BREAKING THE EMBARGO:
A PROPOSAL TO BREAK UK PUBLIC HEALTH MEDICINAL CANNABIS IMPASSE

COMMISSIONING NATIONAL CLINICAL ASSESSMENTS OF CANNABIS-BASED MEDICINAL PRODUCTS IN THE MANAGEMENT OF CHRONIC DISEASE

Co-authored by Dr. Daniel Couch, CMC Council of Clinicians and Scientists, Dr. David Horn, CMC Medical Lead, and Dr. Charles Akle, CMC Council of Clinicians and Scientists.
The CMC | Breaking the Embargo: A proposal to break UK public health medicinal cannabis impasse

**Executive summary**

- More patients are turning to street cannabis for therapeutic use. Despite clinical physicians being able to prescribe CBMPs, very few prescriptions have been issued due to a lack of evidence.

- High profile calls for access to cannabis-based medicines have placed CBMPs on the national agenda.

- Through the creation of a new government authority, this policy intends to:
  - Offer rapid clinical data and insight regarding the use of CBMPs.
  - Provide two routes of access to safe, regulated CBMPs via a trials rather than prescription.

- This authority will generate comprehensive data through clinical trials that will recruit 10,000 patients over 5 years, providing evidence for guidelines to NICE and MHRA.

- Establishment of UK centres of excellence hosting trials will nurture the existing CBMP clinical expertise, and this will expand to tertiary and primary care.

- Funding will be met through deployment of existing CCG and NIHR budgets and early involvement of industry partners. Early involvement allows us to ensure affordability of licensed medicines.

**Current UK Policy context**

As a result of the proven efficacy of CBD in childhood epilepsy syndromes and the failure of alternative agents and treatments in a significant cohort of these children, it became unsustainable in the UK to keep cannabis related medical substances within Schedule 1 of the Misuse of Drugs Act. Following Dame Sally Davies’s report to this effect, and the recommendation of the Advisory Committee on the Misuse of Drugs (ACMD), the previously relating policy of prohibition became abandoned and replaced by one of limited medical access through hospital specialists only, and CBMPs were accordingly entered into Schedule 2 on 1st November 2018. The Medicines Act was altered by the addition of paragraph 16A, to exclude patient access to CBMPs via general practitioner doctors. Since CBMPs remain unlicensed, specialist approved access can only currently be via the extant default pathway as an unlicensed drug commonly known as the Specials route. This route is appropriate to access and stocking for medical trials and occasional use in medical extremis.

There was at this time an expectation in the Home Office and Department of Health and Social Care (DHSC) that NHS prescriptions would follow, particularly in relation to those cases of medical extremis in children that had previously exerted sufficient political pressure to trigger the change in policy. Indeed the DHSC was initially more concerned towards an over relaxation of policy that might afford excessive patient access, and it therefore made significant effort to exhort medical colleges and professional associations to issue professional guidance to make clear that its policy was intended only to empower very narrowly the professional authority to prescribe by appropriate senior consultants in a multidisciplinary context. Nevertheless, there have been to all intents and purposes no prescriptions issued, and the few that have related to private care and not the NHS. The reason for this is a matter of often ill understood impact of UK NHS clinical culture:

1. There is a presumption of causing harm when prescribing without supporting knowledge of safety and efficacy drawn adequately performed randomised controlled trials. The Specials route makes clinicians...
personally liable for attributable medical misadventure, unless this route is used as part of an approved clinical trial. There are no trials yet in operation, as might be expected due to the extensive travails and time necessary to implement them.

2. Doctors’ professional conduct is measured by the UK legal system against the reasonably accepted behaviours of the substantial body of doctors’ peers. Even in the Netherlands, only 15% of doctors prescribe CBMPs, and therefore even here this behaviour is statistically outlying. To prescribe CBMPs in the UK immediately after the repeal of outright prohibition was always going to be exceptional behavior that should not sit well in court if harm should occur. Accordingly, no doctor should be well advised to currently prescribe CBMPs, excepting in such medical extremis that the patient has little to lose, or the context of an approved trial of CBMPs.

3. Without the results of definitive trials showing efficacy, there is nothing to base commissioning decisions upon. Evidence is currently only of sufficient quality relating to the use of CBD in epilepsy syndromes. Whilst there is potential to commission for CBMP use in chemotherapy induced nausea and vomiting (CINV), more effective agents with a preferable side effect profile are already in use. For the diseases relating to current and illicit street cannabis use, there is no formal evidence of efficacy. Without commissioning, there is no funding for CBMP prescriptions, so virtually no specialist doctor is minded to waste the valuable time necessary to go through the extensive bureaucracy to issue one.

Additionally in October 2018, the National Institute of Clinical and Healthcare Excellence (NICE) was tasked to report on how deployment of CBMPs might be widened, in the expectation of any serendipitous but as yet unreported clinical research “in the pipeline” before November 1st 2018. It is now apparent that there is none of significance, and NICE is not expected to make significant alteration to its current recommendations, save as relate perhaps to epilepsy syndromes.

It is therefore now accepted amongst UK governmental policy makers that current policy is fundamentally not likely to adequately deliver patient access to CBMPs within an acceptable time frame. As a result and as a consequence of its relationship with the CBMP industry and worldwide reach in this field, the CMC is invited by the DHSC to now lead the conversation around future enhancement of CBMP development policy. Accordingly, the CMC is engaging with all UK CBMP stakeholders to design, propose and conceptually test an enhanced CBMP development policy within a policy summit. The CMCs proposed policy follows.

The consequences of illegal use

Due to an unmet clinical need with available therapies, NHS patients are turning to street cannabis for symptom relief for conditions such as multiple sclerosis, chronic pain, palliative states and epilepsy. An uncontrolled, illegal market has developed to fill this demand. Patients place themselves at daily risk ofclass-A contaminants, potentially lethal fungal toxins and indeterminate active pharmaceutical ingredient (API) concentration. These patients don't want to break the law; they're driven to do so out of desperation. A survey of UK cannabis users for medical intent indicated that 75% would discontinue their illegal supply if an NHS prescription were available.1 Allowing this illegal use to continue will lead to a rise in police expenditure, morally spurious indictment and increasingly widespread public appreciation that there's no way to impede recreational use while medical use is not formalised.

Weeks before the DHSC asked the CMC for input on the implications of cannabis re-scheduling, the CMC approached the Chair of the NICE to request a specific review of its portfolio in relation to ongoing CBMP development. NICE was formally asked to consider the implications of cannabis re-scheduling for its portfolio. The CMC understands that NICE has since asked the DHSC for further input on this matter.

Whilst it was immediately recognised that trials should be performed, and the National Institute of Health Research (NIHR) was instructed to issue an open-ended call for trials, producing a compliant application takes at least six months and consideration of it commonly takes a further eighteen months. Applications to date are few in number, and it is evident that there is no volume of newly heightened cannabis related clinical research interest, lurking just below the radar consequent upon re-scheduling that may imminently appear.
Historic cannabis legislation

Cannabis sativa has been used for centuries for its psychoactive effects as well as symptomatic relief. Despite it being a criminal offence under the Misuse of Drugs Act, over a million people in the UK illegally obtain and consume cannabis sativa for medical reasons alone.

Even though medical CBMP prescriptions are legal since 1 November 2018, they’re given out very rarely and almost exclusively in private healthcare rather than the NHS.

For decades the NHS has been evaluating and prescribing novel medical therapies, leading to the widespread use of successful life enhancing therapies such as statins, ACE inhibitors, and monoclonal antibodies.

Typically, innovative medicine has been introduced through large scale randomised controlled trials (1000+ patients). The trials assess efficacy of a single API compared to conventional therapy or a placebo. If drugs are introduced without clinical trials they may cause harm, as was the case with the morning sickness drug thalidomide. Sometimes approved drugs are even withdrawn decades after deployment, as happened with certain non-steroidal anti-inflammatory drugs. This is why post-marketing surveillance continues after initial marketing approval is granted by the MHRA. However, street cannabis is already widely in medical use amongst the majority of potential trial participants, albeit without any protection or monitoring.

Understanding the efficacy of cannabis

Understanding the therapeutic effects of cannabis and its constituents is not as simple as identifying a single API and measuring its efficacy. Over 90 compounds within the cannabis plant (the so called “phytocannabinoids”) activate a wide range of receptors in the body with varying, but crucial potency. Deployment of this “entourage” of compounds across varying configurations may be responsible for the wide range of possible therapeutic effects – some of which may not be discovered with the use of a single cannabinoid API such as CBD or THC. That’s why when attempting to assess the efficacy of CBMPs, the complexities of the “entourage effect” may make the use of classical randomised trials problematic. Given that many patients are already at potential health risk, evidence supporting or opposing the clinical use of CBMPs might be more rapidly attained through a more adaptive and novel trial methodology.

Other countries

Alongside the need for clinical data that allows for the formation of national guidelines, public calls for CBMP access have gained increasing traction. Several access schemes have been piloted elsewhere with variable success.

Unregulated prescription and over-the-counter access to patients in North America has led to routine clinical prescribing and dispensing of these medicines, satisfying public demand. However, this hasn’t generated the trial data and evidence required for the NHS. Moreover, fundamental differences in healthcare provision between the UK and the USA mean that UK patient demand is not an important driver for prescriber behaviours: it doesn’t translate into significant patient access in either the UK NHS or private health markets.

An individual access-application scheme in Australia has led to a rapid uptake in the prescribing of CBMPs, which would blueprint easily into UK policy, and match public expectations for access. However, despite the adoption of this more progressive policy, like in the US this hasn’t generated the anticipated drug safety or efficacy data.

Lastly, a recently launched Danish programme links patients with clinical experts for the prescription of CBMPs for key conditions. This scheme, involving >400 willing medical prescribers, continues to recruit large patient numbers, with collection of observational data.

A similar scheme would be desirable in the UK. However: neither the prescribers willing to prescribe in a knowledge vacuum, nor the clinical expertise required are currently evident.
What's next for the UK?

The UK now has the opportunity for a tailored policy intervention that allows access to safe, regulated CBMPs in and NHS setting where there is lawfully unmet clinical need.

Simply generating a lawful “access programme” is in itself not enough without willing UK prescribers. If NHS clinicians feel pressured to participate in what’s seen as a programme where patients can access products as they see fit, the programme will likely fail through their disengagement. The key output of any UK policy must be the generation of world-leading CBMP evidence through a national research initiative. If this policy is to be successful, it must collect rigorous safety and efficacy data. This is needed to quickly create a transparent evidence base to address the current knowledge deficit. Modified prescriber behaviour might be effectively based on this in the future. Any policy intervention must delicately navigate NHS medical culture to gain widespread traction, as current NHS culture remains resistant to the prescribing of cannabis derived drugs.

Clinical research is currently being conducted by academic centres de novo, although on a small scale and in a relatively uncoordinated fashion. This is driven according to individual researcher interest. This is a fundamental National Institute of Health Research (NIHR) tenet. It’s designed to minimise the risk of significant public expenditure becoming orphaned should a researcher choose to withdraw from the intended research due to waning interest. The data from these centres is unlikely to impact the national prescription of CBMPs soon, not only due to limited size and scope, but also because the knowledge acquisition process is gradual. Waiting for data to trickle into the public domain (as is passively facilitated through NIHR funding processes informing NICE and MHRA) won’t satisfy the public and political timeframe.

The new policy should be designed to gain knowledge as well as to build clinical expertise with the use of CBMPs amongst NHS specialists, in order that CBMPs may become more affordable, market volumes being driven by mass access and enhanced demand.

The Cannabinoid Clinical Trials Authority

A purpose-built authority is best suitable to actively generate clinical data, appropriate knowledge and early patient access. It must be specifically empowered to commission critical research on the efficacy and safety of CBMPs within a systematic, focussed and efficient process that provides safe, regulated substances. This might be embodied within a new organisation: the Cannabinoid Clinical Trials Authority (CCTA).

The goal of the CCTA over 5 years will be to accelerate the acquisition of knowledge surrounding the safety and efficacy of CBMPs in areas of greatest clinical need. In the meantime, it will allow access to all appropriate patients who wish to participate in any clinical trials. The CCTA itself would not be responsible for carrying out detailed trial design, patient surveillance, data collection, data processing and statistical analysis, or product licencing, but would instead commission trials through formal procurement exercises, selecting from academic centres of excellence capable of these functions, whilst preventing diversion of CBMPs into recreational use. The CCTA would both set the investigational strategy and agenda to which it would progressively then procure against, in order to effectively drive new policy. The CCTA would define the outline requirements and structure of any given trial required. This policy is to move from the current passive and more random system of NHS funded research based upon applications received from researchers that are according to their personal interest and passion, to an active and more directed, accelerated, and coordinated approach.

Additionally, the CCTA will formally procure support from industry to minimise the cost of trials. This accelerated approach will critically also provide the most rapid response possible to the debate on the efficacy of CBMPs in critical areas of unmet clinical need where patients are already exposed to unregulated cannabinoid substances. This is in contrast to existing NIHR process, that neither fully addresses the urgent need for nationally coordinated CBMP research nor produce the requisite data within the politically appropriate timescale.
Although devolved, the CCTA will be overseen by and answer to an appropriate Member of Parliament. The role of the CCTA won’t be to promote health through the administration of CBMPs, but to further clinical and scientific knowledge of them. It’s beyond the remit of this agency to incorporate CBMPs into regular NHS prescribing. As such the CCTA won’t be under NHS control, but will answer directly to the DHSC and its Department of Drugs Development and Regulation.

**Initial focus of research**

There is evidence for a potential therapeutic effect in multiple disease states, ranging from post-traumatic stress disorder, rheumatoid arthritis through to inflammatory bowel diseases. However, trials conducted must initially focus on areas of critical clinical need. Key conditions, some previously identified by NICE, might form the initial focus:

- Chronic severe pain
- Refractory epilepsy
- Spasticity in multiple sclerosis
- Anxiety
- PTSD
- Sleep disturbance

These form the bulk of current use cases of street cannabis. For these patients, conversion to regulated substances is of immediate clinical benefit. A body of evidence for the use of CBMPs already exists in these areas, although the current clinical evidence is insubstantial and inadequate for the issuing of clinical guidelines. Despite the lack of data, thousands of patients actively source of street cannabis for symptomatic relief in these conditions.

Commissioned trials must fall into one of two study models; observational trials and randomised controlled trials dependent on previous CBMP exposure.

**Modern observational trials**

Whilst it may remain clinically and academically desirable to recruit patients already consuming street cannabis into randomised, placebo-controlled trials, replacing their cannabis with a CBMP, it’s ethically challenging to offer patients an inert placebo. That’s why recruiting patients currently consuming street cannabis for symptomatic control may be more appropriate. Within these trials, patients must voluntarily abstain from the use of street cannabis.

**Typical inclusion criteria are:**

- A documented diagnosis of either:
  - chronic pain
  - spastic multiple sclerosis
  - anxiety
  - PTSD
  - sleep disturbance
- Failure and exhaustion of conventional NHS therapies for the above
- Documented use of street-derived cannabis for the relief of the above
- Willingness to substitute street cannabis with prescription of CBMP

**Exclusion criteria from the trials might include:**

- Concomitant use of an illicit drug other than cannabis for any reason, be it recreational or therapeutic
- Previous absenteeism from the scheme
- Use of street cannabis during the scheme
Recruitment

Patients eligible to take part in the study will, by the nature of their disease, regularly be in contact with their General Practitioner (GP) or hospital specialist. The GP will ask if they use street cannabis to control their symptoms. If so, they’ll be offered to take part in the trial. They’ll be referred to a specialist research unit where appropriate consent and enrolment into the observational trial can begin.

Observation

Once recruited, participants will be provided with a 30-day prescription for an appropriate CBMP, dispensed by the study centre. Participants must return to the study centre to obtain a further 30-day prescription. This requirement prevents loss to follow up and absenteeism from the trial. Participants must follow up regularly with their research centre, with assessment by an appropriate health specialist to ensure compliance, measure symptom response and observe for adverse reactions or interactions. Alongside face-to-face follow up, participants will also be required to collect compliance, symptom and other data through purpose-built IT or app-based research platforms.

Analysis

Data collected from the trial will be collected by the commissioned research centre and analysed centrally by a parent academic institution. Analysed data must then be presented to CCTA for publication and presentation to NICE or the MRHA and be publicly available.

Randomised controlled trials

Although observational trials give access and generate significant data, the open-label nature of these studies allows for considerable bias in data collection and analysis. Trials may also be commissioned employing the existing randomised controlled-trial (RCT) methodology for the following reasons:

1. to facilitate more rapid adoption in future of GP prescribing
2. to validate the new assessment process
3. to elucidate knowledge in clinical areas where the programme methodology might be considered inappropriate (e.g. childhood epilepsy)

Alongside observational trials, conventional, double-blinded, randomised, placebo-controlled trials will be commissioned concurrently.

As residue of cannabis-derived products may persist for several months after ingestion, patients recruited into randomised trials should not have previously used a CBMP, street derived or otherwise, for symptomatic relief.

Inclusion criteria into the trials are:

- A documented diagnosis of either:
  - refractory epilepsy
  - chronic pain
  - spastic multiple sclerosis
  - anxiety
  - PTSD
  - sleep disturbance
  - refractory nausea and vomiting
  - Failure and exhaustion of conventional NHS therapies for the above
  - Willingness to be included in a CBMP trial

Exclusion criteria from the trials:

- Previous or current use of any illicit substance
- Previous inclusion in the observational wing

These conventional randomised studies, conducted and analysed by commissioned research centres, will produce clinical data essential to the establishment of national guidance on prescribing CBMPs.
Although data derived in this way may require more time to emerge, they will be the cornerstone of guidelines developed in the next five years.

**Recruitment**

Similarly to observational trials, patients attending their GP or hospital specialist for chronic and poorly controlled disease will be offered recruitment into an RCT. If they would like to take part, they will be referred to the appropriate specialist research unit for enrolment and consent. Trial observation and data collection will be conducted using the same technology employed in observational trials, with interim and completion analyses reported to the CCTA. Modern data collection allows real-time analyses to inform decisions far earlier than traditional methods, and therefore trials can be halted or modified quickly.

**Research Centres of Excellence - the concentration of knowledge and expertise**

Only a handful of NHS centres have any experience prescribing CBMPs, which means clinical competence is hugely lacking. It’s outside the authority’s scope to dictate which clinical academic centres should take part in the trials, but those selected through the commissioning process must contain clinical units relevant to the studied disease (neurology or paediatric neurology, anaesthetics, psychiatry, oncology and palliative care). Academic clinical specialists within these departments will be required to attend a CBMP training programme. This will be delivered by specialists with relevant expertise and it will include the prevention of diversion.

Encouraging the uptake of knowledge and skills for clinical cannabinoid practice in this way will spread the development of expertise in these and neighbouring centres. This step is crucial to more widespread adoption of CBMPs into regular prescribing practice.

**Impact and timeline**

Based on a Home Office assessment of CBMPs in the UK, an estimated one million patients suffer from a medical condition which may benefit from a CBMP. Invitation of 5% of this population into clinical studies would include 50,000 patients. The Danish access programme is comparable (2,000 patients in 2 years), although 400 specialists had already declared interest and the expertise necessary to host the study. Although interest has not yet been confirmed, a previous report has estimated 5,000 specialists in the UK will be actively affected by CBMPs, and therefore may be approachable to host studies across ten UK specialist centres.

Following publication of the policy, the CCTA would be established in the summer of 2019, with trial commissioning broadcast after consultation by October 2019. Following an appraisal process, academic centres would be recruited by spring 2020, with trials recruiting patients by summer 2020. Within 12 months of establishing academic centres, 1,000 patients are expected to have been recruited, with 10,000 by the close of 2023.

By autumn 2024, 5 years following the establishment of the CCTA, an estimated 10,000 patients will have been included in clinical trials commissioned by the CCTA.

**Funding**

Resources required to fund and sustain this national programme might be obtained from existing budgets, without new finance from the exchequer, and could be sought from NIHR, CCGs and industry. The research of CBMPs in clinical practice is currently within the scope of NIHR, and appropriately budgeted. Similarly, it’s expected that thousands of patients with refractory disease will for example move from opiate based or patented pharmaceuticals with attendant cost currently funded by CCGs to trial-derived and funded CBMPs during the programme. As such, in the medium-term CCG and NIHR budgets may reasonably be diverted without meaningful deleterious effect or serious impact on the existing budgets of each.
Within the CBMP industry itself there is a host of producers with a keen interest in the UK market. As these firms are frequently already established abroad with filed drug patents, there’s willingness in the private sector to provide funding for observational and randomised controlled trials measuring the efficacy of their therapeutic agents. It is therefore reasonable to expect that industry, with the expectation of future market returns, will invest in this programme in the short to medium term.

Procurement, commissioning and licensing expertise

The CCTA’s terms of reference will not be coercive towards existing entities in the current UK drugs licensing pathway. Only the goals of rapid acquisition of requisite knowledge and safe CBMP access, while simultaneously building a sustainable UK CBMP industry serving legitimate and appropriate medical demand in the UK is within CCTA remit. To put this remit into effect, the CCTA will instead co-opt existing stakeholder entities with their expertise and resources to support policy implementation within a collective approach. The CCTA will principally be to act as a facilitator and programme manager across this wide stakeholder spectrum in application of policy that is inclusive of relevant academia and research institutions, clinical experts and institutions. These include the Royal Colleges, clinical associations such as the BPNA, NHS Commissioners (drugs commissioning specifically and wider NHS procurement process expertise), the MHRA (drugs licensing), NICE (clinical recommendation), and DHSC (drug development). The CCTA will permit group ownership of the policy and ensure that CBMPs become rapidly and fully deployed in the UK.

Conclusion

Multiple parties are calling for the legalisation of recreational cannabis, their central argument being a perceived therapeutic benefit in certain medical conditions. The rapid accumulation of observational cohort study and randomised trial data, with administration of CBMPs in a controlled, legal and safe environment diffuses calls for wider deregulation that would encompass recreational use. Enhanced leadership through the establishment of a trials commissioning authority will focus academic attention to effectively and efficiently drive this goal within a politically achievable timeframe, simultaneously satisfying prescribing inhibitions around safety and efficacy. Should the authority be implemented, within 5 years the UK will become the world leader in CBMP prescribing excellence, in place of an ever-growing black market.

2 Home Office. Rescheduling of Cannabis-Based Products for Medicinal Use under the Misuse of Drugs Regulations 2001; 2018.