CANPAIN feasibility study: evaluating the feasibility of subsequently undertaking a pragmatic real world trial investigating CBMP in chronic pain patients

(SHORT) CANPAIN Feasibility study

Chief Investigator:
Dr Shahpoor Sorooshian
Clinical Lead of Harley Street (CPC) limited

Sponsored by:
Harley Street (CPC) Limited
Trading as LVL Health

Protocol version number and date:

CANPAIN feasibility v2 16 02 2022

PROTOCOL VERSIONS

Version Stage	Versions No	Version Date	Protocol updated & finalised by;	Appendix No detail the reason(s) for the protocol update
Current	2	16 02 22	NA	NA
Previous	1	17 08 22	NA	NA

SIGNATURES AND AGREEMENT WITH PROTOCOL

Trial title: CANPAIN feasibility study: evaluating the feasibility of subsequently undertaking a pragmatic real world trial investigating CBMP in chronic pain patients

We, the undersigned, agree to conduct this trial according to this Trial Protocol. We agree that the trial will be carried out in accordance with Good Clinical Practice (GCP), with the Declaration of Helsinki (with amendments) and with the laws and regulations of the countries in which the trial takes place.

On behalf of the Chief Investigator:

Signature:.. **Date. 16/Feb/2022**

Print Name(in full):.....Dr Shahpoor Sorooshian...................

Position:.....................Chief Investigator..........................

On behalf of the Study Sponsor:

Signature:.. **Date..16../.Feb./.2022**

Print Name(in full):.......Gregory Stoloff............................

Position:.......................Director...................................

STUDY SUMMARY

Identifiers	
IRAS Number	304548
REC Reference No	TBD
Sponsor Reference No	CANPAIN feasibility 1
Other research reference number(s) (if applicable)	
Full (Scientific) title	
Health condition(s) or problem(s) studied	Non-cancer chronic pain
Study Type i.e. Cohort etc	Feasibility study
Target sample size	Number collected over a 3 month period but with a minimum target of 100 subjects
STUDY TIMELINES	
Study Duration/length	3 months
Expected Start Date	1st March 2022
End of Study definition and anticipated date	Last patient last visit (2nd June 2022)
FUNDING & Other	
Funding	Study will be funded by the Sponsor
Other support	NA
KEY STUDY CONTACTS	**Study Site: Gregory Stoloff** **Email:gregory.stoloff@lvlhealth.co.uk** **Tel: 0333 366 1033** Full contact details including phone, email and fax numbers
Chief Investigator	Dr Shahpoor Sorooshian

KEY ROLES AND RESPONSIBILITIES

SPONSOR: The Sponsor is responsible for ensuring before a study begins that arrangements are in place for the researchers to deliver the research as proposed and allocate responsibilities for the management, monitoring and reporting of the research.

CHIEF INVESTIGATOR (CI): The person who takes overall responsibility for the design, conduct and reporting of a study.

The CI role is to complete and to ensure that all relevant regulatory approvals are in place before the study begins. Ensure arrangements are in place for good study conduct and reporting.

CONTENTS

1 INTRODUCTION

The below proposed study will recruit existing patients of the private clinic who have already consented to and agreed to receive and self-fund the cannabis-based medicinal product offered by the clinic.

The CANPAIN study has been devised to evaluate the efficacy and safety of a defined cannabis based medicinal product (CBMP) delivered by inhalation to patients with chronic pain attending a private clinic. Prior to commencing the CANPAIN study, and as suggested by the Oxford A REC, we propose to conduct a feasibility study. This study will aid in establishing likely rates of patient recruitment, duration of participant enrolment in the study, the demographic and geographic spread of patients, patient acceptability of data collection and identify any issues with technological and drug delivery logistics.

2   BACKGROUND AND RATIONALE

The CANPAIN protocol has been submitted previously to the Oxford A REC for ethical review (see Appendix 1), but a non-acceptance opinion was received. It was recommended that a feasibility study be considered to address concerns regarding recruitment rates and acceptability of the study. The feasibility study will be based within a private clinic setting and will only involve existing patients of the clinic. The treatment regime, tests that the patients are required to take, the clinical information they are required to provide, and the informed consent required for treatment, will all follow the clinical protocol in Appendix 1. We wish to assess the feasibility of conducting the study within the private clinic to aid a future submission to Oxford A REC of the CANPAIN study. This subsequent application will aim to address the Oxford A REC concerns around the control group.

Patient Clinical Pathway
This section provides an overview of the clinical pathway patients at the clinic will follow from initial assessment through to provision of CBMP and vaporiser device.

Prior to receiving the clinical service, the prospective patient's application and medical information will be assessed by a multi-disciplinary team to determine if they are suitable for CBMP treatment. This assessment will utilise the inclusion and exclusion criteria outlined below as well as the clinicians' experience and will comply with NHS England and GMC guidance on prescribing both CBMP and unlicensed medications.
If the patient meets the requirements for CBMP treatment, they will sign a consent form for undertaking certain screening tests. Once consent has been gained patients will be sent a urine pregnancy test (if applicable), a urine cannabis test to establish existing cannabis use and a saliva genetic test to subsequently determine if genetic markers can determine sensitivity to cannabis. If the patient is pregnant, they will not be able to attend the clinic. If they fail the cannabis test, they will have to stop use for 3 weeks and provide a negative urine test before they can commence treatment at the clinic.
The patient will then book a consultation at the clinic. They will review the treatment consent prior to the consultation and will be explained the treatment and safety consideration by the specialist doctor at the clinic and if they are in agreement to receive the unlicensed medicines, they will sign the consent form in front of the doctor. The doctor will then prescribe the medication using his private controlled drug PIN on a FP10PCD form and send this to the pharmacy. The inhalation device with instructions and the medicines will be couriered to the patient using controlled drug procedures. The patient will need to fill out baseline pain and quality of life questionnaires to ascertain their base level before taking the medicines for the first time. After each inhalation session the patient must fill in safety questions, which are reviewed by the clinic, before they can use the medication again. The

patient has to fill out pain questionnaires once a week and a quality-of-life questionnaire once a quarter. If they do not do so they cannot continue using their medication. The patients will also be asked to fill out a questionnaire on quality of the service and any complaints they have.

The feasibility study will be conducted over a 3-month period with a minimum target recruitment number of 100 patients. Feasibility will be assessed through 3 distinct domains: Recruitment and patient experience, medication logistics and data management.

Patient experiences (part of domain 3) will be captured using comment forms, requesting feedback on ease of onboarding, ease of answering questionnaires, evidence of questionnaire fatigue and their satisfaction of service.

3 OBJECTIVES

3.1 Primary Objective
Domain 1
1) Assess rate of recruitment to the clinic.
2) Assess the number/proportion of patients that cease treatment at the Clinic.
3) Assess the number of patients that complete all questionnaires required.
4) Assess the number of patients that experience safety issues.

Domain 2
1) Assess the timeliness and efficiency of CBMP delivery to the patient.
2) Assess the presence of issues with the usability of the inhalation device.

Domain 3
1) Assess the study acceptability via answers to comment forms:
   a. ease of onboarding.
   b. ease of answering questionnaires.
   c. evidence of questionnaire fatigue.
   d. satisfaction of service.

3.2 Secondary Objectives
1) Assess the socio-economic status and geographic origin of patients.
2) Assess the number of enquiries to webpage and completion of registration forms.

4 CONSENT

Informed consent will be obtained from participants when onboarding to the clinical service for treatment with a CBMP. If they subsequently decide to join the feasibility study, then they will sign a separate consent form for the study.

5   ELIGIBILITY CRITERIA

5.1   Inclusion Criteria

1. A consented patient at the clinic;

2. Male or female 18-85 years old;

3. Diagnosed with chronic non-cancer pain;

4. Is currently receiving standard of care but still has pain, has completed standard of care pain treatment, does not want standard of care treatment, or standard of care is contraindicated. An inadequate response is defined as the subject receiving standard analgesic agents and still has pain, has unpleasant side effects or wishes to reduce their intake of standard of care analgesic agents, e.g. a subject receiving opioids who wishes to dose reduce in light of the "opioid crisis";

5. Despite being on or having received standard of care and has still pain (>3 on the Pain NRS); and

6. Signed and dated consent form from the patient.

7.2   Exclusion Criteria

1. Pregnant or lactating females or females who are planning a pregnancy during the study;

2. Positive pregnancy test at time of joining the clinic;

3. Major organ failure, renal, lung or liver failure;

4. Participants having active liver disease or unexplained persistent elevation of serum transaminases > 3 times the upper limit of normal;

5. Participants with a creatinine clearance < 60mL/min;

6. History of cardiac or respiratory failure;

7. History of recent myocardial infarction or poorly controlled ischaemic heart disease;

8. Severe respiratory disease (e.g., GOLD 3 for COPD or asthmatics requiring high doses of oral corticosteroids);

9. History or presence of alcohol or substance abuse, including analgesics used as standard of care;

10. Participation in a clinical trial of an investigational medicinal product;

11. With any known or suspected history or family history of schizophrenia, or other psychotic illness; history of severe personality disorder or other significant psychiatric disorder disorders other than depression associated with their underlying condition;

12. Known hypersensitivity to cannabis or allergy to cannabis or CBMP; and

13. Currently taking cannabis and does not agree to a 3 week wash out period.

6   DATA HANDLING AND MANAGEMENT

Information related to feasibility study will be extracted from the participating clinical sites electronic health record (EHR) system which will contain all the relevant patient information, prescribing information, safety information and questionnaires completed. At the end of the feasibility study information on the relevant domains will be extracted and collated into a feasibility study report.

7   MONITORING AND AUDITING

The Chief Investigator will ensure there are adequate quality controls in place for conducting the feasibility study by the Sponsor. This will include adherence to the protocol and ensuring adequate data quality.

The Chief Investigator will inform the Sponsor should he/she have concerns which have arisen from monitoring activities, and/or if there are problems with oversight/monitoring procedures.

8   TRAINING

The Chief Investigator will review and provide assurances of the training and experience of all research-relevant staff working within the Sponsor. All staff involved in the study will have up to date GCP and other training necessary for working in such a clinic.

9   APPENDICES

- CANPAIN clinical study protocol v7

Feasibility Protocol Appendix 1.

Clinical Trial Protocol

A PRAGMATIC NON-RANDOMISED, NON-BLINDED REAL WORLD TRIAL OF THE SAFETY, TOLERABILITY AND EFFECTIVENESS OF A CANNABIS BASED MEDICINAL PRODUCT (CBMP) FOR THE TREATMENT OF CHRONIC NON-CANCER PAIN COMPARED AGAINST MATCHED CONTROLS RECEIVING STANDARD OF CARE PAIN MANAGEMENT

Trial Name: CANPAIN Trial (Cannabis treatments for chronic pain)

Protocol Number: Chronic Pain 001

EudraCT number: 2019-003035-34

Principal Investigator: Dr Shahpoor Sorooshian MB, ChB, FFPM, DPM, DA, FRCA

> Harley Street (CPC) Limited,
> 76 Harley Street
> London, W1G 7HH
> United Kingdom

Sponsor: Harley Street (CPC) Limited

> 76 Harley Street
> London, W1G 7HH
> United Kingdom

GCP statement
This trial will be performed in compliance with Good Clinical Practice (GCP), the Declaration of Helsinki (with amendments) and local legal and regulatory requirements.

1.   SIGNATURES AND AGREEMENT WITH PROTOCOL

Principal Investigator: Dr Shahpoor Sorooshian

                                               MB, ChB, FFPM, DPM, DA,

                                               FRCA

                                               Harley Street (CPC) Limited,

                                               76 Harley Street
                                               London, W1G 7HH
                                               United Kingdom

                                               Date   Signature

Sponsor's representative: Gregory Stoloff

                                               London Bioscience Innovation Centre

                                               2 Royal College Street

                                               London, NW1 0NH

                                               Date   Signature

Trial title: A pragmatic non-randomised, non-blinded real world study of the safety, tolerability and effectiveness of a cannabis based medicinal product (CBMP) for the treatment of non-cancer chronic pain compared against matched controls receiving standard of care pain management.

We, the undersigned, agree to conduct this trial according to this Trial Protocol. We agree that the trial will be carried out in accordance with Good Clinical Practice (GCP), with the Declaration of Helsinki (with amendments) and with the laws and regulations of the countries in which the trial takes place.

TRIAL SYNOPSIS

Name of Sponsor:	Name of finished products:	Name of Active ingredients:
Harley Street (CPC) Limited	Cannabis based medicinal product comprising of: Cannabis flower blend (low and balanced; 8% THC, 8% CBD Vaporised and inhaled	Δ9-tetrahydrocannabinol (THC) Cannabidiol (CBD)

Title of trial	A pragmatic non-randomised, non-blinded real-world trial of the safety, tolerability and effectiveness of a cannabis based medicinal product (CBMP) for the treatment of chronic non-cancer pain compared against matched controls receiving standard of care pain management. (Protocol number: Chronic Pain 001; Trial Name: CANPAIN)
Coordinating Trial Centre	Harley Street (CPC) Limited
Duration of trial	3 years with a minimal planned sample size of 5000 participants who have completed at least 12 months of treatment with CBMP.
Objectives	To determine the safety and the effectiveness of a medical cannabis treatment for moderate to severe chronic non-cancer pain in a real world setting on pain numerical rating scores (NRS) scores, quality of life measures, sleep scores, personal wellbeing, global impression of change and changes in the dosing of concomitant analgesic treatments, compared with appropriate matched controls receiving opioids and/or other neuropathic pain relief. To determine the tolerability of a medical cannabis treatment in patients by assessing psychological morbidity such as anxiety and effects on gut function, and dizziness measurements.
Rationale	Medicinal cannabis has recently been re-categorised from Schedule 1 to Schedule 2 in the misuse of drugs regulations, meaning it is recognised to have medical applications and can now be prescribed to patients suffering from conditions where clinical evidence exists for its use. One of the conditions where the scientific literature contains evidence for the utility of medicinal cannabis is chronic non-cancer pain. Further data on effectiveness and tolerability is required and synthesis of this data is the main purpose of this study. Globally, three types of medical cannabis products are commonly used to treat chronic non-cancer pain. These products contain either a high, medium or low content of THC balanced by reciprocal ratios of CBD. We believe that the evidence base indicates that whole flower products with balanced THC and CBD content and levels of other phytochemicals unaffected by extraction, give the maximum levels of efficacy. However, more evidence is needed on the use of these forms of medical cannabis to assess efficacy and tolerability. In addition, data will be collected on the concomitant dosing of medications such as opioids and anti-neuropathic adjuvant analgesics, as part of a patient's standard of care, thereby enabling the impact of medicinal cannabis on the use of standard of care treatment to be assessed.

Design	This trial will be conducted in a single private health clinic, staffed by clinicians experienced in prescribing and managing the use of medicinal cannabis or who will be trained to do so. The trial will use established treatment protocols which originate from experienced healthcare practitioners working at established medical cannabis clinics in comparable healthcare environments to the UK. Participant's data will be collected as they are treated.
	The trial is an open-label, real-world study reporting on the treatment outcomes across a range of chronic non-cancer pain disorders.
	This is a prospective trial to determine the effects of medical cannabis ("Treatment") in chronic non-cancer pain subjects on:
	- Pain NRS - Quality of Life (QoL) - Sleep quality NRS - Anxiety NRS - Fatigue NRS - Nausea NRS - Depression NRS - Shortness of breath NRS - Dizziness (NRS) - Appetite (NRS) - Global Impression of Change (since commencing treatment) - Personal Wellbeing Score (NRS) - Changes in concomitant analgesic medication use
	and to assess the safety and tolerability of adding medicinal cannabis to the subject's standard of care.
Planned number of participants	Planned sample size of 5000 participants.
Enrolment criteria	**Inclusion criteria** 1. Male or female 18-85 years old; 2. Diagnosed with chronic non-cancer pain and; 3. A consented patient at the Harley Street (CPC) clinic 4. Is receiving standard of care therapy with inadequate response or has completed standard of care treatment, does not want standard of care treatment, or standard of care is contraindicated. An inadequate response is defined as the subject receiving standard analgesic agents and still has pain, has unpleasant side effects or wishes to reduce their intake of standard of care analgesic agents, e.g. a subject receiving opioids who wishes to dose reduce in light of the "opioid

	crisis".”
	4. Despite being on or having standard of care and still has pain (>3 on the Pain NRS); and
	5. Signed and dated written informed consent from the subject.
	Exclusion criteria
	1. Pregnant or lactating females or females who are planning a pregnancy during the study;
	2. Positive pregnancy test at screening;
	3. Major organ failure, renal, lung and liver failure;
	4. Participants having active liver disease or unexplained persistent elevation of serum transaminases > 3 times the upper limit of normal;
	5. Participants with a creatinine clearance < 60mL/min;
	6. History of cardiac or respiratory failure;
	7. History of recent myocardial infarction or poorly controlled ischaemic heart disease;
	8. Severe respiratory disease (e.g., GOLD 3 for COPD or asthmatics requiring high doses of oral corticosteroids).
	9. History or presence of alcohol or substance abuse, including analgesics used as standard of care.
	10. Participation in a clinical trial of an investigational medicinal product;
	11. With any known or suspected history or family history of schizophrenia, or other psychotic illness; history of severe personality disorder or other significant psychiatric disorder disorders other than depression associated with their underlying condition.
	12. Known hypersensitivity to cannabis or allergy to cannabis or CBMP and
	13. Direct employee of the study site.
Test product, dosage and mode of administration	The treatment regimen is as follows. In addition to standard of care management provided by their regular health care practitioner, participants will receive defined doses of inhaled CBMP namely Equipose 8-8 with a balanced ratio of THC and CBD as a dried cannabis flower. **Inhaled delivery** Cannabis flower containing mid and balanced levels of THC and CBD (Equipose 8-8), will be vaporised using a CE marked, handheld device with dose counting and Bluetooth connectivity to a smart device (Ryah). Dosing will be recorded by the study participant entering their data into the ePRO data collection system through an application on their mobile phone. Participants will receive prompts to enter data and must do so to continue in the study.

Duration of treatment	3 years
Crieria for evaluation (Outcome variables)	**Effectiveness:** Primary variables (comparable to matched controls): • Pain scores (NRS) summated and by pain types. Secondary variables (not comparable to matched controls): • Quality of life scores; 12 item short form health survey (SF-12), summated and by pain type • Sleep quality scores (NRS) • Anxiety (NRS) • Depression (NRS) • Fatigue (NRS) • Appetite (NRS) • Nausea NRS • Wellbeing score (NRS) • Global impression of change • Concomitant use of pain medications (doses per subject per week), summated and by pain type. In the case of opioids daily opioid uptake will be converted to morphine equivalent daily dose (MEDD) **Safety and tolerability** Daily analysis of THC specific effects: • Anxiety (NRS), • Drowsiness (NRS) • Dizziness (NRS) • Shortness of breath (NRS) • Adverse events reported
Statistical considerations	Tabulations will be produced for appropriate effectiveness and safety parameters. For categorical variables, summary tabulations of the number and percentage of participants within each category (with a category for missing data where applicable) of the parameter will be presented. For continuous variables, the number of participants, mean, standard deviation (SD), median, minimum, and maximum values will be presented. Statistics may be presented for cohorts of interest (e.g. by subtypes of chronic pain) if sample size permits. Inferential statistical methods will only be employed to highlight data of interest. Any p-values will be interpreted descriptively, and 95% confidence intervals (CIs) will be presented as appropriate. The analysis of effectiveness will be controlled by comparison with matched controls identified from a database of comparable subjects with chronic non-malignant pain. In order to reduce bias and to balance the distribution of covariates in the treated and control groups, multiple regression analysis will be used, adjusting for potential confounders. Matching methods such as propensity scoring methods may also be used.

| | Statistical analysis, data listings, graphs and summary tables will be produced using SAS®, version 9.2 or above.

Full details, including the use of the matched control database(s), of the interim and final statistical analyses to be performed will be described in detail in the Statistical Analysis Plan (SAP). |

Table 1-1: Schedule of Assessments

	Initiation visit Day 0 (Baseline)	Daily data collection	Weekly data collection	Monthly data collection	Follow up visits (every 3 months[a])
Pre-read of patient information sheet and informed consent document	X				
Written Informed Consent	X				
Check of inclusion/exclusion criteria	X				
Demographic data	X				
Medical history	X				X
Standard of care medication (number of doses given in previous period of time)	X		X		X
Site of pain reported in NRS	X		X		X
Additional efficacy assessments			X		
Quality of life score	X				X
Blood reports[b]	X				X
Genetic test for cannabis tolerance validation study	X				
Continuous cannabis intolerance assessments: red flags		X			X
Overall assessment of efficacy and tolerability			X		X
Scan or additional tests [b]	X				X
Determination of state of disease	X				X
Adverse events	X	X	X		X
Prescription and treatment regimen compliance	X		X		X

a. Follow-up visit can be done in person or over the phone.
   If available.

2.   TABLE OF CONTENTS

<u>**Appendices:**</u>

1. Declaration of Helsinki

2. List of names and addresses

3. Summary of Concomitant Medicine Restrictions

3. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

3.1 List of Abbreviations

2-AG	2-arachidonoylglycerol
ADT	Abstract Data Type
AE	Adverse Event
AERS	Adverse Effects Reporting System
aHR	adjusted Hazard Ratio
CA	Competent Authority
CB1	Cannabinoid receptor type 1
CB1A	Cannabinoid receptor type 1A
CB2	Cannabinoid receptor type 2
CB2A	Cannabinoid receptor type 2A
CBC	Cannabichromene
CBD	Cannabidiol
CBDV	Cannabidivarin
CBG	Cannabigerol
CBGV	Cannabigerivarin
CBMP	Cannabis based medicinal product
CBN	Cannabinol
CCI	Chronic Constriction Injury
CD4	Cluster of differentiation 4
CD8	Cluster of differentiation 8
CFA	Complete Freund's Adjuvant
CI	Confidence interval
CINV	Chemotherapy Induced Nausea and Vomiting
CNS	Central Nervous System
COMT	Catechol-O-Methyltransferase
CPC	Care Pain Clinic
CRF	Case Report Form
CUD	Cannabis use disorder
CXCR4	C-X-C chemokine receptor type 4
CYP1A2	Cytochrome P450 1A2
CYP3A4	Cytochrome P450 3A4
CYP2B6	Cytochrome P450 2B6
CYP2C9	Cytochrome P450 2C9
CYP2C19	Cytochrome P450 2C19
ECS	Endocannabinoid system

ePRO	electronic Patient Reported Outcome
ERK1/2	Extracellular signal–regulated kinases 1/
GCP	Good Clinical Practice
GMC	General Medical Council
GPCR	G protein coupled receptor
HHV	Healthy Human Volunteer
HIV	Human Immunodeficiency Virus
IBD	Inflammatory Bowel Disease
IGSoC	Information Governance Statement of Compliance
IL-1β	Interleukin-1beta
IL-6	Interleukin-6
ITT	Intention to Treat
LAR	Legally Authorized Representative
MAPK	Mitogen-activated protein kinase
MDI	Meter Doses Inhalers
MEDD	Morphine equivalent daily dose
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Health Products Regulatory Agency
mmHg	millimetres of mercury
NK	Natural Killer
NRS	Numerical Rating Scale
OUD	Opioid Use Disorder
PEA	Palmitoylethanolamide
PGIC	Patient's Global Impression of Change
PNL	Partial Sciatic Nerve Ligation
PP	Per Protocol
PPAR	Peroxisome Proliferator Activating Receptor
PPARγ	Peroxisome Proliferator Activating Receptor Gamma
PRN	Pro Re Nata
PT	Preferred Term
QoL	Quality of Life
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAEs	Serious Adverse Effects
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System (Software)

SD	Standard Deviation
SF-12	12 item short form health survey
SNL	Spinal Nerve Ligation
SOC	System Organ Class
SOP	Standard Operating Procedure
SSL	Secure Socket Layer
SUSARs	Suspected Unrelated Serious Adverse Reactions
THC	Δ9-tetrahydrocannabinol
THC-acid	2-COOH-Δ9-tetrahydrocannabinol
THCV	Tetrahydrocannabivarin
TNFα	Tumour Necrosis Factor alpha
TRPM8	Transient receptor potential cation channel subfamily M member 8
TRPV1	Transient receptor potential cation channel subfamily V member 1
UV	Ultraviolet
WMA	World Medical Association

3.1   Definitions of terms

Treatment regimen:	All participants will be given the same regimen for each chronic pain disease outlined in this protocol.
Abstinence:	Refraining from heterosexual intercourse during the entire period of risk associated with the study treatments
Acceptable contraception methods:	Birth control methods which may be considered as highly effective, achieving a failure rate of less than 1% per year when used consistently and correctly, include: Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[1] (oral, intravaginal, transdermal). Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable[2]). Intrauterine device (IUD)[2]. Intrauterine hormone-releasing system (IUS)[2]. Bilateral tubal occlusion[2]. Vasectomised partner[2,3]. Sexual abstinence[4]. Acceptable contraception method but may not be as highly effective, that result in a failure rate of more than 1% per year include: Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action. Male or female condom with or without spermicide[5]. Cap, diaphragm, or sponge with spermicide[5]. [1] Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method. [2] Contraception methods that in the context of this guidance are considered to have low user dependency. [3] Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the trial participant and that the vasectomised partner has received medical assessment of the surgical success. [4] In the context of this guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject. [5] A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are also considered acceptable but not highly effective, birth control methods
Unacceptable contraception methods:	Periodic abstinence (calendar, sympothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception. Female condom and male condom should not be used together.
Women of child bearing potential:	For the purpose of this document, a woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
End of the trial:	The length of the trial for each participant is a maximum of 3 years.

4.   INTRODUCTION

4.1   Background of the trial

On the 1st of November 2018 the Home Office in response to guidance from the Chief Medical Officer and the Department of Health, announced that cannabis-based products for medicinal use were to be moved from Schedule 1 to Schedule 2 status in the misuse of drugs regulations, reflecting the view that these agents possess medical utility.

Due to its unlicensed status, medical cannabis must be prescribed in clinical practice through a 'Specials License' and prescribing must remain wholly under the control of a GMC registered Specialist, who have been made responsible for determining who is eligible to receive medical cannabis, satisfying two predetermined criteria: 1) that unmet clinical need exists and that there must be enough evidence that the subject would receive benefit, and 2) the subject must have exhausted all other established treatment options. Specialists should possess the correct knowledge to determine whether all established treatment options have been exhausted or inappropriate. However, in addition to this, most specialists will need training on the evidence base and the current clinical approach to the use of medicinal cannabis.

Cannabis derives from two main strains of plant; *Cannabis Sativa* and *Cannabis Indica*. Over the last 50 years, these strains have been repeatedly cross bred to create many new varieties and hybrids each with unique chemical compositions. Chemically, cannabis strains are immensely complex, with cannabinoids and other phytochemicals, making up a large array of biologically active compounds all with potential clinical utility. Most of the cannabis research has focused on cannabinoids, of which almost 200 have so far been identified (Hanus et al., 2016). Eight of these cannabinoids are thought to be responsible for most of the effects of medicinal cannabis and so are routinely measured (Aizpurua-Olaizola et al., 2016). There is now acceptance that cannabis has demonstrable medical utility, at varying levels of evidence quality, in conditions including chronic pain, multiple sclerosis, anxiety, depression, sleep disorders, inflammatory bowel disease (IBD) and epilepsy (Barnes and Barnes, 2016). However, due to the plant's chemical complexity it is difficult to fully define which chemicals contribute to the pharmacology of cannabis. Much scientific work is underway to elucidate this.

Cannabinoids are synthesised by the plant in a carboxylic acid form, for example THC exists as THC-acid. To exert a pharmacological effect, carboxylic acids require conversion to their decarboxylated forms through either heat or light (Wang et al., 2016). The literature indicates that THC and CBD are of primary importance in eliciting the clinical effects of medical cannabis. There is substantial peer-reviewed evidence which supports the utility of medical cannabis. The evidence for some of its individual constituents (primarily THC and CBD) for treating diseases and their symptoms, will be outlined in detail.

Cannabis flower, hashish and whole plant extracts currently predominate in medical cannabis therapy, although the production of isolated cannabinoids is currently being investigated through chemical and biotechnology routes of synthesis. Current products are derived from strains of cannabis which produce, in the flower, high concentrations of the eight major cannabinoids in varying ratios and amounts (see table 1). The two cannabinoids that are predominantly focused on, due to their relative abundance and complimentary pharmacological profiles are THC and CBD.

It is essential that CBMPs are safe and reliable pharmaceutical grade products and must be produced to good manufacturing practice (GMP) standard. To satisfy these requirements, CBMPs are tested to confirm that they are derived from a cannabis plant and that it contains the principle

active ingredients, listed in the product's predefined specification. CBMPs may require gamma irradiation to sterilize them and are tested for the presence of microorganisms harmful to health. Additionally, CBMPs are tested for the presence of pesticides, heavy metals and must be free of these harmful substances as well as contaminants such as soil. The total water content must be below a predefined specification to ensure it is suitable for vaporisation.

The inhaled route of delivery is the most controllable and predictable route of delivery for the administration of CBMPs. Heating a 250 mg sachet of CBMP in the medical grade vaporisers produces vapor which contains consistent quantities of active phytochemicals, is quickly absorbed with rapid onset of action. The rapid kinetics allow a faster dose titration, enabling the correct dose to be achieved while minimising side effects. Importantly, vaporised CBMP produces blood levels of active ingredients, principally THC and CBD, with a relatively short duration of activity (up to 1 hour), which reduces the risk of a long-lasting side effects, of importance if the subject receives an accidental overdose. This is a distinct advantage over other routes of deliverysuch as oral and sublingual which have substantially longer durations of activity (6 to 8 hours).

Table 1) List of eight major cannabinoids found in medical cannabis in their active decarboxylated forms

Name (abbreviation)	Structure
(−)trans-Δ^9-tetrahydrocannabinol (THC)	
Cannabidiol (CBD)	
CBG	
CBN	
CBC	
THCV	
CBDV	
CBGV	

In cannabis, alongside cannabinoids, there are 11 major terpenes (*a*-pinene, *β*-pinene, *β*-myrcene, limonene, terpinolene, linalool, *a*-terpineol, *β*-caryophyllene, *a*-humulene, and caryophyllene oxide) (Ibrahim et al., 2019). It is thought these compounds in various concentrations interact with cannabinoids to produce the variety of medicinal effects found in the cannabis strains used by medicinal cannabis patients (Russo, 2011), through the entourage effect.

There are strains that produce high levels of THC and low levels of CBD, strains that have the opposite profile and strains that are balanced. The medical cannabis community describe products in terms of their THC and CBD content:

1) High THC (>10 %) / low CBD (<3 %)

2) Mid THC / mid CBD (balanced THC to CBD, at approximately 10 %)

3) Low THC (<3 %) / high CBD (>10 %).

The safety profile of cannabis has been extensively studied revealing that the majority of adverse events are attributable to one of its constituents, THC. THC induces acute adverse effects such as anxiety and chronic effects such as increased risk of psychosis and addiction/dependence (D'Souza et al., 2004; Zehra et al., 2018). The acute effects are largely avoidable if either the dose is kept low (<3 mg per day) or the cannabis extract has enough CBD to counteract THC- induced anxiety (MacCallum and Russo, 2018). The risk of long-term psychoses and depression is substantially reduced if the cannabis is not used during adolescence (Gobbi et al., 2019).
The addiction potential of cannabis has also been well studied and in susceptible individuals, chronic dosing of very high THC strains of cannabis can lead to addictive behaviour (termed cannabis misuse disorder). To minimise risk, it is essential to; 1) restrict access by the paediatric patient population, 2) ensure that starting doses are kept low, particularly for THC high products, 3) use balanced THC: CBD cannabis products and 4) monitor the quantity of medicinal cannabis consumed to ensure excessive consumption is limited.

These strategies are designed to limit the risk of addictive behaviour and psychoses in susceptible individuals. Whilst there is evidence that THC has health benefits, certain individuals have increased risk of acute anxiety and dependence with chronic use. There is emerging pharmacogenetic evidence for determinants of susceptibility for THC-induced anxiety. Polymorphisms in effector, metabolism and ancillary genes effect how individuals respond to THC exposure. CB1 receptor genes are the most widely studied, but other genes controlling metabolism such as CYP3A4 and COMT are also implicated (Hyrhorowicz et al., 2018). As well as complementing the benefits of THC, CBD counteracts THC induced adverse events such as anxiety in susceptible individuals (Russo, 2011). Patients using THC, require a THC/CBD ratio that provides the right pharmacological effect, while minimising that individual's risk of THC induced psychological morbidity.

CBD when given without THC, need to be given in high doses to achieve a therapeutic effect (300 mg to 1000 mg per day), and when used on its own it is associated with adverse events such as somnolence, GI upset and the more serious but rarer adverse event of raised liver enzymes (Stockings et al., 2018).

Whilst it is very important to address the addiction potential of medicinal cannabis, it is also important to emphasise that the risks associated with cannabis are comparatively lower than other analgesics utilised in chronic pain conditions, namely opioids and other anti-neuropathic agents. Medicinal cannabis is now considered to be a potential adjunct to opioid based analgesia, boosting opioid efficacy and there is evidence that the addition of medicinal cannabis lowers the dose and time required to reach analgesia for opioids, reducing dose burden and moving patients away from opioid use disorder (OUD) (Wiese and Wilson-Poe, 2018).

The pharmacokinetics of CBD and THC have been thoroughly described (Sativex product monograph). THC and CBD are both absorbed and metabolized in a similar manner. They have poor oral bioavailability (around 6%), are both widely distributed into lipid tissues due to their highly lipophilic physicochemical properties and also demonstrate high protein binding (~97%). They are both primarily metabolised by cytochrome P450 enzymes (CYP3A4, 1A2, 2B6, 2C9 and 2C19), with relatively short initial half-life of about 5 hours but a long terminal half-life of between

24 and 36 hours. The primary differences that exist for medicinal cannabis products are the route of delivery. Inhaled cannabis is rapidly absorbed (Tmax= ~10 minutes) and has a relatively rapid initial half-life (1 to 2 hours), while cannabis ingested through the oral route has a much-delayed absorption kinetic (Tmax= 1 to 2 hours) and importantly higher levels of the high potency psychoactive metabolite 11-OH-THC are present after oral absorption (Sharma et al., 2012), which increases the risk of this route of delivery for THC sensitive individuals.

The aim of our clinical study is to provide cannabis based medical product in the form of cannabis flower with mid-levels of THC (8%) balanced by 8% CBD given to subjects with an unmet clinical need through a single route of delivery (vaporised; inhaled) under the medical guidance for a GMC registered specialist clinician. We will collect data from subjects receiving medicinal cannabis therapy; assessing how participants respond, how well they tolerate it and their patterns of use. Data will be collected via connected devices and validated ePRO tools. In addition, data regarding side effects will be collected and reported in a timely manner.

4.1.1 Medical cannabis

Mechanism

Cannabinoids sourced from the cannabis plant (phytocannabinoids) are known to interact with endogenous cannabinoid receptors which is thought to be their principle mechanism of action (Ligresti et al., 2016). In 1990 Matsuda's group first described a cannabinoid receptor found in several species including human, which was named the CB1 receptor. Subsequently the cannabinoid receptors have been shown to possess an additional subtype, the CB2 receptor (Munro et al., 1993).

Although the effects of phytocannabinoids are attributable to the cannabinoid receptors, it is only recently that the endogenous ligands to the CB1 and CB2 receptors have been elucidated (Di Marzo et al., 1999). Endogenous ligands are lipid membrane derived molecules consisting of arachidonic acid derived 2-arachidonoylglycerol (2-AG) and anandamide (Lu and Mackie, 2016). 2-AG is thought to be the primary endocannabinoid with full agonism at the CB1 and CB2 receptors, while anandamide acts as a partial agonist at the same receptors. There are other endocannabinoids which are thought to act through potentiating the CB1 and CB2 effects of endocannabinoids. For example, palmitoylethanolamide (PEA) which acts through PPARα agonism (Verme et al., 2005) and interactions with cannabinoid like G protein coupled receptors (Kramar et al., 2017). The endocannabinoid system (ECS) has a wide-ranging series of physiological functions which are only now being understood but includes the modulation of pain perception, appetite, immune function and the level of general neural activity within the brain and the peripheral nervous system with implications in autonomic function, sleep and cognitive function (Pacher and Kunos, 2013).

There is good evidence of increased ECS activity when the brain is exposed to environmental stress (Morena et al., 2016), which is likely to provide a protective function for the brain. An imbalanced ECS contributes to pathological processes associated with stress such as anxiety and depression and that modulation of the ECS with cannabinoids will affect that stress response (Hillard, 2014) and pain states (Woodhams et al., 2015). If the right cannabinoids are utilised in the right doses then a rebalance of the ECS system could be achieved, but over stimulation can be problematic and requires careful consideration. This will be achieved by up-titrating the dose of the CBMP provided to the subject via the vaporizing device from one dose to two doses per day, depending on response and tolerability to treatment.

CB1 receptors

CB1 receptors are found throughout the central nervous system (CNS) (Mackie, 2005), in the peripheral and autonomic nervous system (Vianna et al., 2012), in the immune system (Galiegue et al., 1995), reproductive system (Correa et al., 2016) and in the gastrointestinal tract (Pertwee, 2001). They are lower receptor densities in the bladder (Walczak and Cervero, 2011), heart (Montecucco and Marzo, 2012) and lung (Makwana et al., 2015). The CB1 receptor is a G protein

coupled receptor (GPCR) which acts as an effector protein for a retrograde signalling system which modulates both inhibitory (GABAergic) and excitatory presynaptic neurones (glutamatergic) (Busquets-Garcia, et al., 2018). When stimulated, CB1 receptors interact with Gi/o proteins to inhibit adenylyl cyclase, activate mitogen-activated protein kinases (MAPK), inhibit voltage-gated Ca^{2+} channels, activate K^+ currents, and influence Nitric Oxide signalling (Howlett et al., 2010). This decreases presynaptic membrane potential, decreasing the likelihood of the transmitter release and postsynaptic signalling (Dasgupta et al., 2017).

The CB1 receptor has specific presynaptic signalling characteristics, dependent on the presynaptic neuron, on which it is located, and to what ancillary proteins and structures it is associated. The receptor exists as either monomers, homo-dimers or hetero-dimers with a wide variety of GPCR receptors from dopamine to chemokine receptors (Busquets-Garcia et al., 2018). This gives the CB1 receptor flexibility in response to interactions by endocannabinoids and phytocannabinoids. The precise mechanism by which this flexibility is managed has yet to be elucidated but the functional effects of cannabinoids are well defined, through extensive human use of cannabis and the expanding medical literature. CB1 activation induces analgesia in preclinical and clinical models of pain, which has translated through to good evidence in chronic non-cancer pain clinical studies.

Phytocannabinoid ligands at the CB1 receptor include: THC (partial agonist), CBD (inverse agonist), THCV (antagonist). The endocannabinoid 2-AG is a full agonist.

CB2 receptors

CB2 receptors are found predominantly in the periphery, primarily associated with immune cells and immune tissue, including the thymus, tonsils, B lymphocytes, T lymphocytes, macrophages, monocytes, natural killer (NK) cells, and polymorphonuclear cells (Cabral and Griffin-Thomas, 2009). They are also present on microglia in the CNS (Cassano et al., 2017) and in the reproductive system (Battista et al., 2015). First cloned by Munro et al., 1993, from the promyelocytic cell line (HL60). Like the CB1 receptor, the CB2 receptor is a GPCR protein, but it primarily couples to Gi/o proteins modulating adenylyl cyclase and extracellular signal–regulated kinases 1/2 (ERK1/2) to produce largely immune related cellular effects (Dhopeshwarkar and Mackie, 2014). These effects are the same as those seen during immune cell phenotype changes induced by inflammation derived mononuclear cell activation (M1) and subsequent repair (M2) (Askari and Shafiee-Nick, 2019). Ranking of CB2 expression levels in immune cell populations is as follows: B cells > NK cells > macrophages > polymorphonuclear cells > CD8 T cells > CD4 T cells (Malfitano et al., 2014). Importantly this indicates that CB2 receptor signalling does not affect T-lymphocyte function but primarily B cells and NK cells and macrophages. CB2 receptors, like their CB1 isoform, are likely to exists as homo and heterodimers giving them the same large potential varieties of responses to ligand interaction, this has now been reported for the CXCR4 receptor (Scarlett et al., 2018). Two isoforms of the CB2 receptor exist; CB2A and CB2B (Liu et al., 2009). CB2A is found in high concentration within the testis and the brain (microglia), while CB2B has high amount in other peripheral tissues. CB2 receptors are implicated in the pathogenesis of peripheral inflammatory disease, such as rheumatoid arthritis (Ismail and Khawaja, 2018) and Crohn's disease (Leinwand et al., 2017). Endogenous signalling at the CB2 receptor fine tunes the innate and cellular immune response to pathogens (McCoy, 2016). They are upregulated in neuroinflammatory disorders and so are also implicated in the pathogenesis of CNS inflammatory disorders such as Alzheimer's, depression and Parkinson's (Cassano et al., 2017).

Ligands at the CB2 receptor include; THC (partial agonist), CBD (inverse agonist), β-caryophyllene (full agonist), anandamide (partial agonist) and 2-AG (full agonist), which is thought to be the endogenous ligand for the CB2 receptor.

CB2 receptor activation is an effective mechanism for inhibiting pro-inflammatory mechanisms in a variety of inflammatory systems (Kapellos et al., 2019), translating into an extensive preclinical evidence base in inflammatory models of disease and expanding clinical evidence base for inflammatory diseases, particularly in inflammatory pain.

Orphan receptors: GPR18 and GPR55

A novel synthetic cannabinoid (abnormal cannabidiol) has elicited the discovery of possible new cannabinoid receptor; GPR18. In rats, abnormal cannabidiol stimulates this G protein coupled receptor to lower blood pressures not interacting with CB1 or CB2 (Penumarti and Abdel-Rahman, 2014). GPRE18 has been identified primarily in CNS tissue. GPR55 has seven conserved transmembrane sequences and has been shown to be activated by exogenous cannabinoids such as THC, CBD, and by the endogenous cannabinoids, anandamide and 2-AG (Schicho and Storr, 2012). GPR55 is not activated by the synthetic CB1/CB2 agonist WIN55212-2 and is coupled to a G-alpha (Gα) protein, increasing intracellular calcium when stimulated. GPR55 expression has been identified in a variety of tissues including spleen, gastrointestinal and brain. The physiological and pharmacological functional relevance of GPR18 and GPR55 is not yet understood, but it is proposed that once they are fully characterised, they may be defined as additional cannabinoid receptors.

Peroxisome proliferator-activated receptors (PPAR)

Cannabinoids modulate the PPAR system. The best evidence exists for PPARγ where THC, CBD, CBG and CBC bind and stimulate transcription of this nuclear receptor (O'Sullivan, 2016). It is widely recognised that PPARγ is a very important system controlling immune and inflammatory processes and hence this is an important mechanism for the cannabinoids to interact with and likely to be one of the key mechanisms responsible for the pleotropic anti- inflammatory effects of the cannabinoids contained within medicinal cannabis,

Transient Receptor Potential Vanilloid 1 (TRPV1)

CBD stimulates the TRPV1 receptor (De Petrocellis et al., 2011), which has been shown to contribute to its anti-inflammatory properties which are blocked by a TRPV1 antagonist (Costa et al., 2004). It has been demonstrated that the TRPV1 receptor is an important effector target for the endogenous cannabinoids such as PEA and that the TRPV1 and CB1 receptor co-localisation on peripheral sensory neurons (Chen et al., 2016) which suggest that the effects of THC may have an indirect interaction with TPRV1 sgnalling.

Sodium channel blocking

CBD blocks voltage gated sodium channels (Ghovanloo et al., 2018) which are a pharmacological target for pain.

Medicinal cannabis

Phytocannabinoids; Human Data in chronic non-cancer pain

A high dose of cannabis derived THC (50 mg per day) markedly reduced opioid consumption when used during the day of a Flare of Mediterranean Familial Fever (Holdcroft et al., 1997), which supports the opioid sparing effect of medicinal cannabis. In a human healthy volunteer study (Wallace et al., 2007) used low doses of smoked cannabis to effectively treat a capsaicin (TRPV1) induced model of pain. Interestingly, high doses exacerbated the capsaicin induced pain indicating that high doses stimulate TRPV1 receptors. Abrams et al., 2007 assessed the effects of smoked cannabis (3.56% THC) given as required in HIV sensory neuropathy patients, utilising an RCT design with 50 patients treated for 5 days and established efficacy in treating pain. Subsequently, Kraft et al. (2008) using a single oral dose of whole spectrum extract of THC (20 mg) showed no analgesia in human pain model (sun burn), indicating that UV initiated pain is not responsive to cannabis therapy, although only female HHV were studied. Single dose design studies suggest that acute dosing of medicinal cannabis is not effective. In an early RCT looking at all comer users of medicinal cannabis and selecting their primary symptom. Wilsey et al., (2008) produced a positive dataset with smoked cannabis decreasing neuropathic pain symptoms.
In a well conducted cross over design RCT, Ellis et al., (2009) provided HIV patients with neuropathic pain cannabis cigarettes which were titrated up to a potential maximum dose of 8% THC (127 subjects). In these patients, neuropathic pain scores were decreased after 5 days of

treatment (one cannabis cigarette three times a day), indicating that 5 days is a sufficient dosing period to produce analgesia.

Ware et al., (2010), dosed neuropathic pain patients with 25 mg of cannabis with 9.6% THC, three times a day combusted in a pipe, which was effective at treating pain and improving sleep quality. In a similar study, low dose vaporized cannabis was used to effectively treat pain and related symptoms in neuropathic pain patients (Wilsey et al., 2013). The same group (Wilsey et al., 2016) looked at low (2.9 %) and high (6.7%) doses of vaporized cannabis versus placebo in spinal cord injury patients. Both doses were equivalent but highly effective in treating pain and neuropathy. Finally, Wallace et al., (2015), provided 7% THC cannabis flower in a placebo-controlled cross over design study in diabetic neuropathy patients, producing robust evidence that this treatment is effective in reducing pain scores in this patient population.

There are a number of studies underway which are investigating the use of medicinal cannabis in the control of non-cancer chronic pain and whose publication will add to this evidence base in the coming months and years (clinicaltrials.gov).

Opioid sparing effects

Cannabinoid and opioid receptors are expressed in several brain regions involved in the regulation of pain and have been shown to co-localise (be expressed next to each other on the cell membrane). Numerous animal studies have now shown that there is a synergistic effect from opioid and cannabinoid co-administration (Neilsen et al., 2017). The effect of medicinal cannabis on the use of opioids in the chronic pain population has been reviewed (Campbell et al., 2018). A more recent study from Michigan published in 2019 showed that approximately 80% of 1,321 chronic pain patients reported substituting cannabis for traditional pain medications (53% for opioids, 22% for benzodiazepines), citing fewer side effects and better symptom management as their rationale for doing so (Boehnke et al., 2019). Data from Canada published in 2019 also suggests that patients report they are using less opioids and other analgesic drugs, alcohol, tobacco, and illicit substances (Lucas et al., 2019). There is evidence that cannabis increases the efficacy of opioid therapy and can reduce the opioid dose burden.

More evidence is needed to fully establish the opioid sparing effects of CBMP.

Animal studies in chronic non-cancer pain

In the chronic constrictive injury (CCI) model of neuropathic pain, a full spectrum phytocannabinoid (THC, CBD and terpenes) extract from cannabis produced substantial effects in inhibiting pain behaviour. The authors suggested that CBD acting through TRPV1 produced the pharmacodynamic effect (Comelli et al.,2008).

4.1.2   THC

What is THC?

THC is a single entity cannabinoid with a history of clinical use as a licensed product, outside of chronic non-cancer pain. THC has been registered for use in chemotherapy induced nausea and vomiting (CINV) under the proprietary name dronabinol. Dronabinol is the drug product that has been utilised when evaluating the effects of THC in chronic non-cancer pain.

Mechanism

THC acts via the CB1 and CB2 receptors, as full and partial agonists, respectively.

Synthetic THC Human Data in chronic non-cancer pain

In a heterogenous chronic pain population the dosing of oral THC (titrated up to 9 mg per day) produced no change in pain scores compared with placebo group, after 52 days of dosing. However, in this study there was an imbalance in baseline pain scores between THC and placebo groups, which was a clear confound to this result (de Vries et al., 2017). In healthy human volunteer (HHV) pain models, THC had no effect on heat, cold or electric stimulated pain

challenge (Naef et al.,2003), which strongly indicates that THC is not a substance that performs well in HHV pain models. These studies although limited in number, suggest that purified THC may not be as effective as THC as part of a full spectrum cannabis extract for the treatment of chronic non-cancer pain. Although, when THC was used as an adjunct therapy to potentiate the effects of opioid analgesia it was significantly effective (Narang et al., 2009), suggesting that THC could be useful in this regard.

Animal studies in chronic pain
Neuropathic pain models

The analgesic effects of THC have been known in a chronic constriction injury (CCI) model of neuropathic pain for over a decade. It has been demonstrated that, alongside several other neuropathic pain agents, to be effective at controlling both mechanical and thermal hyperalgesia at doses of 3 and 6 mg/kg (po) respectively (De Vry et al., 2004). In the Freund's adjuvant arthritis model, which is inflammatory and chronic in nature, THC was shown to be active in inhibiting pain behaviour in rats, which was CB1 driven but also involved an endogenous opioid pathway. In this study, synergy was found between THC and morphine and there was evidence that morphine tolerance was reduced (Cox et al., 2007a), interestingly this effect in a related study was attributed to CB2 stimulation, supporting an anti-inflammatory, immunomodulatory role for THC in chronic pain (Cox et al., 2007b). THC has been shown to be synergistic in its activity in the CCI model when combined with gabapentin, suggesting that the addition of THC to current standards of care for neuropathic pain warrants further investigation (Atwal et al., 2019).

4.1.3 CBD

Mechanism

CBD acts as a CB1 and CB2 receptor inverse agonist (Thomas et al, 2007). The CB1 inverse agonism is responsible for the inhibitory effects of CBD against THC mediated anxiety events in susceptible individuals. CBD is also known to agonise PPARγ, and TRPV1 while inhibit voltage gated sodium channels (Morales et al., 2017; Gaston and Friedman, 2017), all of which are mechanisms associated with the treatment of inflammation and pain.

Synthetic CBD Human data in chronic non-cancer pain

CBD is a component of nabiximols and found in some strains of cannabis flower. CBD as a component of nabiximols (Sativex) has been studied in chronic pain, with good levels of evidence (Nurmikko et al., 2007; Berman et al., 2004). However, no clinical studies of CBD have been conducted as a single agent which investigate its effects in chronic pain. It is apparent that these studies should be undertaken, however due to a lack of supporting evidence, CBD alone must be used with caution in chronic pain patients.

Preclinical data in chronic non-cancer pain

Although there is little clinical evidence, CBD has been shown to have clear effects in several animal models of chronic pain. There is evidence for efficacy in streptozocin induced neuropathic pain (Jesus et al., 2019) and neuropathy (De Gregorio et al., 2019; Li et al., 2018). CBD has been shown to reverse opioid-induced tolerance in an inflammatory pain model (Rodriguez-Munoz et al., 2018). It also strongly inhibits pain in sodium iodoacetate induced osteoarthritis in a neuroprotective manner (Philpott et al., 2017), CBD is also effective in Freund's induced arthritic pain (a rheumatoid arthritis model) (Hammell et al., 2016). Although not chronic in nature, CBD has shown to be effective in animal models of acute pain such as post-incisional pain (Genaro et al., 2017).

THC: CBD (Nabiximols)

Nabiximols is a purified THC and CBD oromucosal spray that has a license for use as a treatment for multiple sclerosis induced spasticity. It has been studied extensively in chronic non-cancer pain but has not received a license in the UK for that use.

Nabiximols; Human data in chronic non-cancer pain

In a homogenous population experiencing severe neuropathic pain (Brachial plexus avulsion), nabiximols administered in conjunction with standard of care over a 2-week period, was shown to have a small but highly significant effect on pain score when compared to placebo (Berman et al., 2004). In a similar study which investigated neuropathic pain patients with allodynia, nabiximols added to standard of care had a small but highly significant effects on pain scores, sleep and allodynia scores, when compared to placebo when dosed over a 5-week period (Nurmikko et al., 2007). In an open label study nabiximols was found to be effective and maintained its effectiveness over a 9-month period in neuropathic pain patients, with good tolerability (Hoggart et al., 2015). In a 15-week study nabiximols was administered to peripheral neuropathic pain patients with clinically significant decreases in pain versus placebo, suggesting that the longer-term treatment of medicinal cannabis provides better treatment effects.

Preclinical data in chronic non-cancer pain

In animal studies of pain (paw withdrawal and paw pressure tests), CBD modulates the acute analgesic properties of THC (van de Donk et al., 2019). In a CCI model of neuropathic pain, low doses of THC and CBD were effective at inhibiting pain behaviours, whilst higher doses were less effective but had clear effects against allodynia (Casey et al., 2017), demonstrating highly synergistic effects in combinations versus THC and CBD used in isolation.

4.1.4 Terpenoids and Terpenes

Mechanism of action

β-caryophyllene is a full agonist at the CB2 receptor. The precise mechanisms of action for the other terpenoids is not known. However, they have a wide range of functional effects such as sedation (e.g. β-myrcene), anxiolysis (e.g. limonene) and antibacterial effects (e.g. linalool) having been described.

Terpenes; Human data

There are no clinical studies that specifically evaluate the effects in chronic pain types. However, it is widely postulated that terpenes play a role in the efficacy of cannabis in chronic pain. This theory is reinforced by semi-anecdotal clinical knowledge of the differing effects of medical cannabis strains in painful conditions which do not appear to be directly associated simply with cannabinoid content. However, the benefits observed in the early clinical studies on medicinal cannabis in chronic pain and those reported anecdotally by consumers of medical cannabis worldwide, are not in-line with the underwhelming data for THC and CBD as single chemical entities. These insights support the importance of the entourage effect described by Russo (2011) and reinforce the hypothesis that terpenes have an important contribution to the beneficial effects of medicinal cannabis in treating pain.

4.2   Risk and Benefit Section

4.2.1   Medical Cannabis (balanced THC and CBD)

Cannabis has a long history of use as a medicine, being included in the British Pharmacopoeia until 1932 (Brown and Farquhar-Smith 2018), it was made illegal first in 1928 (as part of the International Opium convention), then in 1971 it was controlled by the Single UN Convention on psychotropic substances (Barnes and Barnes, 2016). It has been used extensively for both recreational and for therapeutic uses. During this time the amount of THC has risen substantially from 2% in hashish and cannabis flower in the 1960's, often with CBD to counteract the negative effects of THC, through to >20% THC in modern strains, which are typically of reduced CBD content (Stuyt 2018). This change has led to concerns regarding the effects of these high THC containing strains on the UK population when consumed for both recreational and medicinal reasons. This situation also results in a large range of cannabis preparations being used, therefore heterogeneity of IMP across studies makes interpretation difficult.

Within the field of medical cannabis, despite the high levels of THC in modern strains, no increases have been observed for SAEs in patients taking medicinal cannabis with standard of care, versus standard of care alone (Ware et al., 2016). Additionally, with the heterogeneity of medicinal cannabis products currently available for prescription, we believe that standardisation of medicinal cannabis is required to improve the risk-benefit profile for patients.

The products to be studied are either a strain of medical cannabis with a balanced THC and CBD ratio with minor cannabinoids and terpenes supplied as vaporisable flower. This balanced CBMP has been selected to provide the maximum possible benefit through the pharmacodynamic effects provided by THC, whilst having enough CBD content to minimise THC induced anxiety and psychosis in susceptible patients. In addition, doses will be kept low and titrated up slowly to reach the maximum benefit whilst minimise the acute and chronic risks associated with excessiveTHC exposure, which is widely believed to be the cannabinoid of primary safety concern. This gradual up-titration mirrors the "start low go slow" dosing strategy that is widely used in the medicinal cannabis community (Lucas et al., 2018), designed to minimise the risk of THC exposure in patients sensitive to THC. This approach will be adopted by the study physicians andis commonly used in pain medicine practice with other agents such as anti-neuropathics. We believe the literature supports the view that a cannabis product with the full spectrum of active ingredients will have the maximum benefit to sufferers of non-cancer chronic pain, through the entourage effect (Russo, 2011). As a result, we will study a full spectrum medicinal cannabis product with a balanced THC and CBD profile to maximise the benefit to the patient and minimise the risk associated with THC induced adverse effects.

It is well described in the literature that CBMPs requires careful dosing to avoid tolerability concerns. However, in terms of overall safety, cannabis presents a relatively low risk to patients, compared to other analgesics, particularly in overdose. In a recent review of acute toxicities observed within two Poisoning units in Oregon and Alaska it was observed that neuroexcitation is the primary reason for admission with overdose of cannabis (47.1%), followed by sedation (40.5%). Out of 253 individuals admitted 28.1% were <12 years old and almost all of those accidentally ingested the cannabis, 16.6% were adolescents and 55.3% were adults. Eight individuals were admitted to ICU and one death was reported (Noble et al., 2019).

There is evidence that medicinal cannabis reduces the consumption of opioids in countries where medicinal cannabis has been legalized (Bradford et al., 2018). Medicinal cannabis is now being proposed as a treatment or adjunct to the treatment of opioid use disorder (OUD) (Wiese and Wilson-Poe, 2018). There is a growing evidence base that suggests a potentially de-risking strategy for medicinal cannabis in OUD.

Importantly there is extensive safety evidence for the THC and CBD balanced cannabis based pharmaceutical product from nabiximols (Sativex) although this product is not full spectrum. During its development nabiximols was found to have an excellent safety profile with regards to the development of potential THC induced adverse events such as anxiety as well as generally.

These findings provide further support to our risk mitigation strategy of providing a balanced THC and CBD medicinal cannabis product to the participants in our study.

Acute use of THC at higher doses can potentially cause reflex tachycardia in response to changes in blood pressure, with higher doses causing orthostatic hypotension and syncope. However, chronic users may develop bradycardia. (Handbook on Cannabis 2015). Cannabis can cause an acute increase in blood pressure, increasing the risk of angina (Goyal et al 2017) and it has been reported that cannabis can rarely trigger acute myocardial infarction (Mittleman et al 2001). However, in patients who have had a myocardial infarction, an 18-year follow up study showed no conclusive evidence that smoking marijuana increased mortality (Goyal et al 2017).

There is some evidence that THC has an association with road traffic accidents, and the strongest association exists with fatal road traffic accidents (Bondallaz et al., 2016). As a result, care must be taken with using medical cannabis particularly with high THC strains. As we are studying a balanced THC/CBD strain it is likely that our subject's risk will be diminished but the risk must be considered and appropriate warnings that comply with current Driver and Vehicle Licensing Agency (DVLA) guidance will be provided.

There is literature that suggests there is a genetic risk to a patient's response to THC. To assess these genetic risks to subjects enrolling on the study we will carry out a genetic test prior to subjects receiving a CBMP using the Illumina "Genome Wide" chip to analyse an individual's genetic variance in association with cannabis tolerance and risk of cannabis use disorders (CUD). This information will be used to study the genetic risks of acute THC induced anxiety. This will involve cross validating observed patient reported outcomes related to anxiety and reported clinical anxiety adverse events, to the selected SNPs we have predicted to determine a subject's sensitivity to THC.

Conclusion

There is a long history of use of medicinal cannabis and evidence supports the concept that cannabis is generally well tolerated (especially when compared with current agents routinely used to treat chronic pain). Recently, THC levels have increased substantially for cannabis strains used recreationally which has raised concerns for the UK population in relation to addiction and the development of psychosis. Consuming a balanced THC and CBD medicinal cannabis product is known to substantially lower this risk, whilst having a full-spectrum cannabis product including minor cannabinoids and terpenes is thought to maximise the benefits to the chronic pain patient.

The full-spectrum, 8% THC/8% CBD cannabis product which will be prescribed in this study has the optimum risk benefit profile. Additionally, there could be a beneficial effect for medicinal cannabis in opioid use disorder (OUD). There is evidence of cardiovascular effects associated with THC and care must be taken with patients prone to syncope, links, although uncommon and unproven, with myocardial infarction require consideration. There is an association with road traffic accidents although the THC/CBD balanced product proposed for this study is likely to minimise this risk.

4.2.2   Reference Safety Information

Nabiximols is a licensed medicine containing THC and CBD as active pharmaceutical ingredients. A thorough review of the safety of the two important phytocannabinoids have been undertaken and reported in the nabiximols SPC.

5. STUDY OBJECTIVES

- The primary objective is to evaluate the effectiveness of the treatment regimen on reducing the average intensity of pain of subjects with chronic non-cancer pain compared to matched controls.

- The secondary objective is to evaluate the effectiveness of the treatment regimen on quality of life measurement, global impression of change, well-being, appetite, sleep scores and changes in concomitant medicine of chronic non cancer pain sufferers compared to matched controls.

- Safety and tolerability of the treatment regimen in chronic non-cancer pain subjects will also be assessed.

6. INVESTIGATIONAL PLAN

6.1 Overall study design and plan

This is a non-randomised, non-blinded single arm real world data collection study investigating the safety, tolerability and effectiveness of medicinal cannabis in chronic non-cancer pain subjects. The study will be conducted in a CBMP treatment clinic that has staff experienced at administering and managing the use of CBMP in its current unlicensed status. At time of enrolment, baseline data will be provided by the participant's health care team who is managing their chronic non-cancer pain (to current standard of care) and collected at the clinical study site. This will provide information on the type of chronic non-cancer pain the subject has (including relevant investigations previously conducted) and the types of drugs and non-pharmacological interventions that the subject is receiving or has received. The standard of care treatment and patient management will be determined by the treating physician. All study treatments and/or any change to treatment or management of the disease that occur throughout participation in the study will be recorded as well as being communicated to the subject's GP. Data will be collected either by the Physician during the study visit or via real time collection via an application (ePRO)provided to the subject. Data will be collected retrospectively and prospectively. A sample size of 5000 participants is planned.
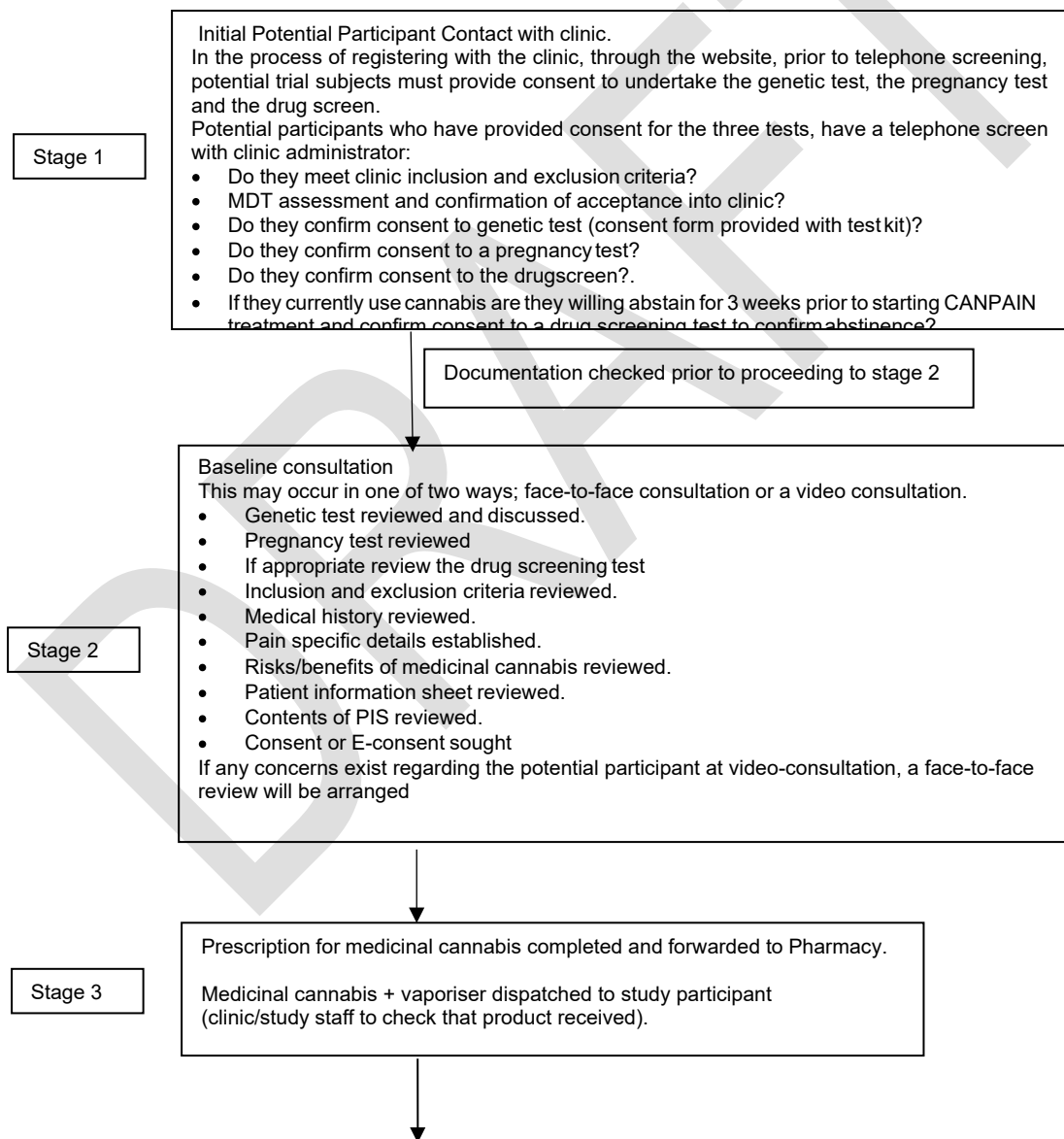
Trial subjects will come from patients who have consented to receive treatment at the Harley Street (CPC) clinic. The study will consist of an initiation visit (or call) to allow screening and base line data to be taken and then a follow up visit (or call) every three months thereafter, until the end of the study (after the last subject's 3 years of treatment). Day 0 (baseline) for each subject will be the initiation visit when study treatment is started (first prescription written) (see figure 1). Prior to conducting any data collection, eligibility for enrolment will be assessed, oral consent will be requested for conductance of a genetic test and if appropriate a pregnancy test. A full medical history will be taken to assess suitability for treatment with medical cannabis; focusing on pain aetiology, subject's current standard of care and previous history of medical cannabis, if any use. Each participant will be provided with study documents to allow them to consider whether they want to have their data collected prior to providing written informed consent.

Informed consent documents (consent form and patient information sheet) will be sent to patients at least 2 days prior to the initial consultation to allow patients time to review them. At the time of initial consultation, the clinician will review the documents with the participant again and explain them in detail. If the subject agrees to provide informed consent, the clinician will witness the subject signing the consent form. If this takes place over video conference the clinician will witness and record the signing event. In addition, the subject will provide photographic identification prior to consultation, permitting confirmation of the participants identification at the time of the remote consultation. Free prescriptions for the study regimen will be provided. Subjects will provide saliva samples for genetic single nucleotide polymorphism (SNP) genetic analysis to study the genetic risk of an individual's sensitivity to THC. Subjects will be continuously monitored via real time reporting of patient reported outcomes and cannabis use information delivered by vaporiser and its bluetooth connected mobile phone application. Tolerability-related patient reported outcome

data will trigger automatic alerts to clinicians who will contact those subjects for assessment. Subjects will have quarterly consultations with specialists to discuss their treatment and to collect adverse events, until the end of the 3 years of treatment. On each 3 monthly follow up, an updated medical history will be taken, alongside information on current standard of care treatment and a review of the CBMP prescribed will be undertaken (see figure 1).

Under the supervision of an appropriately qualified and trained physician, all subjects will be prescribed a dose of CBMP product that is appropriate for their type of chronic non-cancer pain, their medical history and their previous experience with cannabis. Cannabis tolerance will be monitored via ePRO data collection with tolerability questions asked after each vaporisation session. After 1 month of treatment at the low dose, this information will be used, alongside regular monitoring of the subject, to guide the Investigator on whether the subject can be titrated to the higher dose. The length of the trial for each participant is 3 years. Treatment will continue until the end of the study (see figure 1). An overview on the study procedures is given in the schedule of assessments (Table 1-1).

Figure 1; schematic of patient journey

Stage 1

Initial Potential Participant Contact with clinic.
In the process of registering with the clinic, through the website, prior to telephone screening, potential trial subjects must provide consent to undertake the genetic test, the pregnancy test and the drug screen.
Potential participants who have provided consent for the three tests, have a telephone screen with clinic administrator:
- Do they meet clinic inclusion and exclusion criteria?
- MDT assessment and confirmation of acceptance into clinic?
- Do they confirm consent to genetic test (consent form provided with test kit)?
- Do they confirm consent to a pregnancy test?
- Do they confirm consent to the drugscreen?.
- If they currently use cannabis are they willing abstain for 3 weeks prior to starting CANPAIN treatment and confirm consent to a drug screening test to confirm abstinence?

Documentation checked prior to proceeding to stage 2

Stage 2

Baseline consultation
This may occur in one of two ways; face-to-face consultation or a video consultation.
- Genetic test reviewed and discussed.
- Pregnancy test reviewed
- If appropriate review the drug screening test
- Inclusion and exclusion criteria reviewed.
- Medical history reviewed.
- Pain specific details established.
- Risks/benefits of medicinal cannabis reviewed.
- Patient information sheet reviewed.
- Contents of PIS reviewed.
- Consent or E-consent sought
If any concerns exist regarding the potential participant at video-consultation, a face-to-face review will be arranged

Stage 3

Prescription for medicinal cannabis completed and forwarded to Pharmacy.

Medicinal cannabis + vaporiser dispatched to study participant
(clinic/study staff to check that product received).

<table>
<tr><td>Stage 4</td><td>

Clinic treatment phase

Predominantly application-based data collection, video consultation/face-to-face reviews at 3-month timepoints. Review tolerability, treatment effects and concomitant changes to standard of care

Patients asked if they want to join CANPAIN study and are provided with PIS about study and draft study consent form.

If they want to enter study inclusion/exclusion criteria confirmed and meeting arranged to review study consent form and get it signed.

Study protocol followed for this patient from this point on until end of maximum of 3 years

</td></tr>
</table>

6.2 Discussion of study design and choice of control groups

The aim of the study is to evaluate whether the addition of medical cannabis to standard of care or at the completion of standard of care is beneficial with regards to pain scores, quality of life, quality of sleep and changes in the use of concomitant medication, as well as being safe and tolerable in subjects suffering from chronic non-cancer pain. The study will utilise a combination of patient reported outcomes and data from the NHS (chronic pain diagnosis, standard of care and health related laboratory tests) to provide a holistic evaluation of the CBMP treatment when combined with standard of care. The patient reported outcomes and NHS data will be transferred into an electronic health repository which will manage their day to day care, provide reports and alerts on the tolerability of the cannabis for each subject and will form the clinical trial database. The matched controls will exclude those potential participants who are consuming illicit cannabis, identified by drug screening. If participants are using illicit cannabis, they will be given the option to stop with a 3-week wash out period. If participants are not willing to cease, they will not be eligible for inclusion in the matched control cohort.

Controls

The analyses of effectiveness will be conducted through comparison with matched controls obtained from NHS sites established to enable data collection from consented subjects receiving standard of care only. Subjects who consent to have their data collected will be asked to provide essential demographic information, details on their chronic pain type, their standard of care and whether they are currently using medical cannabis to help with their pain. This information will be used to match the subject to subjects on the trial. The data collected in the match cohort will mirror the data collected from the CANPAIN minus tolerability data which will not be required.

The CANPAIN study will follow a pragmatic, real-world, 'all-comers' design with wide inclusion criteria, which is designed to result in a more representative sample of the target population and of the matched controls. Baseline characteristics of treated participants may still differ systematically from those of the matched control group and one must account for these systematic differences when estimating the effect of treatment on outcomes.

In order to reduce bias and to balance the distribution of covariates in the treated and control groups, multiple regression analysis will be used adjusting for potential confounders. Matching methods such as propensity scoring methods may also be used. The propensity score facilitates the construction of matched sets with similar distributions of the covariates, without requiring close or exact matches on all of the individual variables. However, unmeasured confounding may still be present after matching and should be recognized as a limitation.

Baseline Controls

All analyses will be baseline-compared (i.e. using changes from baseline).

6.3 Study Duration

The study duration is 3 years. Subjects will only be followed for as long as the individual investigator or individual subject agrees.

6.4   Selection of Study Population

6.4.1   Inclusion Criteria

Participants must meet all the following inclusion criteria to be eligible for enrolment into the study;

1. Male or female 18-85 years old;

2. Diagnosed with chronic non-cancer pain

3. A consented patient at the Harley Street (CPC) clinic.

4. Is receiving standard of care therapy with inadequate response or has completed standard of care treatment, does not want standard of care treatment, or standard of care is contraindicated (Inadequate response is defined as the subject receiving standard analgesic agents and still has pain, has unpleasant side effects or wishes to reduce their intake of standard of care analgesic agents, e.g. a subject receiving opioids who wishes to dose reduce in light of the "opioid crisis");

5. Despite being on or having standard of care and still has pain (>3 on the Pain NRS); and

6. Signed and dated written informed consent from the subject.

6.4.2   Exclusion criteria

Study exclusions will be assessed by the study clinician in light of established cannabis restrictions. However, in general participants meeting any of the following exclusion criteria will not be included in the study;

1. Pregnant or lactating females or females who are planning a pregnancy during the study;

2. Positive pregnancy test at screening;

3. Major organ failure, renal, lung and liver failure;

4. Participants having active liver disease or unexplained persistent elevation of serum transaminases > 3 times the upper limit of normal;

5. Participants with a creatinine clearance < 60mL/min; History of cardiac or respiratory failure;

6. History of cardiac or respiratory failure;

7. History of recent myocardial infarction or poorly controlled ischaemic heart disease;

8. Severe respiratory disease (e.g., GOLD 3 for COPD or asthmatics requiring high doses of oral corticosteroids).

9. History or presence of alcohol or substance abuse, including analgesics used as standard of care.

10. Participation in a clinical trial of an investigational medicinal product;

11. With any known or suspected history or family history of schizophrenia, or other psychotic illness; history of severe personality disorder or other significant psychiatric disorder other than depression associated with their underlying condition.

12. Known hypersensitivity to cannabis or allergy to cannabis or CBMP and

13. Direct employee of the study site.

6.4.3   Contraceptive Guidance

The safety and tolerability of medicinal cannabis has been studied and the adverse event and safety profile is well understood. The use of CBMP is not advisable during pregnancy, therefore we will ask for provision of evidence of a negative pregnancy test for women of child-bearing age, before treatment can commence.   Evidence of a negative pregnancy test for women of child-bearing age (section 3.1 for definition) needs to be provided at screening and 3 months after the completion of the treatment period. It is mandated that males and females of a child bearing age use an acceptable barrier methods of contraception (see section 3.1 for definition) is used during the duration of the study (irrespective of whether the participant is using a hormonal contraceptive) from screening throughout the study and for 3 months after the last dose of the study treatment. The effectiveness of systemically acting hormonal contraceptives may be reduced by CBMP, therefore female participants using systemically acting hormonal contraceptives must add an additional second barrier method.

6.4.4 Study Drug Discontinuation

Reasons for the discontinuation of study drug may include, but are not limited, to the following:

1. An AE, SAE, drug reaction, or complication, whether related or not to the treatment drug, which precludes continuation of dosing with study drug.

2. Abnormal laboratory results that lead the Investigator to diagnose a poorer prognosis for subject health.

3. Noncompliance with study drug dosing.

4. Noncompliance with study procedures.

5. Subject's right to withdraw consent at any time during the study, with or without a stated reason.

6. Three separate pieces of evidence that the subject is self-administering other cannabis treatments outside of the prescribed study treatment (three strikes rule). Prior users of non-prescription cannabis will be monitored for any indication that they are using non-trial sources of CBMP, through regular explicit questioning and monitoring of patient reported outcome responses.

7. The investigator's opinion that it is not in the subject's best interest to continue study participation.

8. Sponsor's decision to terminate the study.

9. Pregnancy.

6.4.5 Premature removal from study

Participants may withdraw from the study at any time at their own request, or at the discretion of the investigator or sponsor for safety, behavioural, or administrative reasons. If a participant does not return for a scheduled visit, every effort will be made to contact them and to document participant outcome, wherever possible. The investigator will establish the reason for withdrawal. If the participant withdraws consent for disclosure of future information, no additional data will be collected for the study. The sponsor will retain and continue to use any data collected before such withdrawal of consent.

6.4.6 Withdrawal due to an adverse event

Withdrawal due to an adverse event should be distinguished from that due to participant perceived lack of treatment response or any other reason for withdrawal and this will be recorded. The study doctor must report this event to the study sponsor. The sponsor clinician must determine if this adverse event was as a result of the study medication. If this is the case the sponsor clinician must report the case to the regulator on an appropriate adverse event form. If this has implications to other participants, all study doctors must be immediately informed and subjects that are at risk must be immediately contacted and all or part of their treatment as appropriate must be stopped. Any future subject that may be impacted by this adverse event must not be recruited into the study or treated at the clinic.

If a participant withdraws due to a serious adverse event, the serious adverse event must be reported in accordance with the reporting requirements defined in Section 7.3 and if this has application to other subjects, all study doctors must be immediately informed and subjects that are at risk must be immediately contacted and all or part of their treatment as appropriate must be stopped. Any future subject that may be impacted by this adverse event must not be recruited into the study or treated at the clinic.

If a serious adverse event is determined to be at least possibly related to one of the treatment drugs and a change to the study management is warranted, the trial will be stopped as per current legislation and UK guidance. Any resultant change to the protocol which is to be implemented will be notified to the REC and MHRA via a substantial amendment. If a change is required

immediately to protect the safety of trial participants, then notification of Urgent Safety Measures will be made to the REC and MHRA according to the current legislation and UK guidance.

6.4.7   Study termination

The sponsor reserves the right to modify or terminate the study at any time. Possible reasons for termination are:

- Safety reasons – the incidence of AEs in this or any other study using the same treatment regimen indicates a potential health risk for the participants.

- New scientific knowledge becomes known that makes the objectives of the study no longer feasible/valid.

- Unsatisfactory enrolment of participants.

- Regulatory requirement.

- Drug manufacturing/stability issues.

- Force majeure events.

6.4.8   Study Treatment Discontinuation

The primary reason for study treatment discontinuation will be documented as extensively as possible. Subjects who discontinue study treatment prematurely will be followed-up until the end of study, or until they withdraw consent.

6.5   Treatment Drug

The treatment drug will be prescribed as an IMP to study participants and dispensed by a registered UK pharmacist. The treatment drug will be labelled in English and packaged in accordance with the regulations that apply to dispensed relevant medicinal products (in accordance with the requirements of Schedule 5 to the Medicines for Human Use (SI 1994/3194) Regulations 1994).

6.5.1   Treatments administered

The treatment regimen will be as follows; a vaporised/inhaled medical cannabis strain (CBMP), namely Equipose 8-8 with a balanced 8% THC and 8% CBD content. Treatment is a full spectrum medical cannabis product presented as dried flower:

The cannabis will be delivered by a smart vaporiser device manufactured by Ryah. This is CE marked having passed CE-RED NB and IEC 60601 medical device safety tests. It is a temperature-controlled vaporiser with flow sensors that connects remotely with a smart-device. hosted application which collects dosing data from the vaporiser and patient reported outcomes, permitting further dosing only after completion of required data entry. The CBMP is placed in a prefilled cartridge which contains 250 mg of product. This cartridge is QR coded and must be read by the mobile application prior to loading into the vaporiser. Detailed instructions on how to use the vaporiser will be provided with each vaporiser and a UK-based technical helpline will be provided in case the subject needs to be assisted with vaporiser use.

Treatment is determined by the study Physicians based on the subject's medical history, their subtype of chronic pain and their experience with CBMP use. Study Physician will be given extensive guidance on state of the art of CBMP prescribing, ensuring that subjects can tolerate the CBMP and are not given a dose of THC that might cause excessive adverse events. All subjects will be prescribed an initial low dose of CBMP. Real-time evaluation of efficacy and tolerability will allow dose to be titrated appropriately.

Using the principles of universal precaution all subjects will start the protocol at a low dose.
At the low dose the subject will commence with one 1 vape session (250 mg of cannabis) in the evening only. All subjects will progress to the higher dose at 1 month after baseline, unless

instructed not to by the study clinician, who will review how well the subject has tolerated the CBMP. The higher dose will consist of 2 vape sessions (250 mg total cannabis flos per cartridge) one in the morning and one in the evening.

6.5.2   Selection of doses in the study:

A considerable body of clinical studies support the use of medicinal cannabis in chronic non-cancer pain. The optimal treatment for chronic pain is achieved by dosing carefully with titration to achieve the required pharmacological effects. The study clinician will closely monitor the dosage during the treatment of the participant. Titrating if necessary, to improve response to treatment and ensure the treatment is well tolerated.

6.5.3   Treatment compliance

Treatment compliance will be monitored by regular and prompted ePRO interactions via the study mobile phone application and by contacting the subjects directly to discuss the progress of medication protocol. These contacts will be recorded in the subject record under "Documents"in the medical management database used for this study "Heydoc". Due to the self-fundedaspect of the study and the nature of the condition being treated, good trial protocol compliance is expected.

In addition, at each quarterly review, study clinicians will ask the subjects about their medicine taking experience and their compliance and they will also note this in the subject record under "Consultations" in the medical management database used for this study "Heydoc".

6.5.4   Contraindicated Medicines

After oral intake, THC is mainly metabolized in the liver by cytochrome P450 (CYP) 2C9, 2C19 and 3A4 to much more psychoactive 11-hydroxy-Δ9-THC and inactive 11-nor-9-carboxy-Δ9-THC (Abraham et al., 2007). Cannabinoids are weak inhibitors of cytochrome P450 (CYP). Δ9-THC inhibits CYP3A4, 3A5, 2C9 and 2C19. CBD inhibits CYP2C19, 3A4 and 3A5, although this can be observed only at doses higher than clinically used. Nevertheless, caution is advised with concomitant fentanyl and amitriptyline use, as both are metabolized through CYP3A4, and 2C19 (Sativex product monograph). Most drug interactions are an effect of the concurrent use of other agents' depression of the central nervous system. Clinically significant interactions are rare, and cannabis may be combined safely with many medications (McCallum and Russo, 2018).

6.5.5   Treatment after end of study

Subjects will be free to continue to receive treatment and medical care at the clinic after termination of the study, in compliance with local regulations. Those not receiving ongoing treatment at the clinic, no further follow up or data will be collected on these subjects. Any data from patients who continue to receive treatment after the 3-year study period will be outside the study and will not contribute to the study database.

6.6   Assessments and schedule of measurements (overview)

The following assessments and measurements will be carried out at the times specified in the schedule of assessments (Table 1-1).

Informed consent will be obtained prior to any study-related procedures.

6.6.1   Assessments during the study

- **Initiation visit/call (Day 0)**

Day 0 (baseline) for each subject will be the initial clinic visit when treatment is started. Alongside the daily monitoring of CBMP tolerability through the patient reported outcomes,

subjects will have 3 monthly consultations..

- Complete medical questionnaire form
- Review of medical history and relevant investigations
- Review current treatment being received or proposed
- Assess inclusion and exclusion criteria
- Written informed consent obtained
- Discuss the medicinal cannabis therapy
- Go through dosing instructions with participants (i.e., how to use the device, when to use the CBMP and how to enter data onto their smart device).
- If appropriate arrange the prescription

Daily assessments (concomitant with dosing)

- Tolerability NRS measurements (anxiety, drowsiness, dizziness, shortness of breath)

The tolerability measures collected 30 minutes after dosing with the CBMP are collected and fed back to Heydoc. Any NRS score >5 causes an alert, which triggers a study physician to contact the subject to assess their status and to elicit an appropriate response.

Weekly assessments

- Efficacy NRS measurements (pain, well-being, sleep quality, fatigue, nausea, depression, appetite)
- Global impression of change

3 monthly assessments

- Quality of life (SF-12)

3 monthly visits/call

- Review of efficacy and tolerability of medicinal cannabis and establishing the subject's overall impression on how they have responded to the CBMP
- Review current treatment being received or proposed
- Adverse events
- Renew prescriptions. Remind the participants of dosing instructions

6.6.2   Additional (safety) examinations

If the subject has a history of mild to moderate psychiatric ill-health that could indicate a potential sensitivity to a CBMP that subject will be referred to a specialist psychiatrist for psychiatric evaluation to further assess the risk of receiving a CBMP. In addition, if there are any unclear chronic pain related symptoms or observations the responsible physician in charge may perform further medical examinations, other than outlined in this protocol, including further clinical laboratory tests, in order to clarify the relevance or to diagnose symptoms.

6.7   Effectiveness, tolerability and safety measurements

6.7.1   Effectiveness measurements

Change from baseline in pain intensity (pain NRS).

Change from baseline in quality of life measure (SF-12)

Change from baseline in well-being (well-being NRS)

Change from baseline in fatigue (fatigue NRS)

Change from baseline in nausea (nausea NRS)

Change from baseline in depression (depression NRS)

Change from baseline in anxiety (anxiety NRS)

Change from baseline in appetite (appetite NRS)

Change from baseline in sleep quality (sleep NRS)

Change from baseline in use of concomitant pain medications

Patient's global impression of change (PGIC)

Generally, these quarterly reports compare the results to the previous quarterly results and the Specialist can make comments about the changes from the previous period.

Numerical data will be collated and reports made on the baseline changes for pain, QoL, well-being, fatigue, nausea, depression, appetite, sleep quality, anxiety, global impression of change and concomitant medication, to define whether the subject has received benefit.

6.7.2   Safety and tolerability measurements

Safety endpoints will include the following:

- Assessment of AEs, including SAEs
- Safety clinical laboratory tests

6.7.2.1 Adverse Events

Definitions and instructions for AE monitoring and reporting, are provided in Section 7.

All AEs will be coded using the version of Medical Dictionary for Regulatory Activities (MedDRA).

Safety laboratory tests

A copy of all the diagnostic and laboratory reports arranged for by the participant's Health Care Professional will be obtained at or around the time of initial visit/call and for each quarterly visit. If any adverse results are seen, the subject will either not be permitted into the study or will be asked to stop taking the CBMP at the time of a quarterly review.

7.   Adverse events

7.1   Definitions

An **adverse event** is any untoward medical occurrence in **a participant who has been administered a cannabis product** and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether related to the medicinal product.

Adverse events will be graded with respect to <u>intensity</u> and classified as either <u>serious or non-serious</u> according to the World Health Organisation classification.

Classification of adverse events

Intensity	*Mild*	Some awareness of symptoms, but easily tolerated.
	Moderate	Symptoms causing enough discomfort to interfere with usual activity.
	Severe	Incapacitating event causing inability to work or to perform usual activity.
Seriousness	*Serious*	Any untoward medical occurrence that at any dose: - results in death - is life-threatening - requires participant hospitalisation or prolongation of existing hospitalisation - results in persistent or significant disability/incapacity - is a congenital anomaly / birth defect - is an important medical event.
	Non-serious:	Any other adverse event.

Note: The term "life-threatening" implies only the fact that the participant was at immediate risk of death. The term "life-threatening" does not imply a possible future course which might or might not have happened but was prevented due to adequate physician's action. For example: A simple bacterial wound infection can lead to gangrene, sepsis and eventually to death; while sepsis is usually regarded as a Serious Adverse Event because of the known high mortality, the primary wound infection itself is usually not regarded as a Serious Adverse Event. In analogy, a newly diagnosed malignant disease is usually regarded as a Serious Adverse Event because malignant diseases usually have a high mortality rate and are, therefore, life-threatening.

Hospitalisation is usually defined as an overnight stay, i.e. admission prior to midnight and continuing into the following day. A visit to an out-patient facility or Emergency Department is not necessarily a hospitalisation, although the event leading to the visit could be an SAE. Hospitalisation for elective treatment of a pre-existing condition that did not worsen during the study is not considered a Serious Adverse Event unless a complication occurs during the hospitalisation.

Adverse Event Causality

The drug regimen -event relationship will be assessed using the following criteria:

Certain: A clinical event, including laboratory test abnormality occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically

plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.

Probable /likely: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition.

Possible: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

Unlikely: A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.

Not assessable/unclassifiable: A report suggesting an adverse reaction, which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.

Unrelated: A clinical event that is judged to be clearly and incontrovertibly due to extraneous causes (disease, environment, etc.) and meet the following criteria:
- The AE does not have a reasonable temporal relationship and can be explained by a commonly occurring alternative aetiology, or
- The AE is unrelated to the study *e.g.* automobile accident - unless it can be demonstrated that the treatment could have caused the event.

7.2   Assessment and reporting of adverse events

The occurrence of adverse events will be assessed by non-directive questioning of the participant at each visit. Further, adverse events volunteered by the participant during or between visits or detected through observation, physical examination, laboratory test, or other assessments during the observation period, will be documented. Participants will be instructed that they must immediately report any adverse events, subjective complaints or objective changes in their well-being to the study doctor or the clinic personnel, regardless of the perceived relationship between event and test product.

All AEs will be recorded by the study doctor or clinic personnel in the CRF and subject notes from the signing of informed consent until the end of the trial (3 years of treatment). The AEs will be followed until resolved, if applicable.

7.3   Reporting of serious adverse events

All serious adverse events (SAEs) are to be recorded in the CRF and subject's notes from the signing of informed consent until the end of the trial (after 3 years of treatment).

SAEs must be reported immediately to the sponsor. The study doctors or clinic staff are required to notify the sponsor by completing the Serious Adverse Event template and emailing or faxing the sponsor, within 24 hours of them becoming aware of the occurrence of a serious adverse event. The sponsor is responsible for notification to the appropriate authorities, if applicable (A serious adverse event reporting form template must be prepared and made available to the investigators for quick reporting).

All SAEs should be reported promptly to the REC, if applicable in accordance with the International Conference on Harmonisation Good Clinical Practice (ICH GCP) E6, (Section 4.11.1). The SAE will then be followed until resolved, if applicable.

If the SAE was unexpected, it is then defined as a Suspected Unexpected Serious Adverse Reaction (SUSAR) and should be reported by the sponsor to the MHRA and relevant REC. If the SUSAR is fatal or life threatening, then these should be reported immediately and at least not later than seven days after the sponsor was first aware of the reaction. Any additional relevant

information should be sent within eight days of the report. Electronic reporting will be adopted using the MHRA's eSUSAR website, the EudraVigilance Gateway or EVWEB. The sponsor shall keep detailed records of all adverse events relating to the clinical trial which are reported to it by the study doctors or clinic staff for the trial. The Licensing Authority may require the sponsor to send those records, or copies of such records, to the authority. For all other SUSARs the sponsor must inform the MHRA and relevant REC within 15 working days of them becoming aware of the SUSAR.

7.4   Actions to be undertaken

The responsible study doctor will initiate appropriate treatment according to his/her medical judgment and will decide whether to withdraw the subject from the study if an adverse event or a concurrent health condition occurs. The subject must be followed-up by additional examinations according to the medical judgment of the study doctor, until the abnormal condition is resolved, or the study doctor deems further observations or examinations to be no longer medically required.

7.5   Stopping Criteria

Close monitoring of the subjects during the study will be performed. Any decision to stop the study will be immediately communicated to all investigators and to the relevant regulatory authorities.

8.   DATA MANAGEMENT AND QUALITY CONTROL

8.1   Case report forms and data management

An independent data management party will prepare a CRF at the time of analysis for each subject. The CRF will record the subject number which will be obtained from the subject database Heydoc which is an automatically generated subject number. No other subject personal details will appear on the CRF. The clinical personnel at the site will obtain from the Heydoc system the date that the subject entered the study and the date the subject was either removed from the study, died or the date being five years after entering the study if none of the previous dates are applicable and record this information on the CRF.

In addition, the site will obtain from the Heydoc system for each subject the scanned in external quarterly reports obtained from the subjects. The sponsor will ensure that the CRF is correctly completed. The CRF will be signed by the investigator signifying agreement with and responsibility for the recorded data.

A list of all data fields to be recorded in the CRF, will be generated by the sponsor and which documents are the sources for that data (i.e. the source documents) and which data, can be directly entered into the CRF.

8.2   Quality control

The study will be supervised by the sponsor. The sponsor will contact the clinical trial site regularly to discuss the progress of the study and to check the study documents including the informed consent forms for completeness and consistency.

The sponsor will verify the data entered in the CRF at the time it has been recorded on the CRF with the source data at the study centre in order to confirm accuracy and adherence to the study protocol.

The Heydoc system which records all the subject data and stores all the subject information and documents is an externally run and controlled database that has been audited and verified as being acceptable for medical record keeping, data protection and back up and access purposes. Every user has their own log in details and passwords that have to be changed every month. Any change made to the system is recorded by the person making such change and every change is auditable and non-removable so that any changes can be tracked and verified.

Heydoc is the online practice management software solution, which has been designed and developed by Heydoc.

Heydoc is one of the leading online system available on the UK market, and the only full-service solution that enables single and multiple location private medical practices to connect securely to their data from any location worldwide.

The data is stored at a high security and internationally approved data centre based in the United Kingdom. Hardware is monitored 24/7 in a temperature-controlled environment with a battery and generator standby for use in the event of power failure. The Heydoc technology creates a secure connection that transports data entered by authorised users through the World Wide Web, allowing protection from viruses, spy ware, SPAM, and other unwanted Web browser traffic. The system operates in the same environment commonly used by Banks and UK Government departments to handle information transfers. All data transmitted through Heydoc is encrypted using Secure Socket Layer (SSL), the highest form of internet data encryption. Algorithms scramble data so that unauthorized users cannot view it, keeping all subject data safe from data pirates or hackers.

Heydoc is registered as a Data Controller with the Information Commissioners Office and is subject to the Data Protection Act. The company is accredited by Lloyd's Register Quality Assurance to ISO27001 standards and complies with NHS Information Governance Statement of Compliance (IGSoC).

9.   STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

9.1   General considerations

The aim of the study is to evaluate whether a medical cannabis treatment in addition to standardof care is beneficial with regards to pain scores, quality of life measures, sleep scores, changes in concomitant medication use, subject's global impression of change and general wellbeing score, as well as being safe and tolerable. The study is a non-randomised, non-blinded, single arm study with comparisons being made against matched control database(s) where available and applicable.

There are many causes of chronic pain, which can be described as either neuropathic or non-neuropathic. In addition to those two main subtypes, there are 10 further subtypes which are as follows: systemic inflammatory disease, osteoarthritis, lower back pain, inflammatory bowel pain, neurogenic pain, post cancer pain, post trauma pain, psychogenic pain, genitourinary pain and vascular pain. These pain types will be recruited into both the CANPAIN cohort and matched cohorts.

The use of matched controls instead of a randomised control design is the best approach to studying medicinal cannabis due to the inherent difficulties of blinding trial subjects to the effects of cannabis. Protocol designs for the study of medicinal cannabis have been recently reviewed in a BMJ editorial (Freeman and Morgan 2019) which support the use study designs such as ours in the generation of evidence in medicinal cannabis use. Subjects in the active and control cohorts will be matched on a range of demographics, socio-economic, pain, and health related variables (see response to comment 1d). Certain covariates (such as gender) may be considered for exact matching if appropriate. Subjects will be matched using an optimal matching algorithm. For the primary analyses, a 1-1 matching algorithm will be used. At a predefined interval (12 months), a multiple regression analysis will be undertaken on subjects in the matched control cohort to assess which co-variates (e.g. categories of standard of care,pain type or location of pain). are important for the matching process with the CANPAIN cohort. Subgroups of special interest include type of pain, inclusion of gabapentinoids, age and gender. Subgroups of exploratory interest include but are not limited to, standard of care, site of pain and prior cannabis use. These will be fully defined in the SAP.

Full details, including the use of the matched control database(s), of the interim and final statistical analyses to be performed will be described in detail in the Statistical Analysis Plan (SAP). The SAP will be developed to specify the statistical methods to be used and it will be finalized prior to the final or interim data cut-offs.

The progress of each subject identified for participation in the trial will be documented in a flowchart so that all subjects are accounted for, whether or not they go on to enter the trial itself. This flowchart will also show the number of subjects with data available as well as the incidence of withdrawal from treatment. All data obtained in this study will be presented in individual subject data listings.

The analyses will be exploratory and primarily make use of descriptive statistical methods. Tabulations will be produced for appropriate effectiveness and safety parameters. For categorical variables, summary tabulations of the number and percentage of participants within each category (with a category for missing data where applicable) of the parameter will be presented. For continuous variables, the number of participants, mean, standard deviation (SD), median, minimum, and maximum values will be presented. Statistics may be presented for cohorts of interest (e.g. by pain type) if sample size permits.

Inferential statistical methods will only be employed to highlight interesting aspects of the data. Any p-values will be interpreted descriptively; no adjustment for multiple testing to control type-1 error will be done. 95% confidence intervals (CIs) will be presented as appropriate.

Statistical analysis, data listings, graphs and summary tables will be produced using SAS®, version 9.2 or above.

9.2 Determination of Sample Size

The sample size was calculated based on the objective of showing a greater proportion of patients experiencing an improvement in NRS score, from baseline to 12 months, when using CBMP in addition to the standard of care as compared to the standard of care alone. We assume that 25% of matched controls will experience an improvement in NRS score (O'Brien and Breivik, 2011). A sample size of 3600 patients using CBMP plus 3600 matched controls will provide at least 80% power to detect an increase in the proportion of patients experiencing a 28% improvement, using a two-sided z-test test for proportions with a Type I error rate of 5%. After adjusting for 10% non- evaluable rate and a 20% match failure rate, the sample size is 5000 CBMP patients plus 5000 matched controls.

Thus the null hypothesis H0: P=0.8 is tested against the one-sided alternative H1: P>0.80 Assuming that the expected pain reduction at 18 months for the treated subjects is P1=86%, a minimum sample size of 500 subjects for each type of chronic pain, with a total minimum number of 5000 subjects, is needed to design the study at 80% power, using a one-sided level 0.05 test for single proportion and the variance from the empirical estimate.

9.3 Analysis Sets

Data from all subjects recruited to the study will be analysed using an Intention-to-treat (ITT) approach, therefore data will be included in the primary analysis irrespective of whether the stipulated dose regimen or all the study medicines were followed throughout the study. All participants who receive at least one dose of any of the study drugs will be included in the safety analysis set (SAF). A Per Protocol (PP) analysis may also be conducted, comprising those subjects who adhere to the regimen as per protocol, as defined by the database entry and excluding subjects with major protocol deviations.

9.4 Summary of treatment group comparability

Demographic and baseline characteristics and disease characteristics will be summarized and compared between the treated subjects and the subjects from matched control group(s) for the ITT and the PP populations.

9.5 Methods of analysis

9.5.1 Effectiveness

The ITT Population will be used for all effectiveness analyses. Selected analyses may also be performed using the PP population. Effectiveness analyses will be presented for the overall populations and by subgroup of subjects (e.g. cause of chronic pain), as appropriate.

9.5.1.1 Change in baseline pain NRS

The change in baseline pain NRS will be defined as the difference between chronic pain state at the beginning of the study versus the end of the study (after 3 years of treatment).

The primary analysis will be a difference analysis with comparison to appropriately selected matched controls. The endpoint will be tested using a two-sided z-test test to compare results between the prospectively enrolled treated participants and external matched controls. The impact of confounding factors will be reduced as much as possible by including values of important covariates in the model and by performing sub-analyses. Covariates included in the model will be selected based on:

(1) Base line pain scores

(2) Cannabis consumption experience and/or

(3) Cause of chronic pain

A propensity score analysis may also be performed to match subjects between the treated and matched control groups. The propensity score is the probability of treatment assignment conditional on observed baseline characteristics. Propensity score matching entails forming

matched sets of treated and untreated participants who share a similar value of the propensity score (Rosenbaum PR & Rubin DB, 1983a and 1985).

Secondary measure outcome variables

Descriptive statistics will be presented for Quality of life changes, sleep NRS changes, Anxiety changes, confusion changes, dizziness changes, and changes in the use of concomitant medicines. Change from baseline to a number of analysis time points (including 12 months) will be assessed. Repeated measures analyses will be undertaken to allow for the evaluation of outcomes at any timepoint. In addition, multi-state modelling (MSM) will be undertaken to assess time-varying confounds. These will be described in detail in the SAP.

A comparison between treated subjects and matched control may be performed if similar endpoints are collected in both databases. Time to event analysis, multiple regression analysis for continuous and/or categorical outputs and/or propensity score analysis may be performed as appropriate.

To deal with missing data in subjects over the 3 year period, patterns of missingness will be evaluated including missing completely at random (MCAR), missing at random (MAR) or missing not at random (MNAR) will assessed, this will be described in detail in the SAP.

9.5.2   Safety and tolerability data

The SAF Population will be used for all safety analyses. Safety analyses will be presented overall and by subgroup of subjects (e.g. cause of chronic pain), as appropriate.

9.5.2.1 Adverse events

Adverse events will be summarized according to the Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT). Any "higher-than-expected" event frequency will be investigated.

The number and percentage of subjects reporting each PT and SOC will be tabulated. A subject experiencing the same AE multiple times will only be counted once for the corresponding PT. Similarly, if a subject experiences multiple AEs within the same SOC, the individual will be counted only once for that SOC.

Similar tables will be presented for treatment-related AEs, Serious Adverse Events (SAEs), treatment related SAEs and AEs leading to discontinuation of study regimen. AEs that are reported as "possibly", "probably/likely" or "certainly" related to combination of study medication will be considered treatment related. AEs may also be summarized by highest severity and relationship to treatment. AEs will be listed for each subject.

Subject Death reported during the study will be summarized.

9.5.2.2 Other Safety Data

Drug Regimen exposure and standard of care analgesic therapy will be summarized.

9.6   Measures to reduce bias

See Section 7.2.

10.   ETHICS AND REGULATIONS

10.1   Research ethics committees and competent authority

The clinical trial authorisation granted by MHRA and a favourable opinion from the relevant research ethics committee (REC) will be obtained prior to the start of the study. The local authorities will be notified about the study as required by law.

The MHRA and the REC will be notified about the end of the trial and a report summarising the study results will be sent to the MHRA and the REC within one year after the end of the trial. If the trial is terminated early, the MHRA and the REC will be notified within 15 days.

10.2   Ethical conduct of the study

The study will be conducted in accordance with the ethical principles set forth in the Declaration of Helsinki (including amendments). A copy of the declaration is included in Appendix 1 of this protocol.

10.3   Participant information and consent

Written informed consent will be obtained from all participants prior to entry into the study. The investigator will explain to each participant orally and in writing, the nature, significance, risks and implications of the trial before inclusion. In particular, the participants will be informed about the following:

- the possibility of withdrawing from the clinical trial at any time by revoking the consent and without any resulting disadvantage.
- how personal and health-related data will be collected and used during the study.

All participants will receive a copy of their signed and dated informed consent form.

10.4   Legal and regulatory requirements

This trial will be carried out in accordance with

- Good Clinical Practice (GCP) as required by EU Directive 2001/20/EC, the relevant laws and regulations of the country in which the study takes place.
- Standard operating procedures (SOPs for clinical investigation and documentation).

11.   STUDY ADMINISTRATION

11.1   Responsibilities

Harley Street (CPC) Limited is the sponsor of this study and will organise the performance of this study. The representative for the sponsor is Gregory Stoloff.

11.2   Protocol changes

Amendments to this study protocol may be made following the procedures specified by local laws and regulations. Substantial amendments to this study protocol may be implemented only if the approval of the MHRA and/or a favourable opinion of the REC have been obtained.

Substantial amendments to the conduct of the clinical trial may arise from changes to the protocol or from new information relating to the scientific documents in support of the trial. Amendments to the trial are regarded as "substantial" where they are likely to have a significant impact on:

- the safety, physical health and mental integrity of the participants;
- the scientific value of the trial; or
- the conduct or management of the trial.

If a new event occurs related to the conduct of the trial which may affect the safety of the participants, the sponsor and the investigator will take appropriate safety measures to protect the participants against any immediate hazard. The sponsor will immediately inform the MHRA and REC of the new events and the measures taken.

11.3   Publication of results

The original CRFs and the data otherwise obtained during the study under this study protocol will become the property of the sponsor.

Information about this trial and the results will be posted according to applicable national or regional regulations and laws.

11.4   Clinical study report

After completion of the study, the results will be tabulated, evaluated and issued as a complete final clinical study report according to the ICH-E3 Note for guidance on structure and content of clinical study reports.

The sponsor will send a summary of this clinical study report to the REC and MHRA within one year after the end of the trial (after the last participant's treatment).

11.5   Retention of study records

Records and documents pertaining to the conduct of the study and the distribution of the treatment drug (e.g. ICFs, laboratory slips, medication inventory records, and other pertinent information) must be retained by the Investigator for a period of at least 10 years.

CRF data will be kept for a period of least 15 years.

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APPENDIX 1

Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Participants

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53th WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1.   The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2.   Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3.   The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

4.   It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5.   Medical progress is based on research that ultimately must include studies involving human subjects.

6.   The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7.   Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8.   While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9.   It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10.   Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11.   Medical research should be conducted in a manner that minimises possible harm to the environment.

12.   Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13.   Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14.   Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15.   Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16.   In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17.   All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18.   Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19.   Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20.   Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21.   Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22.   The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23.   The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24.   Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25.   Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26.   In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study

and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27.   When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28.   For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29.   When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30.   Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31.   The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32.   For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33.   The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34.   In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35.   Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36.   Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37.   In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

C.   ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31.   The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research participants.

32.   The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:
   - The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
   - Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

33.   At the conclusion of the study, participants entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.

34.   The physician must fully inform the participant which aspects of the care are related to the research. The refusal of a participant to participate in a study or the participant's decision to withdraw from the study must never interfere with the participant-physician relationship.

35.   In the treatment of a participant, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the participant or a legally authorized representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

APPENDIX 2

List of names and addresses:

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APPENDIX 3

Concomitant medication limitations

Medical Cannabis
THC and CBD are metabolized by CYP3A4 and CYP2C9 (Yamaori et al 2012, Watanabe et al 2007). CYP3A4 inhibitors slightly increase THC levels. CYP3A4 inducers slightly decrease THC and CBD levels. CBD, but not THC, is metabolized by CYP2C19 (Stout and Cimino 2014).
Theoretically, THC can decrease serum concentrations of clozapine, duloxetine, naproxen, cyclobenzaprine, olanzapine, haloperidol, and chlorpromazine (Flockhart 2007, Watanabe et al 2007).
As CYP3A4 metabolizes about a quarter of all drugs, CBD may increase serum concentrations of macrolides, calcium channel blockers, benzodiazepines, cyclosporine, sildenafil (and other PDE5 inhibitors), antihistamines, haloperidol, antiretrovirals, and some statins (atorvastatin and simvastatin, but not pravastatin or rosuvastatin).
CYP2D6 metabolizes many antidepressants, so CBD may increase serum concentrations of SSRIs, tricyclic antidepressants, antipsychotics, beta blockers and opioids (including codeine and oxycodone).

Drug interaction studies
THC and CBD increase warfarin levels (Yamaori et al 2012). Alcohol may increase THC levels (Hartman 2015). Smoked cannabis can decrease theophylline levels (Stout and Cimino 2014). In children treated with CBD for epilepsy, CBD increased clobazam levels (Geffrey et al 2015).

Conclusion
Cannabis enhances CNS depressant effects when combined with alcohol, barbiturates and benzodiazepines, but probably not opioids. THC induces CYP1A2, and can reduce levels of drugs metabolized by CYP1A2. CBD inhibits CYP3A4 and CYP2D6, and can increase levels of drugs metabolized by these isoenzymes. CPY3A4 metabolizes about a quarter of all drugs.

The Sativex SPC (Sativex SPC) provides a thorough review of a balanced THC/CBD cannabis pharmaceutical product which is a purified version of the strain of cannabis being studied in this protocol. Although our strain has a range of minor cannabinoids and terpenes that Sativex has removed by purification, the Sativex SPC provides further guidance on the concomitant medication limitations of the two major cannabinoids contained within the strain under investigation.