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Expert Review of Clinical Pharmacology

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ierj20

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To cite this article: Michael Harris, Simon Erridge, Mehmet Ergisi, Devaki Nimalan, Michal Kawka, Oliver Salazar, Rayyan Ali, Katerina Loupasaki, Carl Holvey, Ross Coomber, Azfer Usmani, Mohammed Sajad, Jonathan Hoare, James J Rucker, Michael Platt & Mikael H Sodergren (2022) UK Medical Cannabis registry: an analysis of clinical outcomes of medicinal cannabis therapy for chronic pain conditions, Expert Review of Clinical Pharmacology, 15:4, 473-485, DOI: 10.1080/17512433.2022.2017771

To link to this article: https://doi.org/10.1080/17512433.2022.2017771

Published online: 31 Dec 2021.

EXPERT REVIEW OF CLINICAL PHARMACOLOGY
2022, VOL. 15, NO. 4, 473–485
https://doi.org/10.1080/17512433.2022.2017771

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ORIGINAL RESEARCH

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UK Medical Cannabis registry: an analysis of clinical outcomes of medicinal cannabis therapy for chronic pain conditions

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ABSTRACT

Objectives: To explore pain-specific, general health-related quality of life (HRQoL), and safety outcomes of chronic pain patients prescribed cannabis-based medicinal products (CBMPs).

Methods: A case series was performed using patients with chronic pain from the UK Medical Cannabis Registry. Primary outcomes were changes in Brief Pain Inventory short-form (BPI), Short-form McGill Pain Questionnaire-2 (SF-MPQ-2), Visual Analogue Scale-Pain (VAS), General Anxiety Disorder-7 (GAD-7), Sleep Quality Scale (SQS), and EQ-5D-5L, at 1, 3, and 6 months from baseline. Statistical significance was defined at p-value<0.050.

Results: 190 patients were included. Median initial Δ^9-tetrahydrocannabinol and cannabidiol daily doses were 2.0mg (range:0.0–442.0mg) and 20.0mg (range:0.0–188.0mg) respectively. Significant improvements were observed within BPI, SF-MPQ-2, GAD-7, SQS, EQ-5D-5 L index, and VAS measures at all timepoints (p<0.050). Seventy-five adverse events (39.47%) were reported, of which 37 (19.47%) were rated as mild, 23 (12.11%) as moderate, and 14 (7.37%) as severe. Nausea (n=11; 5.8%) was the most frequent adverse event.

Conclusion: An association was identified between patients with chronic pain prescribed CBMPs and improvements in pain-specific and general HRQoL outcomes. Most adverse events were mild to moderate in severity, indicating CBMPs were well tolerated. Inherent limitations of study design limit its overall applicability.

ARTICLE HISTORY
Received 27 July 2021
Accepted 14 November 2021

KEYWORDS
Medical cannabis; chronic pain; pharmacotherapy; pain severity; pain interference; health-related quality of life; opioid dosing

1. Introduction

Chronic pain is defined as 'persistent or recurrent pain lasting longer than 3 months' and is estimated to affect between 35.0–51.3% of the UK population [1,2]. Chronic pain is associated with increased incidence of anxiety and depression, disability, and reduced health-related quality of life (HRQoL) [3–5]. Furthermore, chronic pain is associated with high socioeconomic costs due to increased absenteeism and unemployment, alongside reduced productivity [6]. Indeed, the economic cost of chronic back pain to the UK was estimated at £12.3 billion GBP in 2000 (£21.2 billion GBP at present inflation) [7]; current associated costs are likely to be higher secondary to a growing and aging population [8].

Currently, there are limited pharmacological options for the management of chronic pain of all etiologies. For example, the National Institute for Clinical Excellence (NICE) exclusively recommends antidepressant medications for the management of chronic primary pain [9]. However, pharmacological management of chronic pain in a clinical setting often involves medications which NICE describes as having insufficient or poor-quality evidence to support their use, including non-opioid, and opioid analgesics [9]. Nonsteroidal anti-inflammatory drugs are frequently prescribed for musculoskeletal chronic pain conditions yet are increasingly associated with serious dose-dependent adverse effects [10,11]. Opioid medications are widely used in clinical practice for multiple etiologies of chronic pain [12]. Yet, randomized controlled trials (RCTs) involving opioids have largely been performed in acute pain settings, with limited evidence to support benefit in chronic pain, particularly in light of their well-known adverse effects [13]. Gabapentinoids similarly lack sufficient evidence to support the extent to which they are currently prescribed in clinical practice, and are increasingly associated with individual harm with long-term use [14–17]. Research and development of novel pharmaceutical agents, in addition to repurposed drugs, is therefore essential to tackle this growing epidemic.

The endocannabinoid system has subsequently become an established target for drug development due to its implicated role in both central and peripheral pain pathways. Cannabis plants, including *Cannabis sativa* and *Cannabis indica*, contain

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greater than 144 unique phytocannabinoids, the most researched of which are Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD) [18]. THC is a partial agonist for cannabinoid receptors type 1 and 2 (CB1-R and CB2-R), which are G-protein coupled receptors of the endocannabinoid system [19,20]. CBD acts in a comparatively more complex manner. CBD is a negative allosteric modulator of CB1-R, modifying the clinical effects of THC and other agonists [21]. CBD appears to alter the outcome profile of THC by reducing the likelihood of adverse events resultant of THC [19,22]. Furthermore, CBD also inhibits fatty acid amino hydrolase, increasing levels of anandamide, an endogenous CB1-R and CB2-R agonist [23]. CB1-R is expressed in the central and peripheral nervous systems, and is dense within areas associated with central nociceptive processing [19]. CB1-R agonism inhibits voltage-sensitive calcium channels, ultimately preventing neurotransmission in these regions of the brain [24,25]. It is this mechanism by which CB1-R agonism is thought to provide analgesic and psychotropic effects. The CB2-R is predominantly expressed on immune cells. Accordingly, its primary known function is to modulate inflammatory cytokines; whether this contributes to the proposed analgesic properties of cannabinoids is unknown [26–28]. CB2-Rs are also expressed in central nervous system cells, albeit to a much lesser extent than the immune system; the extent to which phytocannabinoids may affect these receptors located in differing bodily systems is currently not well described in the literature [28].

Cannabinoids also produce effects at other endogenous drug targets, including opioid, transient receptor potential cation channel subfamily V member 1 and serotonin receptors [29]. These supplementary targets are also involved in central and peripheral pain signaling pathways, with in vitro data supporting their role in any proposed clinical effect in relieving pain [30,31].

Observational studies have found associations between chronic pain patients on cannabis-based medicinal product (CBMP) therapy with significant reductions in pain severity and interference, and improvements in overall HRQoL measures [32–34]. However, RCTs investigating CBMPs in the setting of chronic pain have largely been of indifferent quality, leading to conflicting conclusions and subsequent guidance from regulatory and advisory bodies [35–37]. In the setting of neuropathic pain, double-blind RCTs have demonstrated significant improvements in pain intensity, and HRQoL measures compared to placebo [38,39]. Wilsey *et al*., investigating the effect of vaporized cannabis on central neuropathic pain, also demonstrated dose-dependent improvements in neuropathic pain scores. Yet, false-discovery rate adjustment demonstrated these reductions to be statistically non-significant [40]. Overall, the evidence base is limited by the quality of trials, which are generally underpowered, have limited generalizability, and are inconsistent in reporting outcomes [41]. Most studies involving CBMPs are performed in acute settings, meaning there is a paucity of evidence regarding long-term effects of cannabis in chronic pain, with further research required [26].

Patient registries offer an increasingly important source of observational data, providing evidence in a resource-efficient manner within a real-world setting. Patient registries hold the advantage of collecting naturalistic real-world data, enhancing external validity, whilst compromising on internal validity. The UK Medical Cannabis Registry (UKMCR) was established in December 2019 to prospectively collect data of patient outcomes, allowing exploration of the benefit-risk profile for numerous medical conditions, and assessment of long-term safety and efficacy of CBMP therapy [42].

Herein, this study presents an analysis the outcomes of chronic pain patients registered in the UKMCR. The primary aims being to explore changes in validated patient-reported outcome measures (PROMs), incidence of adverse events, and changes in daily oral morphine equivalent doses.

2. Methods

2.1. Study design

Data was extracted from the prospectively designed UKMCR of patients treated with CBMPs for chronic pain. Patients who gave fully informed written consent were prompted to complete questionnaires at baseline, 1 month, 3 months, and 6 months. Herein, this study is reported in accordance with the STROBE guidelines for reporting observational studies [43]. In line with NHS Health Research Authority and Research Ethics Committees guidance, this study was considered not to require formal ethical approval (Appendix A).

2.2. Setting and participants

The UKMCR is a patient registry established in December 2019, which longitudinally captures pseudonymised data of patients prescribed CBMPs in the UK and Channel Islands, and is privately owned by Sapphire Medical Clinics. Inclusion criteria for this study were: individuals aged greater than 18 years old with chronic pain lasting >3 months, commenced on CBMP therapy. Patients who were treated primarily for a chronic pain condition, including cancer pain, complex regional pain syndrome, Ehlers-Danlos syndrome, fibromyalgia, and neuropathic pain, were included. Patients who had chronic pain caused by alternate pathophysiology were also included under 'chronic pain of undefined aetiology.' Diagnosis was assigned by a specialist pain physician following clinical assessment. Patients treated with CBMPs for alternate conditions with a secondary indication of chronic pain were excluded. Patients were excluded if they had not completed a baseline PROMs assessment or had been enrolled in the UKMCR less than 1 month.

2.3. Outcomes of interest

The baseline questionnaires captured demographic data including age, sex, occupation, and medical history. The Body Mass Index (BMI) was also calculated for each participant. Primary, secondary, and tertiary conditions for which CBMPs were prescribed were recorded. The incidence of comorbidities including hypertension, depression and/or anxiety, arthritis, epilepsy, and endocrine dysfunction were also recorded. The Charlson Co-morbidity Index, a tool which predicts the ten-year mortality for an individual, was calculated

for each participant [44]. Parameters including drug and alcohol data, smoking status, and past cannabis use were recorded.

Data regarding CBMP prescriptions were recorded at each follow-up, including manufacturing company, formulation, route of administration, THC and CBD concentrations and doses, and type of strain. All CBMP prescriptions were manufactured according to Good Manufacturing Practice (GMP) criteria [45].

Adverse events were either self-reported by patients at each remote follow-up, or were recorded following disclosure to their clinician during a routine visit. Adverse events were categorized in accordance with the Common Terminology Criteria for Adverse Events v4.0 [46].

Medication data was recorded for prescriptions in the following British National Formulary (BNF) chapters:

- Analgesics
- Anticoagulants and protamine
- Antidepressants
- Antidiabetic Drugs
- Antiplatelets
- Hypnotics and Anxiolytics

Oral morphine equivalent doses were calculated in line with conversion factors quoted by the BNF, apart from tapentadol, which was converted using figures quoted by the Royal College of Anaesthetists as it was unavailable from the BNF [47,48].

The gold standard for assessing chronic pain conditions is self-reporting via PROMs [49]. Approaches aiming to assess pain intensity and severity include categorical scales (i.e. mild, moderate, severe), numerical rating scales (NRS), and visual analogue scales (VAS) [49]. The following PROMs were collected at baseline, and at 1, 3, and 6 months.

2.3.1. Brief Pain Inventory short form (BPI)

A two-part NRS which captures Pain Severity ('0' = 'no pain' to '10' = 'pain as bad as you can imagine') and Pain Interference ('0' = 'does not interfere' to '10' = 'completely interferes').

2.3.2. Short-form McGill Pain Questionnaire-2 (SF-MPQ-2)

A NRS consisting primarily of 4 major classes of word descriptors. For each class, patients are asked to numerically rate ('0' = 'none' to '10' = 'worst possible pain intensity') the intensity of pain and pain-related symptoms over the past week. A mean score between 0 to 10 is generated for each pain subscale, as well as a mean overall pain score [50].

2.3.3. Generalized Anxiety Disorder-7 (GAD-7)

A 7-item NRS which captures generalized anxiety in a population. Patients are asked how often they have been bothered by various symptoms of anxiety over the last two weeks ('0' = 'not at all' to '3' = 'nearly every day'). The scores are totaled to generate a score from 0 to 21, with mild, moderate, and severe anxiety described as ≥5, ≥10, and ≥15, respectively [51].

2.3.4. EQ-5D-5L

A two-part tool utilized to measure the overall HRQoL in a population. The first part is a NRS measuring five domains, (mobility, self-care, usual activities, pain or discomfort, anxiety or depression) with five levels of severity ('1' = 'no problems' to '5' = 'extreme problems'). From these, a 5-digit code is generated, then mapped to EQ-5D-5L index values as described by van Hout *et al*., the preferred methodology of measuring HRQoL by NICE [52,53]. An EQ-5D-5L index score of 1 represents full health, whereas a score of <0 represents a health-status that is worse than death. The second part is the EQ-VAS, which asks patients how they would rate their health from 0 to 100 ('0' = 'the worst health you can imagine' to '100' = 'the best health you can imagine').

2.3.5. Sleep Quality Scale (SQS)

A single-item measure utilizing a VAS, which captures quality of sleep. Patients are asked how they would rate their sleep quality ('0' = 'terrible' to '10' = 'excellent') over the past 7 days [54].

2.3.6. VAS-pain

A VAS capturing how severely patients are experiencing their pain. Patients are asked to rate their pain ('0' = 'no pain' to '10' = 'pain as bad as it could be') at that moment.

2.4. Outcome measures

Primary outcomes were changes from baseline in BPI, SF-MPQ-2, VAS Pain, GAD-7, SQS, and EQ-5D-5 L PROMs, at 1, 3, and 6 months. Secondary outcomes included adverse event incidence, and changes in daily oral morphine equivalent doses.

2.5. Statistical methods

Patient data was extracted from the UKMCR according to recorded diagnosis. Demographic variables, patient conditions, cannabis status, tobacco and alcohol use, medication data and adverse events were analyzed using descriptive statistics. PROM analysis involved comparisons with baseline at 1, 3, and 6 months; 1 month, 3 month, and 6 month PROMs were compared with baseline readings independently, so that patients with missing follow-up PROMs may still be included utilizing listwise deletion. The normality of the distributions of each data set was determined utilizing the Shapiro-Wilk test. Unless otherwise stated, parametric continuous data are presented as mean (± standard deviation (±S.D.)), and non-parametric continuous data are presented as median (range). Statistical analysis was performed using the student paired t-test or the Wilcoxon rank sum test, if data were parametric or non-parametric, respectively. Statistical significance was defined as $p < 0.050$. Demographic data and adverse event data were analyzed using Statistical Package for Social Sciences (SPSS) [IBM Statistics version 27 SPSS Inc] [55]. PROMs were analyzed using GraphPad Prism [GraphPad Prism for Windows version 9.0.0, GraphPad software Inc] [56]

3. Results

3.1. Patient data

Preliminary data extraction from the registry included 289 patients with a chronic pain diagnosis. Patients without completion of a baseline PROM were excluded, and patients who were enrolled in the registry for less than 1 month at the time of extraction were also excluded, leaving 190 patients included for final analysis (Figure 1). Of these, 135 patients had recorded PROMs at 1 month, 68 patients had recorded PROMs at 3 months, and 44 patients had recorded PROMs at 6 months.

Baseline demographic details are displayed in Table 1. The mean age of patients was 47.50 (±14.88) years. One hundred and four (54.7%) patients were female. The highest occupation recorded was 'other occupation' (n = 112; 58.9%); of these, 57 (30.0%) were unemployed. The mean BMI of patients was 26.98 kg/m^2 (±7.34).

Table 2 displays the diagnoses for which CBMP treatment was indicated. The most common primary diagnosis was chronic pain of undefined etiology (n = 98; 51.6%), followed by neuropathic pain (n = 43; 22.6%), and fibromyalgia (n = 31; 16.3%). A total of 71 (37.4%) and 11 (5.8%) patients, respectively, were diagnosed with secondary and tertiary chronic pain indications for treatment. The median Charlson Comorbidity Index was 1 (range:0–9). The incidence of hypertension (n = 23; 12.1%), depression and/or anxiety (n = 76; 40.0%), arthritis (n = 50; 26.3%); epilepsy (n = 1; 0.5%); endocrine dysfunction (n = 16; 8.4%) were also recorded.

Eighty-nine (46.8%) patients had never smoked cigarettes, 61 (32.1%) were ex-smokers, and 39 (20.5%) were current smokers. Median alcohol consumption was 1 unit per week (range: 0–120). Ninety-five (50.0%) patients had never used cannabis, 23 (12.1%) were ex-users, and 71 (37.4%) were current cannabis users.

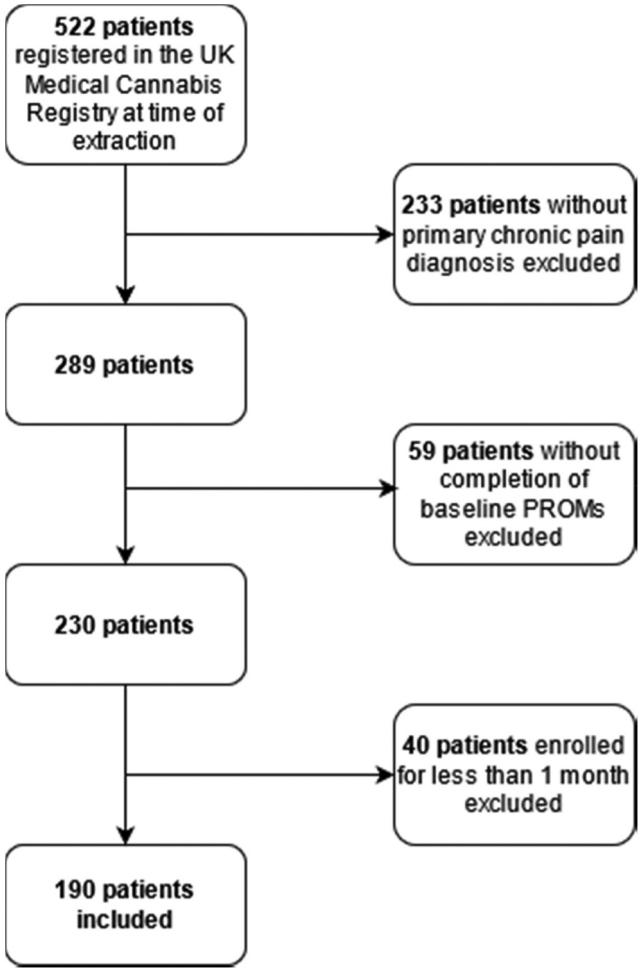

Figure 1. A flow diagram depicting the inclusion and exclusion of patients.

Table 1. Baseline demographics of study participants (n = 190).

Demographic Details	n (%)/mean (± S.D)
Sex	
Female	104 (54.7%)
Male	86 (45.3%)
Age	47.50 ± 14.88
Occupation	
Clerical support workers	1 (0.5%)
Craft and related trades workers	7 (3.7%)
Elementary occupations	9 (4.7%)
Managers	9 (4.7%)
Plant and machine operators, and assemblers	4 (2.1%)
Professional	29 (15.3%)
Service and sales workers	4 (2.1%)
Skilled agricultural, forestry and fishery workers	2 (1.1%)
Technicians and associate professionals	13 (6.8%)
Other occupation*	112 (58.9%)
Body Mass Index	26.98 ± 7.34

*Other occupations – Unemployed (n = 57; 30.0%), Unspecified (n = 41; 21.5%), Retired (n = 9; 4.7%), Student (n = 3; 1.6%), all else (n = 2; 1.1%).

Table 2. Primary, secondary, and tertiary diagnoses of patients with chronic pain indications. (n = 190).

Diagnosis	Primary n (%)	Secondary n (%)	Tertiary n (%)
Chronic pain of undefined etiology	98 (51.6%)	26 (13.7%)	3 (1.6%)
Neuropathic pain	43 (22.6%)	15 (7.9%)	4 (2.1%)
Fibromyalgia	31 (16.3%)	20 (10.5%)	1 (0.5%)
Ehlers-Danlos	14 (7.4%)	9 (4.7%)	3 (1.6%)
Cancer pain	2 (1.1%)	1 (0.5%)	0 (0.0%)
Complex regional pain syndrome	2 (1.1%)	0 (0.0%)	0 (0.0%)
Anxiety	0 (0.0%)	7 (3.7%)	6 (3.2%)
Insomnia	0 (0.0%)	7 (3.7%)	0 (0.0%)
Migraine	0 (0.0%)	4 (2.1%)	5 (2.6%)
PTSD	0 (0.0%)	4 (2.1%)	2 (1.1%)
Autistic spectrum disorder	0 (0.0%)	2 (1.1%)	2 (1.1%)
Depression	0 (0.0%)	2 (1.1%)	6 (3.2%)
Cluster headaches	0 (0.0%)	1 (0.5%)	0 (0.0%)
Crohn's Disease	0 (0.0%)	1 (0.5%)	0 (0.0%)
Epilepsy adult	0 (0.0%)	1 (0.5%)	0 (0.0%)
Headache	0 (0.0%)	1 (0.5%)	0 (0.0%)
Ulcerative colitis	0 (0.0%)	1 (0.5%)	0 (0.0%)
Agoraphobia	0 (0.0%)	0 (0.0%)	1 (0.5%)
Social phobia	0 (0.0%)	0 (0.0%)	1 (0.5%)

3.2. CBMP dosing and mode of administration

The median number of CBMPs prescribed at baseline was 2, with 16 (8.4%), 137 (72.1%), 29 (15.3%), and 7 (3.7%) patients being prescribed 1 to 4 different CMBPs, respectively. CBMPs were administered via oral, sublingual, or vaporized routes of administration. The vast majority (n = 177; 93.2%) of patients were prescribed at least 1 oil preparation, administered via either oral or sublingual routes. The most commonly

prescribed therapies were Adven 20 and Adven 50 sublingual medium-chain triglyceride oils (Curaleaf International, Guernsey, UK). Thirty-eight (20.0%) patients were prescribed 1 vapourised dry flower preparation, and 10 (5.3%) were prescribed 2 such preparations. The median initial daily THC dose was 2.0 mg (0.0 mg-442.0 mg). The median initial daily CBD dose was 20.0 mg (range: 0.0 mg-188.0 mg).

3.3. Patient reported outcome measures

Table 3 outlines the results at 1, 3, and 6 months for the GAD-7, SQS, and EQ-5D-5 L HRQoL measures. Statistically significant improvements were observed at 1, 3, and 6 months for GAD-7, SQS, the EQ-5D-5L pain and discomfort subscore, and the EQ-5D-5L Index Value ($p < 0.050$). Statistically significant improvements were observed at 1 and 3 months for EQ-5D-5L mobility, and EQ-VAS subscores ($p < 0.050$). A significant improvement at 1 month was observed in the EQ-5D-5L anxiety and depression subscore ($p < 0.050$).

Table 4 outlines the results for the BPI, SF-MPQ-2, and VAS-Pain outcome measures. Statistically significant improvements were seen for all measures at all time points ($p < 0.050$).

Table 3. Paired baseline and follow-up scores for GAD-7, SQS, and EQ-5D-5L measures at 1, 3 and 6 months.

		n	Scores at Baseline	Scores at Follow-Up	p-value
GAD-7	1 month	135	5.00 (0.00–23.00)	4.00 (0.00–22.00)	0.025
	3 month	68	5.50 (0.00–23.00)	4.00 (0.00–21.00)	0.001
	6 month	44	6.00 (0.00–23.00)	4.50 (0.00–23.00)	0.032
SQS	1 month	113	5.00 (0.00–10.00)	5.00 (0.00–9.00)	<0.001
	3 month	55	4.00 (0.00–9.00)	6.00 (0.00–10.00)	<0.001
	6 month	33	4.00 (0.00–9.00)	6.00 (1.00–9.00)	0.002
EQ-5D-5L Mobility	1 month	128	3.00 (1.00–5.00)	3.00 (1.00–5.00)	0.002
	3 month	67	3.00 (1.00–5.00)	3.00 (1.00–5.00)	0.043
	6 month	41	3.00 (1.00–5.00)	3.00 (1.00–5.00)	0.291
EQ-5D-5L Self-Care	1 month	128	2.00 (1.00–5.00)	2.00 (1.00–5.00)	0.134
	3 month	67	2.00 (1.00–5.00)	2.00 (1.00–5.00)	0.216
	6 month	41	2.00 (1.00–5.00)	2.00 (1.00–5.00)	0.798
EQ-5D-5L Usual Activities	1 month	128	3.00 (1.00–5.00)	2.50 (1.00–5.00)	<0.001
	3 month	67	3.00 (1.00–5.00)	2.00 (1.00–5.00)	<0.001
	6 month	41	3.00 (1.00–5.00)	3.00 (1.00–5.00)	0.031
EQ-5D-5L Pain and Discomfort	1 month	128	4.00 (1.00–5.00)	3.00 (1.00–5.00)	<0.001
	3 month	67	4.00 (1.00–5.00)	3.00 (1.00–5.00)	<0.001
	6 month	41	4.00 (2.00–5.00)	3.00 (2.00–5.00)	<0.001
EQ-5D-5L Anxiety and Depression	1 month	127	2.00 (1.00–5.00)	2.00 (1.00–4.00)	0.002
	3 month	67	2.00 (1.00–5.00)	2.00 (1.00–4.00)	0.137
	6 month	41	2.00 (1.00–5.00)	2.00 (1.00–5.00)	0.372
EQ-VAS	1 month	128	49.51 ± 20.49	53.05 ± 21.27	0.024
	3 month	66	48.11 ± 20.69	56.59 ± 20.63	0.001
	6 month	40	46.28 ± 21.12	50.80 ± 22.05	0.284
EQ-5D-5L Crosswalk Index Value	1 month	126	0.41 (−0.36–1.00)	0.55 (−0.36–0.88)	<0.001
	3 month	62	0.37 (−0.28–1.00)	0.54 (0.05–1.00)	<0.001
	6 month	41	0.30 (−0.33–0.77)	0.49 (−0.27–0.84)	0.005

GAD-7 – General Anxiety Disorder-7; SQS – Sleep Quality Scale; EQ-VAS – EQ-visual analogue scale

Table 4. Paired baseline and follow-up measures for validated pain outcome measures at 1; 3; 6 months.

		n	Scores at Baseline	Scores at Follow-Up	p-value
BPI Pain Severity	1 month	93	5.50 ± 1.83	5.11 ± 1.86	0.001
	3 month	50	5.67 ± 1.90	4.68 ± 1.70	<0.001
	6 month	31	5.70 ± 1.84	4.42 ± 2.26	<0.001
BPI Pain Interference	1 month	93	5.52 ± 2.27	4.83 ± 2.31	<0.001
	3 month	50	5.62 ± 2.23	4.45 ± 2.55	<0.001
	6 month	31	6.01 ± 2.05	4.42 ± 2.26	<0.001
SF-MPQ-2 Neuropathic Pain	1 month	86	3.09 (0.00–8.00)	2.67 (0.00–8.17)	<0.001
	3 month	48	3.17 (0.00–8.00)	2.00 (0.00–7.00)	<0.001
	6 month	28	3.42 (0.00–7.67)	2.59 (0.00–5.67)	0.002
SF-MPQ-2 Continuous Pain	1 month	86	4.67 (0.00–10.00)	3.83 (0.17–9.50)	0.021
	3 month	48	4.50 (0.33–10.00)	3.17 (0.17–7.83)	<0.001
	6 month	28	4.50 (0.33–9.33)	3.25 (0.00–8.00)	<0.001
SF-MPQ-2 Intermittent Pain	1 month	86	4.59 (0.00–9.83)	3.50 (0.00–8.83)	0.008
	3 month	48	4.42 (0.00–9.83)	3.00 (0.00–8.71)	<0.001
	6 month	28	3.75 (0.00–9.83)	2.50 (0.00–9.33)	<0.001
SF-MPQ-2 Affective Pain	1 month	87	3.75 (0.00–9.25)	3.00 (0.00–9.50)	0.036
	3 month	48	4.63 (0.00–9.25)	2.75 (0.00–8.00)	<0.001
	6 month	28	4.75 (0.25–9.25)	2.75 (0.00–7.00)	<0.001
SF-MPQ-2 Overall Pain Score	1 month	86	4.08 (0.44–8.27)	3.32 (0.46–8.19)	<0.001
	3 month	48	4.46 (0.44–8.27)	2.71 (0.09–7.60)	<0.001
	6 month	28	4.37 (0.44–7.73)	3.15 (0.04–5.50)	<0.001
VAS-Pain	1 month	104	7.00 (0.00–10.00)	7.00 (0.00–10.00)	0.011
	3 month	56	7.00 (0.00–10.00)	6.00 (0.00–10.00)	<0.001
	6 month	36	7.00 (2.00–10.00)	5.50 (0.00–9.00)	<0.001

BPI – Brief Pain Inventory; SF-MPQ-2 – Short-form McGill Pain Questionnaire-2; VAS – Visual Analogue Scale

3.4. Oral morphine equivalent

At baseline, the median oral morphine equivalent of those prescribed opioid medication was 24.0 mg (n = 91; range: 3.0 mg – 960.0 mg). The baseline median oral morphine equivalent of the entire patient cohort was 0.0 mg (range: 0.0 mg-960.0 mg).

No significant differences were observed in oral morphine equivalent doses after 1 month ($p > 0.050$). Compared to baseline, the median oral morphine equivalent was significantly reduced at 3 months (n = 15; median of differences = −15.00 mg; $p = 0.004$), and 6 months (n = 10; median of differences = −10.50 mg; $p = 0.030$) (Figure 2.).

3.5. Adverse events

Reported adverse events are outlined in full within Table 5. Forty-three (18.7%) patients reported at least one adverse event, with 20 (8.7%) patients reporting two or more adverse events. There were 75 (39.47%) adverse events in total. The most common adverse events were nausea (n = 11; 5.8%) and fatigue (n = 6, 3.2%). Relative to the number of total adverse events, 49.3% were mild, 30.7% were moderate, and 18.7% were severe. There was one (0.53%) disabling adverse event of insomnia, which lasted for 4 days.

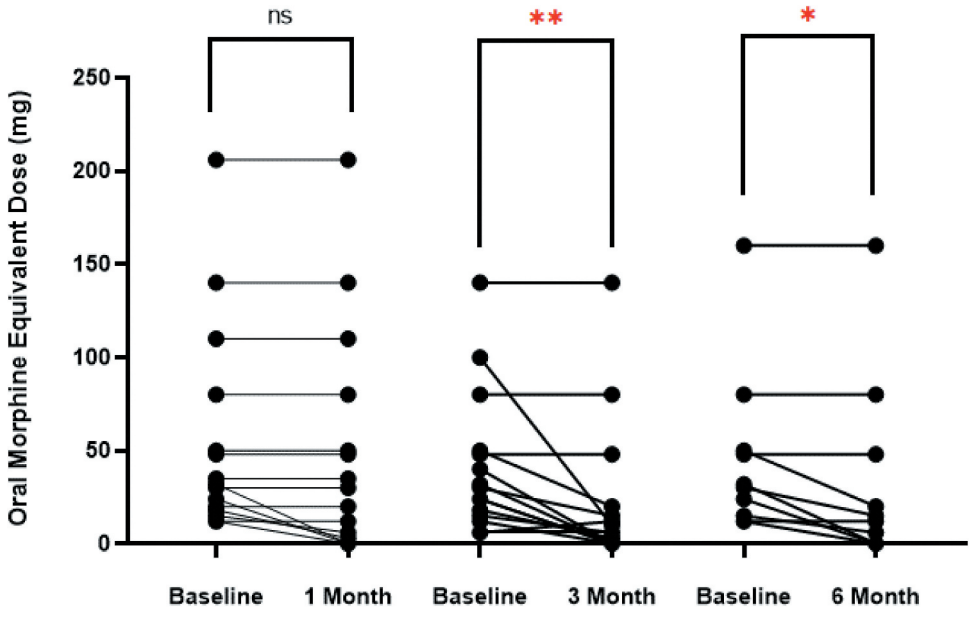

Figure 2. Paired baseline and follow-up oral morphine equivalent doses at 1, 3, and 6 months. '*' $p < 0.050$; '**' $p < 0.010$. n = 15;15;10 for 1-month, 3-month, and 6-month cohorts, respectively.

Table 5. Adverse events by participants (n = 190).

Adverse Events	Mild	Moderate	Severe	Life-threatening /disabling	Total (%)
Abdominal pain upper	1	0	0	0	1 (0.53%)
Amnesia (memory loss)	1	0	0	0	1 (0.53%)
Anorexia (lack of appetite)	0	1	0	0	1 (0.53%)
Blurred vision	1	0	0	0	1 (0.53%)
Cognitive disturbance	1	1	1	0	3 (1.58%)
Concentration impairment	0	2	0	0	2 (1.05%)
Constipation	3	1	0	0	4 (2.11%)
Coordination/balance/speech	0	1	0	0	1 (0.53%)
Dizziness	2	1	2	0	5 (2.63%)
Dry mouth	6	0	0	0	6 (3.16%)
Dyspepsia	1	1	0	0	2 (1.05%)
Fall	0	1	0	0	1 (0.53%)
Fatigue	3	1	2	0	6 (3.16%)
Headache	0	3	2	0	5 (2.63%)
Insomnia (inability to sleep)	1	0	0	1	2 (1.05%)
Lethargy	0	1	1	0	2 (1.05%)
Memory impairment	0	2	0	0	2 (1.05%)
Nausea	10	1	0	0	11 (5.79%)
Other	5	1	2	0	8 (4.21%)
Rash	0	1	0	0	1 (0.53%)
Somnolence (sleepy/drowsy)	0	3	1	0	4 (2.11%)
Spasticity	0	1	1	0	2 (1.05%)
Tremor	0	0	1	0	1 (0.53%)
Vertigo (spinning/dizziness)	1	0	1	0	2 (1.05%)
Vomiting	1	0	0	0	1 (0.53%)
Total	37 (19.47%)	23 (12.11%)	14 (7.37%)	1 (0.53%)	75 (39.47%)

4. Discussion

This case series of chronic pain patients from the UKMCR demonstrated a potential association between CBMPs and improved outcomes in pain-specific and general HRQoL measures, over the short to medium term. There were statistically significant improvements in multiple domains, including pain and discomfort, anxiety and depression, and sleep quality scales ($p < 0.050$). Additionally, statistically significant reductions in opioid administration, were observed ($p < 0.050$). The adverse event incidence was 39.47%; most adverse effects were mild to moderate in severity. These findings, whilst statistically significant, should be interpreted with a high degree of caution, due to pertinent limitations in study design.

In this case series, CBMP prescriptions were associated with significant reductions in pain severity and interference scores at one month, with further improvements realized at 3 and 6 months ($p < 0.050$). A 2016 open-label study suggested a 1.25-point reduction in BPI severity and a 1.43-point reduction in BPI interference following 6 months of CBMPs, which is consistent with the respective reductions of 1.28 and 1.59 reported in the present study [33]. These findings are further corroborated by a recent 12-month longitudinal study of 751 chronic pain patients who experienced a statistically significant reduction in pain severity after commencing CBMPs ($p < 0.050$) [32]. Whilst their reported BPI severity reduction of 1.59 points is greater than seen in our study, the difference is small enough to potentially represent natural variation between studies which might be anticipated; factors affecting this may include dissimilar cohort sizes, natural demographic variation, and differing mean severities of pain at baseline [32]. Similarly, this may indicate the responsiveness of their study to a highly sensitive test, meaning clinically significant differences between both cohorts of patients may be difficult to detect.

Contrastingly, an observational study of Australian patients with non-cancer chronic pain on opioid medication failed to show improved pain severity or interference, as determined using the BPI, in those consuming illicitly sourced cannabis [57]. Though their results were adjusted to account for concurrent opioid use when considering reductions in pain severity, a key limitation is illicitly obtained cannabis has variable consistency in cannabinoid, terpene and flavonoid content, both between patients and in the same patient over time, unlike CBMPs [58]. Furthermore, illicit cannabis may also contain substances harmful to human health, including pesticides and lead [32,59,60]. Not only might these factors have contributed toward maintenance of pain interference and severity scores, but inconsistency of constituent compounds in the cannabis, compounded by irregular dosing patterns reported by this study, likely biased results toward the null [61]. Our study, in comparison, analyzed outcomes on prescriptions of CBMPs made in accordance with GMP, ensuring batch to batch consistency of constitutive compounds within the medication. With a median cohort oral morphine equivalent of 0 mg, it is unlikely opioid dosing considerably affected BPI severity and interference scores. Future analyses involving the UKMCR should, however, aim to account for potential confounding factors.

The improvements seen within the SQS scale corroborate the literature demonstrating CBMPs' potential role in improving sleep [62]; THC is associated with sedative effects, and CBD with biphasic, dose-dependent stimulatory/sedating effects on sleep [63]. Chronic pain is associated with an increased incidence of comorbid insomnia, leading to poorer HRQoL outcomes [64]. In a recent cross-sectional study of chronic pain patients, CBMPs were associated with fewer problems with disrupted sleep compared to controls [65]. However, more frequent use of CBMPs for sleep was linked with an increase in problems falling asleep; tolerance to the sleep-aid properties of THC was suggested as the cause of sleep-related adverse effects [65]. Furthermore, withdrawal from long-term recreational cannabis use is strongly associated with decreased quality of sleep, and the long-term effects of cannabis withdrawal on sleep are not well documented [63,66]. The upcoming CANSLEEP RCT will aim to comprehensively assess the acute effects of 1:1 THC and CBD single-dose co-administration on measures of sleep quality in patients with insomnia [67]. In the context of chronic pain, however, further research is required to establish therapeutic margins for CBMP-modulated sleep, especially in the case of chronic THC tolerance.

CBMPs have a proposed role in reducing the opioid burden in chronic pain patients. A hypothesized mechanism of action involves interaction of cannabinoids and opioids at the level of their signal-transduction mechanisms, as cannabinoid and opioid G-protein coupled receptors are linked to similar inhibitory effects on intracellular adenylyl cyclase and calcium currents [29,68]. In a prior open-label study, CBMP administration was not associated with a significant reduction in oral morphine equivalent doses following 6 months of CBMP therapy [33]. We, however, observed statistically significant median oral morphine equivalent reductions of 79% and 56% at 3 and 6 months, respectively ($p < 0.050$). Our findings are supported by the recent multicentre prospective trial, which reported a significant 78% mean reduction in oral morphine equivalent dose after 6 months of CBMP treatment ($p < 0.050$) [69]. Though the findings in our paper are confounded by the comparatively small sample size, they are in line with developing literature, and will be explored further in future studies involving the UKMCR as the total number of participants continues to increase.

Following initiation of treatment with CBMPs there was a significant improvement in anxiety at all follow-up points measured with the GAD-7, as well as significant improvements for quality of life as measured by the EQ-5D-5L index and EQ-VAS ($p < 0.050$). This is corroborated by growing evidence supporting the association with improved anxiety within the context of anxiety disorders, as well as the psychological morbidity of chronic disease. To date, there are only two RCTs in anxiety disorders focusing on social anxiety, albeit each demonstrates notable improvements in self-reported anxiety on provocation tests [70,71]. In addition, studies within chronic pain settings have similarly resulted in improved anxiety outcomes [72,73]. Improvement of anxiety may, therefore, be a particularly beneficial aspect of CBMPs in the setting of chronic pain.

The all-cause adverse event incidence in this study was 39.47%, the majority of which (80.0%) were mild or moderate in severity. Common acute adverse effects resultant from illicit

cannabis consumption commonly include nausea, tachycardia, and altered cognitive states [74]. The adverse event incidence for CBMPs varies in the published literature. Whiting *et al.* reported an 80.1% all-cause adverse event incidence [62]. One potential explanation for the lower adverse event incidence in our study is the predominant prescription of oral/sublingual oils, with the majority prescribed orally administered preparations exclusively. This may have led to fewer bronchopulmonary adverse events, resultant of smoked/vaporized cannabis. Observational post-marketing studies investigating nabiximols reported all-cause adverse event incidences of 27.9%, and 31.3% [75,76]. This implies the acceptable adverse event incidence reported in our study more closely reflects the adverse event incidence of oil-based preparations.

4.1. Limitations

This study presents a longitudinal, observational case series. Whilst comparatively resource-efficient compared to RCTs, observational studies lack the appropriate methodology to determine causal associations. The lack of placebo control introduces bias, especially so when patients self-report their outcomes; non-blinded patients have previously been found to exaggerate the mean difference of treatment effect by an average of one standard deviation [77]. Heterogenous variables such as variable cannabinoid doses, and the inclusion of numerous chronic pain conditions, introduce confounding bias. Furthermore, this study employed the use of multiple endpoints and timepoints, introducing potential for 'false-positive' statistical findings. CBMP treatment was accessed privately at cost to patients; although the data fails to fully portray the socio-economic demographics of the cohort, this data may not be generalizable to low-middle income groups. However, the proportion of unemployed patients (30.0%), implies that a bias toward wealthy participants is not implicit. Additional selection bias exists in the prevalence of current/ex-cannabis users, representing a combined 50.0% of the cohort – patients who are treatment-experienced may not only be more likely to tolerate CBMP therapy, but, again, may be more likely to overstate the effect size. Conversely, patients experienced with illicit cannabis may have reached a ceiling effect with their treatment, and may fail to realize the same benefits. In the UK population, 69.7% of people have never consumed cannabis in their lives, meaning the proportion of cannabis-naïve patients (50.0%) in our study is lower than the national average [78]. Recall bias may further affect study outcomes as all PROMs are collected at distinct time periods and are reliant on retrospective recollection over a defined period; this may be further compounded by the known action of cannabis to negatively affect aspects of executive cortical function [74]. Follow-up PROMs were limited to a maximum of 6 months, due to insufficient data at later timepoints. Final titrated CBMP doses were not able to be analyzed meaning that the doses of CBMPs do not represent the maximum tolerated doses achieved over the study period. Since the initiation of this study, the UKMCR has undergone data-linkage with prescription data. Unpublished data extracted from the UK Medical Cannabis Registry on 31 August 2021 is available for 741 patients with the same conditions as this analysis. 289 patients were on oil CBMPs only (mean CBD dose: 14.1 mg/day; mean THC dose: 23.0 mg), 423 were on both oil (mean CBD dose: 36.6 mg/day; mean THC dose: 12.6 mg) and flower CBMPs (mean flower dose: 2.1 g/day), and 29 patients were on flower CBMPs only (mean flower dose: 2.2 g/day). Future analyses will benefit from this richer data on CBMP prescribing, enabling bespoke analysis of individual CBMPs [79]. Long-term adverse events and outcomes were not captured. Subsequent analyses utilizing the UKMCR should aim to incorporate statistical regression, controlling for demographic and pharmacological confounders.

5. Conclusion

These results suggest that treatment of chronic pain with CBMPs is associated with significant improvements in self-reported pain-specific and general HRQoL outcomes in the short to medium term in this patient cohort ($p < 0.050$). Yet, numerous limitations restrict the capacity to draw definite conclusions regarding causality and the efficacy of treatment, particularly in comparison to currently available medications. Significant improvements were observed within HRQoL domains ($p < 0.050$), alongside an acceptable adverse event profile, which is supported by previously published literature. The significant reduction in opioid doses ($p < 0.050$) demonstrates promise, but requires further exploration via future analyses and comparison with emerging studies. These results, and their discussed limitations, can assist future RCTs in the field to develop accurate power calculations regarding patient-specific outcomes.

Funding

This paper was not funded.

Declaration of interest

MH Sodergren is a consultant hepatopancreatobiliary surgeon, a director and a shareholder at Sapphire Medical Clinics, a consultant at Imperial College NHS Trust, a senior clinical lecturer at Imperial College London, and the research director at Curaleaf International. S Erridge is a junior doctor and undertakes paid consultancy work at Sapphire Medical Clinics, an honorary clinical research fellow at Imperial College London, and has no shareholdings in pharmaceutical companies. C Holvey is a chief clinical pharmacist at Sapphire Medical Clinics and has no shareholdings in pharmaceutical companies. R Coomber is a consultant orthopaedic surgeon, a director and shareholder at Sapphire Medical Clinics, a consultant at St. George's Hospital, and has no shareholdings in pharmaceutical companies. A Usmani and M Sajad are pain specialists at Sapphire Medical Clinics, consultants at Dartford and Gravesham NHS Trust, and have no shareholdings in pharmaceutical companies. J Hoare is a consultant gastroenterologist, a director and shareholder at Sapphire Medical Clinics, a consultant at Imperial College NHS Healthcare Trust, and has no shareholdings in pharmaceutical companies.

JJ Rucker is a consultant psychiatrist, a director and a shareholder at Sapphire Medical Clinics, an honorary consultant psychiatrist at The South London & Maudsley NHS Foundation Trust, and an NIHR Clinician Scientist Fellow at the Centre for Affective Disorders at King's College London. JJ Rucker is funded by a fellowship (CS-2017-17-007) from the National Institute for Health Research (NIHR). JJ Rucker leads the Psychedelic Trials Group at King's College London. King's College London receives grant funding from COMPASS Pathways PLC to undertake phase 1 and

phase 2 trials with psilocybin. COMPASS Pathways PLC has paid for JJ Rucker to attend trial related meetings and conferences to present the results of research using psilocybin. JJ Rucker has undertaken paid consultancy work for Beckley PsyTech and Clerkenwell Health. Payments for consultancy work are received and managed by King's College London and JJ Rucker does not benefit personally. JJ Rucker has no shareholdings in pharmaceutical companies. M Platt is a consultant in pain services and a director and shareholder at Sapphire Medical Clinics, and has no shareholdings in pharmaceutical companies. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Author contributions

M Harris, S Erridge, C Holvey, R Coomber, JJ Rucker, M Platt and MH Sodergren contributed to the study conception and design; M Harris, S Erridge, M Ergisi, D Nimalan, M Kawka, O Salazar, R Ali, K Loupasaki, C Holvey, A Usmani, M Sajad, JJ Rucker and M Platt contributed to the acquisition of data; M Harris, S Erridge and MH Sodergren contributed to the analysis and interpretation of data; M Harris, S Erridge and MH Sodergren contributed to the drafting of the manuscript; and M Harris, S Erridge, M Ergisi, D Nimalan, M Kawka, O Salazar, R Ali, K Loupasaki, C Holvey, R Coomber, A Usmani, JJ Rucker, M Platt and MH Sodergren contributed to critical revision.

Disclaimer

The authors confirm that the PI for this paper is MH Sodergren and that he had direct clinical responsibility for patients. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

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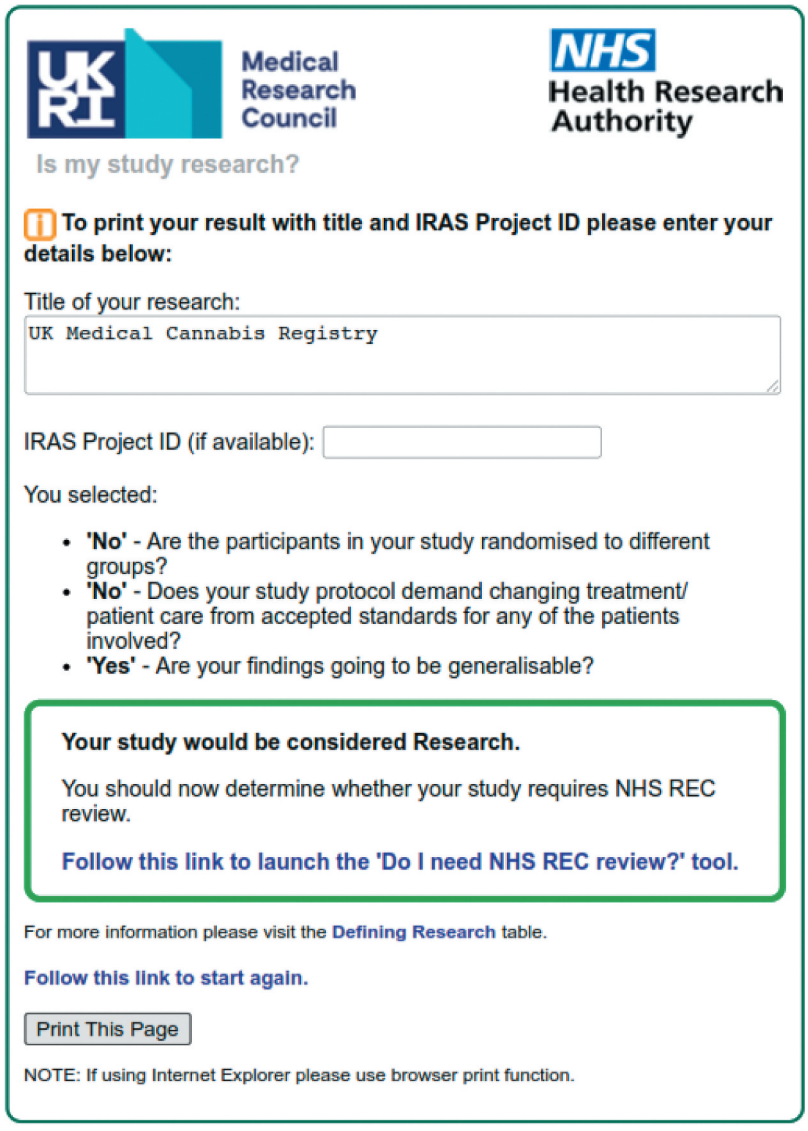
Appendix

A.



Medical Research Council

NHS Health Research Authority

Is my study research?

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

Title of your research:

UK Medical Cannabis Registry

IRAS Project ID (if available):

You selected:

- **'No'** - Are the participants in your study randomised to different groups?
- **'No'** - Does your study protocol demand changing treatment/ patient care from accepted standards for any of the patients involved?
- **'Yes'** - Are your findings going to be generalisable?

Your study would be considered Research.

You should now determine whether your study requires NHS REC review.

Follow this link to launch the 'Do I need NHS REC review?' tool.

For more information please visit the **Defining Research** table.

Follow this link to start again.

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Medical Research Council

NHS Health Research Authority

Do I need NHS REC review?

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

Title of your research:

UK Medical Cannabis Registry

IRAS Project ID (if available):

Your answers to the following questions indicate that **you do not need NHS REC review for sites in England.**

This tool only considers whether NHS REC review is required, it does not consider whether other approvals are needed. You should check what other approvals are required for your research.

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 (NHS and adult social care), including participants recruited through these services as healthy controls?
- Will your research involve prospective collection of tissue (i.e. any material consisting of or including human cells) from any past or present users of these services (NHS and adult social care)?
- Will your research involve prospective collection of information from any past or present users of these services (NHS and adult social care)?
- Will your research involve the use of previously collected tissue and/or information from which individual past or present users of these services (NHS and adult social care), are likely to be identified by the researchers 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 (NHS and adult social care)?

Question Set 3

- Will your research involve the storage of relevant material from the living or the deceased on premises in England, Wales or Northern Ireland without a storage licence from the Human Tissue Authority (HTA)?
- 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 for research from the donors?
- Will your research involve the analysis of human DNA in cellular material (relevant 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 human 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 procedures (including use of identifiable tissue samples or personal information) involving 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 offenders?
- Does your research involve xenotransplantation?
- Is your research a social care project funded by the Department of Health and Social Care (England)?
- Will the research involve processing confidential information of patients or service users outside of the care team without consent? And/ or: Does your research have Section 251 Support or will you be making an application to the Confidentiality Advisory Committee (CAG) for Section 251 Support?

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

OTHER UK COUNTRIES

If, after visiting all relevant UK countries, this decision tool suggests that you do not require NHS REC review follow this link for final confirmation and further information.

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