Project TWENTY21

REGISTRY PROTOCOL

Version: 2

Date: 08-Jan-2021

Sponsor: Drug Science

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Version 1.0   10-Jan-2020

Revision History

Version	Date	Summary of Changes
1.0	10-Jan-2020	Initial Version

List of Abbreviations

BPI-SF	Brief Pain Inventory-Short Form
CBD	Cannabidiol
DSM-5	Diagnostic and Statistical Manual of Mental Disorders
EDSS	Expanded Disability Status Scale
EQ-5D	EuroQol 5 Dimensions
GAD-7	Generalized Anxiety Disorder – 7 Item Scale
PCL-C	Post Traumatic Stress Disorder Checklist - Civilian Version
PGIC	Patient's Global Impression of Change
PHQ-9	Patient Health Questionnaire
PTSD	Post Traumatic Stress Disorder
QOLIE-10-P	Patient Weighted Quality of Life in Epilepsy
RWD	Real-World Data
SDS	Severity of Dependence Scale
THC	Delta-9-tetrahydrocannabinol
UK	United Kingdom
YGTSS	Yale Global Tic Severity Scale

Summary

Sponsor	Drug Science
Methodology	Prospective observational multi-center registry
Background and Objectives	The cannabis plant has recently generated considerable attention among both the medical community and general population for its potential medicinal capabilities. Although many countries have endorsed cannabis as a medical treatment, there remains a lack of evidence to definitively support its prescription and use. This gap in evidence has influenced its accessibility for patients in the United Kingdom. The patient registry aims to provide extensive effectiveness and safety data that will help identify the role that medical cannabis may play in symptom management for the included indications.
Population	The registry population is individuals presenting to a prescribing physician seeking medical cannabis for any of the seven included indications, namely: (i) chronic pain, (ii) post-traumatic stress disorder, (iii) anxiety, (iv) multiple sclerosis, (v) Tourette's syndrome, (vi) epilepsy, and (vii) substance use disorder.
Outcomes	The outcome measures include a health outcome questionnaire specific to each included indication, depression (where relevant), a general health-related quality of life questionnaire, patients' impression of change, impact on sleep quality, and reported safety data.
Follow-Up	Patients will be followed for two years.
Sample Size	20,000 patients will be included in the registry.

1.0 Introduction

1.1 Cannabis as a Medical Treatment

The cannabis plant has been used in traditional medicine for centuries, recently generating considerable attention among both the general population and medical communities for its potential medicinal capabilities.[1] Cannabis contains more than 100 different chemical compounds, known as cannabinoids, that act primarily on the human endocannabinoid system via interaction with cell receptors throughout the body. These compounds alter neurotransmitter function in the brain, affecting physiological functions from inflammation and pain to sleep, memory, and digestion.[2] Of these compounds, Delta-9-tetrahydrocannabinol (THC) and, to a lesser extent, cannabidiol (CBD) have undergone the most scientific study and their effects are the most well known. THC is the most abundant of the cannabinoids and is psychoactive in nature, leading to temporary changes in a users' mood, behaviour, and perception (which is why it is controlled under the UK Misuse of Drugs Act 1971). CBD, on the other hand, is the second most abundant cannabinoid and is considered to be non-psychoactive, with little to no side effects (which is why it is not controlled under the UK Misuse of Drugs Act 1971).[3]

The interest in medical cannabis has led to an increase in its use to treat medical conditions, either through individuals accessing the drug via the recreational or illicit markets or via medical cannabis programs in regions where regulations permit. Chronic pain, anxiety and depression/mood are three of the most common reasons patients use medical cannabis[4]; however, it is currently being prescribed for numerous conditions including epilepsy, Tourette's Syndrome, insomnia, and multiple sclerosis, to name a few.[5,6]

1.2 Medical Cannabis in the United Kingdom

In November 2018, unlicensed cannabis-based products became a Schedule 2 drug[7] in the United Kingdom (UK), allowing physicians on the General Medical Council Specialist Register to prescribe it to their patients.[8] However, to date, very few patients have received a prescription for medical cannabis, despite lobby and patient groups suggesting that as many as 1,000,000 potential patients in the UK may benefit from treatment. A lack of evidence surrounding the use of medical cannabis has influenced its accessibility for patients in need, and this prohibitionist approach to medical cannabis access in the UK has the potential to increase harm by driving patients to the illicit market, fuelling an illegal supply chain that will be difficult, if not impossible, to dismantle in the future.

1.3 The Need for Real-World Data

It is widely recognized that there is a need for additional research to support the prescription and use of medical cannabis worldwide, as the rapid rise in the use of medical cannabis has not yet been accompanied by conclusive evidence of its efficacy. Although randomized controlled trials are regarded as the gold standard of evidence, the unique properties of cannabis and the acceptance of its medicinal use in many countries worldwide presents an opportunity for the use of real-world data (RWD). RWD is an umbrella term for data regarding the effects of health interventions that are not collected in the context of highly-controlled trials.[9] Instead, RWD can either be primary research data collected in a manner which reflects how interventions would be used in routine clinical practice or secondary research data derived from routinely collected data.[9]

This registry seeks to develop a body of RWD to inform on the effectiveness and safety of medical cannabis for seven indications for patients in the UK, namely: (i) chronic pain, (ii) post-traumatic stress disorder (PTSD), (iii) anxiety, (iv) multiple sclerosis, (v) Tourette's syndrome, (vi) epilepsy and (vii) substance use

disorder. These indications were chosen for the potential benefit that medical cannabis may offer in those patients whom alternative treatments have failed, as outlined below.

1.3.1 Medical Cannabis for Chronic Pain

Chronic pain is extremely prevalent in the UK, with an estimated 28 million adults suffering from it.[10] Chronic pain is uncurable in the traditional sense; patients instead must work with their care providers to find ways to manage their pain to a level that is satisfactory.[11] A study that surveyed 1,000 dispensary customers in the adult use market of Colorado, USA, indicated that 65% of respondents reported using cannabis specifically to relieve pain. Of these participants, 80% reported that cannabis effectively reduced pain and over 80% reported reducing their opioid use.[12] This anecdotal evidence indicates that some patients with chronic pain are successfully using cannabis as a treatment, which is encouraging and would benefit from further investigation in the UK market.

1.3.2 Medical Cannabis for Post-Traumatic Stress Disorder

Post-traumatic stress disorder (PTSD) is defined as the "persistent difficulty in processing of previously experienced extreme life-threatening situations," such as combat violence, natural disasters, assault, or critical illness.[13] It is a common morbidity among military and veteran populations,[14] as well as being prevalent in the general wider population.[15] A systematic review of cannabis use for mental health demonstrated preliminary evidence of its potential benefit for individuals diagnosed with PTSD, including reduced restlessness, irritability, and sleep difficulties in addition to reports of greater emotional regulation, reduced feelings of anxiety, and improved functioning overall.[16]

1.3.3 Medical Cannabis for Anxiety Disorders

Anxiety is an umbrella term for a group of disorders, all of which can affect the physical and mental health of an individual, often leading to their inability to work, socialize, study, or manage daily tasks of living.[17] It is estimated that there are over 8 million individuals in the UK with an anxiety disorder,[18] and those diagnosed often face excessive and irrational fear, apprehensive and tense feelings, and distress related to performing certain tasks. Where mainstay medications for anxiety have failed, or for patients seeking alternate treatment options, cannabis has become a common choice.[16] However, with the complexity of anxiety disorders and the many formulations of cannabis as a medication, further data are needed.

1.3.4 Medical Cannabis for Multiple Sclerosis

Multiple sclerosis is a disease of the central nervous system that results in an autoimmune response against the myelin sheath that protects nerve fibers, that can potentially result in progressive neurodegeneration and disability.[19] Individuals living with multiple sclerosis often suffer from high levels of disability and impaired quality of life for prolonged periods of time. In 2010, it was estimated that 127,000 people in the UK were living with multiple sclerosis.[20] A mixture of pure THC and CBD (Sativex) is licensed for the treatment of spasticity in multiple sclerosis but full plant extract cannabis is preferred by many people with this disorder. There is some available evidence to support its positive effects on muscle spasticity and pain; however, additional data and evidence are required to support its value.[21]

1.3.5 Medical Cannabis for Tourette's Syndrome

Tourette's syndrome is a neuropsychiatric disorder that causes involuntary motor and vocal tics.[22] It is a genetic condition that often begins in childhood with no known cure and affects approximately 1% of school-aged children and an estimated 0.3%-0.5% of adults in the UK.[23] The goals of treatment of Tourette's syndrome focuses mainly on reducing or controlling the tics through behavioural, rather than

medicinal, intervention, due to potential side effects of available medications.[22,23] Cannabis may have a positive impact within this population, as preliminary evidence from a retrospective study demonstrated promising results, warranting further investigation.[22]

1.3.6 Medical Cannabis for Epilepsy

Epilepsy is one of the most common neurological disorders, with an estimated prevalence of 6 million people in Europe and over 500,000 people in the UK.[24,25,26] Approximately one third of the total epileptic population have seizures that are resistant to treatment with anti-epileptics, demonstrating the need for alternative treatment options.[24] Studies undertaken during the 1960's and 1970's have shown that cannabinoids have potential anti-convulsive effects and, therefore, could be utilized as a potential treatment option for seizure management.[27] However, the safety and efficacy profiles of cannabinoid use in the short term, as well as in the long term as a therapy for epilepsy, still require further investigation.[28]

1.3.7 Medical Cannabis for Substance Use Disorder

Substance use disorder is often classified along with other mental health diagnoses and includes the misuse of nicotine, alcohol, pharmaceutical and illicit drugs.[29,30] In the UK, almost 3% of the population have a current substance use disorder, causing significant burden on the health care system.[29] Treatment of substance use disorder may include therapies, medicinal treatments, detoxification, or support groups.[31] Despite being a recreational drug itself, cannabinoids have shown promise as a treatment option for substance use disorder as substitution of more harmful substances (e.g. opioids and cocaine.[32] Moreover many people with cannabis use disorder are addicted to strong cannabis (skunk) that is deficient in CBD. Prescribing a lower THC balanced plant extract might also help these individuals cut down their high THC use.

1.4 Rationale

Despite progress being made in terms of access to medical cannabis in many western countries, patients in the UK have been left behind; in the year since cannabis was made a Schedule 2 medicine, less than 50 prescriptions have been issued. As it is estimated that over 200,000 UK patients use illegally sourced medical cannabis, this gap is alarming since they are unable to legally access treatment that they may benefit from. Project TWENTY21 seeks to close this gap in access by providing data to help facilitate decision making about the use of medicinal cannabis in the UK.

2.0 Study Objectives

The primary objective of Project TWENTY21 is to develop a substantial body of evidence using a RWD registry to document clinical effectiveness, safety, quality-adjusted life years, and patient-reported outcomes in those prescribed medical cannabis. Project TWENTY21 will include patients diagnosed with the following indications: (i) chronic pain, (ii) PTSD, (iii) anxiety, (iv) multiple sclerosis, (v) Tourette's syndrome, (vi) epilepsy and (vii) substance use disorder.

These data and findings from the registry will be provided to regulatory bodies such as the National Institute for Health and Care Excellence and to the Medicines and Healthcare products Regulatory Agency to facilitate decision making surrounding the regulatory system for medical cannabis in the UK.

3.0 Study Design

This study is a multi-centre, prospective, observational patient registry of RWD that aims to include 20,000 patients eligible for medical cannabis. Patients will be entered into the registry and followed for two years for data collection purposes at the same intervals used in standard of care.

4.0 Methods

4.1 Study Population

The registry will include patients with one of seven indications who are seeking access to medical cannabis after failure of at least two non-cannabis management options for their condition. The seven eligible indications are as follows:

- Chronic pain
- PTSD
- Anxiety
- Multiple sclerosis
- Tourette's syndrome
- Epilepsy
- Substance use disorder

4.2 Recruitment Strategy and Consent

All patients presenting to a participating prescribing physician will be screened for inclusion in the registry via the Sail software. Patients will self-refer to a prescribing physician at a clinic and are required to present all necessary documentation from their general practitioner, including:

- Evidence of diagnosis meeting one of the seven clinical indications
- Evidence of failure of two other non-cannabis treatment options
- Past medical history and co-morbidities
- Current medications

Patients with evidence of one of the seven indications will be invited to participate in the registry. If they agree, consent will be obtained following Good Clinical Practice guidelines. As there is no clinical intervention as part of participation in the registry, patients will consent only to the collection of their data. Patients under the age of 16 will require proxy consent by a parent or guardian. Patients who participate in the registry will be prescribed a product from one of the licensed producers partnered on the registry and will receive their prescription at a discounted flat rate.

The patient should notify the clinic when booking the initial consultation if they are already registered as a T21 patient at another clinic. Then the clinic looking to accept the patient must notify the original clinic (CC'ing in Drug Science) referencing the patient whose file they require and the clinic the patient data is to be transferred over to. Once approval has been given, CB2 will facilitate the transfer.

4.3 Data Collection

All pertinent demographic, medical and condition-specific history will be entered into the Sail software as part of the registry data. This will be completed at the patient's initial visit with their prescribing physician. The patient's medical cannabis prescription information will be recorded in the registry database and updated every time the patient renews their prescription.

4.4 Outcome Measures

In order to fulfill the primary objective of Project TWENTY21, each indication included in the registry has its own condition-specific outcome measure associated with it. In addition, as described below, all patients will also complete a health-related quality of life questionnaire, a questionnaire to assess their perception of their treatment, questions regarding sleep and insomnia, and select patients will complete an outcome questionnaire related to depression. The outcome measures will be completed at the patient's first visit to the clinic and at subsequent visits that the patient attends, as per standard of care at the clinics. The outcome measures are as follows:

4.4.1 Chronic Pain

The primary outcome measure for patients with chronic pain is the Brief Pain Inventory Short Form (BPI-SF). The BPI-SF is validated for use in patients with both cancer and non-cancer pain[33] and is one of the most commonly used measurement tools for evaluating clinical pain, including pain severity and the interference of pain on feeling and function.[34]

4.4.2 PTSD

The primary outcome measure for patients with PTSD is the Post Traumatic Stress Disorder Checklist - Civilian Version (PCL-C). The PCL-C is a reliable and validated tool to provide assessment on PTSD symptom change and is a widely used self-report measure to assess the symptoms of PTSD, as well as being a tool for the provisional PTSD diagnosis.[35]

4.4.3 Anxiety

The primary outcome measure for patients with anxiety is the Generalized Anxiety Disorder 7-Item Scale (GAD-7). The GAD-7 is one of the most frequently used, validated, self-reported questionnaires that is used to screen for, diagnose, and assess the severity of generalized anxiety disorder.[36]

4.4.4 Multiple Sclerosis

The primary outcome measure for patients with pain from multiple sclerosis is the BPI-SF. In addition to this, the Expanded Disability Status Scale (EDSS) will also be used. The EDSS is an internationally accepted, widely used tool to measure the disease progression in multiple sclerosis that has been evaluated for its validity and reliability.[37]

4.4.5 Tourette's Syndrome

The primary outcome measure for patients with Tourette's syndrome is the Yale Global Tic Severity Scale (YGTSS). The YGTSS is a reliable tool for measuring tic severity in Tourette's syndrome[38] and is reported to be internally consistent for its measures across adults and children.[38]

4.4.6 Epilepsy

The primary outcome measure for patients with epilepsy is the Patient Weighted Quality of Life in Epilepsy (QOLIE-10-P). The QOLIE-10-P is a 10-item questionnaire containing epilepsy-specific dimensions and is a reliable and sensitive instrument for assessing quality of life in epilepsy patients.[39] The approximate number and severity of seizures will also be reported.

4.4.7 Substance Use Disorders

The primary outcome measure for patients with substance use disorder is the Severity of Dependence Scale (SDS). The SDS is a short, 5-item scale for measuring the degree of dependence experienced by

users[40] and its score is related to behavioural patterns of drug use, which indicates substance dependence. The psychometric properties of the SDS are very reliable across different populations.[40]

4.4.8 Health-Related Quality of Life

The health-related quality of life instrument that will be used in this registry is the EuroQol 5 Dimensions (EQ-5D). It is a widely used, validated, and reliable tool that assesses the quality of life of patients in many disease areas[41] through assessment of the severity of each of 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression).

4.4.9 Depression

The outcome measure that will be used for depression is the Patient Health Questionnaire (PHQ-9). The PHQ-9 is a reliable and valid measure of depression severity and is comprised of a 9-item self-rated instrument that has been validated in general populations, medical populations and psychiatric samples.[42] Registry patients with chronic pain, PTSD, anxiety and substance use disorder will complete this questionnaire at their first visit to the clinic and at subsequent follow-up visits.

4.4.10 Perceived Adequacy of Treatment

Patients will be asked as part of their follow-up visits whether they believe that their prescribed medical cannabis has been adequate in treating their respective condition. Patients will also complete the Patients' Global Impression of Change (PGIC) scale, regarded as an important indicator of the impact of treatments,[43] at each follow-up visit.

4.5 Patient Follow-up

Patient follow-up will adhere to standard of care at each clinic and will not differ based on inclusion in the registry. Follow-up is typically completed every three months (13 weeks) and patients will complete all standard follow-up questions, including questions pertaining to insomnia and health-outcome questionnaires at any visits they attend.

If a patient does not return to the clinic during a follow-up window, the visit will be marked as incomplete. To ensure the greatest likelihood of collecting data, visit windows will touch. For example, the 3-month visit window will stretch from 6.5 weeks post-enrollment to 19.5 weeks, and the 6-month visit window will stretch from 19.5 weeks to 32.5 weeks. If a patient attends the clinic multiple times within a visit window, the full follow-up visit assessment will only be completed once; any additional visits will be recorded as an unscheduled visit if necessary.

4.6 Final Patient Status

Patients will remain in the registry for two years. For patients who cease attendance at a clinic for their medical cannabis prescription, all data entered prior will remain in the database. If a patient chooses not to have a prescription renewed, the reason will be recorded, if possible.

5.0 Data Management

5.1 Data Access

All data for the registry will be entered via the Sail software and will be reviewed for completeness and accuracy. Clinicians who require access at the participating clinics will have access to the Sail software via user accounts with unique login credentials. The access to patient data will be governed by the user

account permissions based on the requirements of the clinician, and they will only be able to review data for patients at their own clinic.

Access to the entire database is governed by Drug Science, including provision of anonymized data sets to any collaborators per official requests.

5.2 Database & Security

The Sail software, as part of the CB2 Insights umbrella of technology, is committed to the privacy and protection of patient data and the data of its clients. The Sail software meets both Health Insurance Portability and Accountability Act and General Data Protection Regulation compliance standards. CB2 Insights utilizes a third party, iSecurity consulting, to ensure that all standards are met and to employ regular cybersecurity testing.

CB2 Insights is a data, analytics and technology company that provides software and services for managing clinical data collection and clinical decision support. CB2 manages several patient registries in North America and Europe.

6.0 Statistical Methods

The registry will generate considerable volumes of data, including self-reported symptoms assessed at the start of treatment (i.e., covering the 'before treatment' period) and at regular intervals assessed prospectively throughout the course of treatment. The availability of this rich RWD set will enable analysis of the dataset utilizing a number of statistical methods in order to gain insight into the impact that medical cannabis has had on patient reported outcomes.

Methods will include: a) comparisons of symptom intensity before and after the onset of treatment, and b) analyses of the repeated measures data to examine changes in symptomatology over time. A variety of statistical approaches will be utilized including regression-based methods, survival analysis (if, for specific conditions, there is a clearly defined end point) and trajectory-based methods, such as latent trajectory analyses. Such methods allow for the identification of specific symptom trajectories (e.g., gradual reduction in symptoms vs. rapid reduction) and examination of whether individuals following these different trajectories vary on personal characteristics (e.g., gender, symptom intensity at start of treatment) or treatment characteristics (e.g., product type, dose).

7.0 Ethics

According to the National Health Service Health Research Authority, the Project TWENTY21 is classified as research; however, based on the Medical Research Council decision tools, Research Ethics Committee review and approval is not required.

A copy of this decision tool verdict is available in Appendix 1.

8.0 Confidentiality

All records containing identifying information will be kept confidential, and only delegated individuals will have physical and/or electronic access to them. All patients entered in to the registry will have a unique patient identification number assigned to them. Any data exported from the registry will only use the patient identification number; patient names will not be distributed in any way.

9.0 Adverse Effects

Patients will be asked to self-report any adverse effects or negative side effects they experience as a result of their medical cannabis prescription. Physicians will be responsible to reporting these events as per regulatory requirements.

10.0 Knowledge Translation

A publication policy will be developed in order to facilitate the translation of knowledge gained as a result of this registry.

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Appendix 1: Research Ethics Committee Requirement

MRC | Medical Research Council

NHS Health Research Authority

Do I need NHS REC approval?

To print your result with title and IRAS Project ID please enter your details below:

Title of your research:

Project TWENTY21

IRAS Project ID (if available):

N/A

Your answers to the following questions indicate that **you do not need NHS REC approval** for sites in England. However, you may need other approvals.

You have answered *'YES'* to: Is your study research?

You answered *'NO'* to all of these questions:

Question Set 1

- Is your study a clinical trial of an investigational medicinal product?
- Is your study one or more of the following: A non-CE marked medical device, or a device which has been modified or is being used outside of its CE mark intended purpose, and the study is conducted by or with the support of the manufacturer or another commercial company (including university spin-out company) to provide data for CE marking purposes?
- Does your study involve exposure to any ionising radiation?
- Does your study involve the processing of disclosable protected information on the Register of the Human Fertilisation and Embryology Authority by researchers, without consent?

Question Set 2

- Will your study involve potential research participants identified in the context of, or in connection with, their past or present use of services (adult and children's healthcare within the NHS and adult social care), including participants recruited through these services as healthy controls?

- Will your research involve collection of tissue or information from any users of these services (adult and children's healthcare within the NHS and adult social care)? This may include users who have died within the last 100 years.
- Will your research involve the use of previously collected tissue or information from which the research team could identify individual past or present users of these services (adult and children's healthcare within the NHS and adult social care), either directly from that tissue or information, or from its combination with other tissue or information likely to come into their possession?
- Will your research involve potential research participants identified because of their status as relatives or carers of past or present users of these services (adult and children's healthcare within the NHS and adult social care)?

Question Set 3

- Will your research involve the storage of relevant material from the living or deceased on premises in the UK, but not Scotland, without an appropriate licence from the Human Tissue Authority (HTA)? This includes storage of imported material.
- Will your research involve storage or use of relevant material from the living, collected on or after 1st September 2006, and the research is not within the terms of consent from the donors, and the research does not come under another NHS REC approval?
- Will your research involve the analysis of DNA from bodily material, collected on or after 1st September 2006, and this analysis is not within the terms of consent for research from the donor? And/or: Will your research involve the analysis of DNA from materials that do not contain cells (for example: serum or processed bodily fluids such as plasma and semen) and this analysis is not within the terms of consent for research from the donor?

Question Set 4

- Will your research involve at any stage intrusive procedures with adults who lack capacity to consent for themselves, including participants retained in study following the loss of capacity?
- Is your research health-related and involving prisoners?
- Does your research involve xenotransplantation?
- Is your research a social care project funded by the Department of Health and Social Care (England)?

If your research extends beyond **England** find out if you need NHS REC approval by selecting the *'OTHER UK COUNTRIES'* button below.