems. Forms, lists, logbooks, appointment books, and any other listings that link participant ID numbers to other identifying information will be stored in a separate, locked file in an area with limited access.

Participants' study information will not be released outside of the study without the written permission of the participant.

17 Access to data

17.1 Data handling

The Chief Investigator will act as custodian for the trial data. The following guidelines will be strictly adhered to:

Patient data will be pseudo-anonymised.

1. All pseudo-anonymised data will be stored on a password protected computer.

2. All trial data will be stored in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006 and the Data Protection Act and archived in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006 as defined in the Kings Health Partners Clinical Trials Office Archiving SOP

17.2. Direct Access to Source Data and Documents

Principal Investigators will have direct access to their own site's data sets and will have access to other sites data by request. To ensure confidentiality, data dispersed to study team members will be blinded of any identifying participant information consistent with the General Data Protection Regulation (GDPR).

The Investigator(s) will permit trial-related monitoring, audits, REC review, and regulatory inspections by providing the Sponsor(s), Regulators and REC direct access to source data and other documents (e.g. patients' case sheets, blood test reports, etc.).

18 Patient and Public Involvement (PPI)

Service users and carers have already identified early intervention as a research priority for the Maudsley Biomedical Research Centre for Mental Health at King's College London and South London & Maudsley NHS foundation trust (https://www.ncbi.nlm.nih.gov/pubmed/27068151).
We also surveyed clinical high-risk of psychosis patients during our previous proof-of-concept CBD study. Patients felt that their current treatments, often psychological and occasionally pharmacological (typically anxiolytic/antidepressant medications), were not optimal. One of the key priorities that they identified was the need for new pharmacological treatments that were safe and tolerated well, as opposed to currently available antipsychotic medications, which they found unacceptable owing to side effects. They also expressed an interest in taking CBD if it was found to be safe and effective and identified this as an important research priority.
Finally, for the current proposal a participant from our proof-of-concept study using CBD has been formally involved in the development of the application at the full application stage and has also agreed to be involved at the trial stage.

Patient and Public involvement will continue to be a critical part of the study. The aforementioned service user has agreed to be involved with practical aspects of developing the study protocol including training of research staff employed on the study, especially during CAARMS training and inter-rater reliability exercises and will also be part of our Patient Advisory Group. We are also in the process of establishing this group. We will also involve our service user group early on in supporting the issues of compliance.

Involving a service user group will ensure that the views of CHR patients and those with psychosis fully inform (i) every stage of the study especially at the planning stages (ii) practical aspects of the study protocol including patient information sheets such that these are feasible and easy to understand; and research visits and packaging of study drug are acceptable to the target population to maximize response, retention and compliance rates, and (iii) help interpret and disseminate study findings in a way that optimizes impact. Service users will be reimbursed for their time and expenses as per INVOLVE guideline.

19 Dissemination Policy

It is intended that the results of the study will be reported and disseminated at national/ international conferences and in peer-reviewed scientific journals. We aim to submit for publication the main results of the trial within two years of last patient recruitment.

19.1 Publication Policy

The CANTOP central team will prepare a structured publication policy, approved by the CI and TMG. It will include the main publications with lead author, and core writing group, with anticipated date of publication.

20 Insurance / Indemnity

South London & Maudsley NHS Foundation Trust and King’s College London indemnity insurance applies.

21 Financial Aspects

Funding to conduct the trial is provided by the NIHR Efficacy and Mechanism Evaluation programme (Ref: **EME Project: 16/126/53)**

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Appendix "Protocol for the mechanistic sub-study"

1 Sub-study Synopsis

Title of clinical trial sub-study	***CAN*nabidiol as a *T*reatment f*O*r *P*sychosis clinical high-risk state- a *R*andomised *C*ontrolled Clinical *T*rial (CANTOP-RCT) mechanism Sub-Study**
Protocol Short Title/Acronym	**CANTOP-RCT SS**
Purpose of clinical trial sub-study	To understand the neurochemical and neurophysiological basis of cannabidiol (CBD) effects added to treatment as usual, in people at clinical high-risk (CHR) of developing psychosis
Mechanism objective (s)	To test: When added to treatment as usual in CHR patients, whether the clinical effects of CBD are mediated by its effects on brain function and glutamate levels in the medial temporal cortex and basal ganglia
Endpoints	**Secondary mechanism sub-study outcomes (measured at visit 1, day 28) :** ***These outcomes will be based on measures made at visit 1, day 28, relative to those made at baseline:*** 1) Within-subject change in glutamate levels in the left hippocamus and caudate measured using ^{1}H-MRS 2) Within-subject change in activation (indexed using the blood oxygen level dependent signal; BOLD) in the medial temporal cortex (MTL) and basal ganglia during a verbal memory task, and during an emotional (fear) processing task. 3) Within-subject change in resting state MTL and basal ganglia perfusion, as indexed using arterial spin labelling (ASL).
Sample Size	One hundred (Total N=100; n=50 each from the CBD and placebo treatment arms) CHR-APS patients drawn from the main clinical trial
Version and date of protocol	Version 1, 10th January 2018
Protocol Development (amendments, version date)	Not applicable

2 Background & Rationale

Previous research data and proof-of concept studies suggest that the therapeutic effects of CBD may reflect its ability to correct neurophysiological abnormalities in the medial temporal cortex and striatum. We therefore propose to investigate this further in a mechanism study, nested within a fully powered RCT. As well as advancing our understanding of the mechanism of action of CBD, assessing brain function prior to treatment might also help to predict which CHR patients will respond best to treatment with CBD. At present there is no way of predicting this on clinical grounds, but recent evidence from studies in psychosis suggests that neuroimaging measures can distinguish patients who will or will not respond to antipsychotic medication[1].

3 Trial Sub-Study Objectives

We aim to understand the neurochemical and neurophysiological mechanisms through which CBD exerts its beneficial effects in CHR patients.

3.1 Mechanism Research Questions

Our mechanism research questions are:
Are the clinical effects of CBD mediated by the effects on the function of the medial temporal cortex and basal ganglia, and on glutamate levels in the medial temporal cortex and basal ganglia?

3.2 Mechanism endpoints

These outcomes will be based on measures made at visit 1, day 28, relative to those made at baseline:
Mechanism sub-study outcomes (measured at visit 1, day 28) :
1) Within-subject change in glutamate levels in the left hippocamus and caudate measured using ^{1}H-MRS.
2) Within-subject change in activation (indexed using the blood oxygen level dependent signal; BOLD) in the medial temporal cortex (MTL) and basal ganglia during a verbal memory task, and during an emotional (fear) processing task.
3) Within-subject change in resting state MTL and basal ganglia perfusion, as indexed using arterial spin labelling (ASL).

3.3 Trial Sub-Study Flowchart

Imaging and related activities only at London site

Outcome	Screening	0	1	2	3	4
Week No.	**-1 to -3**	**1**	**4 (±3day)**	**13 (±7days)**	**26 (±14days)**	**30 (±7days)**
MRI Study Exclusion criteria check	**X**	**X**				
MRI Scanning (fMRI, 1H-MRS, ASL)		**X**	**X**			
Pre-scanning Alcohol breathalyser		**X**	**X**			
Pre-scanning Nicotine smokerlyser		**X**	**X**			

4 Visit assessments

Baseline Visit (Randomisation, on Day 0) and Month One Visit (Visit window 1, at approximately day 28): Patients from the London hub who are participating in the Mechanism sub-study will take part in a neuroimaging session.

5 Outcomes

5.1 Mechanism sub-study outcome assessment

Neuroimaging data (^{1}H-MR spectroscopy, fMRI, and ASL) will be acquired using well-established protocols (below) on the 3T MRI scanner at the Centre for Neuroimaging sciences, King's College London. Each scanning session will last approximately 90 minutes.

5.1.1 Functional MRI (fMRI)

The BOLD signal will be acquired while participants perform a verbal memory task and an emotional processing task. Both paradigms have been used in previous fMRI studies of the effects of CBD [2,3] and the verbal memory task was also used in our proof-of-concept study.

1. Verbal memory task: In an encoding condition, subjects will be shown word pairs and asked to say ('yes' or 'no') if the words 'go together'. In a subsequent retrieval condition, they will be shown one from each pair and asked to say the word that it was previously paired with. Stimuli will be presented every 5secs in alternating blocks of 8 pairs and verbal responses will be recorded on-line.

2. Emotional (fear) processing task: Subjects will be 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 will be asked to indicate the gender of each face by pressing one of two buttons. Thirty different facial stimuli will be presented twice each for 2 seconds with the order of facial identities and expression type pseudo-randomized such that the same identity or facial expression type will not be presented successively.

5.1.2 Magnetic resonance spectroscopy (^{1}H-MRS)

Glutamate (Glu) levels in the hippocampus and caudate will be measured from a spectroscopic voxel placed over the left hippocampus and left caudate head, respectively (2cm^{3}), using ^{1}H-MRS spectra (PRESS - Point RESolved Spectroscopy; TE = 30 ms; TR = 3000 ms; 96 averages) as previously employed at our centre [4,5]. We will employ the standard GE probe (proton brain examination) sequence, which uses a standardised chemically selective suppression (CHESS) water suppression routine. Although measuring Glu in these brain areas is technically difficult, a conventional PRESS acquisition following the techniques employed previously has provided good quality Glu signal [4] in CHR patients and allowed quantification of the major metabolites (Glu, Gln, NAA, Cho, Cr, mI). Shimming and water suppression will be optimised for each location, aiming for a line-width of less than 7Hz.

5.1.3 Arterial Spin labeling (ASL)

Resting cerebral blood flow (rCBF) will be measured using Continuous Arterial Spin labelling (CASL) scans acquired with a 3D Fast Spin Echo (FSE) spiral multi-shot readout, following a post-labelling delay of 1.5s using a sequence that we have employed before in this age group[6]. The spiral acquisition will use a short (4ms) TE, and 8 spiral-arms (interleaves) with 512 points in each arm.

5.1.4 Structural MRI

For image registration, both a high resolution T2-weighted Fast Spin Echo (FSE) image and high resolution T1-weighted Spoiled Gradient Recalled (SPGR) image will be acquired.

5.2. Mechanism sub-study Assessment of Efficacy

Mechanism sub-study outcomes (measured at visit 1, day 28):
These outcomes will be based on measures made at visit 1, day 28, relative to those made at baseline.
Our mechanism sub-study parameters will be measured using the neuroimaging techniques: proton magnetic resonance spectroscopy (^{1}H-MR spectroscopy), functional magnetic resonance imaging (fMRI), and arterial spin labelling (ASL) (as described further in sections below), acquired using well-established protocols on the 3T MRI scanner at the Centre for Neuroimaging sciences, King's College London.
The outcomes to be measured are:
1) Within-subject change in glutamate levels in the left hippocamus and caudate measured using ^{1}H-MRS.
2) Within-subject change in activation (indexed using the blood oxygen level dependent signal; BOLD) in the medial temporal cortex (MTL) and basal ganglia during a verbal memory task, and during an emotional (fear) processing task.
3) Within-subject change in resting state MTL and basal ganglia perfusion, as indexed using arterial spin labelling (ASL).

6 Sample size

6.1 Mechanism sub-study proposed sample size

One hundred CHR patients drawn from the main clinical trial; n=50 each from the CBD and placebo treatment arms.

6.2 Mechanism sub-study sample size justification

In our previous study [7] comparing hippocampal glutamate levels in CHR patients who make a transition to psychosis (Mean±SD: 7.81±1.01) compared to those who do not (Mean±SD: 7.06±1.23), the effect-size for the difference in hippocampal glutamate between the groups was 0.67 (estimated as standardized mean difference). Assuming that the effect of CBD treatment on hippocampal glutamate will be of a similar magnitude we estimated that to have 80% power to detect a difference between CBD and placebo on hippocampal glutamate at 28 days with an effect size of 0.67, using a two-sided t-test at p=0.05, we would require a sample size of n=37 per treatment arm. After inflating our sample assuming a 25% drop-out, we would need to recruit 100 participants for a minimum of 80% power.

In our proof-of concept study, we observed the within-subject change (day 1 minus day 21) in parahippocampal cortex activation (as estimated from the BOLD signal) in CHR patients during the verbal memory task between the CBD (Mean change ±SD: 0.015±0.04) and the placebo (Mean change ±SD: -0.042±0.05) treatment arms corresponded to an effect size of 1.25 (estimated as standardized mean difference). Assuming a similar effect-size in our proposed study, we estimated that to have 80% power to detect a difference between CBD and placebo on medial temporal cortex activation following 28 days treatment with an effect size of 1.25, using a two-sided t-test at p=0.05, we would require a sample size of n=11 per treatment arm.

In our proof-of concept study, we observed the within-subject change (day 1 minus day 21) in left putamen activation (as estimated from the BOLD signal) in CHR patients during the verbal memory task (encoding condition) between the CBD (Mean change ±SD: -0.018±0.05) and the placebo (Mean change ±SD: 0.043±0.06) treatment arms corresponded to an effect size of 1.10 (estimated as standardized mean difference). Assuming a similar effect-size in our proposed study, we estimated that to have 80% power to detect a difference between CBD and placebo on basal ganglia activation following 28 days treatment with an effect size of 1.1, using a two-sided t-test at p=0.05, we would require a sample size of n=14 per treatment arm.

7 Methods

7.1 Analysis of Clinical Efficacy Measures

For the mechanism (neuroimaging) sub-study outcomes (which focus on change from pre-treatment estimate to 28-day post-treatment estimate), only those with complete data for each of the mechanism outcomes will be analysed.

7.2 Imaging data analysis

Imaging analysis will be overseen by the imaging expert Prof Mick Brammer. In line with our hypotheses, for the purposes of our statistical analyses with the fMRI and ASL data, we will focus on two hypothesized regions of interest (ROI), based on previous literature and our pilot data. We will create two ROI masks: one for the 'medial temporal cortex' (which will include bilateral medial temporal cortices including hippocampi and parahippocampal gyri) and another for the 'basal ganglia' (which will include caudate, putamen and pallidum bilaterally) combined in separate study-specific masks.

7.2.1 fMRI analysis

fMRI data from the verbal memory and emotional (fear) processing tasks will be pre-processed 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[2,3]. Prof Michael Brammer, one of the developers of the XBAM image analysis package and a co-investigator will advise on the analysis of imaging data. For each fMRI paradigm, we will examine whether the within-subject change in BOLD signal (at 28 days relative to baseline) within pre-specified ROIs differs between the two treatment conditions by examining the interaction between time (baseline and 28 days) and treatment (CBD vs placebo) in a repeated measures non-parametric analysis of co-variance (ANCOVA).

7.2.2 cASL analysis

rCBF images will be processed using FMRIB software library (FSL) software applications (www.fmrib.ox.ac.uk). Statistical analyses of rCBF data will be performed using the "randomise" program implemented within FSL, which uses a nonparametric permutation–based approach to infer statistical significance against a null data set generated by random permutation using approaches that we have employed before [6]. We will examine whether the within-subject change in rCBF (at 28 days relative to baseline) within pre-specified ROIs differs between the two treatment conditions by examining the interaction between time (baseline and 28 days) and treatment (CBD vs placebo) in a repeated measures non-parametric ANCOVA.

7.2.3. ^{1}H-MRS quantification and analysis

All spectra will be analysed with LCModel version 6.3-0A [8] using 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 with the same field strength (3 Tesla), localisation sequence (PRESS), and echo time (30 ms). Model metabolites and concentrations used in the basis set are fully detailed in the LCModel manual (http://s-provencher-.com/pages/lcmmanual.shtml). Poorly fitted metabolite peaks (Cramer-Rao minimum variance bounds of >20% as reported by LCModel) will be excluded from further analysis. Values of the water-scaled measure of

glutamate will be corrected for CSF content of the ROI using approaches employed before [9]. We will examine whether the within-subject change in Glutamate level in the hippocampus and caudate (at 28 days relative to baseline) differs 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.

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