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**UK Medical Cannabis Registry**

**Protocol**

**Version 2.1**

**Date: 8th November 2022**

**Sponsor: Sapphire Medical Clinics**

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|  |  |  |
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| Version Number | Date | Key Updates |
| V2.00 | 15th July 2022 | Change in hosting platform for Registry |
| V1.00 | 1st December 2019 | - |

**Abbreviations**

|  |  |
| --- | --- |
| Δ9-THC | (–)-Trans-Δ9-tetrahydrocannabinol |
| 5-HT3 | 5-hydroxytryptamine 3 |
| CB1 | Cannabinoid type 1 |
| CB2 | Cannabinoid type 2 |
| CBMPs | Cannabis-based medicinal products |
| CBD | Cannabidiol |
| DMP | Data management plan |
| GABA | γ-aminobutyric acid |
| GCP | Good Clinical Practice |
| HRA | Health Research Authority |
| HRQoL | Health-related quality of life |
| NICE | National Institute for Health and Care Excellence |
| PPAR-γ | Peroxisome proliferator-activated receptor-γ |
| PPIE | Patient and public interaction and engagement |
| PROMs | Patient reported outcome measures |
| RCTs | Randomised controlled trials |
| REC | Research Ethics Committee |
| TRP | Transient receptor potential |
| UK | United Kingdom |
| UKMCR | UK Medical Cannabis Registry |

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## Introduction

In 2018, cannabis-based medicinal products (CBMPs) were rescheduled in the United Kingdom (UK) under the Misuse of Drugs Regulations 2001, moving them from Schedule 1 (controlled drugs considered to have no medicinal value) to Schedule 2 (controlled drugs acknowledged to have medicinal benefits) (1). The National Institute for Health and Care Excellence (NICE) has provided guidance to support the utilisation of licensed CBMPs (nabilone, Epidyolex® and Sativex®) in the setting of chemotherapy induced nausea and vomiting, treatment-resistant epilepsy in Dravet and Lennox-Gastaut Syndromes, and multiple-sclerosis-associated spasticity (1,2). However, they did not provide any recommendation regarding the prescribing of unlicensed CBMPs (1,2). However, for conditions where sufficient prior clinical evidence exists, unlicensed CBMPs can be initiated by members of the General Medical Council’s Specialist Register for patients who have failed to achieve a satisfactory clinical response to licensed therapies (1). These conditions comprise of an array of pain, psychiatric, gastrointestinal, neurological, and dermatological conditions, in addition to the symptoms of cancer and/or its treatment (3-10).

CBMPs are derived from species of the cannabis plant (*Cannabis sativa*, *Cannabis indica*, and *Cannabis ruderalis*) which have previously been described as containing a ‘pharmacological treasure trove’ of active pharmaceutical ingredients (11). The major compounds contained within CBMPs are the cannabinoids cannabidiol (CBD) and (–)-trans-Δ9-tetrahydrocannabinol (Δ9-THC). However, there are potentially over 400 potential active pharmaceutical ingredients contained within the cannabis plant (12,13). Hence, the pharmacology and resultant effects of cannabis, and products made thereof, vary between different chemovars of cannabis according to the concentrations and interactions of these compounds (12,13). Cannabinoids are known for their effects on the endocannabinoid system, an endogenous system of ligands, receptors, and enzymes which are ubiquitous throughout the central nervous system, but also peripheral tissues and play a regulatory role in neurotransmission.

Δ9-THC is a partial agonist of cannabinoid type 1 (CB1) and type 2 (CB2) receptors (14). CB1 receptors are concentrated in the central nervous system, particularly presynaptic terminals in the cerebellum, basal ganglia, and hippocampus (15). Activation of CB1 receptors inhibits calcium ion influx resulting in reduced synaptic release of neurotransmitters such as glutamate and γ-aminobutyric acid (GABA) (15). It is this mechanism which mediates the cognitive, emotional, memory, and euphoric effects of Δ9-THC (15,16). CB2 receptors were initially believed to be found exclusively on peripheral immune cells, however there is also evidence of their presence on microglial cells (17,18). Activation of CB2 receptors is associated with inhibition of immune signalling, particularly interleukin-1 and tumour necrosis factor- α pathways (17,18). This has been implicated in a diverse set of pre-clinical models for immune-related diseases, as well as pain (17,18). Beyond effects at canonical cannabinoid receptors Δ9-THC has also demonstrated evidence of interacting the following receptors with varying potencies: 5-hydroxytryptamine 3 (5-HT3), GPR18, GPR55, peroxisome proliferator-activated receptor-γ (PPAR-γ), and opioid receptors, as well as transient receptor potential (TRP) channels (19-23). Comparatively CBD is a negative allosteric modulator of CB1/2 receptors (24), however its main mechanism of action is to increase the concentration of anandamide through preventing re-uptake via fatty acid binding ligands and degradation via fatty acid amid hydrolase (25,26). Similar to Δ9-THC, CBD has demonstrated a diverse spectrum of additional receptor and enzyme targets in vitro (27). Both major cannabinoids have subsequently been associated with analgesic, anti-inflammatory, anti-emetic, anti-spasticity, anti-psychotic, anticonvulsant, anxiolytic, appetite-stimulating, and neuroprotective effects (10,12,13,28-32).

This multitude of effects through interaction with a diverse range of targets has been suggested as a mechanism for improvement of health-related quality of life (HRQoL) with respect to chronic disease. There have been attempts to assess this within well-defined cohorts with respect to geographical location, treatment modality, and condition. A Canadian clinic assessed the outcomes of patients prescribed for CBMPs for up to 6 months for a range of conditions (33). This study which was limited to CBD-rich CBMPs products found an improvement in pain, anxiety, depression, and overall wellbeing, however it was only able to report findings on 279 out of the 715 which were eligible for inclusion (33). An observational study assessing the role of CBMPs in patients with chronic pain, showed that, after 12 months, significant improvements were seen in pain intensity, pain disability, anxiety, and depression. However, the greatest improvement was seen between baseline and three months (32). Another observational study of 400 patients in New Zealand concluded that CBD was associated with reduced depression, anxiety, and pain symptoms in patients treated for mental health symptoms and non-cancer pain. In addition, an overall improvement was seen in general HRQoL assessed by the EQ-Visual Analogue Scale (34). Likewise, earlier publications from the UK Medical Cannabis Registry (UKMCR), analysing patient reported outcome measures (PROMs) after 1, 3, and 6 months, suggest that CBMPs may improve HRQoL for patients with various chronic conditions (35,36). Several randomised controlled trials have also recorded improved quality of life as a secondary outcome (30). Turcott et al. investigated Nabilone, a synthetic Δ9-THC analogue, as a treatment for cancer-related cachexia over a period of 8 weeks. Whilst only limited improvements were seen in appetite and cachexia-associated symptoms, several quality-of-life measures were significantly improved (30). However, a recent systematic review investigating the relationship between medical cannabis and HRQoL was inconclusive, citing significant heterogeneity of the current literature (37).

## Rationale

High-quality evidence is critical in clinical translation of new pharmaceuticals. Randomised controlled trials (RCTs) are undoubtedly of great importance in evaluating efficacy and safety of medical products. The diversity of molecular targets and active pharmaceutical ingredients is in part responsible for the broad range of effects and potential clinical uses for CBMPs. This heterogeneity, however, adds to the complexity of performing high-quality research on CBMPs and the ability to arrive at a consensus on its effects on HRQoL across different chemovars, formulations, and routes of administration for each clinical indication (38). RCTs will ultimately be necessary to determine the appropriate utilisation of CBMPs however there are several barriers to their conduct, in addition to the complex pharmacology of the plant, most notably the lack of an appropriate placebo control and costs (38). Observational evidence, collected in a prospectively enrolled patient registry has the potential to inform prescribing guidelines, regulations, and the quality and design of RCTs via a top-down approach (38).

In 2019, NHS England and Improvement performed a review on barriers to accessing CBMPs on prescription (39). Within this, they reiterated the paucity of high-quality evidence on the safety and efficacy of CBMPs (39). Moreover, the authors highlighted that parents, carers, and clinicians believed RCTs would not be available in a timely manner and that a structured dataset needed to be collected on those patients being prescribed CBMPs to add to current evidence and inform future RCTs (39). This subsequently led to the authors issuing a recommendation that a national patient registry should be established to collect outcomes across all indications for which CBMPs are prescribed in the UK. The UKMCR was subsequently devised to meet this unmet need for further evidence on efficacy and safety.

## 3. Registry Objectives

The primary objective of the UKMCR is to collect a comprehensive data source of real-world evidence that can be utilised by researchers to answer outstanding questions such as the following:

1. To study the epidemiological and clinic-pathological characteristics of patients prescribed CBMPs in the UK and Channel Islands.
2. To study the safety of CBMPs.
3. To study effects of CBMPs on concomitantly prescribed medications.
4. To study the effects of prior cannabis, alcohol, and tobacco consumption on outcomes of patients prescribed CBMPs.
5. To study the socio-economic effects of CBMPs.
6. To study the effectiveness of CBMPs.

## 4. Methods

### 4.1 Patient Identification

Patients are identified from those enrolled at clinics which have agreed to contribute to the UKMCR. Eligible participants are subsequently identified by the local clinical care team. Inclusion criteria extends to patients who are prescribed CBMPs. CBMPs must adhere to the criteria for Good Manufacturing Practice (1). These can contain either isolated cannabinoids or be a broad/full spectrum extract. For broad/full spectrum extracts and dry flower the chemovars were either Cannabis sativa, Cannabis indica, or a hybrid species. CBMPs must only be initiated by clinicians abiding by the latest national guidance (1).

### 4.2 Enrolment and Consent

Patients are enrolled prospectively prior to first appointment. Patients shall be approached to provide informed consent in line with Good Clinical Practice (GCP) guidelines (40). Participants are not required to provide informed consent within any specific timeframe to allow them to fully consider the implications of enrolling and discuss enrolment with local research/clinical team as appropriate. Consent will be provided electronically, and a copy will be held in a patient’s electronic health records. A copy will be available to the participant. As there is no required clinical intervention as part of participation in the registry, patients will only consent to the collection of their data. Patients under the age of 16 will require proxy consent by a parent or guardian.

Patient enrolment into the study will occur once consent is taken and eligibility criteria is met. A randomised 20-character unique registry identification number is generated utilising computer-based fair randomisation for each patient for pseudonymisation of data.

### 4.3 Data Collection

Participants will engage with clinic within the guidance of usual care as delivered by participating clinics. There are no additional interventions required through enrolment in the UKMCR to deviate from usual standard of care.

Figure 1 outlines the process for data collection through the UKMCR. The majority of data collected within the UKMCR is required for the delivery of standard of care, except for PROMs which are an additional prospective data source.

All pertinent demographic, medical and condition-specific history, as well as concomitant medications and previous drug and alcohol exposure will be entered into the UKMCR as outlined in the Data Management Plan (DMP). This shall be completed at baseline during the patient’s initial visit by their prescribing physician through inputting of information on the clinical team’s data reporting portal for the UKMCR which is directly linked to the participant’s electronic healthcare record. Concomitant medications can also be inputted directly by participants.

Timeline

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**Figure 1:** Process of data acquisition through the UK Medical Cannabis Registry from provision of consent to completion of follow up data. Follow up patient reported outcome measures are completed at 1, 3, 6 months and every 6 months thereafter. Other follow up data can otherwise be provided at any time interval. *CBMPs – cannabis-based medicinal products; PROMs – patient reported outcome measures.*

Any changes to concomitant medications shall be inputted directly into the registry through the medications form on a participant’s bespoke UKMCR data reporting portal. Alternatively, the patient’s clinical team can also insert current medications at baseline, as well as any changes to medications during the course of treatment with medical cannabis.

The patient’s medical cannabis prescription information, as outlined in the DMP, will be recorded in the UKMCR database and updated every time there is a change to the either the type of CBMP prescribed or dose of medication.

PROMs shall be collected electronically at baseline, prior to treatment beginning, then subsequently at 1 month, 3 months, 6 months, and every 6 months thereafter. These shall be completed online via the UKMCR data reporting portal. Participants shall be prompted to complete the questionnaires via an email directing them to the portal on each follow up date. If the questionnaires are not completed an automated follow up email reminder shall be sent every 72 hours until they have been completed, as this has been shown to improve completion rates of PROMs (41).

Participants are required to record any adverse events they may have experienced, and their severity and duration, prior to completing any PROMs. In addition, participants can report these at any time through a separate form within their bespoke UKMCR data reporting portal page. The clinical team can also record adverse events during clinical consultations.

### 4.4 Outcome Measures

The data sources which comprise the UKMCR are outlined in Table 1 and are described in full in the DMP.

All data sources are collected within the performance of routine clinical care.

The principal outcome measures for the UKMCR are PROMs. For each condition participants are asked to complete a general set of PROMs, in addition to condition-specific measures.

**Table 1.** Data sources of the UK Medical Cannabis Registry

|  |  |
| --- | --- |
| **Data Arm** | **Summary** |
| **Clinicopathological Characteristics** | Demographic details of participants at baseline of study period, supplemented by comorbidities, and drug and alcohol data |
| **Medication Data** | Concomitant medications taken by participants, including information about dose and method of administration |
| **Prescribed CBMPs** | Information regarding prescribed CBMPs, including products prescribed and dose |
| **PROMs** | Validated questionnaires to assess general changes in HRQoL as well as those specific to primary indication for treatment |
| **Adverse Events** | Incidence of adverse events, in addition to length of adverse event and grade |

*CBMPs – cannabis-based medicinal products; HRQoL – health-related quality of life; PROMs – patient reported outcome measures*

### 4.5 Study Duration

There is no time restriction on the UKMCR. For patients who cease to continue treatment with CBMPs for their medical cannabis prescription, all data entered prior will remain in the database. A participant may however request that their record in the UKMCR may be deleted at any time.

### 4.6 European Medical Cannabis Registry

In addition, to the UK Medical Cannabis Registry, at present there are national patient registries undergoing development in other European Countries. These, alongside the UK Medical Cannabis Registry will be incorporated within a pan-European dataset, called the European Medical Cannabis Registry, which is held in the same secure framework and subject to the same data security standards as the UK Medical Cannabis Registry. Currently, similar applications are currently underway with the appropriate institutions in other jurisdictions across Europe.

This will allow for international benchmarking, in addition to comparison in outcomes across different populations and to also accelerate the development of evidence which may best inform practice in UK and internationally.

## 5. Data Analysis and Statistical Considerations

Statistical guidance and study design oversight will be provided by the Registry Steering Group under the leadership of the Chief Investigator. The rich volume of data collected prospectively as outlined in the DMP facilitates several unique analyses. Individual research proposals must be supported by robust scientific methodology.

Analysis may include:

1. Assessment of demographics of patients prescribed CBMPs
2. Evaluation in change in PROMs during treatment compared to baseline
3. Evaluation of associated adverse events following commencement of CBMPs

Analyses may be considered according to individual conditions, CBMPs or both. Statistical design of individual projects must account for the magnitude of any potential differences in effect between underlying patient characteristics, conditions, and CBMPs. Moreover, they should account for different sensitivities in PROMs to detect a change in patient symptomatology or HRQoL.

Each project will require a bespoke statistical methodology which must be reviewed by the Registry Steering Group prior to commencement. However, the diversity of data lends itself to a range of statistical methodologies, including logistic and linear regression, as well as survival analysis to assess the different effects according to condition, clinicopathological characteristics of patients at baseline, prior cannabis exposure, and prescribed CBMPs.

## 6. Data Management

### 6.1 Data Privacy and Monitoring

The data acquisition process has been described above with further detail described within the DMP.

All patient information remains confidential and will be maintained in the following manner:

* Access to patient data will only be permitted to necessary personnel.
* Only the clinical care team will be able to access identifiable patient data.
* All investigational site patient identifiers will be removed, and study-specific identifiers will be assigned and maintained.
* The principal investigator, co-investigators, clinical staff and all other individuals involved in the research study will follow practice according to the International Conference on Harmonization, GCP, the Declaration of Helsinki, UK Policy Framework for Health and Social Care Research, and the Human Tissue Amendment Act.
* The study protocol will be given approval by the appropriate Research Ethics Committee (REC) and Health Research Authority (HRA).

This study may be terminated at the request of the Principal Investigator, if, during the study, concerns about the safety of the patients emerge.

As an observational study all aspects of this study are non-interventional in nature, and there will be no risk to the patient from the collection of their routine clinical data.

### 6.2 Data Security

The UKMCR complies with all legislative and legal requirements. The security of the UKMCR and its associated policies have been assessed and approved by the NHS Data Security and Protection Toolkit, as well as being compliant with BS7799; ISO17799; ISO/EC27002; the Code of Practice for Information Security Management part 1: 1999 and part 2: 2002, and the UK-General Data Protection Regulation (UK-GDPR).

All data is held in a secure cloud-based server provided by Google Cloud Platform. The Google Cloud Platform was chosen from a suite of other providers including Amazon Web Services, Heroku and Azure for hosting of the UKMCR because of robust framework it has adopted not just for healthcare but also for handling healthcare data in the UK, for which it published a white paper in 2020 (42). The Google Cloud Platform operates as a data processor, whilst the Registry Management Group acts as the data controller.

Google Cloud Platform has an internal audit function and regularly engages third parties to conduct independent reviews of the effectiveness of the organisation’s approach to managing information security.

Physical security of the data features a layered security model, including safeguards like custom-designed electronic access cards, alarms, vehicle access barriers, perimeter fencing, metal detectors, and biometrics, and the data centre floor features laser beam intrusion detection. Data centres are monitored 24/7 by high-resolution interior and exterior cameras that can detect and track intruders. Access logs, activity records, and camera footage are available in case an incident occurs. Data centres are also routinely patrolled by experienced security guards who have undergone rigorous background checks and training. As one gets closer to the data centre floor, security measures also increase. Access to the data centre floor is only possible via a security corridor which implements multi-factor access control using security badges and biometrics. Only approved employees with specific roles may enter.

To protect information and that confidentiality is maintained information is only accessible by appropriate and authorised users as assigned by the Registry Management Group. Each clinical team member has a single sign on to the UKMCR data collection platform through which to input clinical information regarding a participant. The access to patient data is governed by user account permission based on the requirements of each member of the patient’s clinical team. They shall only be able to see data from patients at their own clinic. Access is limited to a password protected log-in. The user identification and password management of this adheres to BS 7799 (ISO27001 and IS017799) standard. All those who interact with the UKMCR are required to abide by the Data Protection Act 2018. Access to the UKMCR is only permitted using computers with the latest antivirus/malware software provided by ESET Cloud Admin programme, where operating system versions for users are recorded and monitored.

The security of the technology and processes is annually assessed via penetration testing through an accredited third-party.

Data backups are taken on a weekly basis to ensure there are working backups of the data. These are stored on a separate server and routinely tested to ensure that data and information can be restored.

To ensure that adequate safety protections are in place a process review is held at least once per year or additionally following any data security incidents or near misses. Participation in reviews is comprehensive. If any data breaches/near misses occur, then they shall be reported to the Data Custodian who will consider the nature of the data and report it to the Information Commissioner’s Office appropriately and accordingly.

Participants can only report their relevant outcomes through a bespoke remote data reporting platform. This can only be accessed by participants through a unique web address provided on a named participant basis, which is password protected.

The data outputs of the UKMCR are only available to members of the Registry Management Group through a secure password-protected login. All outputs are pseudonymised using a randomly generated 20-character unique registry identification number.

### Data Access Requests

External data access requests must be processed in accordance with the Research Data Governance Operating Framework. This includes the Data Transfer Specification plan which details the process for data transfer. Recipients of data via data access requests shall only be provided with data that is necessary to complete the desired aims of the approved project. Data must be held and analysed in a secure cloud-based data repository/data safe haven or equivalent that meets UK/European standards for data storage and handling. All data must be analysed within the secure platform and not transferred beyond this. Data shall not be transferred to countries outside of the European Economic Area unless they offer equivalent protection.

Researchers will be required to delete all data within 6 months following publication of the registered studies and to provide signed confirmation back to the UKMCR Committee that this has been completed.

## 7. Confidentiality

The Chief Investigator will preserve the confidentiality of participants taking part in the study under Data Protection Act 2018. Patient confidentiality is of paramount importance and will be strictly observed.

All exported data is linked via a pseudonymised identification code, and the participant shall not be identifiable.

## 8. Regulatory and Ethics Committee Approval

This UKMCR will be conducted in compliance with the protocol, standard operating procedures, policies, local research management guidance, GCP including the UK Policy Framework for Health and Social Care Research and other applicable regulatory requirement(s).

The data obtained from this study will provide important information for the wider community but not influence the patient directly. As an observational registry, the patients shall not be exposed to any additional interventions beyond usual standard of care.

A copy of the protocol, proposed informed consent form and other written patient information, will be submitted to an independent ethics committee and any other relevant regulatory authorities, subject to the regulations of the country of each participating site, for written approval.

The Chief Investigator will submit and, where necessary, obtain approval from the independent ethics committee concerned and any other relevant regulatory authorities for all subsequent protocol amendments. The investigator will notify the same of deviations from the protocol.

## 9. Financing, Indemnity, & Insurance

Sapphire Medical Clinics shall provide funding for the ongoing management of the UKMCR, including ensuring adequate oversight from staff and the maintenance of licenses for relevant PROMs.

In order to ensure sustainability, the UKMCR Steering Group has engaged with discussions with the Department for Health and Social Care and the National Institute for Health Research about funding the UK Medical Cannabis Registry, as well as utilisation by the National Health Service.

As an observational study no specific compensation arrangements exist for harmful events that might arise. However, if any patients are harmed during the during routine clinical care existing statutory mechanisms shall be available to them.

## 10. Patient and Public Interaction and Engagement

The input of both patients and the public have been sought throughout protocol development to plan, manage, design, and eventually conduct the proposed research. The research has been presented to the Sapphire Medical Clinics Patient and Public Interaction and Engagement (PPIE) Group which has provided global feedback for iterative improvements.

In addition, a global survey evaluation has been conducted of participants already enrolled in the UKMCR. In this evaluation, which has been accepted for publication in a peer review journal, participants were asked to rate the importance of the UKMCR, the ease of data completion, and outlined priorities for future research from the UKMCR (43). Participants also provided open text answers which were analysed thematically to provide iterative improvements to the UKMCR.

Over 90% of patients strongly agreed or agreed that it was important to contribute to medical cannabis research such that its effects can be greater understood (43). Moreover, 92.2% of patients strongly agreed or agreed that contributing to the UKMCR would impact the medical care of future patients (43).

The majority of participants (91.6%) found it easy to complete PROMs remotely. Few participants (8.67%) recorded an adverse event, of which 73.1% found it easy to do so (43). Those participants who had used the electronic portal to record their medications 90.4% and 85.0% of patients found it easy to input medication names and dosages respectfully (43). Most participants (86.7%) also found it easy to input the route of administration (43).

## 11. Publication Policy

Results from any UKMCR project will be required to be submitted for publication in a relevant medical journal with authorship according to requirements for manuscripts in the Vancouver Statements.

The results of studies shall be shared directly with participants through the email by which they have enrolled in the UKMCR for reminders to complete PROMs and adverse event questionnaires, except in the condition that they have opted out of these communications.

Furthermore, research results shall be disseminated widely via social media and press releases shall be sent to traditional and trade media to see if there is any interest in publishing the results within news articles.

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