Integrate Study

Statistical Analysis Plan

Does cannabidiol attenuate the acute effects of Δ9-tetrahydrocannabinol intoxication in individuals diagnosed with schizophrenia? A double-blind, randomised, placebo-controlled experimental study

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Study Design

Integrate is a double-blind, randomised, placebo-controlled, crossover, experimental study assessing whether pre-treatment with oral cannabidiol (CBD) can attenuate the negative effects of acute delta-9-tetrahydrocannabinol (THC) intoxication in individuals with schizophrenia or schizoaffective disorder who use cannabis.

Population

The study will recruit 30 participants with a diagnosis of schizophrenia or schizoaffective disorder, who smoke cannabis regularly, are currently receiving treatment with antipsychotic medication, and are clinically stable (no inpatient or intensive community care for at least three months). Full inclusion and exclusion criteria are described in the study protocol.

Drug conditions

There are two drug conditions:

i) CBD 1000mg oral & THC inhaled
ii) Placebo oral & THC inhaled

Each participant will complete two experiments so that they receive each treatment once. The order of CBD/placebo is randomised and double-blind. CBD/placebo capsules are administered with food (two yoghurts).

After completing trial experiments at 10mg and 15mg, the starting dose of THC was set at 20mg (101mg of 19.8% THC ground cannabis flos).

The THC is administered three hours after CBD administration using a medical grade vaporiser device.

Dose escalation

If a participant completes two experimental visits and does not demonstrate a significant response (defined as a PANSS positive subscale score increase of 3 or more), they will be invited to complete another pair of experiments with a higher dose of THC. The dose of CBD will always be 1000mg.

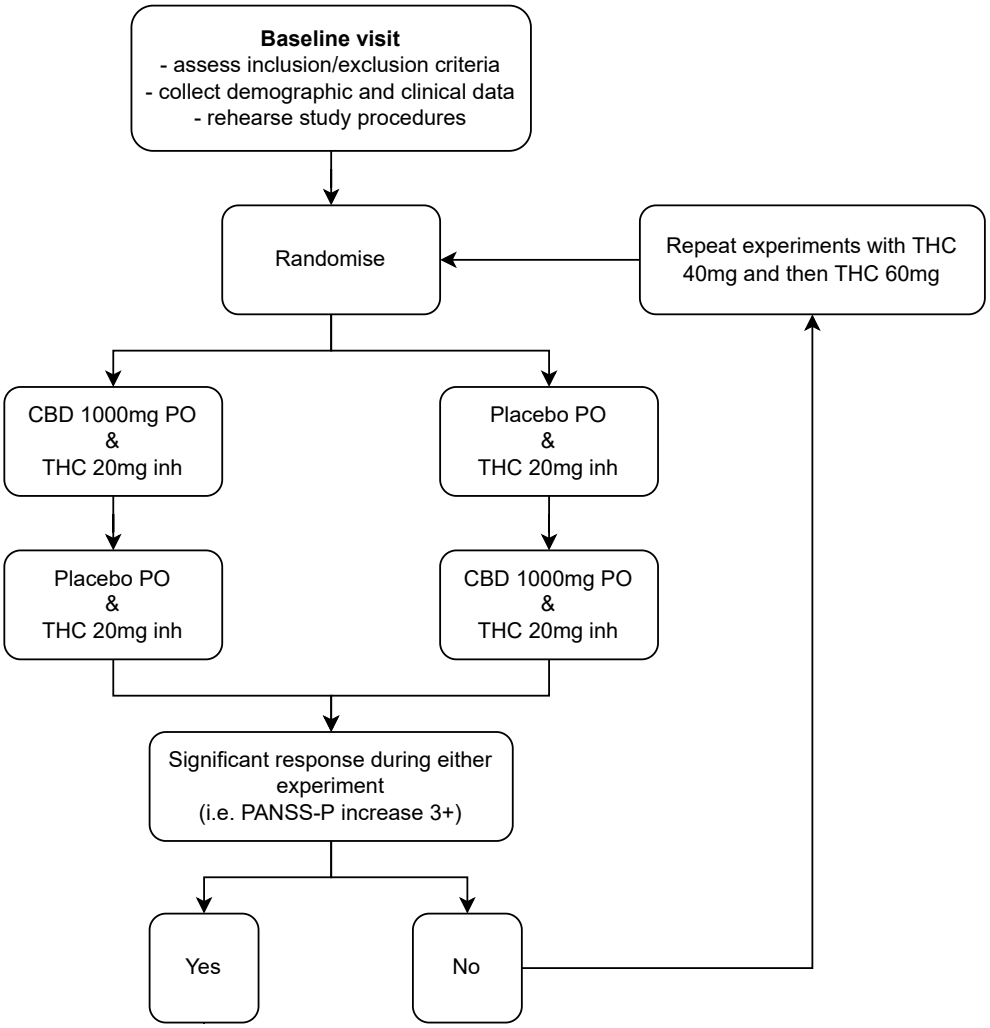
Experiments 1 & 2: 20mg THC inhaled & oral CBD 1000mg/placebo

Experiments 3 & 4: 40mg THC inhaled & oral CBD 1000mg/placebo

Experiments 5 & 6: 60mg THC inhaled & oral CBD 1000mg/placebo

With each pair of experiments participants will be re-randomised to treatment with CBD/placebo.

Flowchart



Study objective

To assess the extent to which, in individuals with schizophrenia, the presence of CBD attenuates the acute effects of THC on cognitive impairment and psychotic symptoms.

Primary hypotheses and outcome measures

Hypothesis 1: CBD will reduce the impairment in delayed verbal recall compared with placebo.
Outcome measure: Hopkins verbal learning task – delayed verbal recall. The total number of words correctly recalled at 20-25 minutes.

Hypothesis 2: CBD will reduce the severity of positive psychotic symptoms compared with placebo.
Outcome measure: Positive and Negative Syndrome Scale (PANSS) - Positive subscale. Change from pre-CBD/placebo to post-THC.

Secondary hypotheses and outcome measures

Hypothesis 3: CBD will reduce state anxiety compared with placebo.
Outcome measure: State-Trait Anxiety Inventory (STAI-S). Change from pre-CBD/placebo to post-THC.

Hypothesis 4: CBD will reduce the impairment in working memory compared with placebo.
Outcome measure: Forward and reverse digit span. The total number of numbers correctly repeated.

Data processing and statistical analysis

Data processing and missing data

Multiple imputation chain equations (MICE) will be used to impute missing values in psychopathological, cognitive, physiological, and pharmacokinetic outcomes using the mice package in R. We will complete sensitivity analyses to assess the effect of data imputation.

Analysis population

Primary analyses will be per-protocol (i.e. data where participants completed a pair of experiments). For participants who completed more than one pair of experiments, the data from the experiments where the highest THC dose was administered will be used. We will complete sensitivity analyses i) using the data from all participants who completed pairs of experiments with 20mg THC; and ii) intention to treat analyses.

Order effects

It will be assumed that there are no carryover effects from the previous experimental session as there was sufficient time for drug washout between session. A period effect may be present due to learning and because participants become more comfortable with the lab environment over time. We will therefore include visit number in all models to account for potential order effects.

Correction for multiple comparisons

Benjamini Hochberg correction will be conducted across outcomes locally i.e. across secondary cognitive outcomes, secondary psychopathological outcomes, visual analogue scales and physiological outcomes.

Analysis of primary and secondary outcome measures

Continuous outcomes will be reported as means with standard deviation. Categorical outcomes will be reported as frequencies.

We will use linear mixed models to assess the effect of CBD on all continuous outcomes. Treatment allocation (CBD/placebo) and visit number will be included as categorical fixed effects, with participant as a random effect to account for the dependency between repeated measures. Estimated marginal means will be calculated and compared in a pairwise test. If residuals do not fit a normal distribution, values will be transformed to fit a normal distribution.

P values below 0.05 will be considered significant. All tests will be two-tailed.

Analysis of VAS

Two comparisons will be made for each outcome: i) effect at 10mins post-THC; and ii) total effect over time (AUC from pre-THC timepoint to End of Study timepoint). For calculation of AUC, the pre-THC timepoint will be set at -20mins and the end of study visit will be set at +135mins post-THC. We will use a linear mixed-model for this comparison.

Analysis of STAI-S

The STAI-state scale was administered at three timepoints during each experiment: pre-CBD/placebo, pre-THC and post-THC. Here, the outcome of primary interest is the difference between baseline anxiety and post-THC anxiety. An additional and separate analysis will be completed to assess whether CBD can reduce anxiety prior to THC intoxication. We will use a linear mixed-model for this comparison.

Pharmacokinetic analyses

Pharmacokinetic parameters will be summarized descriptively. We will report the geometric mean of the AUC_t and C_{max}. THC's AUC will calculated be from 0mins – 90mins.

To compare the C_{max} and AUC_t of THC and its metabolites across treatment arms, we will used a paired sample t-test or a Wilcoxon rank sum test, depending on the distribution of the data.

DOES CANNAB**I**DIOL ATTE**N**UATE THE ACU**T**E **E**FFECTS OF Δ9-TETRAHYDROCANNABINOL INTOXICATION IN INDIVIDUALS DIA**G**NOSED WITH SCHIZOPH**R**ENIA? **A** DOUBLE-BLIND, RANDOMISED, PLACEBO-CON**T**ROLLED **E**XPERIMENTAL STUDY

Study Acronym: INTEGRATE

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Protocol Synopsis

Study title	Does cannabidiol attenuate the acute effects of Δ9-tetrahydrocannabinol intoxication in individuals diagnosed with schizophrenia? A double-blind, randomised, placebo-controlled experimental study
Study acronym	INTEGRATE
Study type	Non-CTIMP Experimental Study
Sponsor	King's College London
Chief Investigator	Prof John Strang
REC number	Health & Social Care Research Ethics Committee A (HSC REC A) Reference Number: 20/NI/0074
Study design	A randomised, double-blind, placebo-controlled, two-arm cross-over experimental study
Primary Objective	To assess the extent to which, in individuals with schizophrenia, the presence of CBD attenuates the acute effects of THC on cognitive impairment and psychotic symptoms.
Secondary Objectives	The secondary aims are to compare CBD pre-treatment with placebo pre-treatment on the following outcomes: 1. Cognition (including verbal learning, delayed recall, working memory) 2. Psychotic symptoms (positive and negative)

	3. Specific psychotic phenomena (auditory hallucinations, persecutory beliefs) 4. Anxiety 5. Other subjective experiences 6. THC, CBD and metabolite plasma levels 7. Plasma endocannabinoid levels and potential biomarkers and inflammatory markers
Primary Endpoint	Difference in delayed verbal recall, as measured by the Hopkins Verbal Learning Test between placebo/THC and CBD/THC.
Secondary Endpoints	All measures will be collected at baseline and then during both test conditions. Endpoints will be the difference between the test conditions. 1. Cognition o HVLT-R Immediate verbal recall o Forward and reverse digit span 2. Psychotic symptoms o Positive and Negative Syndrome Scale (PANSS) ▪ Positive subscale ▪ Negative subscale o State Social Paranoia Scale (SPSS) 3. White Noise Task 4. Advice Taking Task 5. Psychotomimetic States Inventory (PSI) 6. State-Trait Anxiety Inventory (STAI-S) 7. Visual analogue scales: Feel drug effect, Like drug effect, Want more drug, Thinking clearly, Tired, Excited, Want to talk, Anxious, Relaxed, Happy, Irritable, Suspicious, Hearing voices, Dry mouth, Hungry, Vulnerable, Threatened. 8. Preference for overall drug experience and opinion on CBD as a potential harm reduction treatment 9. The difference in plasma levels of THC, CBD, and their metabolites 10. The difference in plasma endocannabinoid levels and potential biomarkers and inflammatory markers

Sample size	The study aims to achieve 30 complete datasets. Accounting for an estimated 25% drop-out rate it is expected to recruit 40 participants.
Summary of eligibility criteria	Inclusion: i. Age 18-65 years. ii. Clinical diagnosis of schizophrenia or schizoaffective disorder (i.e. documented as such in the patient's clinical records and satisfying ICD-10 criteria for F20 or F25) iii. Clinically stable for at least three months (since discharge from hospital, home treatment team, or prior clinical deterioration, and with agreement from the patient's responsible clinician) iv. Regular (at least weekly) cannabis use for the past 3 months or more v. Evidence from either clinicians or from the patient that cannabis use exacerbates their symptoms or increases their risk of relapse vi. Treatment with regular doses of antipsychotic medication for at least 1 month, confirmed by a blood test at the baseline visit if the participant is not prescribed an injectable formulation, and with the participant agreeing to be maintained at a stable dose over the course of the experiment vii. The participant agrees to abstain from cannabis use for at least 24hours prior to study visits viii. The participant is willing to have an intravenous cannula inserted to collect blood samples on experimental visits ix. Sufficiently fluent English x. Providing written informed consent Exclusion: xi. Extreme cannabis use: participant is estimated to be using over 2 grams of cannabis/day xii. Dependence on alcohol or illicit substances other than cannabis as defined by ICD-10 xiii. Pregnancy (current or planned) or breastfeeding xiv. Physical health disorder or another mental health disorder that the study psychiatrist judges may influence the patient's ability to tolerate the procedure, or that may alter the results of the study. xv. Taken part in any drug study within the last 3 months or taking part in another study over the course of the trial xvi. Drug sensitivity/allergy to cannabis or Lorazepam xvii. Unlikely to be able to complete the study sessions for any reason, as judged by the study psychiatrist Additional criteria which must be met on experimental visits xviii. Negative alcohol breath test xix. Negative urine drug screen (apart from cannabis and prescribed medication)

	xx. Negative urine pregnancy test xxi. Stable mental state as judged by the study psychiatrist
Study drug, dosage and administration	Participants will be administered 1000mg CBD orally or a matching placebo. 3 hours later they will inhale a dose of THC (initially set at 20mg, with potential increases to 40mg and 60mg on subsequent visits) or a matching placebo. The THC and placebo cannabis will be GMP approved (or equivalent standards) and be administered using a Volcano Medic Vaporizer (Storz & Bickel), Germany.
Version and date of final protocol	Version 1.0 [10/02/2020] Version 1.1 [03/03/2020] Version 1.2 [21/05/2020] Version 1.3 [15/06/2020]
Version and date of Protocol Amendments	Version 2.0 [27/10/2020] Version 2.1 [05/02/2021] Version 3.0 [05/05/2021] Version 4.0 [01/12/2021] Version 5.0 [08/11/2022]

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1. Summary

Psychotic disorders cause distressing symptoms and severely impact quality of life (Packer et al., 1997). Many patients with schizophrenia smoke cannabis recreationally (Hunt et al., 2018), a behaviour which is associated with negative outcomes including increased risk of relapse (Schoeler et al., 2016) and more severe psychotic symptoms (Henquet et al., 2010). The compound found in cannabis which is responsible for these effects is Δ9-tetrahydrocannabinol (THC). Experimental studies in healthy controls have shown that pre-treatment with cannabidiol (CBD), another compound produced by the cannabis plant, can counteract THC induced psychotic symptoms and cognitive impairment without significantly modifying other subjective effects (Englund et al., 2013) (Haney et al., 2016). No previous study has investigated whether

CBD is able to moderate the effects of acute THC intoxication in individuals diagnosed with a psychotic disorder such as schizophrenia.

The present study will recruit participants with a diagnosis of schizophrenia who use cannabis regularly. Participants will attend the laboratory on three occasions: an initial visit to check that they are safe to join the study, and two experiments. On the morning of experimental visits, each participant will be administered either an oral dose of CBD (1000mg) or a matching placebo. The order of CBD/placebo administration will be randomised across the two visits. Three hours later, they will be administered a dose of vaporised cannabis containing THC. The THC cannabis administration will follow a standardised inhalation procedure using a medical-grade vaporizer device.

Once intoxicated, participants will complete a series of standard cognitive tasks as well as tasks exploring specific psychotic phenomena: the White Noise Task (Galdos et al., 2010) and the Advice Taking Task (Diaconescu et al., 2019). Finally, measures of subjective and objective psychotic phenomena as well as measures of other relevant subjective states (i.e. mood, anxiety, pleasure, hunger) will be collected.

The study will be carried out at the NIHR-Wellcome Trust Clinical Research Facility at King's College Hospital by researchers who have experience of testing cannabinoid compounds in the acute setting and working with people with psychotic disorders. All participants will be individuals who already use cannabis regularly so that they are not exposed to any additional harm. The researchers will closely monitor those taking part to make sure that they are well, both during the visits and for several weeks afterwards. The study will comply with the Declaration of Helsinki and will be conducted in the principles of Good Clinical Practice (GCP). It will be reviewed and approved by a relevant Research Ethics Committee (REC).

2 Objectives

2.1. Primary objective

To assess the extent to which, in individuals with schizophrenia, the presence of CBD attenuates the acute effects of THC on cognitive impairment and psychotic symptoms.

2.2. Secondary objectives

The secondary aims are to compare THC administration following CBD pre-treatment with placebo pre-treatment on the following outcomes:

1. Cognition (including verbal learning, delayed recall, working memory)
2. Psychotic symptoms (positive and negative)
3. Specific psychotic phenomena (auditory hallucinations, persecutory beliefs)
4. Anxiety
5. Other subjective experiences
6. THC, CBD and metabolite plasma levels
7. Plasma endocannabinoid levels and potential biomarkers and inflammatory markers

3 Trial Design

3.1 Trial Design

Randomised, double-blind, placebo-controlled, two-arm, cross-over, within-subjects study.

The study includes one baseline visit followed by two experimental visits, separated by at least one week.

3.2 Study Flowchart

	Initial Brief Screening	Baseline Visit	Experimental Visits 1 &2
Informed consent		x	
Physical examination		X	
Demographic and clinical information	X	X	
Physical Observations		X	X
Alcohol, Drug and Pregnancy Tests		X	X
Blood sampling		X (antipsychotic level only)	X
Cannula			X
CBD/placebo administration			X
THC administration			X
Cognitive and psychopathological testing		X	X
Sobriety test			X
Follow-up call (+ 1 day)			X
Follow-up call (+7-10 days)			X

3.3 Recruitment

The research team will contact local clinical services (ie. inpatient wards and community mental health teams (CMHTs)) and ask them to identify patients who are likely to meet the study's inclusion

criteria. Clinicians will then ask potential participants if they agree to be contacted by the study team. The researchers will also utilise the South London and Maudsley NHS Foundation Trust (SLaM) Consent for Contact initiative in order to recruit Trust patients and will follow the related Trust policy. The researchers will then contact potential participants by telephone or in person to explore their eligibility for the study and answering any questions they have about what participation in the study entails. The researchers will also obtain consent from the participant for the research team to review their clinical notes and discuss their history with their clinical team. If the participants' responses to the initial questions are satisfactory, and there are no issues identified from the review of their clinical notes or discussion with the clinical team, the participant will be invited for a Baseline visit and be provided with a Participant Information Sheet (PIS).

3.1 Inclusion Criteria

Each participant must meet **ALL** of the following criteria:

i. Age 18-65 years
ii. Clinical diagnosis of schizophrenia or schizoaffective disorder (i.e. documented as such in the patient's clinical records and satisfying ICD-10 criteria for F20 or F25)
iii. Clinically stable for at least three months (since discharge from hospital, home treatment team, or prior clinical deterioration, and with agreement from the patient's responsible clinician)
iv. Regular (at least weekly) cannabis use for the past 3 months or more
v. Evidence from either clinicians or from the patient that cannabis use exacerbates their symptoms or increases their risk of relapse
vi. Treatment with regular doses of antipsychotic medication for at least 1 month, confirmed by a blood test at the baseline visit if the participant is not prescribed an injectable formulation, and with the participant agreeing to be maintained at a stable dose over the course of the experiment
vii. The participant agrees to abstain from cannabis use for at least 24hours prior to study visits
viii. The participant is willing to have an intravenous cannula inserted to collect blood samples on experimental visits
ix. Sufficiently fluent English
x. Providing written informed consent

3.3.2 Exclusion Criteria

If the participants **ONE OR MORE** of the following criteria they will be excluded from the study:

i. Extreme cannabis use, participant is estimated to be using over 2 grams of cannabis/day
ii. Dependence on alcohol or illicit substances (other than cannabis) as defined by ICD-10
iii. Pregnancy (current or planned) or breastfeeding
iv. Physical health disorder or another mental health disorder that the study psychiatrist judges may influence the patient's ability to tolerate the procedure, or that may alter the results of the study.
v. The participant has taken part in any drug study within the last 3 months or taking part in another study over the course of the trial
vi. Drug sensitivity/allergy to cannabis or Lorazepam
vii. Unlikely to be able to complete the series of procedures and study sessions for any reason, as judged by the study psychiatrist

3.3.3 Withdrawal of Subjects

Participants are free to withdraw from the study at any stage for any reason. The researchers may withdraw the participant from the study up until they complete their final experimental visit if it becomes apparent that they do not meet all inclusion and exclusion criteria. The researchers may also withdraw the participant due to adverse or serious adverse effects, protocol violations, administrative or other reasons.

The researchers will ask the participant why they have decided to withdraw and will explain that this data will be recorded anonymously. The participant will not be obliged to disclose their reasons for withdrawal. The participant will be able to withdraw their data until two weeks after the final study visit but will not be able to withdraw their data after this point.

3.4 Baseline visit

3.4.1 Consent

The baseline visit will be held at either the participant's CMHT or at the King's Clinical Research Facility (CRF). At the start of the visit the researchers will explain to the participant the aims and procedures of the study once more. The participant will be given time to re-read the PIS and to ask questions about the study. The participant will be informed about what will happen during the rest of baseline visit and experimental sessions including requirements regarding alcohol and other drug use during and between study visits as well as data protection and confidentiality issues. If consenting, the participant and researcher will then read and sign the consent form.

3.4.2 Assessment for Study Eligibility

To assess for eligibility the following assessments will be completed by the study psychiatrist:

i. Mini-International Neuropsychiatric Interview to screen for co-morbid (non-schizophrenia) mental illness
ii. Clinical interview covering medical, psychiatric and substance use histories
iii. Review of electronic health records (electronic Patient Journey System)
iv. Discussion with the participant's Responsible Clinician
v. Mental state examination
vi. A targeted physical examination depending on physical co-morbidities identified during the assessment

3.4.3 Collection of additional demographic and clinical information

The following information will also be collected through interview of the participant and assessment of their electronic health records:

i. Demographics: age, gender, ethnicity, education level, employment, marital status

ii. Clinical information
    a. Current and past diagnosed psychiatric and medical illnesses
    b. Current and past substance use
    c. Current and past prescribed medications including long-acting injectable formulations and clozapine

d. Admissions to psychiatric hospital, their legal status under the Mental Health Act, their duration, and admission to psychiatric intensive care wards
e. History of being subject to a Community Treatment Order
f. Management by forensic mental health services
g. Custodial/prison sentences
h. Health of the Nation Outcomes Scale score (most recent)

iii. Cannabis-Experiences Questionnaire (CEQ). A questionnaire concerned with subjective experiences of cannabis (Barkus et al., 2006). It has 13 questions divided into three subscales: Pleasurable Experiences, Psychosis-Like Experiences and After-Effects.

iv. Timeline Follow-back (Cannabis). This questionnaire obtains a variety of quantitative estimates of substance use.

v. The Cannabis Use Disorder Identification Test – Revised (CUDIT-R) (Adamson 2010)

vi. Substance Use Awareness and Insight Scale (SAS) (Kim 2021)

vii. Psychotomimetic States Inventory (PSI). A 48-item questionnaire that measures psychotic-like experiences. The PSI was developed for use in drug studies, particularly cannabis and ketamine studies (Mason et al., 2008). Items are rated on a 4-point scale (from 0 = never to 3 = strongly). The PSI has subscales of delusionary thinking, perceptual disorders, cognitive disorganisation

viii. Drug Use Disorders Identification Test (DUDIT). An 11-item self-administered screening instrument for drug-related problems.

ix. Alcohol Use Disorders Identification Test (AUDIT). 10 question alcohol harm screening tool.

x. Wechsler Test of Adult Reading (WTAR). This tool is used to provide a measure of premorbid intelligence (Wechsler, 2001).

xi. Revised-Green Paranoid Thoughts Scale. A scale which comprises an eight-item ideas of reference and 10-item ideas of persecution subscale (Freeman et al., 2019).

xii. State Trait Anxiety Scale. This scale differentiates between the temporary condition of "state anxiety" and the more general and long-standing quality of "trait anxiety." The trait scale will also be used as an outcome measure (Spielberger 1983).

xiii. Carbon monoxide breath test. This test uses a simple handheld device. Carbon monoxide levels can be used as a measure of nicotine dependence.

xiv. Height, weight, body mass index, body fat content (%).

3.4.4 Assessment for eligibility to continue with baseline and experimental visits

As well as meeting the study's inclusion and exclusion criteria, participants must fulfil a number of additional criteria at the baseline and experimental visits before completing any outcome measures.

If a participant does not meet these criteria the visit will be postponed. Depending on the individual circumstances, the investigators will consider whether failing these criteria will mean that a participant has to be withdrawn from the study.

i. Negative alcohol breath test
ii. Negative urine drug screen (apart from cannabis and prescribed medication)
iii. Negative urine pregnancy test
iv. Stable mental state, as judged by the investigator and in light of the participant's normal baseline symptomatology

3.4.5 Baseline Antipsychotic Level

During the baseline visit, a single blood sample will be collected to measure plasma levels of prescribed antipsychotic medication in those prescribed an oral formulation. The sample will be collected by the study doctor or CRF nurses in a 5ml EDTA vacutainer. Staff will aim to take a trough sample (i.e. at least 6 hours post dose). The samples will be processed locally at the King's College Hospital/ViaPath Toxicology Unit. If the result of the test implies poor or non-compliance with prescribed antipsychotic medication, the participant will be withdrawn from the study. If a participant is prescribed a long-acting injectable formulation of an antipsychotic, and has been adherent to it for at least the previous three months, they will be able to participate in the study without obtaining plasma antipsychotic levels in advance of experiments.

3.4.6 Practice of Experimental Procedures and Collection of Baseline Outcome Data

At the baseline visit, if no reasons for exclusion are identified, the participant will then practice the inhalation procedure (with air only) and complete the cognitive and psychological test batteries. The cognitive and psychological test batteries are completed at baseline to familiarise the participant with the outcome measures.

3.5 Randomisation & Blinding

On each experimental visit the participant will receive one of the two drug conditions (placebo/THC; CBD/THC). The order in which they are given the two conditions will be randomised across experimental visits. The randomisation will be double blinded to both researchers and participants. The Maudsley Pharmacy will prepare study drug and dispense it to a blinded researcher. A statistician at King's College London who is not otherwise connected to the study in any other way will produce a randomisation list which will be held at the Maudsley Pharmacy. Information on the allocation of participants to experimental arms will concealed from the study team until the study is completed.

3.5 Experimental visits

After successfully completing the baseline visit, the participant will be asked to attend experimental visits. To complete the study, a participant must attend two experimental visits (placebo/THC; CBD/THC). To allow for washout of the study drug, there is a minimum of one week between experimental visits.

3.5.1 Timetable

Experimental Visit Timetable	Event	Time post-completion of THC administration	Expected Time
Preparation & Baseline Psychopathological Testing	Pregnancy, Alcohol & Drug Testing Mental state review Cannula Insertion Blood sampling I Visual Analogue Scales I STAI-S I SSPS I PANSS I PSI	-3.5hrs	10am-10.30am
CBD/Placebo	Oral CBD/Placebo Administration	-3hrs	10.30am
Light lunch	Light lunch Visual Analogue Scales II Blood sampling II	-90min	12pm-12.30pm
THC Administration	Visual Analogue Scales III (pre-dosing) STAI-S II (pre-dosing) Inhalation Procedure	-30mins	1pm-1.30pm
Initial Assessments	Blood sampling III Blood sampling IV Visual Analogue Scales IV PANSS II (initial assessments) Blood sampling V	0min +5min +10min +15min	
Cognitive and Psychopathological Testing	Hopkins Verbal Learning Test (5min) Digit Span (5min) White Noise Task (7min) Advice Taking Task (8 min) Hopkins VLT - delayed recall (2min) Visual Analogue Scales V (2min) Blood sampling VI Visual Analogue Scales VI STAI-S III	+20min +45min +90min	1.50pm 2.15pm 3pm
End of day review and final outcome measures	Visual Analogue Scales VII SSPS II PANSS II (final interview and scoring) PSI	+3.5hrs	5pm
Sobriety Assessment	Sobriety Assessment		
Discharge	Discharge	4hrs	5.30pm

STAI-S: State-Trait Anxiety Inventory-State Scale
SSPS: State Social Paranoia scale
PANSS: Positive and Negative Syndrome Scale
PSI: Psychotomimetic States Inventory

3.5.2 Preparation

Before experimental visits the participant will be asked to:

- abstain from alcohol and cannabis for at least 24 hours before experimental visits
- abstain from other illicit drugs for at least 7 days before experimental visits
- eat their normal breakfast
- have their normal morning caffeine and nicotine
- take their normally prescribed medications

Upon arrival the participant will complete the eligibility tests described in section 3.3.4. If there is no reason to postpone the experimental visit the participant will have an intravenous cannula inserted for blood sampling and a baseline blood sample will be collected. Baseline vital signs (heart rate, blood pressure and, temperature) will also be recorded.

3.5.3 Administration of oral CBD/Placebo

The participant will then be administered oral CBD or a matching placebo. Previous studies have shown that oral CBD reaches peak plasma concentrations within 3 hours. Administration of vaporized THC will therefore be timed to occur 3 hours after administration of the CBD/placebo. The CBD and placebo will be administered with food to improve bioavailability.

3.5.4 Inhalation Procedure

The cannabis will be provided by a manufacturer which adheres to Good Manufacturing Practice (or equivalent standards) and meet the European Medicines Agency's contaminant levels for products used in the respiratory tract (or equivalent regulations).

Participants will be administered 20mg THC for their first two experiments. Those who do not demonstrate a significant response on the PANSS-positive scale (increase ≥3) on either visit will be invited to repeat the two experiments where they are administered 40mg THC. If no PANSS-P response is observed at this dose, they will be invited to return to complete fifth and sixth experiments with 60mg THC. Both the participant and study psychiatrist must approve the dose increases. If it has been a substantial period of time since their last assessment (>3 months) participants will be asked to repeat the parts of the baseline visit to confirm study eligibility and re-familiarise them with the study's procedures and assessments. Participants who completed the study at a lower dose (i.e. 10mg or 15mg on an earlier version of this protocol) will also be invited to complete experiments at 20mg if they did not previously experience a significant PANSS-P response.

The cannabis will be administered via the intra-pulmonary route using a standardised inhalation protocol which has been used in previous comparable studies. The cannabis is prepared and vaporized by nursing staff separate from the study team to maintain blinding to the type of cannabis being administered. The cannabis preparations will be vaporized at 210°C using the Storz-Bickel

Volcano® Medic Vaporizer. This will vaporize the cannabis into a transparent polythene bag with a valve mouthpiece which prevents loss of drug between inhalations.

The inhalation procedure will start when the participant is standing. Participants will be instructed to inhale a medium size breath from the bag, hold their breath for 8 seconds, and then exhale. They will then wait another 8 seconds before taking another breath. They will repeat this process until the balloon has been emptied.

To ensure that the study drug is delivered to the participant this process will be repeated for a second time. The same cannabis plant material will be heated and vaporized for a second time and a second balloon with be filled with the remnants of the study drug. There will be a 1-2minute break between balloons. Once both balloons have been inhaled the participant will be seated or lying down in a bed.

Throughout the inhalation procedure the investigator will monitor the participant for adverse effects or over-intoxication. The details of the safety protocols and procedures are described below (section 3.7).

3.6 Outcome measures

3.6.1 Burden to participants

Together, the cognitive and psychological outcome measures are expected take around 40minutes. Inhalation of 20mg THC leads to a reasonable or high level of intoxication for at least 90minutes. There is therefore no pressure to complete the tasks in rapid succession and participants will be able to take short breaks between measures.

3.6.2 Blood and urine collection, handling and analysis

Urine will be tested using a bedside drug screen and a bedside pregnancy test. One urine sample, collected at the screening or baseline visit will be stored for laboratory analysis of cannabinoids. Urine samples will be decanted into screw-cap collection tubes and be placed in a -20ºC freezer and then -80ºC freezer as soon as possible. The stored samples will be anonymised with participant ID, visit number and time point of collection and freezing. Samples will be analysed and processed according to standard procedures. All other urine samples will be disposed of immediately.

At the baseline visit, a blood sample will be taken to test for prescribed antipsychotic levels. The test will be completed by ViaPath and be processed according to standard clinical procedures.

On experimental visits, participants will have a venous cannula inserted for collection of blood samples. Blood samples will be taken before administration of CBD/placebo, 1.5 hours post CBD administration (30mins pre-THC inhalation) and at 0, 5, 15 and 90minutes after the end of the THC/placebo inhalation procedure. Each sample will be collected in a 5ml EDTA tube (green). Within 10min of collection, the samples will be centrifuged (3000rpm for 10minutes). The plasma will be decanted from the EDTA tube into two screw-cap collection tubes and immediately placed in a -20ºC freezer. The stored samples will be anonymised with participant ID, visit number and time point. Only the research team will be able to link ID number to participant details. The samples will be moved to a -80ºC freezer for longer term storage as soon as possible. Only plasma will be stored so that analyses can be completed. No human tissue will be stored at the end of the research, all

tissues will have been disposed of in accordance with the Human Tissue Authority's Code of Practice

Plasma samples will later be analysed for the levels of prescribed antipsychotic, Δ9-THC, 11-OH-Δ9-THC, 11-COOH-Δ9-THC, CBD, 6-OH-CBD and 7-OH-CBD, potential biomarkers and inflammatory markers using high performance liquid chromatography–mass spectrometry at King's College Hospital and at the University of Turku, Finland.

3.6.3 Cognitive measures

Hopkins verbal learning task – Revised

The investigator reads a list of 12 words to the participant. The participant is then asked to recall as many of the words from the list as they can remember. They repeat this process three times. 20-25 minutes later the participant is asked to recall as many of the words from the list as they can remember. Repetitions and intrusions (words recalled not part of the original list) are recorded for each trial. A different version of the task (i.e. a different list of nouns) will be used on each occasion. (Brandt 1991).

Forward and reverse digit span

In the forward digit span the investigator reads a string of numbers to the participant which the participant repeats back in the same order. If the participant is correct the length of the string of numbers increases by one. The task is ended when the participant fails to give the answer on two consecutive attempts. For the reverse task the participant must recall the list of numbers in reverse order.

3.6.4 Intermediate measures

White Noise Task

This task is designed to provoke illusions of speech in white noise (Galdos et al., 2010). Participants listen to 75 consecutive 1-second audio clips of three different types: white noise only, white noise + barely audible speech, white noise + clearly audible speech. Following each 1-second stimuli, participants indicate whether they heard something, nothing or if they are not sure.

Modified Advice Taking Task

This laptop task is a modified version of the advice-taking task used by Behrens and colleagues (Behrens et al., 2008) (Diaconescu et al., 2019). It provides a measure of social inference which is believed to play a key role in the development of persecutory delusions. On each trial participants try to predict a binary outcome (blue vs. green). They are offered two sources of information with each trial: a social cue (human advisor) and a non-social cue (pie-chart). The pie-chart displays different green-blue ratios (50:50, 55:45, 60:40, and 75:25) thus varying its certainty. Participants are informed that the advisor will vary their intentions to either help or obstruct the participant. They will also be told that the adviser does not have full information and could therefore make unintentional mistakes. Players accrued points with every correct prediction and are provided a reward depending on their overall success.

3.6.5 Psychotic symptom measures

State social paranoia scale (SSPS)
This is a 10-item instrument which measures persecutory thoughts (Freeman et al., 2007). The persecutory items (e.g. 'someone had bad intentions towards me') are presented among 10 neutral items and scored on a 5-point scale (do not agree – totally agree).

Positive and negative syndrome scale (PANSS) – positive subscale and negative subscales
The PANSS is the most common scale to measure psychotic symptoms and commonly used in schizophrenia research (Kay et al., 1987). The positive subscale includes the following symptoms: delusions, conceptual disorganisation, hallucinations, hyperactivity, grandiosity, suspiciousness and hostility. The negative subscale contains these symptoms: blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation, and stereotyped thinking. The symptoms are scored on a 7-point scale from absent-severe. The PANSS is an investigator rated scale and is scored following a semi-structured interview and through observation of the participant during the experimental visit.

3.6.5 Other outcome measures

Psychotomimetic States Inventory (PSI).
A 48-item questionnaire that measures psychotic-like experiences. The PSI was developed for use in drug studies, particularly cannabis and ketamine studies (Mason et al., 2008). Items are rated on a 4-point scale (from 0 = never to 3 = strongly). The PSI has subscales of delusionary thinking, perceptual disorders, cognitive disorganisation

State-Trait Anxiety Inventory-State (STAI-S)
This is a 20-item scale which measures current state of anxiety (Spielberger 1983). Each item is scored from 1 (not at all) to 4 (very much).

Visual analogue scales (VAS)
These will be used to measure contemporary subjective experiences. The scales ranges will range from 0 to 10. The following scales will be used:

- Feel drug effect
- Like drug effect
- Want more drug
- Thinking clearly
- Tired
- Excited
- Want to talk
- Anxious
- Relaxed
- Happy
- Irritable
- Suspicious
- Hearing voices
- Dry mouth
- Hungry

- Vulnerable
- Threatened

As the study progresses, additional visual analogue scales may be added if it becomes apparent that relevant symptoms are not accounted for.

Preference for overall drug experience
At the end of the second experimental visit, participants will be asked which of the two drug experiences they preferred. They will be asked to describe the reasons for this decision.

Opinion on CBD as a potential harm reduction treatment
Participants will be asked to discuss their thoughts regarding CBD as a novel treatment. Before answering questions, they will be asked to assume that CBD is effective at reducing psychosis symptoms and the risk of relapse. They will then answer a series of specific and open-box questions regarding:

- Indication for treatment (psychosis treatment vs. cannabis harm-reduction vs. other indications)
- Polypharmacy with antipsychotic medication (ie. an adjunct to antipsychotic medication vs. to enable antipsychotic dose to be reduced vs. CBD monotherapy)
- Concerns regarding adverse effects
- Formulation (tablets, capsules, oil, other)
- Natural vs. synthetically derived CBD

3.6.6 Next day effects
The day after each experimental visit, participants will be contacted by an investigator to review mental state and adverse effects.

3.7 Safety
The research group at KCL has extensive experience in the experimental administration of cannabinoids and well-established procedures to manage adverse effects. The study will at the CRF which is based within King's College Hospital, a large teaching hospital. It is a short walk away from A&E and has access to all on-call acute medical support.

3.7.1 Baseline safety measures
At the baseline assessment, the participant will be assessed by a psychiatrist who is experienced in working with patients with schizophrenia and with using cannabis preparations in an experimental setting. The psychiatrist will also review the participant's electronic clinical record and discuss the inclusion of the participant with their responsible clinician (ie. Community Mental Health Team Consultant) and their care-coordinator. The care-coordinator and responsible clinician will be provided with the study's PIS and be able to discuss the study with the study psychiatrist. They will also be made aware of the dates of the experimental visits which their patient will be attending the study on. If the participant provides consent, the study team will also inform relevant friends, family or carers of the dates of their experimental visits.

3.7.1 Pre-THC Inhalation

On arrival at the laboratory, participants will complete the assessments described in section 3.3.4. Before the inhalation procedure, the investigator will talk to the participant about what to expect over the rest of the experimental visit.

3.7.2 Post-THC Inhalation

During inhalation the participant will stand next to a chair or bed so that if they feel lightheaded they are able to sit or lie down easily. If this occurs, the inhalation procedure will be paused and the participant will have their physical observations checked.

Physical observations (HR, BP, Temp) will also be collected at baseline, at 0, 5, 15 and 90minutes post-inhalation, and before discharge. If physical observations are of clinical concern, a study doctor, who will be present throughout testing, will continue to monitor their physical observations and overall well-being closely and seek appropriate specialist advice as required

Throughout the inhalation, the investigator continuously monitors for physical and psychological effects of the drug. If the participant appears to be experiencing unpleasant side effects or is unlikely to tolerate the full dose of the study drug, the administration can be paused or halted at any time.

In the unlikely event of distressing side effects (e.g. paranoia, anxiety), rescue medication (lorazepam) will be made available. If symptoms are severe, antipsychotic medication can also be used.

SLaM Pharmacy will serve as the emergency code breaker. In the extremely unlikely case that a clinician requires blinded information from a participants' experimental visit, they can contact SLaM Pharmacy switchboard where they can speak to the on-call pharmacist for code breaking information at all times including out-of-hours. Out of hours, there may be a delay of up to three hours before the pharmacist is able to obtain the relevant information. The contact details for the SLaM switchboard will also be made available to participants.

3.7.3 Sobriety testing

At the end of experimental visits, participants will complete a series of sobriety tests. These will include examination of mental state by a psychiatrist and completion of the Standardized Field Sobriety Test Battery (heel-toe walking and turn, horizontal nystagmus, one leg stand test). These tests will also be completed at baseline to assess participants ability to complete them when sober and make reasonable adjustments on experimental visits if required.

Participants who are not considered to have fully recovered will be permitted to stay in the facility for as long as necessary. In the unlikely event that a participant's symptoms do not resolve by the end of the study session Participants who are not considered to have fully recovered will be permitted to stay in the facility for as long as necessary. In the unlikely event that a participant's symptoms do not resolve by the end of the study session, the following protocol will be adhered to:

1. The participant fails the sobriety test.
2. The study team will explain to the participant that they have failed the test and that they will have to remain under observation until the study psychiatrist agrees that they are psychologically fit to return home.

3. The participant will be able to repeat the sobriety tests and assessment with the study psychiatrist at regular intervals.
4. If it is likely that the participant will need to remain under observation for a significant period of time, the study team will inform the nurse in charge of the CRF of this issue. They will discuss how long the CRF is likely to remain open for.
5. The study team will also offer to contact a family member, carer or friend so that they can be informed that the participant remains under observation in hospital. The study team may contact the family member, carer, or friend without the participant's consent, if the participant had previously provided consent for such contact, they currently lack the mental capacity to make this decision and such action would be in their best interests.
6. If the participant does not agree to remain under observation, the importance of safety and continued observation will be explained to them. If they disagree with study psychiatrists assessment, and request discharge from the unit, the study psychiatrist will consider assessing the participant for section 5.2 of the Mental Health Act.
7. If the CRF closes, the study team will transfer the participant to the A&E department at King's College Hospital. They will inform the Psychiatric Liaison Nurses in A&E and the on-call psychiatry SpR and consultant
8. Once the participant has been transferred to A&E, responsibility for their care will be taken over by SLaM.
9. If the participant is transferred to A&E or another inpatient ward, or is detained under the Mental Health Act, the study's Chief Investigator will be informed at the earliest opportunity.

3.7.4 Follow-up

Participants will receive two follow-up phone calls from the study team on day 1 and between days 7-10 after each experimental visit. The participants will be asked questions relating to their general well-being, sleep, mood, anxiety, psychotic symptoms, and adverse events. Normal clinical care will continue during the course of participation. If a patient becomes unwell during the study or its follow-up period, the study team will inform the participant's community mental health team to request appropriate clinical follow-up.

If a participant doesn't respond to an initial phone call from the study team, the following escalation protocol will be adhered to:

1. Repeat phone calls x2
2. Text message asking the participant to call the study team
3. If the participant has provided consent, the team will contact a family member, carer or friend and ask them to check that the participant is well, and request that the participant contacts the study team
4. If there has been no contact with the participant to confirm that they are well, the study team will contact the participant's care-coordinator and responsible clinician on the morning of the next working day. The study team will ask the care-coordinator and responsible clinician to follow their usual clinical protocol in such circumstances. At this point, the follow-up will be handed over to the Community Mental Health Team.

3.7.5 Covid-19

Local guidance (SLaM and King's College Hospital) on the management of SARS-CoV-2 will be followed throughout the study.

4. Cannabis use outcomes in volunteers who do not meet inclusion criteria

To allow a broader range of participants to be involved in the research study, those who do not meet the criteria described in section 3.3, will be invited to participate in a limited part of the study as long as they meet the following criteria:

1. Diagnosis of a psychotic disorder (including psychosis spectrum (ICD-10: F20-29), bipolar affective disorder (F31), cannabis-induced psychotic disorders (F12.x) and clinical high-risk for psychosis) or control (ie. regular cannabis user without a psychosis diagnosis)
2. Regular cannabis use (at least weekly)
3. Has used cannabis within the past 7 days (self-report)
4. Urine dipstick test positive for cannabis
5. Providing written informed consent

They will be asked to read through the relevant parts of the Participant Information Sheet and sign a consent form (as per section 3.4.1). They will not be required to sign to sections 9, 10 or 14 of the consent form.

They will then answer questions regarding their medical and psychiatric history and substance use (as per section 3.4.3, subsections i-ix). They will provide a single urine sample which will be stored and analysed (as per section 3.6.2). They will also answer questions regarding CBD as a potential harm reduction treatment (section 3.6.5) and complete a PANSS interview. All data will be collected in accordance with the study's ethical standards and data handling protocols (sections 9 and 10). Participants will be reimbursed £20 for their contribution.

5. Trial Statistics

5.1 Sample Size

The relative effects of THC and CBD/THC have never been compared in this population previously. We chose a sample size (n=30) which we believe has adequate power to detect meaningful effects. In a two-tailed paired sample t-test, a sample size of n=30 has 80% power, at alpha=0.05 to detect an effect size of 0.53.In a study comparing the effect of THC relative to CBD/THC on psychotic symptoms in healthy volunteers[27], the effect size for increase in State Social Paranoia Scale was d=0.64. Assuming a drop-out rate of 25% (as in previous studies using this methodology), we plan to initially enrol n=40 patients.

5.2 Analysis

Study data will be analysed following the completion of data collection and database lock. For the primary analysis linear mixed models will be used, with fixed effects of experimental condition and random intercept for repeated measures within participants. Differences in the frequency of categorical data will be analysed using Pearson's Chi-square test or multilevel logistic regression as appropriate. Relationships between cognitive, intermediate and psychosis data will be analysed using

Pearson's or Spearman's rank correlation coefficient. If data do not fit a normal distribution they will be analysed after appropriate transformation. We will present both effect sizes and tests addressing study hypotheses with statistical significance set at $p < 0.05$. All tests will be two-tailed.

6 Participant reimbursement

Participants will be reimbursed for their time at a rate equivalent to the London Living Wage (£10.55/hour). The baseline assessment is expected to take 4 hours and each experimental visit is expected to take up to 8 hours, a total of 20 hours. The total payment for completing the study (ie. two experiments with THC 20mg) will be £200. The participant will be paid £30 for the baseline, £70 for experimental visit 1 and £100 for experimental visit 2. Further reimbursement will be provided if a participant attends experimental visits 3 (£70), 4 (£100), 5 (£70) and 6 (£100). The total payment for attending all visits will be £540. Participants who do not complete all study visits will be reimbursed for the number of study visits they have attended. Participant will be paid either in cash or via bank transfer as per their preference. For bank transfers, bank details will be taken from the participant at the end of the study and payment will be processed 2-4 weeks after the final study visit.

7. Trial Steering Committee

The trial steering committee will supervise the trial on behalf of the sponsor, ensuring that the study is conducted under good clinical practice (GCP). In addition the trial steering committee will monitor progress of the trial, monitor adherence to the protocol and monitor participant safety. The trial steering committee will include Professor Philip McGuire, Professor John Strang, Dr Amir Englund and Dr Edward Chesney.

8. Access to Source Data and Documents

The researchers will permit study-related monitoring, audits, REC review, and regulatory inspections by providing the Sponsor(s), Regulators and REC direct access to source data and other documents.

9. Ethics & Regulatory Approvals

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of Good Clinical Practice (GCP) and in accordance with all applicable regulatory requirements. The study protocol, informed consent form, and participant information sheet will be submitted to an appropriate Research Ethics Committee (REC) and R&D for approval.

Should the protocol require a major amendment, the amended protocol will be sent to the REC and R&D for approval before the changes in the protocol will be implemented. Minor amendments (administrative or logistic) may be implemented immediately, and the REC will be informed of this in writing.

Written informed consent will be obtained from each participant before the initiation of any data collection or study related activity. Consent will be obtained in accordance with REC guidance and GCP and be performed by Edward Chesney or another psychiatrist.

10. Data Handling

The study will adhere to KCL's policy on data management, security and sharing.

Participants will provide written informed consent for the study team to access their medical records. The study team will review their electronic health record (ePJS) for the South London and Maudsley Trust and will also review the Local Care Record which accesses their primary care notes and records across King's Health Partners (ie. Guys, St Thomas, King's Hospitals).

We will ask participants to provide mobile phone numbers and/or email addresses so that we can contact them during the study. We will not request personal address details unless we are booking a taxi for them. If a participant requests, they will be contacted with the study outcome.

The Chief Investigator will act as custodian for the study data and all participant data will be anonymised. Data will be collected using source data questionnaires (pen and paper) and laptop computers (cognitive tasks) on study visits. Each study participant will be given a study ID consisting of a 3 digit number preceded by the study acronym "INTG" (e.g. INTG002). Source documents and electronic data records (SPSS or Excel) will be named with this ID. The source documents will be kept in locked cabinets within access-card locked rooms; electronic data will be backed up onto encrypted external hard-drives.

Only the study research team will have access to participant's non-anonymised personal data during the study. Study data will be analysed at the IoPPN, King's College London, by the research team including study statistician. Data files which will be analysed will contain the participant ID number and contain no identifiable personal data. If participant's bank details are used to provide payment, the information will be not be stored for any longer than necessary and will be destroyed at the earliest opportunity according to standard departmental procedures.

Research data will be stored for a minimum of 10 years following the completion of the study. Case report forms will be scanned so that they can stored electronically along with other data from the study. We plan to store the data on King's Research Data Management system.

11. Publication

The trial protocol will be published in advance on Open Science Framework (www.osf.io/) and clinicaltrials.gov. Hypotheses for each outcome measure will also be pre-registered. It is intended that the results of the study will be reported and disseminated at international conferences and in peer-reviewed scientific journals. Where appropriate, the results will be disseminated to the general public by means of press releases, posts on social media and at public engagement event. As the results of the study may be valuable to public policy, the results may also be shared with governmental advisory groups such as the ACMD. Individual participants will not be identifiable in publications.

12. Finance

The trial is being funded by the National Institute of Health Research Award NIHR300273 (£412,000).

13. Addendum: Rationale for THC and CBD doses and routes of administration

Rationale for CBD dosing and administration route
Intravenous administration of CBD is not an established route. Inhalation of CBD is ineffective at higher doses due to coughing(Solowij et al. 2019). We therefore chose to administer CBD orally.

A recent systematic review of the pharmacokinetics of cannabidiol highlighted the paucity of data from human studies(Millar et al. 2018). The best data, is probably from submissions for EMA approval of epidiolex (cannabidiol oral solution) which says:

> 'Bioavailability of CBD was approximately 6.5 % following oral administration in fasting conditions. Due to significant food effect observed the bioavailability following administration with food can be expected around 14-25%.'
> (https://www.ema.europa.eu/en/documents/assessment-report/epidyolex-epar-public-assessment-report_en.pdf)

We are aware of the food effect of CBD and are requesting that our participants ensure that they eat their normal breakfast before experiments.

In a study of healthy volunteers, 600mg oral CBD led to a significant reduction in the proportion of subjects who developed psychotic symptoms (Englund et al. 2013). There have been two randomized controlled clinical trials of CBD as an add-on treatment for schizophrenia. In one 600mg daily was not effective at reducing psychotic symptoms(Boggs et al. 2018), in the other 1000mg was effective(McGuire et al. 2018). We therefore decided to administer 1000mg of CBD orally.

CBD reaches peak plasma concentration after around 3 hours after oral administration. We will therefore administer the CBD 2 ½ hours before the start of the inhalation procedure which takes up to 30 minutes.

Rationale for THC dosing and administration route
THC can be administered orally, inhaled or intravenously. During the preparation for this study, the study team interviewed patients who said that inhalation of vapor was the most acceptable route as it is the most similar to smoking, the standard route of administration for almost all users. Familiarity with smoking will mean that users are less likely to become over-intoxicated as they are able to titrate the study in their usual manner. There is also significantly less variability in absorption between individuals compared to oral administration. Vaporization is expected to deliver around 30-40% of the total THC dose to the participant (i.e. 3-4mg.)

Regular users to have a much higher tolerance to THC. For example, in one study of frequent cannabis users (53% daily users, mean 21days/month), compared to placebo, a dose of 2.5mg THC IV caused a slight improvement delayed verbal recall, suggesting that these participants experienced withdrawal symptoms during the placebo arm(D'Souza et al. 2008).

Five previous studies have administered THC to people with a psychosis diagnosis in an experimental setting, three of which are discussed here (D'Souza et al. 2005)(Kuepper et al. 2013)(Henquet et al. 2006), while two neuroimaging studies unfortunately provide little information on either the psychological effects or safety of THC in this population (Whitfield-Gabrieli et al. 2018)(Vadhan et al. 2017).

D'Souza et al. used an IV preparation of THC in patients with schizophrenia who did not use cannabis regularly and were prescribed a regular antipsychotic (D'Souza et al. 2005). They compared two doses of THC: 2.5mg and 5mg, equivalent to around 7mg and 14mg of vaporized THC, with placebo. It is important to note that in this study, the IV THC was administered over only 2minutes. Unlike in the INTEGRATE study, this would have prevented early termination of drug administration due to over-intoxication.

There study reported two adverse events related to the study drug:

> 'One subject who failed to disclose a remote history of untreated hypertension at screening experienced hypertension, anxiety, and paranoia after receiving 5 mg delta-9-THC'.
>
> 'One subject diagnosed with paranoid schizophrenia who did not like the effects of delta-9-THC withdrew consent after completing 2 test days and became paranoid about research staff and his clinicians.'

An increase in PANNS-positive score of 3 or more was considered significant. The 2.5mg dose triggered such a reaction in 80% percent of the patient participants (mean increase: 5, range: -2 – 11). The 5mg dose triggered a significant reaction in 75% of participants (mean increase: 5, range: 0 – 12)

Kuepper et al. administered 8mg THC via a vaporizer to 9 *medication-free* patients with a psychotic disorder(Kuepper et al. 2013). Six participants were daily cannabis users, one was a weekly user and two used it monthly or less. They reported no serious adverse events or drop-outs. There was little data on the psychological effects of the drug, but the study reported that THC induced significant increases in visual analogue scales, such as 'feeling high', and that there were no differences in these outcomes compared to two control groups (relatives of patients and healthy controls).

Henquet et al. administered THC to 30 patients with a psychotic disorder, 8 of whom were not prescribed an antipsychotic(Henquet et al. 2006). The dose used was 300ug THC/kg, equivalent to 21mg in a 70kg person. The THC was smoked in cigarettes containing tobacco. In another study comparing smoking of THC with vaporization, the subjective effects of 25mg smoked THC were similar to a 10mg vaporized dose (Spindle et al. 2018). Henquet et al. combined two other groups (relatives of patients and healthy controls) with the patients for all analyses preventing group specific inferences. The study did not report any adverse events.

Using earlier versions of this protocol we administered THC 10mg, 15mg and then 20mg as the starting dose. A total of 19 experiments have been completed by 10 participants. There have been no serious adverse events and no significant episodes of over-intoxication, nausea, drowsiness, dizziness, anxiety, agitation or hostility. All participants who received the study drug completed all study procedures successfully. All participants said that they are willing to enter the study again at a higher dose, except one who didn't want to be cannulated again. We asked participants who completed the study to estimate the dose of THC that they believe they could tolerate without difficulty. Six participants were confident they could tolerate at least 40mg (study psychiatrist agreed in four cases) and two said they could tolerate 60mg THC or more. We have amended the protocol to allow participants who have safely completed experiments to re-enter the study at a higher dose (40mg and then 60mg). We hope that this approach will mean that more participants

will demonstrate a significant response to THC during their experiments, increasing the number of chances that CBD has to block its effects.

The mean daily use of cannabis in the population who either completed a baseline assessment for the main experiment or the substudy (protocol section 4) is 1g per day (n=22). Almost all participants smoked strong cannabis (roughly 15% THC content). A reasonable estimate for average THC consumption in the local schizophrenia population is therefore 150mg daily.

During recruitment around half of potential participants were excluded as their cannabis consumption was too high (i.e. >1g day). We have amended the inclusion criteria to allow participants who use as much as 2g/day (300mg THC/day) to enter the study. We expect that this will immediately provide us with another 10-15 recruits. It is likely that those with a higher cannabis tolerance (i.e. using 1-2g/day) will only demonstrate a psychotic response at higher doses.

We will continue to take a cautious approach to experiments, for example, by first administering higher doses of THC to those who demonstrated the least response to lower doses.

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14. Signature

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Chief Investigator *Print name*	Date