



MEDICINAL CANNABIS IN THE UK:

ABLUEPRINT FOR REFORM

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Foreword

Exactly six months ago from the date of the publication of this first report by the Centre for Medicinal Cannabis, I was at Heathrow Airport's Terminal 5 awaiting the return of Charlotte and Billy Caldwell from Toronto. Two days earlier Charlotte had been prescribed a medical cannabis oil for her severely epileptic son Billy, one that contained large amounts of cannabidiol (CBD) and small amounts of tetrahydrocannabinol (THC) at the world's largest paediatric research hospital. An hour after her return this medicine was confiscated by tearful customs officials. Two hours later I accompanied her to a meeting with the relevant Home Office Minister when she was told nothing could be done to return the medicine.

The rest is history.

Notwithstanding the alacrity of response from the Home Secretary during the summer and the subsequent progress that has been made since, as this report attests, there is a long way to go to formulate policies that will respond to demand for such products within the context of our distinctive healthcare institutions and norms. In the drafting of this report we have been diligent to draw on international practice where it exists, mindful of some of the reservations that many medical professionals have but practical in setting out 30 recommendations that can be considered and adopted across the range of stakeholders involved in policy setting and implementation.

All effective policy needs to be alive to the very particular situational context within which it is being implemented and set goals accordingly. This report frames not just the alleviation of unnecessary human suffering but the depletion of the existing black market and the nurturing of a new industry for the UK as the fruits of successful policy implementation.

We have very deliberately been ambitious in the scope of this report, in our sweep of the available data and in the volume of recommendations. Not everyone will agree with everything we have set out but we firmly feel that this will move the conversation forward.

I hope you enjoy reading this and continue to engage with our work in the coming years.

Steve Moore

The Centre for Medicinal Cannabis

Summary of Recommendations

Recommendation 1 An Intra-Ministerial Group on Medical Cannabis should be instituted to ensure agreement and coordination of all the UK government's policies.

Recommendation 2 The Home Office should transfer responsibility for cannabis policy to the Department of Health and Social Care as an immediate step in advance of a wider review of which department should have responsibility for drug policy.

Recommendation 3 The UK must draw on lessons from comparable countries, especially the recent reforms in Australia and Canada which offer the best policy parallels in a Common Law context.

Recommendation 4 Given the depth of the Canadian experience of more than a decade, a new bilateral policy initiative should be established between the UK and Canada and working groups should be formed to allow Commonwealth counterparts to advise the UK on next steps.

Recommendation 5 The UK Government should establish a dedicated UK Advisory Council on the Medicinal Use of Cannabis (ACMUC) comprised of both academics and practitioners familiar with the scientific and medical applications of cannabinoids.

Recommendation 6 The UK should create a Cannabis Policy Branch within the Department for Health and Social Care to create a hub for expertise and to locate it in the health domain in line with most other jurisdictions where the drug is legal for medical purposes.

Recommendation 7 A new Cannabis Licensing Branch of the relevant government department should be created to ensure an efficient, timely and dedicated service to all those licenses.

Recommendation 8 The MHRA should notify pharmacies of the UK-based specialist firms that can cater to orders for unlicensed medicines to speed up sourcing of imported products.

Recommendation 9 NHS England and their counterparts across the UK should adopt a simple system of categorisation containing the four types of CBMPs for which we have clinical trial evidence and devise policy accordingly for each.

Recommendation 10 NHS England should create a list of approved CBMPs to guide clinicians. Synthetic versions of the THC or CBD molecules are acceptable and practical alternatives. Generic versions of these CBMPs should be available as specials.

Recommendation 11 CBMP changes need to be communicated to those in the supply chain especially the customer-facing pharmacists, with as a minimum, the Royal Pharmaceutical Society communicating to its members.

Recommendation 12 Regulators should clarify the status of CBD since the 1 November rescheduling and where it sits within the general framework for CBMPs.

Recommendation 13 Patients need a diverse range of consumption options, and medicinal cannabis should be available as flower in the UK, to enable some patients to vape their cannabis (but not to smoke it).

Recommendation 14 UK cannabinoid scientists based in recognised academic institutions or industries should be able to apply for research licenses, with less bureaucracy and costs than the current scheme, to carry out research with CB1 agonists.

Recommendation 15 The evidence base around the clinical use of CBMPs should be more widely recognised and disseminated to healthcare professionals. Given the lack of familiarity, it is especially important that new research findings are shared with clinicians.

Recommendation 16 All academic and industry-funded clinical trials investigating CBMPs should abide by law and best practice and publish all outcomes in full, and encourage the retrospective reporting of already complete trial data.

Recommendation 17 Based on our analysis of complete and ongoing trials, the ongoing NICE consultation should be broadened to encompass more indications.

Recommendation 18 Initiate clinical trials and generate data where CBMPs are used alone and compared against current medication to establish any potential superiority or non-inferiority (with reference to side effect profiles or possibly cost implications).

Recommendation 19 Clinical trial partnerships should be encouraged between the NHS, industry partners and condition charities with a focus on conditions where patients are already using CBMPs but sourcing from the black market.

Recommendation 20 There should be an expectation placed on responsible producers of pharmaceutical-grade medicinal cannabis products (that meet a GMP standard) to commit to the long-term benefit of UK patients by helping to fund and facilitate new trials of their medicines within the UK.

Recommendation 21 Develop a network of Medicinal Cannabis Centres of Excellence of scientists, doctors and clinical trial specialists, with links to major condition charities, public and private healthcare system and industry, with the primary aim of generating world-leading research into CBMPs.

Recommendation 22 Government agencies like NIHR should seed-fund Centres of Excellence as collaborations between private industry, the NHS and academia, under the supervision of a new cannabinoid research agency.

Recommendation 23 The Department for Health and Social Care should oversee this new network of regional Centres of Excellence by endowing a new UK Institute of Cannabinoid Research and Evaluation.

Recommendation 24 NHS England, the Royal College of Physicians and the General Medical Council should agree a scheme by which GPs can continue treatments with cannabis-based medicinal products and allow for such follow-on prescribing to be permitted.

Recommendation 25 Private clinicians and clinics should be brought under the umbrella of the Centres of Excellence to ensure that all patients prescribed a CBMP are either part of a clinical trial or have their data captured by other mechanisms.

Recommendation 26 The Home Office and Department for Health and Social Care should jointly establish a time-limited scheme for compassionate use of cannabis for terminally-ill patients, modelled on the system in New South Wales.

Recommendation 27 CBMP-friendly clinicians within the NHS should lobby at a local level within their speciality and within professional societies, to modify guidelines to make prescribing easier.

Recommendation 28 Create a DHSC-funded training package on CBMPs for NHS clinicians, in partnership with the Royal Colleges and medical professional bodies and associations.

Recommendation 29 Create a single patient registry for all those who are prescribed CBMPs – either on the NHS or privately – and use the data as a resource for future studies and novel trial designs.

Recommendation 30 The government should start work on an economic development plan for encouraging and supporting the medical cannabis industry to establish itself in the UK, consistent with the modern industrial strategy and the life sciences sector deal including an economic analysis by HM Treasury.

Contents

Chapter 1	Introduction	8
Chapter 2	Medicinal Cannabis in the UK today	11
Chapter 3	Goals and Trade-offs	15
Chapter 4	Evaluating the New Landscape	17
Chapter 5	A True Picture of the Current Evidence Base	21
Chapter 6	Experience from Abroad	29
Chapter 7	Barriers to a Fully Functioning Medical Market	37
Chapter 8	Delivering a System that Works for the UK	43
Chapter 9	Roadmap for Reform	54
Chapter 10	Conclusion	58

1. Introduction

In the summer of 2018, the newly appointed Conservative Home Secretary, Sajid Javid MP, initiated an urgent review of cannabis-based medicinal products.¹

This was the political response to a high-profile campaign in June-July 2018 focused on the case of Billy Caldwell - a 12-year-old from Northern Ireland suffering from severe epilepsy. Within weeks he had received advice and accepted recommendations² from the Advisory Council on the Misuse of Drugs (ACMD) and the UK's Chief Medical Officer that cannabis had proven medical benefits and that the government should proceed with rescheduling.

The required secondary legislation was prepared and laid before Parliament in October and took the statutory three weeks to come into effect. The result was that by 1 November 2018, after decades of complete prohibition of the drug, cannabis-based medicinal products (CBMPs) could lawfully be prescribed by doctors in certain circumstances for the first time. This enabled medical practice to finally accord with the science, which was summarised by Professor Dame Sally Davies³ in her review:

“There is clear evidence from highly respected and trusted research institutions that some cannabis based medicinal products have therapeutic benefits for some medical conditions.

As Schedule 1 drugs by definition have little or no therapeutic potential, it is therefore now clear that from a scientific point of view keeping cannabis-based medicinal products in Schedule 1 is very difficult to defend.”

The whole process was quick in policy terms, largely uncontroversial in parliamentary terms, and concluded without significant regulatory mis-steps. This important moment was made possible by a small, symbolic and long-overdue change to the law on the scheduling of certain controlled substances. Any previous Home Secretary in the last decade could have commissioned the same review of the evidence and got the same answer. However, the government deserves due recognition that it finally listened to patients and has at least now embarked on this journey. Various agencies have also so far shown a genuine willingness to engage with patients, academics and groups like Families for Access (F4A) and the United Patient's Alliance (UPA) to help them arrive at the right destination.

Nevertheless, the rescheduling, though a necessary step, is not by itself sufficient. Already it is clear it has raised expectations and initiated a much wider and more extensive period of implementation. This is an unfamiliar system in which a drug that has been made permissible to prescribe in law, must now in practice be made accessible to the patients who need it. The current government position is that such decisions on prescribing cannabis-based products are a matter of professional discretion and must be made on a case-by-case basis, and then only when the patient has an unmet special clinical need that cannot be met by licensed products. This report shows why that position is not sustainable and more steps are needed to make a reality of the government's policy goals.

Set in context, the UK's recent reforms are part of a global shift in favour of medicinal cannabis regulation, with access schemes now spreading across the world. This represents more than just a promising drug development. The potential patient applications for medicinal cannabis are significant, as are the economic benefits that an innovative new healthcare sector could provide. The UK's small and important reform to reschedule cannabis should therefore properly be seen as a vital first step, but on its own, very far short of what is needed to seize the opportunity presented by this new frontier in medical science.

1.1 Why this reform matters

The political interest in cannabis policy is growing as more and more countries choose to legalise and regulate the drug for medicinal purposes. The political agenda and the media interest is being driven by the people, not by policy-makers or legislators. In the UK the most powerful advocates for change have been the parents and patients, some of whom have been arguing in favour of reform for decades, and in many cases have been marginalised, ostracised or even criminalised for doing so. But without their testimony and advocacy, reform would have continued to elude us.

We did not arrive here by accident - it happened because parents and patients' voices were finally heard and public support swung behind them.⁴ Clearly many policy reforms have a democratic driver - pressure from beneath that builds up over time and makes the status quo unsustainable - but few have the human urgency and raw emotion of the medicinal cannabis cause.

In countries throughout the world, the urgency felt by parents and patients, and at times the desperation, is a powerful political motivator and in no fewer than 22 countries - including the UK as of 2018 - this patient pressure proved to be a decisive moral argument in overturning laws restricting medical use. As the Australian Government was embarking on reform, they published this statement: *“Cannabis has the potential to provide relief to people living in some of the most difficult and painful circumstances we can experience as human beings. Even the possibility of attaining, or helping a loved one attain, a slight relief from these symptoms is enough to drive law-abiding people into the arms of the black market.”*⁵

Those circumstances are familiar to the UK, where a thriving black market supplies patients who have no other option, and a similar tale is being told in many countries across the world. When forced to choose between obeying the laws that have banned a plant, and being able to obtain pain relief and ease the physical and psychological harm their condition causes, patients invariably choose the latter. That choice puts otherwise law-abiding citizens in an invidious position and one that was eventually acknowledged by the Home Secretary when he announced a review of cannabis.

1.2 A new debate begins

We acknowledge that the medical profession is divided on this issue. In fact, the number of clinical advocates of medicinal cannabis treatments remain a small minority, which is even the case in those countries that have had a legal medical market for many years. Cannabis is not a common part of clinical treatment regimes, training on its use is not mainstream, and the number of approved drugs is very limited so direct experience is poor to non-existent in the National Health Service (NHS) currently.

It is no surprise that doctors are largely unfamiliar with the drug, as many of the specialist clinicians now authorised to prescribe it went to medical school in the 1970s and 1980s before the human endocannabinoid system had even been discovered. They then trained and spent all of their careers in medical practice while the drug was prohibited, and in the UK at least, before any licensed products were adopted by the NHS. In fact, it is still the case that cannabinoid pharmacology is not taught to medical students. Further reluctance arises from practitioner uncertainty about side effects and some negative

associations with the famous (but flawed, and notoriously lax) medical cannabis practices in places like California in the 1990s and 2000s.

Consequently, there is undeniably a lack of experience of and training on the use and the evidence for Cannabis-Based Medicinal Products (CBMPs) within the medical community even at specialist level. Where experience does exist it can be disparate and often associated with a single condition or CBMP. Today, many senior clinicians are doubtful of the claims made for cannabis as a medicine arguing the drug is lacking the research studies and robust clinical trials that would be demanded of other new drugs to prove their efficacy. There exist some professional treatment uncertainties about cannabis, its interaction with other medications, and the long-term impact of prolonged use on cognition and brain development, especially in children and young adults. These and other similar concerns also have implications for professional conduct and liability. All of this goes some way to explain why the first guidelines have been ultra-cautious and restrictive, despite the health benefits claimed by users of illicit cannabis.⁶ In this report we try and address some of these positions and recommend ways in which opposition or simply agnosticism among the medical community can be overcome.

Set against this professional scepticism is a rising tide of support from patients, the public and some highly influential condition charities for medicinal cannabis. Advocates point to benefits reported by patients, and campaigners highlight the long history of folk medicine to argue its safety and efficacy. They further argue that herbal cannabis is denied to patients because of the laws prohibiting recreational use and the inflexibility of medicines regulations that are set up to evaluate tightly defined pharmaceutical products. They also claim that the evidence base is not as weak as is claimed and is being improved by new studies released almost every week.

Arguments between these two constituencies, the sceptics and the champions, have now moved from a theoretical debate about whether a law should be changed, to debating the right way to regulate and implement a system now the law has changed. The UK public debate is now jumping ahead, as it has in many countries already, from being a question of why cannabis should be legalised for medical use, to how it should best be done. The new Centre for Medicinal Cannabis (CMC) exists to help answer the second question.

This report accepts that the ‘how’ question elicits many different opinions and does not lend itself to a simple response, or one that answers the matter definitively. There are many models for how legalisation can be applied. How it should be implemented is also very dependent on the political context and how ambitious legislators wish to be, which varies between countries. Learning from the international experience is vital but so is also creating a distinctive system that suits the UK. Building a system that is robust, fair and sustainable is now at least possible, but will not be achieved in one simple step.

1.3 Why this blueprint is needed now

Since the change in law took effect on 1 November 2018, there has been only minimal feedback on how the rescheduling is working in practice. What information is available comes from patients, many of whom claim they are continuing to struggle to access cannabis medicines and who perceive the barriers to be the same, if not greater, than before the drug was rescheduled. A small number who have been successful so far have nonetheless been frustrated at the very high cost of this type of prescription outside the public system.

This report pinpoints why the current system is deficient and what policy changes are necessary to deliver a regime that works for patients and one that makes good on the promises made by politicians.

No new system for medical access anywhere in the world has been perfect on day one, and every country faces unique cultural and institutional factors that shape how quickly patient access can be delivered, and by what means. As the UK begins on this journey, it is important that the right decisions are taken in the first couple of years in order to shape the market in a way that guarantees a sustainable model that meets the needs of patients over the long-term.

A system that is too restrictive, or even one that is too lax, will undermine the government’s policy aims, erode public support, and disadvantage patients who need reliable access to a good range of quality products from responsible suppliers. As such, the UK needs a system that strikes the proper balance between choice and safety, whilst allowing for future changes as lessons are learnt. As such, this report explores the fundamental policy choices that are necessary when

devising an access regime and the trade offs policy-makers and legislators must make. It will examine alternatives and consider the constraints that will dictate what regime will be workable in the UK.

1.4 About this report

While this report addresses some of the shortcomings of the current UK approach, it is designed to be forward-looking and constructive, in order to help those who are tasked with setting policy, and implementing guidelines and regulations, as well as those who must work on behalf of patients - the physicians, pharmacists, and providers - to navigate this new and unfamiliar system.

For this reason our report is mostly focused on providing constructive suggestions for improving the current medicinal cannabis system, based on better practice elsewhere. It draws on policy insights, scientific data, industry experience, stakeholder perspectives, and patient attitudes.

The report makes 30 recommendations and outlines the steps that should be taken if the policy objectives we describe are to be achieved. It concludes by describing a vision for the future and makes the case for the government to now develop a strategy to deliver that vision.

1.4.1 Forthcoming Work

To supplement this report the Centre for Medicinal Cannabis (CMC) intends to conduct further research into clinicians’ attitudes and priorities and will commission a dedicated survey of a representative sample of UK doctors in 2019.

The CMC also intends to publish a separate study on the mainstream CBD market in the UK and the changes needed to ensure this important class of cannabinoids is well regulated. This is critical so that producers, including UK hemp cultivators, can contribute to a high-quality consumer market of CBD products that benefit users.

As new research results are released on a monthly basis and the field of study is expanding rapidly, the CMC also intends to examine the growing evidence base for the efficacy of a range of cannabis-based medicines on certain health conditions, in partnership with condition charities, over the course of 2019. The CMC will also conduct further research on the

patient demand for medicinal cannabis products, drawing upon NHS data, patient surveys and clinical studies to estimate the numbers in the UK living with conditions that could prove treatable with the use of a CBMP, and the benefits that such coverage would offer.

2. Medicinal Cannabis in the UK today

Until now, only a handful of current medicinal cannabis patients in the UK have been using pharmaceutical grade products. These licensed medications are rare and not routinely prescribed. The vast majority of people are instead smoking, vaping or otherwise consuming illicitly grown herbal cannabis products to self-medicate a wide variety of conditions, many of which will not have been formally diagnosed. Regrettably the illicit market is notorious for the supply of low quality cannabis, often of unknown provenance, including high potency products that are often contaminated, posing serious health risks.⁷

The creation of a new legal medical cannabis market in the UK is happening against this backdrop and policy choices about how to meet the needs of patients must acknowledge this and recognise where we start from. Treatment options derived from cannabis may be a novel concept to the established healthcare system in the UK, but the different strains of cannabis are very familiar to those who have come to rely on the plant for its therapeutic qualities.

The cannabis sativa plant is not a recent discovery and despite its controlled status, its potential health benefits and widespread availability makes it an unusual clinical proposition - and a challenge to many existing health orthodoxies. In many cases patients who are now likely to seek access following medical legalisation are much more experienced with cannabis and its effects than any clinician. Some have been depending on it to alleviate their symptoms and improve their quality of life for years. It is doctors who have a steep learning curve now the drug can be legally prescribed.

2.1 Public attitudes towards medicinal cannabis

What is already apparent is that despite institutional scepticism, public attitudes in advance of legalisation

were already supportive of cannabis use for medical purposes and public opinion has shifted decisively over recent years.

According to the latest survey by Populus⁸ and commissioned by the Centre for Medicinal Cannabis and VolteFace in October 2018, there is broad and deep support for cannabis medicines:

The research showed that the majority of UK public, 76%, would be open to consuming cannabis as a medicine if prescribed to them by a doctor. This was consistent across the demographic groups, with young people aged 18-24 slightly more likely to consume prescribed cannabis medicine at 81%.

Attitudes to the legalisation of cannabis for recreational use fluctuate but are typically much less clear in terms of public support, with surveys in recent years showing a large gap between the levels of support for medical use, and much lower support for general cannabis legalisation. In the public’s mind at least, cannabis is legitimate as a medical product and the law should acknowledge that. It is seen as a separate proposition, and a much disputed one in the UK, whether the drug generally should be made legal for adults to consume recreationally.

That difference in perspectives on the issue also matters in reality because the two systems can involve the same people and in some jurisdictions can and do co-exist. However, fundamentally the two regimes are distinct in both purpose and effect (and even in Canada since federal recreational legalisation, they are distinct in law). Nevertheless, it is also the case that unless a medical cannabis regime is well-regulated and tightly supervised, there is the risk that the lines blur, access is abused and the reputation of the clinicians and the legitimacy of cannabis as a medical treatment is called into question. It is therefore important to establish a medical cannabis system that is very clearly distinct from any general policy to decriminalise use of the drug, especially if patients are to be prioritised and public support for the reform is to be maintained.

2.2 Markets in cannabis

The healthcare market for cannabis medicines is now evolving rapidly in those jurisdictions where it is legal for medical consumers. However, the unique way in which cannabis was excluded from mainstream science and pharmaceutical industry developments for decades has made for an immature

market defined by rapid growth, poor institutional penetration, and variable quality standards.

One of the consequences of the rescheduling of cannabis is that it immediately opens up the market for medicines that, depending on the product, sit somewhere between food supplements and wellness products for health-conscious consumers, and the pharmaceutical grade licensed medications supplied to patients by taxpayer-funded health systems. In this respect, most CBMPs, although they are not licensed medicines in conventional terms, are more than simply health/wellness products. Those sold by the larger EU or Canadian producers are manufactured to a pharmaceutical grade and several product lines already form part of a number of ongoing clinical trials.

1. Pharmaceutical

Proven clinical benefit; full clinical trial data; fully regulated and approved as a licensed treatment by national regulators (MHRA, FDA or EMA); prescribed by all grades of physicians; synthetic or natural (plant-derived); oral delivery most common mode of consumption; potentially available via public healthcare systems. Examples: Sativex (GW Pharmaceuticals; MHRA and EMA approved), Epidiolex (GW Pharmaceuticals; FDA approved); Nabilone (Dales Pharmaceuticals Limited; FDA and MHRA approved) and Dronabinol (Solvay Pharmaceuticals, FDA approved).

2. Medicinal

Some studies that show patient benefits; growing number of observational trials; larger number of full clinical trials underway; regulated as unlicensed medicines in some markets (Australia, UK); products here must meet EU production standards (GMP); marketing restrictions; prescribed by specialist physicians; flower or oil most common modes of consumption. Examples: Jean Guy and Warlock (Tilray), Luna and Tower (Aurora), Tweed and Red No 1 (Canopy Growth).

3. Wellness

No research to date; pure or enriched CBD products at relatively low doses; sold in retail stores and online in the UK; regulated only as a food supplement; derived from industrial hemp/cannabis sativa; no transport or import restrictions as pure CBD is legal in EU countries; variable quality; production controls do not meet medicinal standards; available as pills, oils, creams; banned by law from making health claims. Examples

of producers/suppliers: Dragonfly BioSciences, Jacob Hooy, CBD Brothers, Charlotte's Web.

4. Recreational / Illicit

Very limited public health research; now only possible in two countries with fully federally legal regimes (Canada as of 2018 and Uruguay as of 2016); illegal in most countries in all forms; penalties/enforcement vary; widest range of products (flower, edibles, oils); high value unregulated illicit market, with extensive organised crime elements; no quality controls; little consumer information; irregular production, and risks from potency/toxicity.

2.3 Cannabis in the UK after 1 November 2018

The Conservative Government elected in 2017 had no policy on medicinal cannabis and so the welcome change to the law in the autumn of 2018 was not preordained. Even after the Home Secretary announced a formal review in response to the case of Billy Caldwell, it was not clear what shape any change might take or when it would take effect.

The Government decided to accept the official advice based on the summary of evidence and effect the changes by rescheduling and amending the 2001 regulations setting out the rules on controlled substances. Those amendments to law were done rapidly and without the need for primary legislation, which reduced the time needed to bring them into effect. The speed of this process was welcomed by patients but undoubtedly caught health regulators by surprise.

The updated legislation does not specify or limit the types of conditions that can be considered for treatment by cannabis-based medicinal products (CBMPs) and qualified doctors will no longer need to seek approval from an expert panel (that was convened as a temporary process in June 2018) in order for patients to access the medicines.

The rescheduling allows for certain CBMPs to be prescribed as unlicensed medicines, however they must be prescribed by a specialist clinician not a General Practitioner. These 95,000 doctors (out of 298,000 on the General Medical Council (GMC) register in the UK as of 2018)⁹ focus on one field of medicine such as neurology or paediatrics and are listed on the GMC's specialist register.

While it was drawing up the interim guidance, NHS England, asked the British Paediatric Neurology Association (BPNA) and the Royal College of Physicians to provide clinical advice to doctors ahead of the law change. NHS England specifically asked the BPNA to develop advice on the use of cannabis-based products for medicinal use in certain forms of severe epilepsy. The College of Physicians were asked to develop advice around cannabis-based products for medicinal use in intractable chemotherapy induced nausea, vomiting and chronic pain. Because only these conditions were chosen, there is currently no guidance on using CBMPs in other conditions, making prescriptions very unlikely. The interim guidelines that were pledged were produced on the very eve of the law change, and there was no widespread consultation with stakeholders in advance.

The National Institute for Health and Care Excellence (NICE) was separately commissioned to develop more detailed guidelines for clinicians and the NHS. The scope for this has been released for comment and the final guidelines will be drawn up after extensive consultation with stakeholders and be published no later than October 2019.

2.3.1 Summary of the Changes in the UK

The UK government has taken several necessary steps to legalise cannabis-based medicinal products but there has been no wholesale structural or legislative reform. Compared to countries like Australia and Canada where dedicated legislation and/or bespoke regulations were devised, consulted on, and then issued, the system now operating in the UK is the result of two hastily-prepared expert reports, a simple legal change, and some new professional (albeit interim) guidance.

In summary, the UK system has been stood up in a relatively short period based on only the following elements:

Rescheduling (1st November 2018)

Amendments via secondary legislation (no dedicated parliamentary bill voted on by MPs) to alter existing 2001 regulations on the misuse of drugs that moved cannabinoids for use as medicines in humans from Schedule 1 to Schedule 2. In law this meant they are now recognised as having medical and therapeutic benefits, enabling them to be prescribed.

Official scientific advice (June - September 2018)

The Home Office commissioned two separate pieces of advice on the current evidence base internationally for the medical use of cannabis. Both the report of the Chief Medical Officer¹⁰ and the first part of the advice received by the Advisory Council on the Misuse of Drugs¹¹ concurred that CBMPs should be exempt from the Misuse of Drugs Order 2015, meaning they would no longer be illegal for patients or their carers.¹²

Interim clinical guidance (31st October 2018)

Published by NHS England on the eve of the change to the law, alongside other guidance from specialist professional bodies.

Finalised guideline development (November 2018 - October 19)

Final NICE guidelines for the approved use of CBMPs will be developed over the next year¹³ and published no later than October 2019.

Ongoing consultation

The government and its regulatory agencies (NICE, the MHRA, the FSA and others) have committed to ongoing engagement as this new system is rolled-out.

2.3.2 Ongoing policy work

The National Institute for Health and Care Excellence (NICE) was tasked by the government with producing definitive guidelines by October 2019. As NICE themselves have admitted, this is especially challenging as they usually take 18 months to produce a single guideline for one specific condition. Partly in response to limited capacity, NICE is focused on spending the next 10 months producing guidelines for those conditions for which there is the strongest evidence that CBMPs could prove beneficial. To guide this work, NICE are recruiting to a committee who will lead the consultation and consider responses before definitive guidelines are finalised and propagated throughout the health service.

In addition, further reviews are ongoing or are yet to be published:

- NHS England has also committed to publishing a detailed FAQ to be sent to specialist clinicians in 2019 that will answer some of their questions about this new area of medicine.
- The second part of the ACMD review into cannabis ordered by the Home Secretary.

2.4 What the legal regime now allows

The Government introduced regulations that would keep cannabis-based medicines within existing statutory and regulatory frameworks, and was clear that this was the intent of the policy change which “brings these products explicitly into the existing medicines framework”. They introduced a new definition of ‘cannabis-based product for medicinal use in humans’ which must meet the following three requirements:

1. It needs to be a preparation or product which contains cannabis, cannabis resin, cannabidiol or a cannabidiol derivative;
2. It is produced for medicinal use in humans and;
3. Is a medicinal product, or a substance or preparation for use as an ingredient of, or in the production of an ingredient of, a medicinal product

This is a broad definition that on its own, would enable a wide variety of products to be made available. The Home Secretary’s statement also made clear that “Only products meeting this definition will be rescheduled to Schedule 2 to the 2001 Regulations and de-designated from the 2015 Designation Order. Any product which does not satisfy this definition will remain a Schedule 1 drug and only be available under a Home Office licence.”

The law was then updated further specifying three access routes for order, supply and use of products meeting the above requirements, and these were explicitly stated to be the only permitted paths:

1. A special medicinal product for use in accordance with a prescription or direction of a doctor (who has made the decision to prescribe) on the Specialist Register of the General Medical Council;
2. An investigational medicinal product without marketing authorisation for use in a clinical trial or;

3. A medicinal product with a marketing authorisation.

The emphasis on standard MHRA authorisation and the utilisation in clinical trials is important and necessary but both of those permitted routes for a CBMP do not meet immediate patient need. The first permitted route, via a specialist doctor, is the access that patients were previously denied. The use of CBMPs in clinical trials is likely to be one growth area in coming years (see Chapter 4), however it is the use by doctors in the prescribing of cannabis-based medicines as an unlicensed product that will determine whether this reform leads to widespread patient benefits.

2.5 What has not changed

2.5.1 Criminal law

Since the review of the laws was announced, the Government has been clear that they have no intention of legalising and regulating cannabis for recreational purposes, or of endorsing any changes to categorisation that would in effect lead the UK to follow countries like Portugal in decriminalising cannabis for non-medical use. Rescheduling and the provision of CBMPs through the ‘specials’ route also means that the authorities are not simply allowing any cannabis-based product to be sold.

A common feature of some medicinal access schemes, that patients are permitted to possess the plant and for it to be grown at home, remains banned, and there are no signs that this reform would have political support within the government at the present time. The Home Secretary was explicit on this: “I have been consistently clear that I have no intention of legalising the recreational use of cannabis. To take account of the particular risk of misuse of cannabis by smoking and the operational impacts on enforcement agencies, the 2018 Regulations continue to prohibit smoking of cannabis, including of cannabis-based products for medicinal use in humans.”¹⁵

Furthermore, because medical legalisation has been brought into effect via the rescheduling route, no new laws have been tabled in the UK Parliament and the penalties (including imprisonment) in the criminal law remain intact¹⁶. Whether as a patient or otherwise, the recent reforms provide no additional rights to access cannabis outside of the proper medical channels, and no defence against arrest for doing so. However difficult it may prove for patients to access

cannabis-based medicines via a specialist clinician, either privately or through the NHS, resorting to growing or consuming cannabis acquired illicitly is still a prosecutable offence.

2.5.2 Existing regulations

Furthermore, despite the rescheduling leading to an increase in demand and therefore a realistic expectation that this will be met by additional supply, the current regulations and the application process for becoming a supplier of medicinal cannabis products or the raw plant product itself has not changed. That remains a Home Office system administered by the Drugs, Licensing and Control Unit.

Those seeking to import, export or cultivate cannabis domestically must only do so with a licence issued by the Home Office after one or more applications have been made. There is currently no sign that these regulations will be amended or the application process or licensing fee regime updated to enable supply to come into the market through importation or the opening of new production or processing facilities in the UK itself. There is also limited information on what licensing approval involves beyond the application process and no published data on the type or nature of application sought or granted. This is in contrast to the well-established Canadian system where Health Canada provides detailed guidance on the whole process and is transparent about the volume of applicants and their status in the licensing process.

3. Goals and Trade-Offs

All systems for regulating medicinal cannabis involve many of the same trade-offs. Each country that has legalised has had to frame their regulations in a way that is practical and allows the political goals to be achieved, often similar across all countries, against a set of usually common constraints and local restrictions. The goals are tempered according to the public concerns that exist so for some countries, public health may matter more than supporting a new industry or tackling public safety concerns of the ongoing black market. The constraints also vary according to context, media and political attitudes, the biases and operating habits of practitioners, the institutional preferences of influential professional bodies, and economic considerations of publicly funded healthcare models.

3.1 Political goals

Most medicinal cannabis systems share the same political goals despite being regulated in very different ways. The regime that the UK is now implementing is consistent with the political goals of the federally-legal systems in two comparable Common Law jurisdictions, that of Canada and Australia, insofar as it has three primary objectives:

Political Goals of Medicinal Cannabis Regimes

1. Alleviate human suffering and improve patient care

Improve quality of life by providing access to medical treatments that show promise for a range of conditions, and for which other conventional pharmaceutical drugs have proved ineffective, or only effective with intolerable side-effects.

2. Displace the black market and regulate for safer consumption

Create a regulated supply of high quality products that can be accessed legally through legitimate, predictable and safe channels, thereby displacing demand from unsafe, illicit sources and lifting the threat of criminal prosecution from patients for their self-medicated use of a controlled substance

3. Foster an innovative new healthcare industry

Catalyse more research into, and exploitation of, cannabis as a medical product so as investment flows into trials and R&D, we can create new drugs and better treatments to improve quality of life at the same times as fostering an industry that generates high-skilled jobs, tax receipts, and contributes to economic growth.

Each regime around the world embodies a different balancing act that reflects local factors including the degree of normalisation of cannabis itself in society. In some systems like Canada, a more familiar and liberal attitude to the drug made it possible to construct a medical system that tolerated patients being able to grow their own plants. The extension of that liberal attitude was also seen in the growth of privately-operated dispensaries selling cannabis to registered patients (among many others) and usually from undocumented and illicit sources, a phenomenon that has not yet happened in the UK or other systems where regulations are more conservative.

2.5 What has not changed

In practical terms, a key trade-off for policy-makers is to decide how special cannabis-based medicines actually are. Clearly as a whole plant product containing in excess of 100 phytocannabinoids, of which we still know an inadequate amount, this makes cannabis distinct from drugs approved via the conventional pharmaceutical paradigm of ‘single compound, single target’. However even though they are unusual and poorly understood, should this mean that cannabis-based medicinal products should be treated differently in regulatory terms? The answer to that question dictates the shape and nature of the medical system that is established.

The UK and Australia landed in the same place, concluding that CBMPs should be subject to conventional licensing and approval processes, and in so far as the majority of products (with the exception of Sativex, Epidiolex, Nabilone and Dronabinol) do not (yet) qualify to be licensed because of a lack of, or inadequate trial results and attainment of other standards. They nonetheless must exist within the unlicensed (or unregistered) regime that already applies to many other drugs.

The Canadian regime, which has had three evolutions since 2001, started from a different position - concluding that whole plant products were legitimate medicines that nonetheless needed special treatment. To this end, even if they reached pharmaceutical standards of production, those producing and supplying raw cannabis or extracts had to abide by a dedicated set of production and labelling standards that were created for this sector and specific to these products, and not simply the generic requirements of all medications produced and sold in Canada.

Another common trade-off for policy-makers is between State control and private provision, where in certain models, the government plays a major role not just as a regulator of commercial entities that supply cannabis, but sometimes as the single wholesaler (as in the Netherlands) or the majority owner of a government-licensed monopoly provider (as was the case originally in Israel). Other trade-offs involve distribution - is this best mediated through a pharmacy model (as in Germany and Australia) or are direct-sales to patients as the distribution model preferred (as in Canada). Or should this be done through a more liberalised private retail (e.g. dispensary) model outside of the regulated healthcare sector?

However, the most important trade-off that medical cannabis regulation must make is that of maximising patient access and the imperative to minimise patient and social harms. If policy seeks to optimise access but not at the expense of safety, and so preferably only to high quality, licensed medicines, then patients needs in the short-term will not be met and the black market will persist. Conversely, if policy seeks to optimise access, even if that encourages a greater share of unlicensed drugs to be prescribed, patient needs will be met faster (and the illicit market undermined), but only by exposing patients to more risk and neglecting the long-term evidence base.

The former approach usually involves narrowing patient options while trials are conducted and the necessary licensing of new drugs takes place, and in the meantime tolerating an ongoing dependence by patients on self-medicating with illicit products, despite the proven risks. The latter approach typically involves more relaxed guidelines designed to encourage greater prescribing so fewer patients have to resort to the black market. Even if this happens outside of proper clinical trial settings and goes against efforts to grow the pipeline of fully-licensed cannabis medications that public healthcare systems could actually adopt widely.

3.2.1 The Trade-Offs the UK System Makes

At present, the system in the UK reflects the former approach, the cautious and conventional approach adopted with other new drugs, which trades away a fair degree of patient access for a greater emphasis on proper licensing processes and encouraging more clinical trials - at least as far as the NHS is concerned. This is acknowledged in the NHS's own patient website which states that “very few people in England are likely to get a prescription for medical cannabis”¹⁸

Later in this report we explore what some of the consequences of this cautious approach could be, and what steps could be taken in the short to medium-term to avoid or mitigate them. Clearly this is not a binary choice and there is no right model for all circumstances. It is a question of balance. Regulations and laws that embody these trade-offs are nonetheless still seeking to achieve certain goals, and have to tolerate certain compromises in order to get there. So what are the common policy objectives of a medical cannabis system and will the current UK model achieve the right balance that ends up delivering them?

3.3 Policy objectives for cannabis regulations

The three core political goals of any medical legalisation are underpinned by several policy objectives. These are invariably the benchmarks against which the reform is judged. Regulations and best practice can be adopted or amended as required to help achieve them, both in light of new evidence and also the experience of how the system actually works for patients, clinicians and the wider industry. The aim throughout is to create and sustain a system that achieves several objectives simultaneously:

Policy objectives of a successful system
Improves health outcomes, reduces social harms and protects patients
Meets diverse patient needs through the timely supply of quality products
Builds the evidence base for medicinal cannabis-based products in the UK
Improves clinicians' knowledge and their confidence to prescribe
Creates regulations that ensure high standards are set and complied with
Increases public awareness and understanding about cannabis as medicine
Stimulates innovation, scientific discovery and economic growth

These policy objectives, alongside the overarching political goals of the reform, provide a framework for us to evaluate whether the medicinal cannabis system being stood up in the UK is working. Evaluating its performance against each of these objectives is not yet possible because the system is in its infancy. However this report attempts to describe the features of a successful access regime, offers some initial assessment of how the UK system is performing, and then devotes most attention to what needs to change.

4. Evaluating the New Landscape

It is too early to begin any evaluation of how the regulations are operating in the UK and to know with certainty where the biggest barriers to an effective and accessible system exist. Nevertheless, in considering the experience of other jurisdictions that have already encountered some well-known problems, it is already possible to identify a range of strengths and weaknesses in how the current system is setup, even if we cannot say with certainty that they will invariably lead to the same problems experienced in other places.

4.1 Strengths and Weaknesses of the UK regulations

How the UK system measures up
Strengths
Doctors professional discretion is respected
Specialists doctors in the NHS can prescribe, so patient access is not based on ability to pay
Prescribing a schedule II product is not restricted to a predefined set of conditions
All forms of cannabis are theoretically prescribable, including herbal flower products

How the UK system measures up

Strengths

Cannabis-based medicines have been incorporated within the established regulatory channel for unlicensed medicines or 'specials'

Smoking of herbal cannabis is not an approved route of administration, but vaporisation is implicit in the products that are permissible (oils and flower)

Private clinics are under no new restrictions and must comply with public sector regulations or processes, or their equivalent

Doctors are encouraged to make decisions based on their professional judgment and the available evidence, having regard to the best interests of their patient

Weaknesses

Doctors remain under an obligation to follow guidelines which are restrictive, and to abide by local policies, which can make prescribing a CBMP impractical

General Practitioners cannot prescribe under any circumstances, not even as a follow-on prescription

Cautious guidelines for major conditions either do not recommend a CBMP or advise its use but not as a first-line treatment

Guidelines recommend only licensed cannabinoid treatments and there is no approved list of flower products to guide prescribers

Prescriptions are bound by the conventional 30-day limit for unlicensed medications, and cannabis medicines are subject to the same local policies that discourage the use of specials on cost and supply grounds

Patients seeking a whole plant product are limited in what products can be legally imported (GMP-certified etc) and product range for oils is narrow.

Private clinics in the UK offer either co-payment upfront or reimbursement through supplementary insurance policies but so far none cover unlicensed CBMPs

There is no education or training material on cannabis medicines being circulated and most doctors of the age and seniority to be able to prescribe lack knowledge of cannabinoids as a relatively new area of medicine

4.2 What has changed for patients?

4.2.1 Available Products

The NHS has written advice for patients on cannabis-based medicines¹⁹. To summarise this, they suggest that Epidiolex can be used for Lennox-Gastaut syndrome and Dravet syndrome; that nabilone can be used for chemotherapy patients and that Sativex can be used for MS patients.

So far, as of 5 December 2018, there has been a single documented case²⁰ of an adult patient receiving a prescription for a flower product from her private clinician under the new CBMP rules, and who was issued a 2 gram per day prescription for 90 days of a product supplied by the Dutch company Bedrocan.²¹ The media also reports a second case of a child being prescribed through a private hospital.

4.2.2 Access through doctors

A prescription for a medicinal cannabis product can only be obtained from a specialist. Preventing General Practitioners from prescribing has several consequences for patients - it immediately presents a barrier to access as patients must be referred by their GP to a specialist and the vast majority of GPs will not have sufficient knowledge to do this. Secondly, it narrows the consultation route so anyone who is prescribed by a specialist must return to that specialist for follow-on prescriptions, even if the GP for that patient is the physician that knows them the best. Thirdly, it means that only those conditions

that are under secondary care would be eligible for a CBMP, and this is not likely for some of the conditions for which people self-medicate with cannabis, such as anxiety, PTSD and insomnia.

4.3 What has changed for clinicians?

Prescribing clinicians will no longer have to resort to either calling upon the Home Secretary to use his executive authority to issue emergency licenses or referring to the panel the Home Office convened to consider such cases in June 2018.²² That panel was constituted as an interim measure and ruled on a number of cases, but as planned, has now disbanded.

However, after a very rapid and public change in the law that allowed for the prescription of CBMPs by consultants, these specialist clinicians have suddenly been faced with patient enquiries and public pressure to begin prescribing CBMPs. Media attention on the issue has driven awareness and it is leading more patients to ask questions of their doctor. However, most doctors will be without the necessary skills or experience to discuss the issue in detail or feel empowered to prescribe. Many will have a very limited knowledge of the science of cannabinoids, and of the potential impact (evidence base) of CBMPs within their speciality. And without any basic guidance from NHS England on what the various different CBMPs even are, it is almost impossible to even undertake this research at an individual level.

For those clinicians who are more open to the concept of CBMPs, local policies and national clinical guidelines mean it is very difficult within the NHS currently to prescribe a CBMP. This has been further restricted by the interim advice from NHS England that CBMPs should only be prescribed in two forms of epilepsy and chemotherapy-induced nausea, using Epidiolex that is either already or is close to being licensed (Epidiolex is already FDA approved in the US) and Nabilone (MHRA approved), and so not in fact ultimately requiring the specials route. The existing regulations on unlicensed medications and guidelines on their prescribing, sourcing and dispensing are set by the MHRA and the latest version²³ (from 2014) has not changed as a result of rescheduling, but additional MHRA guidance on CBMPs has been provided.²⁴

The recent rescheduling and option of the specials route is only relevant therefore if a clinician is inclined to explore a new treatment option, which

depends on the education and familiarity that a specialist has with the whole field of cannabinoids. Since no new training or education initiative for these doctors has been initiated by the NHS (and there is no commitment so far to do so), it is unlikely that knowledge will spread quickly. Until more research is conducted into clinicians' attitudes to cannabis, it is unclear how much of a generational divide their might be. Based on GMC data, 44,731 of the 94,883 doctors (47%) on the specialist register in 2018 are over the age of 50.

For most other clinicians, including GPs and consultants outside of the recommended speciality areas, it is likely that nothing else will have changed for them, other than increased enquiries regarding CBMPs driven by more stories in the media.

4.4 The reality of access today

There have been several surveys in recent years estimating current use of cannabis, and the United Patient Alliance (UPA) 2018 Medical Cannabis Patient Survey investigated the extent and range of the consumption of cannabis for medicinal purposes in the UK and reported effectiveness versus other treatment options.

43% of patients surveyed have been living with their condition for more than a decade. Top physical conditions are Pain, Insomnia, Arthritis, Fibromyalgia, Muscle-Spasms and GastroIntestinal Disorders. Almost a third of respondents (31%) said they consumed cannabis primarily to address mental and behavioural disorders such as Anxiety, PTSD and Depression.

CASE STUDY: Carly's story

'I don't think anyone truly understood how very poorly I was - aside from those very close to me....'

In 2010 I suffered a stroke whilst I was in my third year at University, thankfully I still managed to graduate (stubbornness strikes) and after an agonising circuit of an ice skating rink (yeah I tried to ice skate a month after a stroke) I knew my body wasn't loving life. Two months later I was diagnosed with everything. Everything.

The main condition was Fibromyalgia, the doctor assured me that you don't die of Fibromyalgia, but you will die with Fibromyalgia. Great...is that another challenge?

Over the next five years my stubbornness was tested as my body declined to operate. I was in my twenties and some days I couldn't dress myself, get downstairs or even make a cup of tea. My brain frequently threw raves of the German techno kind, sending signals out like a laser show. This effected everything, from moving to speaking. If I had a job on I would need to spend four days resting in preparation and order a poppy field of morphine to get me through the aftermath. It was messy. My super-wife took over everything...

Towards the end of last year I was having one 'good' day a week if I was lucky. I don't think anyone truly understood how very poorly I was; aside from those very close to me. I am stubborn and I have an excess of pride which is cumbersome at best. Six years hit and I was still in rapid decline. I had been taking morphine and fentanyl in increasing doses for years now. Opiates are great for pain but they also numb all of your other bits. I was struggling to feel the world as I hobbled along in a zombified state - this was not sustainable.

Insomnia is part and parcel of living with 'everything' and when my body stopped responding to four sleeping tablets a night I decided to smoke a joint one night to try and relax my body. Ten mins later I felt like something was missing...What was this?... I froze not wanting the feeling to stop and whispered to "Super-wife". "Hey!.....I am not in any pain!". She looked at me like I had just announced that I was a lizard. We didn't know what to do with that!

This began my research on the use of strain-specific cannabis. I managed to make some contacts through the local cannabis clubs and began using a sativa strain in the daytime and indicas to sleep. I stopped using the morphine altogether and managed to withdraw to half-dose fentanyl without methadone or subutex, just with the use of cannabis. I was finally on top of the pain and the sativa strains were kicking ass with the fatigue, my tremor quietened down, I could get up in the morning without a gruelling battle, I could

think and speak in actual sentences, I even called my doctor enthusiastically to tell him that I was painting a fence. Within four weeks I was walking without my walking stick, I dusted off my hiking boots and started to increase my exercise regime as my body was initially weak and grouchy.

This one little plant has saved the NHS £500 a month on my prescription alone, imagine that scaled up? This one little plant can treat hundreds of conditions and potentially has the ability to save our health service with a boost in what is approximated to be one billion a year in tax revenue and a substantial reduction in people using subsidised medication. I have spoken to several people who are suffering, yet they are so terrified of prosecution that they feel that medicating with cannabis isn't an option for them. We as a society are letting those people down. I am very much enjoying working with the UPA to change that.

Even though 72% of patients source their medicine from black market street dealers, 77% reported that cannabis provided a significant improvement in their condition whereas 49% said prescription medications made them feel worse or provided no relief. In fact, 71% of patients have replaced or significantly reduced analgesic or anti-depressant prescription medications.

While patients are safer consumers with 41% now choosing to vapourise rather than smoke their cannabis as reported by 75% of recreational consumers, nearly half have never discussed their cannabis consumption with their doctor for fear of disapproval or legal consequences. Of the doctors who were informed, only 19% gave negative feedback.

CASE STUDY: Sarah's story ²⁵

"It breaks my heart to think others with a variety of illnesses are going through the same or worse"

I was told, when diagnosed with Relapsing-Remitting Multiple Sclerosis (RRMS) in 2003, to avoid all conventional pharmaceuticals; so

I did! I used cannabis when I could access it, which for years, I was unable to... I suffered the worst pain which left me feeling MS demented, lonely and misunderstood. Having no cannabis to ease my symptoms left me with a mental health problem.... It breaks my heart to think others with a variety of illnesses are going through the same or worse.

Ten years after my diagnosis, on 19th September 2013 I received my first prescription of Sativex. To achieve this I went through an almighty and painful relapse where I couldn't even crawl that well. I had to drag myself to and from the toilet, had to be lifted into the bath (I made sure I clambered out myself. It's important to maintain some pride wherever possible.) Hell continued unabated.

A white box containing 3x10ml bottles of Sativex could have changed my life for the better but I soon found it to be weaker than expected. 3x10ml bottles was used up within a week. My doctor is only at the practice on Thursday morning and all day Friday. She is the only doctor at the practice [able] to prescribe it. Nobody should be expected to keep their doctors holidays in their diary but I do.

Don't get me wrong; my life is much improved because of Sativex. I used to require a 30ml of Sativex per week but thankfully, these days I only use 10ml per week. This is great because I only have to request a new prescription every three weeks. Although Sativex is marketed for spasms I use it mainly for pain relief. When I can escape the pain I can clean up the kitchen and even make dinner. Without this essential pain relief I'm just a mumbling, sobbing, foul-mood zombie. I do nothing.

Yes, my life is infinitely better because of Sativex but I knew my health would continue to go downhill. I also suspect that it could take decades to lessen the laws restricting cannabis. I'm far too impatient for our backward British politics. Four years ago I could not walk more than 20 feet and now I can walk a reasonable distance. I went to extremes and drastically changed my diet and lifestyle. My new medicine is called the Wahls Protocol but the addition of Sativex helps me exercise. I'm still very dizzy, slur my speech and my

vision is still very blurry at times and I've got years of healing to get through. However, both medicines feed the Endocannabinoid system so that the body may work to reverse the symptoms of MS.

Whilst it's a real shame that I still have to break the law to get the level of relief that I need, I can now walk one of my dogs in the fields and ponder the marvels of cannabinoids. I'm also well enough now so that I manufacture cannabis oil for other patients from my cannabis plants. That's my silver lining.

5. The Evidence Base

Scepticism about the efficacy of cannabis-based medicines typically arises from clinicians and scientists who are unconvinced of the scientific validity of the studies undertaken to date, or who simply argue that we do not yet know enough to be confident to prescribe, and that much more high-quality clinical trial data from robust, well-supervised studies is needed. It is therefore important to assess the current state of the research landscape, as many medical stakeholders may not have an understanding of the latest research that is being reported from trials around the world. It is also crucial to realise why the evidence base has gaps, and why the science is now being forced to play catch-up.

5.1 Prohibition effects

The law and science of cannabis have been two forces in clear tension for decades. The mainstream political consensus that banned cannabis in the United Kingdom and many Western countries from the late 1920s existed without successful public challenge for over half a century, and it stifled a huge amount of primary research into the plant itself, as well as the clinical applications.

During the modern prohibition era when new international anti-narcotics treaties were signed, from the 1960s to the late 1980s, there were actually important new scientific discoveries made of the active compounds and their effect on the human body, followed in the early 1990s by the discovery

and mapping of the human endocannabinoid system itself. However, cannabis prohibition stifled research and prevented the science from translating to new medicines.

In fact, after California legalised in 1996 and despite more than a third of US states now having some form of legal medical cannabis system, the drug remains a schedule 1 controlled substance federally in the United States, a country like the UK that often leads the way in new medical discoveries. There still remains an insufficient amount of high-quality scientific research into the medical effects of cannabinoids in humans.

However, over the same period familiarity and awareness of the plant expanded, and democratic pressure to lift this prohibition built up. The advocacy was based largely on the personal (and anecdotal) experience of those who self-medicate with the drug, because research data was largely unavailable. It proved sufficiently compelling to drive a shift in political attitudes in many countries and a series of successful court challenges to existing laws, starting with Canada in 2001. Other libertarian arguments about privacy, or the human right to use a natural psychoactive plant for personal enjoyment were usually far in the background and had much less public support, particularly outside of North America.

Once activism then suddenly delivers a change in the law to legalise cannabis for medical purposes, the pent-up demand for science to fill the gaps in our knowledge has now been unleashed. In each country where it happens, legalisation unlocks the opportunity for research which might otherwise have happened years ago. Cannabinoid scientists in many countries - though not in the US - are now playing catch-up. As Rhys Cohen of the Lambert Initiative at the University of Sydney in Australia remarked: "The historical prohibition of cannabis both in Australia and around the world is the main reason why there's been relatively little proper research on its therapeutic potential. It's the absence of evidence that's the issue [with access]."²⁶

The jurisdictions that legalised medicinal cannabis first have had the longest period to begin building a robust evidence base for its harms and benefits, and the UK is in a disproportionately weak position compared to Israel, Canada or some European countries. Outside of the US, politics is no longer preventing new research, but public and media pressure for science to acknowledge and validate

the benefits that patients ascribe to cannabis is still there. However, the traditional research methods to build a clinical evidence base in the UK, starting with Randomised Controlled Trials (RCTs), the gold standard of clinical research, are likely to prove too slow to satisfy patient and public expectations. It is therefore right that CBMPs can be made available as unlicensed products through the MHRA's existing regime for so-called 'specials'. However, it is also not accurate to say that insufficient evidence exists, as there is much research already out there.

5.2 A true picture of the current evidence base

One of the frequently cited problems is the lack of evidence for the therapeutic benefit of CBMPs. To assess the validity of this assumption we undertook an extensive analysis of the evidence base for CBMPs. Examining the peer reviewed published literature of clinical trials that have investigated the therapeutic benefit of CBMPs in the indications of 1) epilepsy 2) chemotherapy-induced nausea and 3) chronic pain, as these are the three areas NHS England asked for interim guidelines until the publication of the NICE report. In fact, the Royal College of Physicians themselves suggested that 'We recommend that a database is established for the analysis of data from all areas'.²⁷ At present, although there exist several online sources for clinical trials internationally and in the NHS, there is no single database that captures research trials results in the field of CBMPs.²⁸

5.2.1 Peer reviewed published literature

Looking at the history of clinical trials (in any indication) with CBMPs, Figure X shows there has been exponential growth in the number of RCTs published in peer-reviewed journals since the mid 1960s. After the initial discovery of the main phytochemicals within cannabis (THC and CBD), there was a flurry of clinical research which abated in the 1980s for several reasons including the legislative tightening internationally already mentioned. The recent renaissance in this research area was sparked by the discovery of the cannabinoid receptors (CB1 and CB2) and endogenous cannabinoid system in the early 1990s, which prompted many pharmaceutical companies to explore these molecular targets for therapeutic reasons. This was coupled with legislative changes across the world which allowed cannabis to be used for medicinal purposes, facilitating investigator-led clinical trials (initiated by academic or clinical groups) to be carried out.

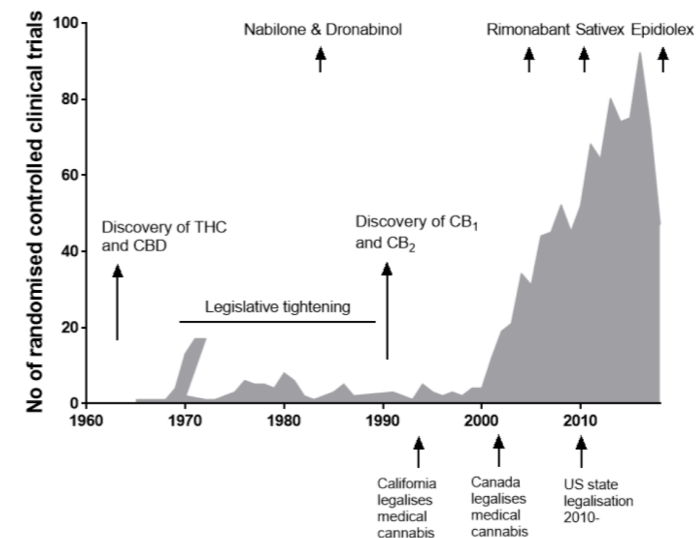


Figure 1. The number of peer-reviewed published randomised controlled trials investigating the therapeutic potential of cannabis-based medicinal products plotted against time, with key influences including scientific discoveries in cannabinoid science and changes in the legality of cannabis use for medicinal reasons across the world.

In the last 10 years, over 700 RCTs investigating the medicinal benefits of various CBMPs have been published across multiple disease areas, demonstrating the escalation of clinical research in this area that continues to provide evidence of the clinical benefit of cannabis-based medicines.

Looking specifically at the evidence base for the use of CBMPs in pain, we found a total of 69 clinical studies published between 1975 and 2018, although only 11 of these studies had greater than 100 patients. We divided these studies into those that examined the effects of the whole plant, pure CBD, pure THC (plant-derived or the pharmaceutical products Dronabinol and Nabilone), or a 1:1 ratio of THC:CBD (Sativex), and a summary of the effectiveness of each compound

is presented in the table below. In general, clinical trials examining the effects of the whole plant (79% of trials were positive) or Sativex (65% of trials were positive) were more likely to show an improvement in pain ratings across a range of pain settings. However, only Sativex has been tested in large patient numbers. In pain studies, the majority of side effects of CBMPs were mild to moderate, but tolerable. Moderate side effects were associated with the psychoactive effects (euphoric or dysphoric effects, mild sedation and drowsiness) and were associated with higher THC doses (15-20mg). Mild side effects were observed in response to Sativex, whole plant extracts and CBD. Typical side effects associated with CBMPs included dizziness, nausea, fatigue and GI related effects.

	Whole plant	Sativex	THC	CBD
Total number of studies	14	17	36	3
Positive trials	11 (79%)	11 (65%)	16 (44%)	3 (100%)
Negative trials	2	1	12	0
Mixed results	1	4	7	0
Positive trials with >100 patients	1/1 (100%)	6/8 (75%)	1/2 (50%)	0
Pain conditions improved in positive trials	Chronic pain, neuropathic pain, fibromyalgia, spinal cord injury, diabetic neuropathy, pain associated with Multiple sclerosis, HIV-associated neuropathy	Pain associated with Multiple sclerosis, cancer-related pain, neuropathic pain, diabetic neuropathy, pain due to rheumatoid arthritis	Multiple sclerosis, chest pain, diabetic neuropathy, headache, neuropathic pain, spasticity-related pain, chronic pain, cancer-related pain	Post-operative pain, dysautonomic syndrome, neuropathic pain

Table 1. A summary of the clinical trials examining the effects of CBMPs in the setting of pain. Positive trials saw a significant change in the primary outcome of the trial and negative trials did not show a change in the primary outcome. Mixed trials failed to change the primary outcome, but showed positive effects in some of the secondary outcomes. For pain studies, this was often a significant improvement for patients in quality of life measures or improvements in sleep and/or anxiety.

Looking at the evidence base for the use of CBMPs in nausea, vomiting and appetite stimulation, we found a total of 63 clinical studies published between 1975 and 2018 (most conducted in the 70s and 80s). Only 9 of these had greater than 100 patients. The majority of trials in this area were carried out with THC (59/64 studies; 26 with Nabilone, 20 with THC, 12 with Dronabinol, and 1 with delta-8-THC), and the majority were in the context of chemotherapy induced nausea and vomiting. In general the results in this area were mixed, with only about half of the studies reporting a significant benefit of the CBMP. However, despite CBMPs often being associated with more side effects, they were generally the patient drug of preference. The data suggests that CBMPs may be

more effective in those patients for whom standard anti-emetics fail. Side effects for CBMPs in these trials included reports of dizziness, drowsiness/sedation/sleepiness, dry mouth, and dysphoria/euphoria. On a few occasions, hallucinations, vertigo, lowered blood pressure, and mood alterations were observed. Generally, the side effects of CBMPs were reported as clinically non-significant and manageable. It is also worth noting that THC was effective in contexts other than chemotherapy-induced nausea including cancer-associated anorexia, HIV(+)-associated anorexia and chronic hepatitis C-associated anorexia, with wider symptom relief including increased appetite and calorific intake.

	Whole plant	Sativex	THC	CBD
Total number of studies	3	1	58	1
Positive trials	2 (66%)	1 (100%)	33 (56%)	0
Negative trials	1	0	12	0
Mixed results	0	0	12	0
Positive trials with >100 patients	0/1	0	2/8 (25%)	0
Contexts in positive trials	HIV(+)	Chemotherapy	Chemotherapy, Cancer associated anorexia, HIV(+), Chronic hepatitis C	
Symptoms improved in positive trials	Increased calorific intake	Reduced vomiting	Reduced vomiting and nausea, improved appetite, increased calorific intake	

Table 2. A summary of the clinical trials examining the effects of CBMPs in the setting of nausea, vomiting and appetite stimulation. Positive trials saw a significant change in the primary outcome of the trial and negative trials did not show a change in the primary outcome. In the nausea setting, mixed trials showed that CBMPs were equally effective as active controls, but not superior (8 studies), or that showed positive effects in secondary outcomes.

Looking at the evidence base for the use of CBMPs in epilepsy, we found a total of 17 clinical studies published between 1980 and 2018 (although 14 of these were published since 2013), and these studies were primarily examining the potential role of CBD in treating epilepsy (16 of the 17 studies) using CBD on its own (Epidiolex, 12 studies) or a plant extract that was enriched with CBD, sometimes containing small levels of THC. 88% of clinical trials in epilepsy were successful using any CBMP and 92% were successful when using CBD alone (usually in the form of Epidiolex). Although Epidiolex now has FDA approval specifically for Lennox-Gastaut syndrome and Dravets syndrome, CBD was able to significantly reduce seizures across many other forms of epilepsy in both

children and adults (see below Table). 3 observational/retrospective studies using a fixed CBD:THC ratio of either 20:1 or 50:1 showed seizure reductions in their patient populations, advocating that randomised controlled trials using these novel ratios should be undertaken. CBMPs were well tolerated by epileptic patients, and the side effects of CBMPs (remembering most of these are pure CBD studies) were sleepiness/sedation, fever, decreased appetite/weight loss, diarrhoea and nausea/vomiting. CBD use in epileptic patients revealed significant drug interactions with other anti-epileptic medications which is thought to be due to CBD inhibiting the liver enzymes that normally break these drugs down.

	Epidiolex	Other CBD	CBD:THC ratios	Whole plant
Total number of studies	12	1	3	1
Positive trials	11/12 (92%)	1 (100%)	3 (100%)	0
Negative trials	0	0	0	0
Mixed results	1	0	1	1
Positive trials with >100 patients	5	0	0	0
Contexts in positive trials	Lennox-Gastaut Syndrome, Dravet syndrome, Sturge-Weber syndrome, refractory epilepsy of multiple types, Febrile Infection-Related Epilepsy Syndrome, Tuberous sclerosis complex	Generalised epilepsy	Childhood refractory epilepsy of mixed causes, Dravet syndrome	n/a
Patient age in positive trials	1-62 years old	14-49 years old	1-20 years old	n/a
Symptoms improved in positive trials	Decrease in seizures, improvement in their overall condition, increased quality of life, cognitive and behavioural improvements	Decrease in seizures		n/a

Table 3. A summary of the clinical trials examining the effects of CBMPs in epilepsy. Positive trials saw a significant change in the primary outcome of the trial and negative trials did not show a change in the primary outcome.

5.2.2 Do we have all the evidence?

Clinical trials are required by law to be registered and reported.²⁹ However in reality, many clinical trials go unreported for a variety of reasons. This is often because the trial was negative (i.e. the drug did not work), although other factors can be at play such as investigators moving jobs or industries refocusing their pipelines. Effectively, this means that there is a positive bias in all published literature towards clinical trials that were successful. For obvious reasons, there is a large movement to increase clinical trial transparency.³⁰ In the research area of CBMPs, the potential lack of all clinical trial data means that we are not equipped with the full breadth of evidence that should be available to us in order to judge the effectiveness of these medicines.

To establish the extent of missing data from clinical trials using a CBMP, we analysed the clinical trials that were registered on clinicaltrial.gov where the study was reported as complete, but no results were reported for that study. We found 97 clinical trials investigating a CBMP product that do not have results

posted where the data would be of benefit to the current discussions of the therapeutic benefits and biological effects (including side effects) of CBMPs. Of these 97 trials unreported on clinicaltrials.gov, it was possible to find peer-reviewed journal articles that generally matched 41 of the registered clinical trials, although the exact details of the studies (such as patient numbers and primary and secondary outcomes) did not always match the registered details on clinicaltrials.gov. However, there were 56 remaining clinical trials investigating a CBMP for which there is no publicly available data on the outcome of the studies, representing nearly 3500 participants/patients. Most worryingly, there were 21 unreported phase 2/3 trials (1716 patients) which are listed in Table 4 and include data on many important indications such as diabetes, motor neurone disease, glioblastoma and cerebral palsy. 62% of these trials were industry sponsored. This represents a significant amount of important missing data.

This finding goes to the issue of research integrity that a October 2018 parliamentary report from the House of Commons Science & Technology Committee raised and which they concluded posed a risk to public health. The Health Research Authority (HRA) in response accepted the findings and pledged to

work harder to address poor compliance, including considering a more robust handling of applications based on abiding by transparency around clinical trial data, and in some cases, sanctions for non-compliance.³¹

NCT Number	Title	Completion	Sponsor/Collaborators	Enrollment	Funded by
Phase 2 trials					
NCT00642499	Dronabinol Versus Placebo in Treatment and Prevention of Highly Active Anti-Retroviral Therapy (HAART)-Related Nausea and Vomiting	Apr-05	Solvay Pharmaceuticals	103	Industry
NCT00123201	Study to Evaluate the Efficacy and Safety of Dronabinol Metered Dose Inhaler (MDI) in Acute Treatment of Migraine Headache	Mar-07	Solvay Pharmaceuticals Nektar Therapeutics	null	Industry
NCT00272207	A Trial Assessing the Effect of Nabilone on Pain and Quality of Life in Patients With Fibromyalgia	Mar-07	Winnipeg Regional Health Authority Valeant Canada Limited	40	Other Industry
NCT00623376	Randomized Double Blind Cross Over Study for Nabilone in Spasticity in Spinal Cord Injury Persons	Dec-07	University of Manitoba Valeant Canada Limited	null	Other Industry
NCT00176163	Supporting Effect of Dronabinol on Behavioral Therapy in Fibromyalgia and Chronic Back Pain	May-09	Heidelberg University Central Institute of Mental Health, Mannheim University of Mannheim	240	Other
NCT01025700	Nabilone & Marijuana Addiction	Oct-10	University of British Columbia	35	Other
NCT00699634	Nabilone for the Treatment of Phantom Limb Pain	Apr-11	University of Manitoba Valeant Canada Limited	50	Other Industry
NCT02006628	A Study of GWP42003 as Adjunctive Therapy in the First Line Treatment of Schizophrenia or Related Psychotic Disorder	Jan-15	GW Research Ltd	88	Industry
NCT01222468	Effect of Cannabinoids on Spasticity and Neuropathic Pain in Spinal Cord Injured Persons	Feb-15	University of Manitoba The Manitoba Spinal Cord Injury Research Fund Canadian Paraplegic Association	12	Other
NCT02115529	Study of Prevention of Postoperative Nausea and Vomiting Using Cesamet	Nov-15	St. Michael's Hospital, Toronto	331	Other
NCT01776970	Safety and Efficacy on Spasticity Symptoms of a Cannabis Sativa Extract in Motor Neuron Disease	Dec-15	Ospedale San Raffaele Fondazione Salvatore Maugeri Niguarda Hospital University of Padova	60	Other
NCT02053272	A Study of GWP42004 as Add on to Metformin in the Treatment of Participants With Type 2 Diabetes	Feb-16	GW Research Ltd	207	Industry
NCT01812616	A Safety Study of Sativex Compared With Placebo (Both With Dose-intense Temozolomide) in Recurrent Glioblastoma Patients	Jun-16	GW Research Ltd	21	Industry
NCT01812603	A Safety Study of Sativex in Combination With Dose-intense Temozolomide in Patients With Recurrent Glioblastoma	Jun-16	GW Research Ltd	6	Industry
NCT02539823	Acute and Short-term Effects of CBD on Cue-induced Craving in Drug-abstinent Heroin-dependent Humans	May-17	Hurd, Yasmin, Ph.D. GW Research Ltd	45	Other Industry

NCT Number	Title	Completion	Sponsor/Collaborators	Enrollment	Funded by
Phase 3 trials					
NCT00642512	Dronabinol Versus Standard Ondansetron Antiemetic Therapy in Preventing Delayed-Onset Chemotherapy-Induced Nausea and Vomiting	Jul-04	Solvay Pharmaceuticals	64	Industry
NCT00959218	Efficacy and Safety of the Pain Relieving Effect of Dronabinol in Central Neuropathic Pain Related to Multiple Sclerosis	Apr-10	Bionorica Research GmbH	240	Industry
NCT00760695	Cannabinoid Receptor (CB1) Agonist Treatment in Severe Chronic Anorexia Nervosa	Dec-11	Odense University Hospital	24	Other
NCT00872144	Sativex for Treatment of Chemotherapy Induced Neuropathic Pain	Mar-13	Mary Lynch Nova Scotia Health Authority	16	Other
NCT01898520	A Safety, Efficacy and Tolerability Study of Sativex for the Treatment of Spasticity in Children with Cerebral Palsy Aged 8 to 18 Years	Mar-17	GW Research Ltd	72	Industry
NCT00553059	Palonosetron and Dexamethasone With or Without Dronabinol in Preventing Nausea and Vomiting in Patients Receiving Chemotherapy For Cancer	null	M.D. Anderson Cancer Center National Cancer Institute (NCI) Solvay Pharmaceuticals	62	Other NIH Industry

Table 4. A list of the phase 2 and 3 clinical trials carried out using a CBMP that have no results reported on clinicaltrials.gov or have no associated peer-reviewed journal articles that could be found, i.e. a list of the trials for which there is no publically available data on the outcome of the studies.

5.2.3 What does the future of evidence with CBMPs look like?

We have already shown that there has been exponential growth in the number of clinical trials carried out with CBMPs in the last ten years, and a forward looking analysis of the ongoing and registered trials (using ClinicalTrials.gov) showed that there are currently a further 124 active clinical trials investigating the therapeutic benefit of CBMPs. Of particular interest is the fact that 18 of these are phase 3 trials and therefore furthest along the drug discovery pipeline³². 50% of the phase 3 trials are industry sponsored and thus likely part of a drug discovery programme. The phase 3 trials cover generalised anxiety disorder, motor neuron disease, marijuana dependence, post-traumatic stress disorder (PTSD), Tourette's syndrome, pain, and nutrition in haemodialysis patients, suggesting these are potentially indications that will be next to have a licensed CBMP. The average success rate for phase 3 trials to progress to drug approval is approximately 60%³³.

The companies that have active and registered trials with a CBMP include GW Pharmaceuticals, INSYS Therapeutics, Zynerba Pharmaceuticals, Tetra Bio-Pharma, Therapix Biosciences, MedReleaf, Prairie Plant Systems, TO Pharmaceuticals and PhytoTech

Therapeutics. The number of pharmaceutical companies in this space shows the industry faith in CBMPs.

Of the 124 active trials, a detailed examination of the types of CBMPs and the indications they are being pursued in was carried out (see below Table). 44 active clinical trials are investigating CBD in multiple indications; 18 of these studies are phase 2 studies and 9 are phase 3. There are 8 clinical active trials investigating a THC:CBD 1:1 product (including but not limited to Sativex); 3 of these are phase 2 and 2 of these are phase 3. There are 7 clinical trials investigating a THC:CBD product in different ratios; 4 of these are phase 2 and 1 of these are phase 3. There are 32 clinical studies registered using a product containing THC; only 6 of these are phase 2 and 4 are phase 3 or 4. 33 studies are registered using a whole plant product; 11 of these are phase 2 and 2 are phase 3.

	CBD	THC	THC:CBD (1:1)	THC:CBD other ratios	Whole plant
Phase 2 trials	<ul style="list-style-type: none"> 4 Epilepsy 3 Schizophrenia 2 Parkinson's disease 2 Prader-Willi syndrome 1 Anxiety 1 Substance use disorder 1 Fragile X syndrome 1 Bipolar disorder 1 Crohn's disease 1 PTSD 1 Chronic non-cancer pain 1 Arthritis 	<ul style="list-style-type: none"> 2 Alzheimer's 1 Low back pain 1 Nausea 1 Trichotillomania 1 Tourette's syndrome 	<ul style="list-style-type: none"> 1 Multiple Sclerosis 1 HIV infections 1 Chronic non-cancer pain 	<ul style="list-style-type: none"> 1 Autistic disorder 1 HIV infections 1 Pancreatic cancer (palliative) 1 Cancer pain 	<ul style="list-style-type: none"> 2 Cancer pain 1 osteoarthritis 1 Low back pain 1 PTSD 1 Chronic obstructive pulmonary disorder (COPD) 1 HIV neuropathic pain 1 HIV cognition/mobility 1 Tourette's 1 Dementia (agitation) 1 Parkinson's
Phase 3 trials	<ul style="list-style-type: none"> 3 Infantile Spasms 2 Epilepsy 2 Tuberous Sclerosis Complex 1 Generalised anxiety disorder 1 Motor neuron disease 	<ul style="list-style-type: none"> 1 Marijuana dependence 1 PTSD 1 Tourette's syndrome 1 Medical abortion pain 	<ul style="list-style-type: none"> 1 Tourette syndrome 1 Chronic pain 	<ul style="list-style-type: none"> 1 Chronic pain 	<ul style="list-style-type: none"> 1 Cancer pain 1 Nutrition in haemodialysis patients

Table 5. A summary of the conditions being investigated using a CBMP at either phase 2 or phase 3.

5.2.4 Where are the gaps in the evidence?

Anecdotal and survey evidence tells us that the primary reasons that patients use CBMPs are for the relief of pain, arthritis/joint pain, anxiety, sleep disorders, depression and cancer and its symptoms³⁴. For many patients within the NHS, these are the conditions that they would like to see a CBMP prescribed. However, none of these conditions have been recommended for medicinal use in the interim guidelines for CBMP prescribing³⁵. None of these conditions have been identified as areas to be covered in the NICE review according to their guidelines scope³⁶. Even if they were conditions in which CBMPs could be prescribed, these patients are unlikely to be under the care of a consultant, and would therefore not be eligible to have a CBMP prescribed. We would encourage high quality, dose-ranging studies in these areas to be carried to help bridge the gap between patient demand and clinical evidence.

The UK's Life Sciences Strategy³⁷ endorses the need for more clinical trials of all kinds, and states that

“the country is well positioned to deliver a host of new innovations in large-scale clinical trials, including the use of digital tools to enhance the quality of data collected and to speed up recruitment.” It is important that medicinal cannabis is a major part of this new push for more clinical trials.

5.3 A medicine of last resort?

NHS England expects that cannabis-based products for medicinal use should only be prescribed for indications where established treatment options have been exhausted³⁸. This is understandable for many reasons, not least because the majority of clinical trials data with CBMPs is generated where the products are added in addition to the patients standard care or where patients have been unresponsive to the usual medications in that indication. However, for some indications, there is a likelihood that CBMPs would be as effective if not better than standard care. Additionally, from patient experience we know that patients often

prefer the side effect profile of CBMPs. As we continue to gather data on CBMPs, it is important that researchers consider (if logistically and ethically feasible) the implications of proving the effectiveness of CBMPs as alternative to standard care.

6. Experience From Abroad

Good policy-making requires a level of subject-matter expertise that can only come from having a broad lens on the full range of developments across the market and throughout the same sector internationally. At times, the UK civil service is prone to considering issues in isolation and ignoring or downplaying the experience of other countries in respect of the same issues. In this area, that tendency among civil servants is even more important to overcome, for two reasons. Firstly because comparable countries have had a lead on the UK in terms of when they legalised cannabis for medical purposes, and therefore have much more direct experience and actual results to share. Secondly, the global nature of this industry, and the very supply of the products that make up the medical supply chain, make it imperative that the issues encountered in other countries are understood and not just seen as unconnected or unique.

The experiences of two Common Law countries in particular, Canada and Australia, are highly instructive and deserve close examination. Australia and Canada are especially useful comparisons because their legal framework and Common Law tradition can make the law and regulatory frameworks for medicinal cannabis familiar and translatable. These countries also have mechanisms to mitigate risks which are common with the UK, and near identical roles for government actors and regulators vis-a-vis the market, albeit variable enforcement and supervision powers.

6.1 AUSTRALIA: A Careful Start and Slow Progress

The Australian medical cannabis system has existed since 2016 and underwent further reforms to streamline prescribing in 2018. Like the UK,

cannabis remains a controlled substance and CBMPs are classified in Schedule 8 (controlled substance) of the Single Uniform Scheduling of Medicines and Poisons (SUSMP) (CBD-only products are in Schedule 4 as 'prescription only'). Australia has a federal constitutional structure where the national government (Commonwealth Department of Health) has a role in regulating the sector as a whole in addition to approving prescriptions. The market in Australia is still relatively new, and with a social insurance model for healthcare that includes both public and private providers, they have experienced many of the access issues that are now apparent or emerging in the UK's new system.

Firstly, wherever they practice, individual doctors in Australia are required to seek approval from both national and regional (State or Territory) governments before patients can have a Schedule 8 cannabis prescription fulfilled. In most jurisdictions, a Schedule 4 prescription only requires national approval. In addition, local rules on prescribing and dispensing unregistered medicines present additional barriers even when federal and State approval for a prescription on a named-patient basis has been issued. Secondly, patient access is constrained because private insurers do not yet cover the products, and as CBMPs are classed as unregistered medicines (similar to unlicensed status in the UK), the public health system does not subsidise them. Thirdly, Australia had no domestic cultivation or processing industry before legalisation, not unlike the UK (with the single exception of GW Pharmaceuticals). As a result, it still relies almost entirely on imported cannabis medicines, which contributes to high prices. Fourthly, and also like the UK, clinical guidelines are similarly tight and do not support widespread use because of the lack of robust trial evidence.

In practice, legal cannabis-based medicines are available but clinicians that seek to prescribe can have their professional decision fettered by either tier of government when the application is sent for approval by health department officials. Australian doctors therefore have less discretion than their counterparts under the UK system, however the pool of doctors who may potentially prescribe is growing. There is no systematic data collection in the Australian system for cannabis and so actual patient numbers are not available, nor is it public information which doctors prescribe and where they are located. Some limited data on the number of prescriptions authorised is available.

The regulator is the federal Therapeutic Goods Administration (TGA) which governs and supervises the supply of all medicines and medical devices in Australia. They have commissioned a meta-analysis of clinical data relevant to the following indications:

- chemotherapy-induced nausea and vomiting
- refractory paediatric epilepsy
- palliative care indications
- cancer pain
- neuropathic pain
- spasticity from neurological conditions
- anorexia and wasting associated with chronic illness (such as cancer).

This is a non-exclusive and non-prescriptive list of possible indications. And, according to the TGA, “a number of applications for indications other than those listed above have also been approved”. This represents a wider list of possible indications than those in interim UK guidelines³⁹.

Several routes exist under which doctors can legally prescribe unapproved medicinal cannabis products. In addition to access via a clinical trial, doctors can request the authority to prescribe a specific product for a named patient on a case-by-case basis (Special Access Scheme Category B). Doctors can apply to become an Authorised Prescriber, permitting them to prescribe a specific product to a class of patients directly under their care without individual prior approval, although receiving this approval is especially difficult. Doctors would normally also have the right to prescribe an unapproved cannabis medicine to a terminally ill patient or one in urgent, life threatening need, without prior approval (Special Access Scheme Category A). But the federal government has ensured that medicinal cannabis remains the only drug inaccessible via Category A⁴⁰.

It would be less bureaucratic to obtain a prescription from an Authorised Prescriber, but it is time-consuming to become registered as an AP and it requires support from a local ethics committee or the relevant Royal College, so many doctors do not seek it. Almost all doctors that do have AP status are paediatric neurologists according to the Lambert Initiative at the University of Sydney and those doctors are more familiar with prescribing unregistered (unlicensed) medications.

Another access issue confronting Australian patients, but which is less of a factor in the UK, is the dispersed geography. Rural citizens must travel long distances to be seen by authorised prescribers who are mostly based in cities. They must also sign waivers that on receipt of medication they will not drive, which further hinders the ability of patients outside of metropolitan areas to easily obtain cannabis, even when they are eligible and prepared to pay.

Patients who are very restricted in what they can access and where they can acquire a prescription, must also then pay out of their own pocket. The lack of competition and the under-developed supply chain also means Australian patients pay very high prices through private clinics and can only obtain the product from pharmacies that can themselves charge a substantial mark-up, estimated to be 25% or more. One analysis of patient costs from 2018 estimated that Australians are currently paying \$353 per month for medicinal cannabis products prescribed to treat chronic pain, or \$992 per month for epilepsy patients – all sourced from private clinics. These prices remain high compared to what Canadian patients pay, and still prove unaffordable for some patients who would otherwise rely on their medicines on a basic publicly subsidised Pharmaceutical Benefits Scheme pricing scale which costs patients between \$6.40 and \$39.50 per prescription⁴¹.

New rules introduced in 2018 should enable easier access, with doctors in New South Wales no longer needing separate State approval if their application to prescribe on a named patient basis has been approved by the Commonwealth Department of Health. Since July 2018 there is also a single online portal for lodging requests which other States and Territories are adopting to reduce bureaucracy and provide speedier decisions. And after two years, licenses and permits for domestic cultivation and processing have been issued and initial supply of Australian-produced cannabis medicines has begun, hopefully putting downward pressure on drug prices. In fact the range of products available is already increasing and prices overall are falling as more producers and volume of supply enters the market.

Private clinics are expanding and more doctors are becoming authorised prescribers so patient access will improve. However, the barriers to access remain substantial and patients who are cared for by an Authorised Prescriber have one of the simplest routes to gain access, but as of November 2018,

there were less than 50 of these doctors across the whole country. That reality, plus the bureaucratic approval process and the high cost of CBMPs explains why there are only an estimated 1,500 patients who have received a prescription, more than two years after the law changed.

Reflecting on progress so far, Rhys Cohen from the Lambert Initiative at the University of Sydney⁴² told the CMC: “*The development of our domestic industry – which was the promised solution to supply and price issues – has been severely delayed due to two main factors. First is the chronic underfunding of the Office of Drug Control which issues licenses and permits to local companies. Companies are waiting more than 6 months before their applications are looked at for the first time. Second is the overly restrictive patient access framework which has, among other things, made Australia an unattractive market for existing and potential companies wanting to operate at scales sufficient to produce lower prices.*”

In order to improve the system, Cohen supports further clinician education and interim measures to provide access to patients who cannot attain at present: “*We need further reforms to empower GPs to prescribe in addition to high-quality clinical education for doctors. And, so long as prices are not subsidised by governments or insurers, we must provide legal amnesty to patients who are compelled to continue sourcing products from the community until such time as cannabis medicines become accessible and affordable.*”

One noticeable feature of the Australian system is the growth of a research and knowledge infrastructure around cannabis. Philanthropically-funded university research groups like the Lambert Initiative co-exist with new organisations established by state governments and backed with taxpayer funding, like the Centre for Cannabis Research and Innovation in New South Wales. These also have committed public funds to new clinical trials to help build the evidence base⁴³.

6.2 CANADA: An Old, Large and Liberal Regime

As of this October, Canada has two legal systems, one medical and one recreational. The country instituted their first federally licensed system for medical access to cannabis in 2001, originally the consequence of a Supreme Court ruling under Canada’s human rights charter. Subsequent

governments have instituted several successive medical systems to grant patients access, building and adapting on lessons learned. Like the UK, the policy shift to concede that cannabis had medicinal benefits was quick and not disorderly, but unlike the UK, the Canadian government’s hand was forced through litigation by organised patient advocates who remain influential to this day.

As a federal constitution, medical cannabis is regulated at both the national and provincial (state) level, until the 2018 Cannabis Act, where there were no changes to its controlled status and existing sanctions in Canada’s criminal code were unaffected by the initiation of medical access.

The current regulations governing the medicinal market in Canada (the so-called) Access to Cannabis for Medicinal Purposes Regulations (ACMPR)⁴⁴ - allows doctors to authorise use and grant patients legal access via online channels, with only fully-regulated cultivators (so-called) Licensed Producers or LPs), able to sell cannabis products over the internet to those registered patients. Importantly, as this regime was created, pharmacists objected and removed themselves from participation, and even today medical cannabis cannot be dispensed over the counter at pharmacies.

Many users who were approved under a previous regulatory system also grow their own cannabis within legal set limits per patient, and many patients still choose to buy cannabis at dispensaries that operate outside the federal law, (but who are subject to sporadic police enforcement). Some of these dispensaries in more liberal provinces are permitted to operate within a municipal licensing regime in certain cities (especially in British Columbia) but they remain illegal businesses who must source their products from the illicit market. Enforcement against such retailers, whilst contested and sporadic, has always depended on policing priorities, local politics, and the conduct and reputation of the dispensaries themselves.

The direct-distribution model of the ACMPR system has been criticized for not being sufficiently patient-centred. So while regulations permit access directly from federally regulated producers, and medicines arrive in the mail, those companies are banned from providing medical advice to patients with further constraints around marketing. And because pharmacies across Canada do not retail cannabis, patients are reliant on advice directly received from their physician, or through staff working in grey market dispensaries.

In practice, advice and education for patients has proved easier in the private clinic domain, and it is the growth of private medical practices that has driven expansion and widened patient access and not uptake by doctors in the public healthcare system. Only in the last two years have major health insurers in Canada offered coverage for cannabis medications, and education and training of clinicians remains an ongoing effort. So after more than 15 years, Canada has an estimated 15,000 doctors who have prescribed medicinal cannabis products (out of 84,000 registered physicians nationally in 2018⁴⁵). Further liberalisation of access is happening, with nurse practitioners now being afforded some of these prescribing rights in certain situations. But even under federal ACMPR rules⁴⁶, individual provinces run healthcare so local policies on prescribing also vary and effect how easily patients can find willing physicians. Some provinces like Quebec have made it more difficult for physicians to issue authorisations.

For some time the majority of registered patients accessing legal cannabis products from Licensed Producers in Canada purchased flower for smoking while also utilising flowers and leaves from any plants they were legally entitled to grow at home. In fact, flower is likely to continue to be a major feature of the Canadian medical market, although since non-medical legalisation, growth in that recreational sector is expected to dominate flower-consumption, with one estimate suggested the recreational demand for flower could be ten times the size of the medical demand by 2022⁴⁷.

Unlike Australia, overall patient numbers are tracked and they grew slowly but steadily until accelerating under the 2016 ACMPR model. The vast majority of the now 300,000+ registered cannabis patients in Canada access their chosen product from the largest LPs that have cultivation and sales license, as it provides a stable, regular supply with guaranteed delivery.

Since October 2018, when recreational cannabis legalisation took effect, the demand for cannabis has risen significantly, leading to supply shortages, and several LPs that service existing medical patients have been unable to maintain stock in response to demand from recreational users and the supply agreements they signed with provincial wholesalers.

The two systems, for medical and recreational, are separate in policy and in law, and the government

has pledged to keep it that way for at least five years when a formal review of the ACMPR is due. However in practice, as LPs with a sales license can cater to both sets of customers, there is a tension now emerging over the legitimate demands of medical patients for a stable supply of a quality product and a new larger group of recreational users. There is also an ongoing dispute about the equity of the federal government taxing both products at the same rate⁴⁸.

As these two systems co-exist - the only industrialised country in the world where that is the case - they now need to define and distinguish themselves. Full legalisation of cannabis in 2018, the first country in the G7 to do so, has brought new challenges, but it has also further legitimised the industry, seen in recent moves by major pharmacy chains like Shoppers Drugmart to apply to become licensed retailers.

The long experience of a medical regime has been a boon for researchers, even if it is still not a mainstream medical practice. The Canadian Institute for Health Research (CIHR) has invested nearly C\$20 million over the last five years in research and Canadian universities and research institutes are now set to lead the world in cannabis research⁴⁹ thanks to the plant's legal status. Plus the relatively long history of a medical system also provides many lessons for the UK.

One clear lesson is how a coordinated and coherent policy framework, set and supervised top-down by the government, can deliver a safe regime, even if full patient access still takes years to realise. In this respect, Health Canada has demonstrated how to regulate a medicinal market that involves a small number of reliable access channels that offer choice for patients, extensive guidelines to doctors⁵⁰, government-backed research and public information campaigns, and robust federal inspection⁵¹ of all production facilities to ensure high standards and good quality production.

Where Canada missed a trick was in data collection from the outset to ensure a comprehensive picture of medicinal cannabis use and its effects. That failing has been made up in the latest legislation with significant funding going towards public education⁵², but also funding for new national studies, longitudinal surveys and swathes of mandatory reporting so future governments can evaluate the impact of legalisation on public health, adolescent brain development, and wider issues like public safety and Canada's economy.

6.3 Key lessons from other systems

There are other legal medical cannabis systems around the world, and many share similar features, but simply based on the case studies of Australia and Canada, the two countries most similar to the UK, we can derive some key lessons.

6.3.1 Every medicinal cannabis regime is different and must fit within national healthcare cultures and institutions

Each medicinal cannabis system is different and every example has emerged as a consequence of different factors that made prescribing possible. The particular context explains why certain systems have features that would not translate to other countries. A succession of human rights based court challenges that eventually led to the creation of Canada's first legal regime afforded registered patients the right to grow their own cannabis plants at home. Equally, the most recent judgment in October 2018 from South Africa's Constitutional Court accepted the privacy case made by the claimants and ruled that it was a civic right for those who wished to grow and consume their own cannabis to do so on their own property, free from State interference. But a system that expressly permitted people, registered as patients or otherwise, to grow their own cannabis plants would not be acceptable in the UK. Apart from requiring more fundamental revisions to the criminal law, that behaviour would be viewed as lax and unsafe, and against the conventions of modern medical practice.

6.3.2 Patient pressure from below, rather than shifting medical establishment opinion, is what triggers and then shapes legalisation

Patient pressure to be allowed to access a drug legally has been a common feature of all jurisdictions that have seen political reforms to permit medicinal use. This can take different forms, from direct patient pressure and lobbying, to litigation efforts and judicial rulings. Successful systems find ways to institutionalise the engagement needed with patients, so that legislators and policy-makers can consult frequently with those groups most affected. Health Canada has extensive consultation functions to ensure its officials are reaching patient groups and harvesting that feedback and expertise, and provides extensive information via its own website on how to access cannabis for medical purposes⁵³.

6.3.3 Strict or limited regulations at the outset can and often are loosened over time.

All medicinal cannabis systems seek a trade off between offering a degree of patient access and insisting on controls for patient safety and a clinician's duty of care, and most start out quite conservative. Common constraints in new systems include limiting who can prescribe, or for what types of conditions and in what circumstances, and often also whether prescribing at all is approved by governing bodies. Initially, clinical guidelines are very influential in all systems but over time it is discretion and direct patient experience that builds confidence among doctors to prescribe, not changes to guidance. Initially however, education for clinicians is key. It is widely accepted that training of doctors is almost always needed to help them to familiarise themselves with the changes to the law, the science of cannabis, and the current state of clinical research into the plant and its potential medical applications. Both Canada and Australia have a number of training products available to GPs. For the UK, the content and delivery mode for such a training programme has not yet been developed or rolled-out, but inspiration from other jurisdictions should guide this process.

6.3.4 The medical community can be nudged in the right direction by the ice-breaker role played by private clinics and sustained advocacy by patients.

The path blazed by those same private clinics along with third-party patient advocacy groups can be influential in encouraging more doctors in the public system to prescribe. Most medicinal cannabis systems start out without widespread support among the medical community, and so prescribing practice is slow to change following legalisation and must be modelled successfully in more innovative and less bureaucratic contexts like private clinics, before other doctors follow suit. Even today, despite some of the highest patient numbers proportionately in the world, Canada still has an active community of patients, scientists, and physicians lobbying for greater awareness and fair treatment⁵⁴.

6.3.5 Patients need support to navigate the system to gain access.

Patients may have personal experience of cannabis but also find the formal routes to legally access medicinal cannabis products highly bureaucratic, confusing, and costly.

Support for patients is therefore key, and this should take many forms. Government agencies should publish clear patient directions for what is available, for whom, and from what sources, and the NHS should provide basic guidance on how to seek a prescription. Third party groups also have a role, and in other countries have provided a valuable service - especially where local conditions and different local regulations apply. The Medical Cannabis Resource Centre Inc (MCRCI) in Canada is a membership body that provides direct support to patients to help them gain access and it receives no funding from producers⁵⁵. A similar role is currently performed pro bono in the UK by patient-support groups like the United Patients Alliance (UPA) and Families4Access, and those efforts will need to expand in future to reach all the patients who need their guidance to navigate an unfamiliar and complicated process.

6.3.6 Healthcare champions emerge as the evidence base expands and professional associations begin to respond to their own members.

No medical community in countries that have legalised medicinal cannabis starts out well-versed in cannabinoid science or the applications of cannabis as a treatment option. All medicinal cannabis systems depend upon a growing evidence base on the efficacy of CBMPs and without trial data doctors are initially, and understandably, sceptical. Professional bodies in other countries devise their own guidelines for licensed physicians and these are often driven by pressure from their own members for clarity and guidance to support them in their roles. Such guidelines can and do get influenced by those in other places, or other medical fields. It is just as important for these senior professional associations to exchange knowledge as it is for policy-makers. For example, Canadian GPs can refer to updated guidance on the prescribing of herbal cannabis for chronic pain and such an example would eventually be very helpful in the creation of a similar set of guidelines in the UK⁵⁶.

6.3.7 Academics and the media play an important role in educating the public about patient experiences and highlighting new research results.

Poor knowledge about the endocannabinoid system and limited awareness of medicinal cannabis is not a peculiar feature of the UK system. In reality it is a fact of life given the state of the science, the legacy of prohibition, and the age and career training of the more senior doctors who are often authorised to prescribe it. Making the findings from peer-reviewed journals digestible and easily accessible so they

can reach a wide audience is a key component of familiarisation. Governments often have a role in producing official information sources for use by the public health authorities like the NHS can also play a role by producing regular fact-check summaries for stories in the media, as offered by the 'Behind the Headlines' blog⁵⁷.

6.4 Risks encountered in other systems

Exploring the risks as well as the benefits of other systems is a good caution for policy-makers because every approach has flaws or experiences unintended consequences. However, some of these risks are more prevalent in (and arise from) under-regulated systems, very different from the UK.

6.4.1 Diversion

From the outset, the UK Government has expressed a concern about the risk of diversion. Essentially, that cannabis medicines could end up being sold and used by those without a condition that gives rise to a legitimate medical claim to them. In the parliamentary statement announcing the rescheduling, the Home Secretary said: *"the Government believes it is important that access to these products is strictly controlled so as to prevent unintended misuse, harm and diversion."*

Avoiding diversion is therefore a declared aim of the government's medicinal cannabis reform, and the strict way in which clinical prescribing has been authorised is a consequence of this concern (among other factors). The Home Office are concerned that legally acquired cannabis medicines, especially flower products, could be diverted into the illicit market (where detection and traceability would be practically impossible). There are reasons why this risk is not significant in the UK system and the experience of other jurisdictions shows why.

Concerns about diversion seems to arise from some experience in North America where controls on access were or are very lax by European standards, or where there was evidence that patients with generous home grow allocations abused the system to sell on their cannabis to others. The limited regulation around patient permissions in US states like Colorado have led to incidences where adolescent use was made possible by the sharing or selling of someone else's medicinal cannabis. In Canada the diversion risk related to home growing: the previous regimes that permitted personal allocations to be pooled,

and examples of police discovering scores of plants being grown for many registered patients at a single address. Before the current Access to Cannabis for Medical Purposes Regulations (ACMPR) came into effect, some of these Canadian patients were found to be abusing the home grow entitlements and supplying dispensaries that were themselves illegal retail enterprises.

The updated regulations which took effect in 2016 require patients to provide a federally-licensed producer of their choice with a physician's authorisation and then their cannabis is ordered online and sold direct to the patient, mitigating any diversion risk and allowing patient identity to be verified and consumption to be tracked. The diversion scenario that has occurred in certain US states is less relevant to the UK which has rightly chosen to make available medical cannabis within the regulated public healthcare system and to control access via prescriptions. This policy anxiety is also now somewhat moot in the example of places like Colorado that have subsequently legalised cannabis for recreational use.

Diversion is a risk in a system where the market for legal product has lax access controls, poor clinical oversight or generous entitlements around personal use that cannot be policed, and none of those features apply in the UK. Ironically, what does feature in the UK is a large and well-established black market in illicit cannabis, one that is so entrenched and so profitable that it is highly unlikely to in any way be affected by the low volumes of prescription cannabis products. Even if there was widespread prescribing of herbal cannabis products in the NHS, it is difficult to see what incentive patients would have for diverting their own supply. The more likely scenario of a medical cannabis system that was functioning well would not be the diversion of product away from legal channels, but the diversion of currently illegal demand towards legal channels and (higher quality) legal products.

6.4.2 Over-consumption

Even in countries where patients can access medicinal cannabis without a prescription, there are often legal limits on personal possession (which also mitigates the diversion risk), and in federally-legal models (i.e. not US states), access is controlled via prescription/pharmacies or via federally-licensed domestic suppliers, so over-prescribing is prevented. For example, in Canada, the health ministry, Health Canada, stipulates that no more than 30 days of

prescribed volume can be possessed by patients (1 gram or 5 gram daily limits and no more than 150 grams per order when supplied via mail by a Licensed Producer). In Australia, the prescription model controls how drugs are obtained and in whose name, and cannabis medicines can only be dispensed to named patients by pharmacies. This regulated distribution also prevents 'doctor shopping'.

6.4.3 Ongoing self-medication

One risk that has been experienced in both the Australian and Canadian system is the behaviour by patients who inevitably find that they cannot obtain access in the legal medicinal channel (for clinical, cost or other reasons). Typically there is widespread self-medication with illicit cannabis by these patients before they are denied legal products by a doctor, and others may continue to rely on black market supply even when they have been able to access cannabis medicines legally (for instance the particular strain or potency they want is not available, or where they can only access pills and oils when vaporising herbal cannabis is their preferred consumption method). To some extent this behaviour, though undesirable and risky, is beyond the influence of regulators. However, when certain patients are refused legal access and feel they have no choice but to continue self-medicating, often those terminally-ill patients who are out of other options and almost out of time, the political pressure to accommodate their needs in some way is significant.

Other countries have wrestled with this conundrum and have adopted different approaches. Some have conceded a limited right for registered patients with a doctor's authorisation to possess cannabis, free of the risk of prosecution, or to permit them to home grow small amounts of cannabis on private property. The Canadian medical cannabis system began that way, before the government changed tack and decided to create a federally licensed class of approved cannabis producers from which patients could be supplied directly.

CASE STUDY: Compassionate Access for Terminally-Ill Patients

A scheme in Australia's most populous state New South Wales provides one example of how governments have sought to regulate use of cannabis for certain-classes of patients who continue to self-medicate. The Medicinal Cannabis Compassionate Use Scheme - which began prior to the 2016 federal legalisation of medical cannabis - created a programme based upon a registry and guidance to police officers not to enforce possession charges for such patients⁵⁸.

Those terminally-ill adults who are certified as such according to the scheme by their physician can apply to be placed on a registry (along with up to two carers) that is accessible by law enforcement⁵⁹. By registering patients in a compassionate use scheme, the government is able to ensure that the police know who is able to use the drug legitimately, and it provides a de facto legal shield against harassment or arrest, if the police follow the guidance (retaining discretion not to in individual cases). An April 2017 review of the scheme by the state's Chief Scientist reported and found that registrations had been increasing and that it was being used by the intended cohort of patients. It recommended some changes, including extending the coverage period from 12 to 24 months, but otherwise endorsed how it was operating. While acknowledging the nationwide reforms since the scheme began in 2014, the review of the scheme concluded that there was still a need for it⁶⁰:

"If the legal pathway for access to cannabis products regulated as medicines was better bedded down, it would be straightforward to recommend that the Scheme be closed down and that all patients wishing to access cannabis or cannabis-derived products do so through the legal route. Yet, while the legal routes have been clarified, at the moment there are a number of steps that can be complex and time consuming, such as the absence of product in Australia and the need to import.... Accordingly, it probably would be imprudent to wind up the Scheme at this time and

the Review recommends it be retained with the current eligibility criteria, but made easier to use for those who are terminally ill."

Although such a scheme is an admission that the law should not be enforced against certain people even though they are accessing a drug illegally, the reality for such patients is that they already are. And while such a scheme does nothing to support those patients to access a quality product, it does lift the threat of prosecution, and in a minority of cases where other medications are no longer effective, it reduces anxiety and helps those patients in the final months of life.

This scheme applies only to personal possession and use, and patients are still not permitted to smoke in public or to grow cannabis themselves. However, in a system that cannot provide medical products that patients need in a timely way, the alternative is for government authorities to continue turning a blind eye to all those who are self-medicating outside of the legal channels, and to give no support to the police who are otherwise required to enforce the law but without the means to identify the legitimate medical use of a controlled substance by a minority.

It is noteworthy that the same argument is ongoing in New Zealand where legislators are debating the merits of law changes there, and in this instance, such a provision, were it to pass, would provide terminally-ill patients with a codified defence in law for their use of cannabis acquired outside of medical channels, and in practice, permission from the state to do so⁶¹.

6.5 International collaborations

6.5.1 Research partnerships

Clinical trials sometimes involve cross-national collaborations involving sponsoring institutions. For some of the rare conditions for which cannabis medicines may provide an effective treatment, a single trial across several countries is a practical way of recruiting sufficient numbers of patients.

Given the growth of medical cannabis research in countries outside the UK, it is likely that there will be both the appetite and the resources to take forward new clinical trials involving patients in several countries at once. The findings of one Randomised Control Trial into the use of cannabidiol to treat Lennox-Gastaut syndrome, a rare form of epilepsy, were published in 2018. This trial⁶² involved 225 participants across 30 hospitals in four countries, UK, US, France and Spain, and was funded by GW Pharmaceuticals, the British company that produces Sativex and Epidiolex.

International collaboration in this fast-evolving frontier of medicine will be increasingly common and should be encouraged. Groups like the CMC can play a role in connecting industry and academia to scope new clinical trials and find sponsoring institutions, especially where that involves a range of international collaborators on the research side. However, such partnerships are still costly and robust clinical trials still take time. For example, one observational study in Philadelphia for children with autism spectrum disorder, seeking 200 participants to begin in 2019, has a three-year follow up period and will publish results in 2023.⁶³ The UK will need many trials of all types starting in 2019 if it wants to inform medical practice. Fortunately, as chapter 5 set out, there are many trials happening across the world that are already far advanced.

6.5.2 Policy exchanges

As the spread of medicinal cannabis legalisation gathers pace, those countries with the most experience are in a good position to advance others on how to tackle common issues that they may face.

The UK is especially well placed to create formal channels between officials in health and public safety departments and their respective regulators in both Canada and Australia.

7. Towards a Fully-Functioning Market

The goals, objectives and trade-offs of any system need consideration by policy-makers but in market economies like the UK, the law and regulations exist to support a fully-functioning market that is expected to deliver against that. In evaluating the current UK system and some of the key lessons from schemes implemented overseas, certain factors stand out as being critical to a fully-functioning medical cannabis market where consumer preferences can be accommodated, supply chains optimised, and demand and supply for products broadly aligned.

7.1 Barriers to a fully-functioning market in the UK

There are major barriers to that fully-functioning market currently in the UK. In addition to the human factor, the issue of clinical attitudes and willingness to prescribe, there are a series of systems and processes that place additional barriers in the path of a patient seeking a prescription for a cannabis medicine.

Features of a Fully-Functioning Medical Cannabis Market		
	Necessary Features	Current Barriers in the UK
PEOPLE	Sufficient Patient Demand	Lack of good information from trusted sources Confusion and misinformation about what is available and for what
	Knowledgeable Clinicians	Limited knowledge of the endocannabinoid system Poor awareness of trial results Lack of direct patient experience
	Empowered prescribers	Doctors' discretion fettered by restrictive local policies, prescribing guidelines and peer opinions
	Experienced pharmacists	Few pharmacists experienced at sourcing unlicensed medicines

Features of a Fully-Functioning Medical Cannabis Market		
	Necessary Features	Current Barriers in the UK
PRODUCTS	Available drug supply	No unlicensed CBMPs stocked domestically. One-off ordering via specialist importers required.
	Diverse product offerings	Limited product selection and all but one must be imported. Every imported product must meet EU GMP standards.
	Competitive pricing	No domestic production so poor competition and inflated drug costs
PROCESS	Multiple access channels	Almost non-existent NHS access presently, and private clinics have not yet emerged or scaled
	Timely sourcing & dispatch	Import license process adds delays. Repeat prescriptions are needed and take as long each time
	Convenient dispensing options	Patients able to obtain their medicine easily from a local pharmacist

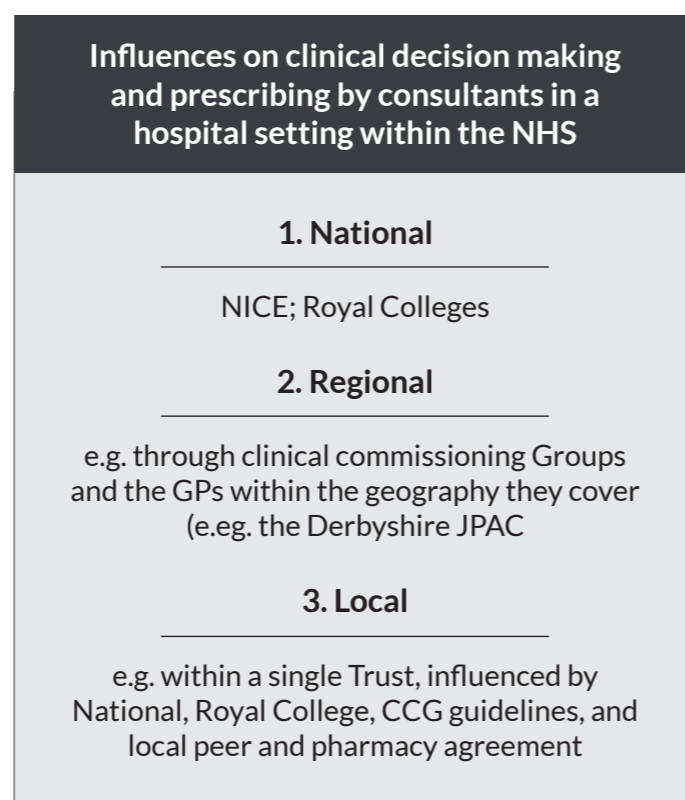
7.2 Constraints on prescribing

The decision for a specialist clinician to prescribe a particular medicine for their patient within the NHS depends on many influences at local and national levels.

In addition to this, the Care Quality Commission (CQC, an executive non-departmental public body of the Department of Health and Social Care of the United Kingdom) oversees patient safety and quality but does not alter guidelines. In the case of a patient safety concern issue, and inspection from the CQC may check as to whether groups are adhering to local and national guidelines. NHS England oversees all of the above and provides the budget to all CCGs, who will commission services within their community from “any willing provider”, including Trusts and private care.

Although the law may have changed, it is still very early days for many of these influences (particularly at local level) to have been affected by the legal availability of CBMPs, which is a major roadblock to their prescription.

These, coupled with a lack of familiarity and confidence in CBMPs, means that the reality of these products actually being prescribed over the next year is bleak.



7.2.1 Clinical Guidelines

As the spread of medicinal cannabis legalisation gathers pace, those countries with the most experience are in a good position to advance others on how to tackle common issues that they may face.

Clinicians refer to guidelines to aid them in their medical practice, but other factors listed above can constrain or otherwise influence clinician behaviour. The Government grants NHS clinicians a wide scope for professional discretion in the exercise of their prescribing function, however, their employers also remind these doctors that they are under other obligations when prescribing unlicensed medications (such as CBMPs), other than just complying with clinical guidelines:

However, all healthcare professionals who can prescribe [unlicensed medicines]... are subject to: their individual clinical competence; the professional codes and ethics of their statutory bodies; and the prescribing policies of their employers⁶⁴.

Clinicians are not expected to prescribe unlicensed medicines for conditions for which they do not have expertise, and must always abide by professional codes. However, the prescribing policies of their employers, typically one or more kind of health authority, can also dictate what prescribing can take place. In practice therefore, professional discretion is tempered by an explicit assumption that doctors will not stray beyond their area of expertise, go against clinical guidelines, or depart from their hospital’s policy on prescribing.

Within the private sector, clinicians are not so strongly subject to the same influences and can prescribe more freely with the consent of the patient, although still liable in the eventuality of anything going wrong. This is primarily why patients within the UK have been able to access CBMPs through private consultants, and remains currently the easiest mechanism for patients to access CBMPs. However, NHS England specifically mentions in its guidance letter on cannabis based products for medicinal use:

We expect clinicians in a non-NHS setting to follow similar standards and equivalent processes for prescribing unlicensed special medicines, bearing in mind GMC and MHRA guidance.⁶⁵

In a joint letter (dated 21 November) to NHS trust chief executives, senior managers, and specialist consultants across the health service, the Chief

Medical Officer for England and her counterparts in the NHS across devolved jurisdictions, gave further advice to clarify the impact of the law change and the status of the interim guidance issued on 31 October. In that, the official advice confirms that specialist clinicians retain their professional discretion, but there is an expectation that they will consider the prescribing guidance, the evidence base, and local policies on unlicensed medications:

“Whilst this interim guidance is available to support specialist doctors on the Specialist Register of the General Medical Council (GMC) in deciding whether to prescribe cannabis-based products for medicinal use in a limited number of conditions, this does not remove or replace the clinical discretion of the prescriber in accordance with their professional duties. We expect clinicians to work with their individual patients or their carers (where appropriate) to agree the best treatment, taking into account the clinical evidence base, GMC prescribing guidance on licensed, off label and unlicensed medicines, and local medicines governance systems. This is in line with normal clinical practice.” [emphasis added]

7.2.2 Local Policies

Below the level of national policies are self-governing NHS Trusts and Clinical Commissioning Groups that have their own local policies on a range of matters, including the prescribing, sourcing and dispensing of unlicensed medications.

Local policies governing the prescribing of unlicensed medicines are not consistent, and as such, the bureaucratic processes needed to access such treatments vary by area. In some places, the approval can only be granted by the Medicines Management Group, and only following review of clinical data and advice from regional commissioners on purchasing, cost and supply chain issues, and only where supply can be secured by a trusted importer⁶⁶. In other areas, there is more light-touch regulation and policies are less formalised⁶⁷.

Some common features of all these policies is a clear onus on the clinician and their designated pharmacist at the hospital, to assume liability for the prescribing of an unlicensed medication. That request should be approved by an internal committee, usually following a process that confirms the non-availability of any alternative licensed medicine, and then a risk assessment as part of the maintenance of proper records and appropriate information given to patients.

Such policies all permit the expedited use of ‘specials’ in an emergency scenario, but all other situations require doctors to abide by the formal approval process.

In this important respect, the ultimate discretion of the specialist clinician to prescribe a CBMP or another type of ‘special’ is fettered. Unlike licensed medications, where approvals are automatic and most drugs that are recommended by NICE are possible to prescribe throughout the NHS, unlicensed medications are treated with caution and processes are in place to limit their uptake, with local areas setting their own processes for granting permission. Before a new special can be approved for prescribing, many decision-makers need to agree and the initial clinical opinion of the specialist doctor concerned is simply one of them.

In practice this means that it is not straightforward for specialist doctors to prescribe a CBMP and those patients who have a supportive clinician, who has judged that they may benefit from a CBMP prescription, therefore cannot be assured that this will actually be made available to them. Depending on where they live and which NHS trust services them, hospital management and internal policies might dictate otherwise.

Local policies that make sourcing unlicensed medicines bureaucratic and slow could be dictated by a view that specials are too complex and expensive to source. Some local policies make reference to the costs of prescribing an unlicensed medicine: *“Where there is a financial concern in terms of the impact on primary care medicine budgets, this needs to be clarified before treatment is initiated.”*⁶⁸ Some local policies emphasise the legal duty on prescribers, and reference professional liability: *“Doctors can prescribe unlicensed medicines, or licensed medicines for unlicensed uses (off-label/off license prescribing). In these situations the doctor is legally responsible for the medicine. They may be called upon to justify their actions in the event of an adverse reaction. Doctors are expected to take “reasonable care” in common law, and to act in a way which is consistent with the practice of a responsible body of their peers of similar professional standing.”*⁶⁹

Beyond this, there are the complicated processes for approving the prescription of an unlicensed medicine, with the East Cheshire NHS Trust⁷⁰ being one example of why clinicians could be disincentivised from recommending a CBMP – particularly where

that necessitates sourcing a product from overseas. See that Trust’s ‘Decision Tree’ as an example (Annex). Largely because local policies will allow variation in the use and uptake of ‘specials’, the Government remains concerned to monitor how CBMPs are used, and to track the dispensing of them across the NHS, committing that:

The NHS England local lead Controlled Drug Accountable Officers (CDAO) will be liaising with their CDAO colleagues Officers (CDAO) will be liaising with their CDAO colleagues in Hospitals to ensure that the introduction of these products is monitored.

7.2.3 Rules on Unlicensed Medicines

The MHRA have issued specific guidance on the supply, manufacture, importation and distribution of unlicensed cannabis-based products for medicinal use⁷¹.

A summary of the requirements set out include:

1. Unlicensed CBPMs must be manufactured and assembled in accordance with the specification of a person who is a registered doctor listed on the GMC’s Specialist Register.
2. As with other Schedule 2 drugs, organisations wishing to possess, supply, produce or manufacture these products will require a Home Office Controlled Drug licence to lawfully undertake these activities.
3. The storage requirements for unlicensed CBPM will be the same as for other Schedule 2 controlled drugs.
4. A Home Office licence will also be required to import or export these controlled drugs.
5. The manufacturer or assembler of “specials” must hold a Manufacturer’s (Specials) Licence granted by the Licensing Authority and in most cases, a Home Office Licence.
6. The Specialist Importer of an unlicensed CBPM into the UK must hold either a Wholesale Dealer’s Licence if the product is to be imported from an EEA member state or a Manufacturer’s (Specials) Licence if the product is to be imported from a non-EEA country.
7. An unlicensed CBPM may only be supplied in order to meet the special needs of an individual patient. This product should not be supplied where a licensed medicinal product can meet the special needs of the patient.
8. All involved in the supply chain should be aware

of the unlicensed status of the CBPM. It should be clear from the product’s packaging that the product is unlicensed because there will be no marketing authorisation/product licence number on it.

9. The Specialist Importer must notify the MHRA at least 28 days before the date of the intended import. The MHRA may choose to permit import before 28 days from the date of its acknowledgment. This is usually only used in the case of immediate import of medicines for life threatening or immediately injurious clinical emergencies.

10. Any person who sells or supplies the unlicensed CBPM in the UK must maintain a record for at least five years.

11. A “specials” manufacturer, importer or wholesaler may advertise the service he provides but particular “specials” must not be advertised as provided by condition B of regulation 167 of the Human Medicines Regulations 2012.

12. For CBPMs, the MHRA requires reporting of ALL suspected adverse reactions (serious and non-serious, whether the product is licensed or unlicensed), including reports of failure of efficacy. Given the limited safety data that is currently available on the products, the MHRA will be conducting enhanced vigilance activities to support their safe use.

7.2.4 Maximum quantities on a prescription

The Department of Health and Social Care and the Scottish Government have issued a strong recommendation that the maximum quantity of Schedule 2, 3 or 4 Controlled Drugs prescribed should not exceed 30 days; exceptionally, to cover a justifiable clinical need and after consideration of any risk, a prescription can be issued for a longer period, but the reasons for the decision should be recorded on the patient’s notes.

In practice this means that patients who are prescribed a CBMP by their specialist are likely to need multiple ongoing prescriptions, following separate consultations. Each of these prescriptions has the ordering delays common to the sourcing of unlicensed medicines that are imported.

7.3 A complex, under-developed supply chain

Whether it is GPs at a local NHS practice or consultants at a hospital, all doctors must be able to

depend on a pharmacy to have stock of the product that they recommend for their patient, or to be able to source it relatively quickly. At present for unlicensed medicines, in particular for CBMPs where there is no domestic producer, that guarantee of availability and timely dispensing is not there.

Because all CBMPs have been classified as unlicensed ‘specials’, this inevitably leads to⁷²:

- a fragmented and complex supply chain.
- inability to promote or educate leading to a lack of awareness of the medicinal products on the market (form, dose, cannabinoid content etc).
- significant cost-impact to either the NHS or patient due to the complex supply chain of supplying a single named patient, and the additional costs (transportation, import fees) incurred.

In fact across the whole supply chain, the UK is drastically under-served by well-established customer channels and few if any domestic companies. It is therefore opening up a new medical cannabis market on the presumption that demand from UK patients will be fulfilled through imports from foreign suppliers.

7.3.1 Cultivation

There is no official data on the number of current/active cultivation licences that have been issued by the Home Office, though it is understood the majority are for research purposes to universities and other similar organisations, and there are few if any issued for commercial producers. The exception is the British company GW Pharmaceuticals, which holds a cultivation license and continues to operate a large cultivation programme as part of the British Sugar facility in East Anglia. In response to a recent Freedom of Information Request and after a review of the public interest, the government refused to publish this data on the grounds that “could damage the commercial interests of the companies licensed by the Home Office and would also make them potential targets of criminal activity.”⁷³

7.3.2 Producers

Companies seeking licenses to import cannabis-based medicines or other raw material into the UK must comply with the general restrictions on the cross border movement of controlled substances⁷⁴.

If those products have a prior medicines approval in another jurisdiction, that does not mean they will automatically qualify under the specials regime being applied in the UK. Furthermore no unlicensed medicine from outside the EEA can be imported unless it meets GMP-certification. A recent report set out in detail the GMP standard that companies around the world must meet in order to service the medicinal cannabis markets in the countries of the European Union⁷⁵. A separate study released in December 2018 in response to growing interest in the issue examined medicinal cannabis systems across the continent alongside the authorisation processes for medicines at EU levels and what rules producers/suppliers inside and outside the EEA need to follow⁷⁶.

7.3.3 Importers and distributors

A small number of dedicated firms exist to source unlicensed medicines on behalf of pharmacy and private clinic clients. These companies must comply with all applicable laws on importation, storage and transportation of controlled substances. However, they are usually the firms that pharmacies trust to have the expertise and the processes to supply the products to meet their order, and their volumes are low.

7.3.4 Pharmacies

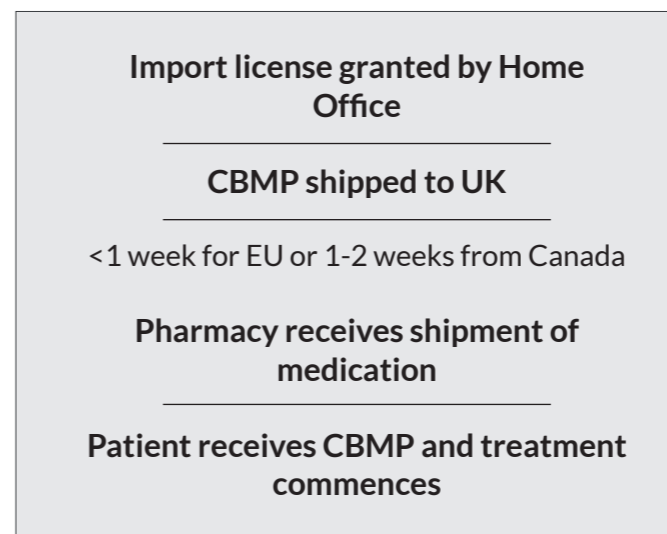
The UK has a mixed economy of pharmacy providers, including several private retail chains that have a presence in every town and city, such as Boots and Lloyds, and hospital pharmacies that can source and stock rarer drugs and specially-ordered medications. The CBMPs that are now available to be prescribed by specialist clinicians in theory, would in practice be ordered by a pharmacist based at the prescribing hospital and only once successfully imported and received onsite, could they be obtained by the patient. However, some private pharmacists do exist to cater to less common pharmaceutical products, and in addition to CBMPs, the widespread demand for CBD-only wellness products (not classed as a CBMP under the regulations because CBD is not a controlled substance in the UK) has led to them being stocked in some high-street pharmacies, as well as a number of health food stores such as Holland & Barrett.

7.4 What these barriers mean for patients today

There is currently a mismatch between patient expectations and the reality. Media coverage of the high-profile patient cases in the summer of 2018 and

the subsequent law change have led to widespread awareness of the new law and an expectation among patients that not only will cannabis medicines be available soon, but that access will be through convenient and familiar channels. In the survey conducted by Populus, 13% of respondents said they planned to ask their GP about medicinal cannabis - in excess of 6 million people in the UK. Most would not be eligible to receive a CBMP and no GP under the current rules could issue a prescription even to those patients who might be. It nonetheless illustrates the stark contrast between the law as it stands and the patient reality.

Even for those patients who have a condition that could be treatable by a CBMP and are in the position of having a supportive specialist who then issues the required prescription, the timeline to obtain that medicine is excessively long. The following outlines the required steps that must be followed and an estimate of how long a patient in this scenario would have to wait between first visiting their doctor to having their prescription fulfilled at the pharmacy counter.



In summary, the current UK system is not designed to enable patients to receive cannabis medicines quickly, even where the barriers to access are otherwise overcome. The lack of a domestic medical cannabis industry and poor product availability via conventional pharmacy routes makes the process of sourcing a CBMP prescribed a long and difficult one. This is then compounded by the cap placed on the amount of an unlicensed medication that can be issued at any time. Supply chains might be optimised over time if sufficient demand is forthcoming, otherwise in the absence of that, local relationships between pharmacists, specialist distributors, and import companies will be necessary to expedite the process of supplying imported CBMPs to UK patients.

8. Delivering a System that Works for the UK

It may be too soon to definitively evaluate the UK's system and to know where the biggest barriers to access for patients are. However the research for this report suggests a need to conduct a strategic policy review to identify the key benchmarks against which policy should be judged, and to develop that on the basis of serious engagement with international experience to date. The evidence base is critical for the confidence of both practitioners, professional bodies and for regulators, but it is also key for policy-makers so they feel able to liberalise the controls that currently exist.

The purpose of a strategic review is to not just identify the policy objectives and to set out a framework

to judge progress, but to signal to the private and third sectors and other key professional healthcare stakeholders that the emergence of a medicinal cannabis market in the UK is part of a comprehensive ambition. That vision needs articulating by the Government, and we suggest what that should amount to in the next chapter. To get us there, we need a strategy that is underpinned by some structural reforms (affecting governance, regulation and policy development), and then a series of steps that could be taken now, and over the next two years, to lay the ground for a viable market that delivers for patients.

A comprehensive strategy of this type can only be created and promoted by Government, but it must be informed by those outside and those in other sectors affected by it. The following are some necessary changes that the CMC believes are indispensable in any future strategy.

8.1 The right policy, governance and regulatory structures

Countries like Australia and Canada that have created medicinal cannabis markets have also moved to institute new bodies, or governing processes, or alternatively to repurpose existing institutions. Devoting the necessary time, expertise and resources to the proper oversight, evidence gathering, and supervision of the market. The UK has none of these institutions or cannabis-specific governance arrangements at present, and without those foundations, no credible strategy can be built.

8.1.1 Policy coherence

As it has been for a century, drug policy in the UK is set and owned by the Home Office, also responsible for policing, borders and counter-terrorism. The structure of any medical system will be shaped largely by healthcare interests, but unless and until there is a machinery of government change (a portfolio change in ministerial responsibility) the final decisions on the system and whether and how it evolves in future will be taken by the Home Secretary. His view will be informed by a longer term review underway by the department's advisory committee, the Advisory Council on the Misuse of Drugs (ACMD) and will no doubt also involve consultation and agreement with Cabinet colleagues and in particular the Secretary of State for Health and Social Care.

However cannabis as an issue, now being the source of legal health products, naturally fits more into the healthcare domain and bears directly on medical and scientific stakeholders and industry groups more than it does policing and the security sector.

To this end unless and until cannabis policy is moved from the Home Office and becomes owned by the Department for Health, key decisions will continue to be governed, or at least skewed by, wider security concerns related to other controlled substances. It is now common in the UK for the Cabinet Office to support a number of cross-departmental Intra-Ministerial Groups where a small number of Cabinet Ministers convene quarterly to agree policy that cuts across individual departments. Medicinal cannabis is such a policy and to formalise the split responsibility that already exists in practice, the civil service should support the creation of such a group, in addition to the Home Secretary, should include the Secretary of State for Health, the Environment, and Business, covering as it does the wider issues affecting the health, science, agriculture, and trade and business sectors. A key priority for such a group should be to capture the international experience to date and to formalise those ties with policy exchanges between officials in UK and their counterparts in Canada and Australia.

Recommendation 1: An Intra-Ministerial Group on cannabis should be instituted to ensure agreement and coordination of all the UK government's policies as they relate to the medical cannabis sector and the industry and regulations needed to support it.

Recommendation 2: Cannabis policy should transfer from the Home Office to the Department of Health and Social Care as an immediate step in advance of a wider review to consider whether to relocate policy and regulation of all controlled drugs to the health domain, akin to the Office for Drug Control within the Australian system⁷⁸.

Recommendation 3: The UK must not seek to reinvent the wheel but instead draw on lessons from comparable countries. The recent reforms in Australia and Canada offer the best policy parallels for a federally-legal model where policy changes and regulations have been amended in light of experience.

Recommendation 4: Given the depth of the Canadian experience of more than a decade, a new bilateral policy initiative should be established between the UK and Canada so their respective

government departments, health regulators and medical professional bodies, can share policy insights, national data, and clinician and stakeholder experiences to inform how the UK model should develop. The Health Secretary should initiate working groups comprising Canadian and Australian delegates to inform UK policy development and their counterparts from Health Canada and the Australian Department of Health should be invited to the UK to observe our system and advise DHSC and health regulators on possible next steps.

The Advisory Council on the Misuse of Drugs was originally set up to advise the Home Secretary on drug policy and they are currently engaged on the second part of their commission into policy on cannabis, due to report by July 2019. While it is unclear what this review will add to the shaping of the current medical market, it is important that this review is completed in a timely way. In the past, many of the ACMD's recommendations have not been followed (including some of its initial advice in 2018 on how CBMPs should be defined), nevertheless, the council plays an important role vis-à-vis current and emerging drugs that have a controlled status.

Given the effect of rescheduling in shifting cannabis decisively towards the healthcare domain, if wider governance changes are instituted it becomes harder to justify why the ACMD should continue to cover cannabis policy in their advice to Ministers, as if it was completely prohibited. It arguably makes more sense for cannabinoids in all their forms to be taken out of the ACMD's remit insofar as advice to Ministers on the medicinal applications of the drug are concerned. While it remains a controlled substance, the importance of recent developments for the healthcare sector and the arrival of a market in CBMPs justifies a standalone committee to advise the government going forward, reporting principally to the Secretary of State for Health and Social Care.

Recommendation 5: Similar to the Australian body⁷⁹ created for this purpose, the UK Government should establish a dedicated UK Advisory Council on the Medicinal Use of Cannabis (ACMUC) comprised of both academics and practitioners familiar with the scientific and medical applications of cannabinoids and reporting to Ministers in the DHSC.

8.1.2 Dedicated Policy Hub

Many countries that have instituted a medicinal cannabis regime have also created a dedicated policy directorate or regulatory branch within

government. This achieves two objectives – it separates cannabis policy development and analysis from wider drug policy geared around prohibition of controlled substances, and it provides a central place to coordinate activity that touches several areas of government activity, while creating a hub for knowledge and improved expertise among policy officials and regulators.

The Netherlands has created such a body to regulate its own medicinal cannabis system. The Dutch Office of Medicinal Cannabis (OMC)⁸⁰ also serves as the only authority for importing or exporting cannabis and other drugs into the country. Applications by businesses or individuals to bring in or take out cannabis, in whatever form for whatever purpose, must be approved by the OMC who then applies for, issues and charges for licenses on the applicant's behalf, and arranges transport. The OMC also acts as the single hub for information and guidance for patients and clinicians. For example, it has produced guidelines on vaping, which is precisely the type of output that UK medical practitioners would need.

Recommendation 6: The UK should create a Cannabis Policy Branch within the Department for Health and Social Care to create a hub for expertise and to locate it in the health domain in line with most other jurisdictions where the drug is legal for medical purposes.

8.1.3 Dedicated Regulatory Machinery

The current processes for issuing licenses for the importation of unlicensed medicines are unlikely to prove sufficient to meet the future demands if prescriptions for CBMPs increase in future years. The estimate patient timeline in Chapter 5 illustrated how long the process can take under current procedures, and this by itself imposes a delay on patients receiving medications which is hard to justify. Over time, if demand from clinicians reaches a certain level, local hospital trusts will need to allocate a part of their prescription drug budgets to CBMPs and institute regular ordering via pharmacies. This will generate more applications for the required importation permits and necessitate a revamp of the current Home Office procedure so licenses can be issued more quickly and in greater volume. As this unit is the same one that handles licensing for all import/export and processing of all controlled substances, it is arguably too poorly resourced to cope with a large increase in applications involving cannabis - either importation licenses or other types.

In some other jurisdictions, (although not Australia), the government have instituted a dedicated administrative office for the processing of cannabis licenses, whether that is part of the security or interior ministry, or the health department. In anticipation of future demand, and to deliver a better service that will result in faster receipt of medications for patients in need, the Home Office should consider creating a similar bureau so licenses can be evaluated and issued in the most efficient way. Licensing offices in government set fees according to the cost of processing and over-recovery, to generate income, is generally not permitted. However in this instance, increasing current fees could justify an expanded staff to handle applications and guarantee a service level where applicants could be assured of a maximum turnaround time. This would also enable pharmacists and clinicians to set patient expectations.

Recommendation 7: A new Cannabis Licensing Branch of the relevant government department should be created to ensure an efficient, timely and dedicated service to all those in the healthcare sector seeking importation or processing licenses to meet pharmacy orders. Licensing fees for importation of controlled substances should be adjusted to support the additional costs of this dedicated unit in return for a commitment to speedier service.

Recommendation 8: In future the growth of domestic suppliers of CBMPs will reduce the need for slow process of ordering via specialist importers, but in the meantime, the MHRA should notify pharmacies of the UK-based specialist firms that can cater to orders for unlicensed medicines to speed up sourcing.

8.2 The right products and modes of consumption

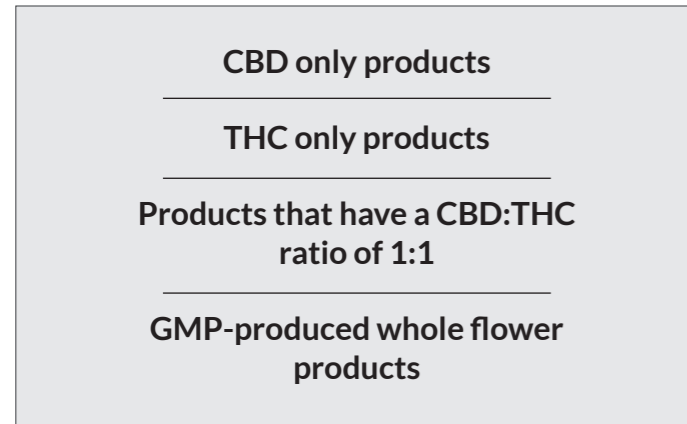
8.2.1 Permissible products

As outlined in October and contained in the regulations, the formal definition of a CBMP is as follows⁸¹:

- the product is or contains cannabis, cannabis resin, cannabinol or cannabinol derivatives
- the product must be produced for medicinal use in humans
- it must be a product that is regulated as a medicinal product or an ingredient of a medicinal product

This represents an incredibly broad potential range of products and complicates clinical decision making in an already unfamiliar territory.

The CMC recommend that there are effectively four CBMPs for which we have clinical trial evidence (see Chapter 5) and these categories should be adopted:



The interim guidance from NHS England really only recommends the use of Epidiolex in 2 forms of epilepsy and Nabilone in chemotherapy patients. As these are both already licensed medications, it seems that the change in law and ability to prescribe these CBMPs within the specials category is redundant.

	CBMP	Examples	Symptom relief
1	Pure CBD	Epidiolex or a similar pure CBD compound	Seizure reduction, pain
1	Pure THC	Nabilone, Dronabinol or a similar pure THC compound	Pain, suppression of nausea/vomiting, appetite suppression
1	THC:CBD 1:1	Sativex or similar 1:1 ratio product	Decrease in spasticity, pain
1	GMP produced flower of known and fixed THC:CBD content	Bedrocan Flos	Pain, suppression of nausea/vomiting

Table 6. List of recommended CBMPs for which there is clinical evidence.

We recognise that it is best practice to recommend licensed medicines, but from a pharmacological point of view, there is no reason to think that a generic product would not have the same efficacy. From a cost comparison point of view, our research indicates that generic versions of CBMPs could cost between 33 and 66% less than the licensed medications recommended. This could make a significant impact on the cost benefit conversations that might be held at a local or national level.

8.2.2 A place for synthetics

The two licensed medicines based on THC, Nabilone and Dronabinol, are both synthetically produced. Some pure CBD medicines that are being developed (for example by InSys Therapeutic Inc) are also synthetically derived. We see no reason why synthetic compounds that are based on the naturally-occurring products should not be classed as CBMPs.

A very clear distinction needs to be made between synthetic versions of THC or CBD (or indeed any of the phytocannabinoids) and street drugs (often called spice, or synthetic cannabis, which were outlawed by the 2016 New Psychoactive Substances Act) that are not structurally related to naturally occurring cannabinoids.

8.2.3 Clarity on Cannabidiol (CBD)

The current guidance issued by the MRHA, Home Office and the interim guidance documents issued on CBMPs⁸² in relation to CBD containing medicinal products (where it is the intention of the prescriber to provide a product that contains only CBD in its pure form) is not clear and could therefore lead to patients being denied access to this important medicine. Namely:

- Currently it is not clear as to whether a preparation containing only CBD is included in the CBMP legislation. Pure CBD is not a scheduled drug; however Home Office guidance recommends caution on the “presumption that a CBD containing product would be controlled under the MDA 1971 / MDR 2001 as a result of its other cannabinoid [controlled] content”⁸³.
- Current CBMP guidance does not allow for synthetic cannabinoids to be prescribed except for those already with a legal classification under the misuse of drugs act i.e. dronabinol and nabilone. Synthetic CBD is available within Europe as a GMP substance with an associated drug master file and its status as a CBMP or indeed the ability for it to be prescribed as a non-CBMP is unclear.

Patients and clinicians need clarity and so the relevant regulatory bodies (MHRA, FSA, NHS and Home Office) should clarify the status of CBD since the 1 November rescheduling.

Recommendation 9: Adopt a simple system of categorisation containing the four types of CBMPs for which we have clinical trial evidence and devise policy accordingly for each.

Recommendation 10: NHS England should create a list of approved CBMPs to guide clinicians. Synthetic versions of the THC or CBD molecules are acceptable and practical alternatives. Generic versions of these CBMPs should be available as specials.

Recommendation 11: Regulators should communicate the CBMP changes to those in the supply chain especially the customer-facing pharmacists so that prescriptions can be dispensed in a timely manner, with as a minimum Royal Pharmaceutical Society communicating to its members.

Recommendation 12: Regulators should clarify the status of CBD since the 1 November rescheduling and where it sits within the general framework for CBMPs.

8.2.4 Modes of consumption

Consuming cannabis products through smoking in the traditional format is permitted in some established medicinal cannabis regimes (e.g. Canada), and many people who access the drug illegally have used it this way because of the ease of availability and preparation. However the advantages for patients of quicker onset of effects through smoking cannabis should be offset by the long-term negative health impacts of inhaling combustible plant material, even if it is uncontaminated. Evidence is mixed on the harms that smoking cannabis alone can cause, however it is less harmful, and much less addictive, than tobacco.

Nevertheless in the UK context, it is unlikely that smoking cannabis for medicinal benefits would be endorsed by healthcare professionals, and a major diversion from medical norms to prescribe such a product. For several decades, taxes have been levied and significant funds spent by public health bodies to reduce rates of smoking and to limit the places in which it is possible to smoke.

In the UK, the government plans to permit flower products but expects that patients will consume them via vaporisers, which are classified as a medical device in Canada and they are subject to the same rules around public consumption as tobacco. Vaping devices have become very popular modes of consumption and due to the lack of combustion they pose far fewer risks to health.

Recommendation 13: Patients need a diverse range of consumption options, and medicinal cannabis should be available as flower in the UK, to enable some patients to vape their cannabis (but not to smoke it).

8.3 The right ecosystem for research and innovation

Rescheduling should serve as an impetus to consider all the steps that could be taken now to expand this evidence base as quickly as possible, including removing barriers to basic science to enable researchers in universities to conduct experiments. The right ecosystem should also foster more clinical trials which are critical for long-term adoption throughout the public system, but in themselves also have a short-term benefit in being a mechanism to expand patient access (as they qualify as one of the three approved paths for prescribing a CBMP).

8.3.1 More basic research

Progress on scientific research on the effects and medicinal benefits of THC or other CB₁ agonists in the UK has been hampered by the fact that these are scheduled drugs and thus require a home office license for researchers to work with them. This has meant that many scientists have been unable to carry out the important innovative research that they would like, fully investigating the biological effects of CB₁ activation. Unfortunately the recent revise in the law will not change this for cannabinoid scientists in the UK as the tools they would work with in laboratory and preclinical (animal research) would not be classified as CBMPs according to the Home Office definition, and thus remain scheduled drugs.

Recommendation 14: UK cannabinoid scientists based in recognised academic institutions or industries should be able to apply for research licenses, with less bureaucracy and costs than the current scheme, to carry out research with CB1 agonists.

Throughout the world there is a broad consensus that given the insufficient amount of high quality evidence into the efficacy of cannabis-based medicines, more must be done to initiate high quality, dose-ranging, phase 3 trials, and that enabling such research should be a priority in those jurisdictions where medical cannabis has already been legalised. Even countries like Australia and Canada that have an imperfect medical cannabis market that still does not provide adequate access for patients, legalisation there has allowed important steps to be taken to improve the evidence base and begin investing in the scientific trials that this new medical frontier demands. However policy should be set with the explicit aim of speeding up the research needed to fully exploit the therapeutic potential that cannabis could deliver for patients⁸⁴.

It is encouraging that the National Institute for Health Research (NIHR) has issued a call for applications for clinical trials in this space, with a closing date of March 2019. The brief asks for applicants for “primary clinical research to evaluate the safety and clinical efficacy or clinical effectiveness of cannabis-based products for medicinal use in humans”, with prospective trials taking place under one of two managed research programmes, depending on the product or technology being evaluated⁸⁵. The NIHR funding is aimed at late phase clinical work, therefore we would also recommend that other research councils such

as the MRC and BBSRC issue calls for preclinical and early phase clinical work in the development of CBMPs, particularly in indications where the evidence is still very limited but anecdotal data and patient experience suggests a benefit of CBMPs.

Recommendation 15: The evidence base around the clinical use of CBMPs should be more widely recognised and disseminated to healthcare professionals. Given the lack of familiarity, it is especially important that new research findings are shared with clinicians.

Recommendation 16: All academic and industry-funded clinical trials investigating CBMPs should abide by the law and best practice and publish all outcomes in full, and encourage the retrospective reporting of already complete trial data.

Recommendation 17: Based on our analysis of complete and ongoing trials, we would recommend to broaden the NICE consultation to encompass more indications.

Recommendation 18: Initiate clinical trials and generate data where CBMPs are used alone and compared against current medication to establish any potential superiority or non-inferiority (with reference to side effect profiles or possibly cost implications).

8.3.2 The role of government

In the UK, government officials regard clinical trials with British patient subjects to be important, but they believe that industry itself, in common with other drug developments, has the incentive and the obligation to invest in these trials itself. The government takes the view that those companies seeking to access new markets like the UK should find partners and invest their own resources in new clinical trials, and limited public funding is necessary to encourage these to take place.

The world needs more trials of all kinds into the benefits of cannabis-based medicines and the UK especially would derive huge value from having its own domestic trials. Even with limited available public funds, to encourage more trials to begin more quickly, the government must play an active role in creating an ecosystem that supports more research and innovation. This cannot be left solely to individual companies to initiate.

The Government ought to create the right conditions for private investment to support new clinical trials, and ensure that any that are initiated, are brought within the proper research channels of the Health Research Authority to help build up the evidence-base. To ensure integrity and transparency, the outcomes and data of such trials should be published in all but exceptional cases, as recommended by a recent Parliamentary committee. Government ought to have a mechanism to collate and disseminate the latest research findings to those in the healthcare system.⁸⁶ Fully government-funded research efforts are not feasible in this area of medicine, but the UK authorities ought to set a goal of creating the right ecosystem for innovative trials to happen, and where appropriate, consider making strategic investments in those partnerships that bring the most potential value, for instance research into some of the most acute conditions. The Canadian government has invested in these kinds of research projects [X] in several provinces across Canada with university partners, and in Australia, the government in New South Wales, as part of a \$12m investment over four years, has created the Centre for Medical Cannabis Research and Innovation⁸⁷ to advise patients and clinicians, oversee the state’s funded trials, and support new research. The Czech Republic, where medical cannabis has been legal since 2013, now hosts the world’s first research consortia dedicated to cannabinoid trials, through the International Cannabis and Cannabinoids Institute, specifically to address the gaps in clinical evidence that exist and the absence of adequate government-backed research⁸⁹.

Recommendation 19: Established grant channels should be used to catalyse more clinical trials through consortia with industry partners and condition charities with a focus on conditions where patients are already using CBMPs but sourcing from the black market.

8.3.3 The role of industry

In North America, where wider legalisation of cannabis is taking place, the role of private companies in pursuing new research efforts is significant - including established pharmaceutical companies hitherto unconnected to cannabinoid research. The pursuit of early competitive advantages in a rapidly expanding consumer industry is driving investment in all research fields associated with the plant, with efforts being made to secure intellectual property and patents⁹⁰.

As this global industry develops, major companies will emerge with large budgets for R&D and for forming partnerships with academic institutions. We should expect such companies to commit to an expansion of the evidence base and to support efforts to grow a community of cannabinoid researchers and scientists, who can advance our understanding and deliver innovative new drugs and medical products to patients. As one of the fastest growing medical sectors in the world, private industry has a major role to play in legitimising cannabis as a drug for medical use.

Recommendation 20: There should be an expectation placed on responsible producers of pharmaceutical-grade medicinal cannabis products (that meet a GMP standard) to commit to the long-term benefit of UK patients by helping to fund and facilitate new trials of their medicines within the UK.

8.4 Medicinal Cannabis Centres of Excellence

The CMC believe that whilst the rescheduling of CBMPs to allow legal patient access under medical supervision is to be welcomed, this report has set out where there remain significant barriers for doctors to be able to prescribe and for patients to have CBMPs dispensed to them to alleviate their suffering.⁹¹ And so whilst we expect there to be increasing use of CBMPs within the NHS framework, it will take time.

Given that the barriers in the public system are very serious but that private doctors can also prescribe a CBMP under the same rules, we believe this will leave a significant role for the private medical care system to ensure that for those patients who have exhausted routes within the NHS or are wanting a more rapid assessment of their suitability and are willing and able to pay, can also access CBMPs.

As with other complex areas of medical intervention, supported by numerous examples within the NHS and across the world the CMC believes that an approach for consideration by stakeholders is for the support, funding and adoption of a small number of Centres of Excellence (CoE) to provide access to CBMP across the UK^{92, 93, 94}. The creation of such CoEs would be centred at existing locations that have a strong academic and clinical heritage in using and researching cannabinoids and cannabis-based medicines, and the various constituents of cannabis for medical conditions.

They would bring together in a public-private partnership the strengths of Universities, NHS trusts, charities, private medical providers and interested industrial parties (i.e. CBMP manufacturers and biotech) who wish to research or supply high quality CBMPs.

The CMC believe that the CoE model would confer numerous benefits to all stakeholders associated with CBMPs, namely:

- A concentration of like-minded, motivated, skilled and focused health care professionals (HCPs) focused on delivering optimal cannabis centric medical interventions based on the available evidence, whilst importantly applying accepted medical research practise to further the knowledge base in the area.
- Shared learning and experience amongst HCPs using a multi-disciplinary approach so that best clinical practise can be rapidly adopted into all areas concerning the use of CBMPs (i.e. dosing and titration schedules, managing adverse drug reactions, improving formulations and delivery systems etc).
- An integrated research environment in which academic, clinical and industrial partners could rapidly deliver quality research at all levels of the evidence hierarchy from prospective case-control through to randomised controlled trials. Regional CoEs would be able to coordinate together under one ethics committee to provide rapid access to patient recruitment, coordinate data collection and processing and have a common goal for rapid publication to further patient benefit. By integrating private medical practise into the CoE this group of patients normally excluded from medical research could also be captured⁹⁵.
- Recognising the challenges of sourcing and supplying CBMPs of the required quality in a timely and cost efficient manner the pharmacy departments within the CoEs could establish a quality assured supply chain and maintain a registry of CBMPs that are available for use “off-the-shelf” and work with specials manufacturers to ensure supply of bespoke products where required⁴⁶.
- The CoEs would act as tertiary referral centres for physical patient referrals, but would also provide ongoing medical and scientific education and consultation into local specialists where patients will be treated locally and could offer a

satellite service into regional hospitals where this service is deemed viable.

- Would help support the UK as a major global hub for Life Science, research and innovation which is at the centre of the government’s Industrial Strategy. CoE are likely to attract both global talent in the field of cannabis research as well as industrial funding within this high growth sector and cement the notion that the UK is open for business and investing in Life Science R&D post-Brexit ⁹⁶.

Creating regional CoEs to spread innovation at pace and scale as well as providing the best possible immediate care and access to both NHS and private patients will ensure that the Government’s stated policy and vision for CBMPs is most effectively established over the short to medium term horizon.

Centres of Excellence would serve to concentrate some of the complex logistical and sourcing issues of CBMPs in one place, bringing scientists and clinicians together, and creating a hub where the research into and the prescribing of CBMPs can be properly coordinated. Over time, satellites could be established at regional hospitals. Patients would have a place to go to, and clinicians would have a dedicated centre to refer patients to.

Recommendation 21: Develop a network of Centres of Excellence of scientists, doctors and clinical trial specialists, with links to major condition charities, public and private healthcare system and industry, with the primary aim of generating world-leading research into CBMPs. The generation of Centres of Excellence will facilitate rapid and cutting-edge basic and clinical research, while providing a new access channel for patients.

Recommendation 22: Through established grant channels, government agencies like NIHR should seed-fund Centres of Excellence as collaborations between private industry, the NHS and academia, under the supervision of a new cannabinoid research agency.

Recommendation 23: The Department for Health and Social Care should oversee this new network of regional Centres of Excellence by endowing a new UK Institute of Cannabinoid Research and Evaluation.

8.5 The right access model for patients

Under the new system as of 1 November 2018, specialist clinicians are the only doctors with the authority to prescribe medicinal cannabis products in the UK, which will give them significant influence over the trends in uptake within the public healthcare system in the future. As UK patients can only obtain cannabis medicines via prescription, the role and attitude of the prescriber is often the decisive factor in whether patients can legally obtain the product. This gate-keeping role, designed to keep tight controls on the use of CBMPs and to avoid overly-lax prescribing, is reserved for senior doctors, and is not unusual for unlicensed medicines. It is also unlikely to change in the short-term. But what could be done to widen clinician’s authority?

8.5.1 Prescribing authority

Many new medical cannabis regimes begin by restricting prescribing authority to specialist doctors. Some systems have loosened these constraints over time, and recent changes to the Australian system now enable GPs there to make an application for a cannabis prescription for the first time.

An important exception outlined by the government was that if a patient is participating in a clinical trial, any clinician (i.e. not just specialists) can prescribe the medicine as part of the approved clinical trial protocol. This is not different to what is normally practised in the development of new medicinal products. This should be recognised as an important mechanism to increase access of CBMPs to patients, and is further rationale to rapidly promote new clinical trials with CBMPs.

While restricting prescribing authority at the outset of a new system is rational, it does expose a discrepancy in that other doctors are already permitted to prescribe certain medications with a higher potential for misuse (e.g. opioids for pain), as part of a patient’s treatment plan, and the NHS and medical professional bodies place great emphasis on the patient-doctor relationship embodied in the general practitioner model.

Encouraging greater uptake among clinicians cannot happen overnight because the NHS is a large and complex organisation and familiarisation among practitioners is a gradual process. Drawing on Canada’s experience, the majority of doctors do not and even after a decade or more, will not prescribe

CBMPs. However a minority will, and the key to building a system of coverage that offers meaningful access is to connect those doctors to the larger pool of patients.

In practice, this means enabling the patients who need a CBMP to receive it via their most common clinical relationship, rather than expecting them to navigate a complex healthcare system to seek out the small number of supportive clinicians, among a tier of specialist doctors. In the UK, that is a patient’s General Practitioner (GPs) who represents the most common clinical relationship because they are based in the community, see the same patients regularly, and typically maintain patient relationships for years or even decades.

8.5.2 A role for GPs?

This report recommends ways to make specialists more familiar with the CBMPs available, to invest in the education needed to encourage more of them to prescribe, and to advance the research into cannabis medicines so specialists can refer to clinical data to help them reach a decision. All of this is necessary and will increase the numbers of specialists prescribing - alongside personal networks and peer influence that policy alone cannot influence. However, one of the underlying factors that may retard the spread of cannabis prescribing in the NHS comes down to the different relationship that patients have with specialists. Specialists are not only fewer in number and harder to access, they also see patients less often. That means if they are hesitant about prescribing, their lack of regular contact with the patient to monitor for adverse side-effects will make them more so. The rules on unlicensed medicines would require specialists to review a prescription every 30 days, but that may be yet another reason why many doctors are reluctant to issue ‘specials’ in the first instance.

A general authority for all doctors throughout the NHS to prescribe unlicensed CBMPs would be a sudden and major expansion of access that Ministers would only approve in response to studies confirming the wider organisational implications (including supply chain capacity and the cost impact on NHS prescriber budgets). There is also no guarantee that such a shift would automatically bring patients greater access, given that lack of education and experience of cannabis medicines is not found only at the level of specialists.

It would be practical, however, to relax the current authority to prescribe by enabling GPs who had referred a named patient to a given specialist who had then chosen to initiate treatment with a CBMP, to then continue follow-on prescribing for that same patient. The initial discretion to authorise would continue to vest in a hospital consultant, and they would at any time have the power to end a treatment plan using CBMPs, but the doctor who has the strongest relationship with the patient and can see them most often would be granted the right to continue a cannabis-prescription if it was proving efficacious. In such a model the onus would still be on the GP to flag concerns, monitor patient responses to the drug (including alerting to any side-effects of unlicensed products through the MHRA's 'Yellow Card' ⁹⁷ system).

This change would by itself help to increase GP awareness of cannabis medicines which is important for the long-term normalisation of the field within mainstream public healthcare culture. Follow-on prescribing by GPs would also make access more convenient for patients, who are otherwise required to travel to the same hospital for a consultation with their specialist, which could be far from home. Because of the repeat prescription requirements under the specials regime, efficient and timely sourcing of unlicensed CBMPs would be a prerequisite of such a model working well, but those supply chain issues need resolving whoever authorises a prescription.

Recommendation 24: NHS England, the Royal College of Physicians and the General Medical Council should agree a scheme by which GPs can continue treatments with cannabis-based medicinal products and allow for such follow-on prescribing to be permitted once a specialist has issued the first CBMP prescription.

8.5.3 Access outside the public system

Within the private sector, clinicians are not regulated by the same constraints as those within the NHS and can prescribe more freely with the consent of the patient. Already within the UK, there are a small number of private doctors who prescribe CBMPs as off-label prescriptions (licensed medications, but for a different indication that the licensing allows: an example of this would be Sativex prescribed for cancer pain) or specials (for example CBD in cancer patients⁹⁸)

This market is likely to expand significantly as a consequence of the recent apparent acceptance and legitimisation of CBMPs through media and indeed by the government itself. This has generated a large number of patients who want to access CBMPs but find themselves unable to because of the applied restrictions. The private sector will grow to meet this demand. However, it is essential that the data generated from these patients is not lost. We must also acknowledge that the growth of the private sector will lead it to an inequality of healthcare provision between NHS patients and those who are in a financial position to avail of private healthcare. Such a two-tier system, while unavoidable in the short-term, is not a good outcome and could be viewed as a sure sign of failure (see chapter 9).

Recommendation 25: Private clinicians and clinics should be brought under the umbrella of the Centres of Excellence to ensure that all patients prescribed a CBMP are either part of a clinical trial or have their data captured by other mechanisms for drug efficacy and side effects.

8.5.4 Exceptional Cases

There are many tens of thousands of patients in the UK who already access cannabis from illicit sources and self-medicate to help them manage pain or other symptoms of chronic or terminal conditions. These people currently have no choice but to rely on a new medical regime that in practice cannot provide them with cannabis medicines unless and until more evidence from UK clinical trials is available. This is a familiar problem when new medical cannabis laws are passed and before full patient access has been achieved.

According to the United Patients Alliance⁹⁹, terminally-ill cancer patients are already self-medicating with cannabis products that they have no choice but to obtain illegally, and which provide them with health benefits in the final months of life. Many grow their own herbal cannabis or acquire it from family or close friends. At present, such patients and their carers are treated no differently in law to the recreational drug user buying skunk from a street dealer.

Therefore, as a pragmatic step forward and in advance of a fully developed medical system that ensures full and fair access for all, there is a need to address this policy conundrum. As a temporary measure, and in recognition of the inevitable ongoing use of illicit cannabis products to self-medicate, other

jurisdictions have created schemes to regulate the possession for such patients, without decriminalising the wider use of cannabis for non-medical purposes. The UK should study the scheme in New South Wales (see case study) that applies to terminally ill patients only.

An analogous UK scheme, created explicitly as an interim measure to be formally reviewed after two years, would be a practical and modest step recognising that the risk of arrest for cannabis users is unjustified and unnecessary in the case of the small number of terminally ill patients, a community who simply use the drug to ease their symptoms in advance of death, and should be given some reassurance so that they do not continue to live in fear of prosecution. This would involve issuing guidance to clinicians and further operational guidance to police Chief Constables, recommending that police officers do not arrest patients registered under the scheme for possession of the drug (although it would not amount to a defence in law and any consumption of cannabis in public would remain unlawful).

When full access to CBMPs is available across the NHS, such an exceptional scheme would become redundant and could be closed down¹⁰⁰.

Recommendation 26: The Home Office and Department for Health and Social Care should jointly establish a time-limited scheme for compassionate use of cannabis for terminally-ill patients, modelled on the system in New South Wales.

8.6 The right support system for clinicians

The recent change in law happened rapidly and publically, and clinicians are now in a position where there is patient and public pressure to begin prescribing CBMPs. However, most UK clinical specialists would have a very limited knowledge of the endocannabinoid system as this is not taught on the medical curriculum or of the evidence base of CBMPs in various indications. They also have no experience of the vast range of CBMPs that are technically available now under law. Understandably this means there is a very limited number of clinicians who are currently open to prescribing CBMPs within their speciality. This is further restricted by the interim guidelines issued by NHS England that makes very narrow recommendations on how CBMPs should be prescribed within the NHS. Together with the range of local restrictions already

outlined, this has created a situation where although technically possible, the reality is that almost no clinicians within the NHS will actually prescribe a CBMP, and particularly an unlicensed CBMP. This is demonstrated in the figure below where we have a bottom heavy system.

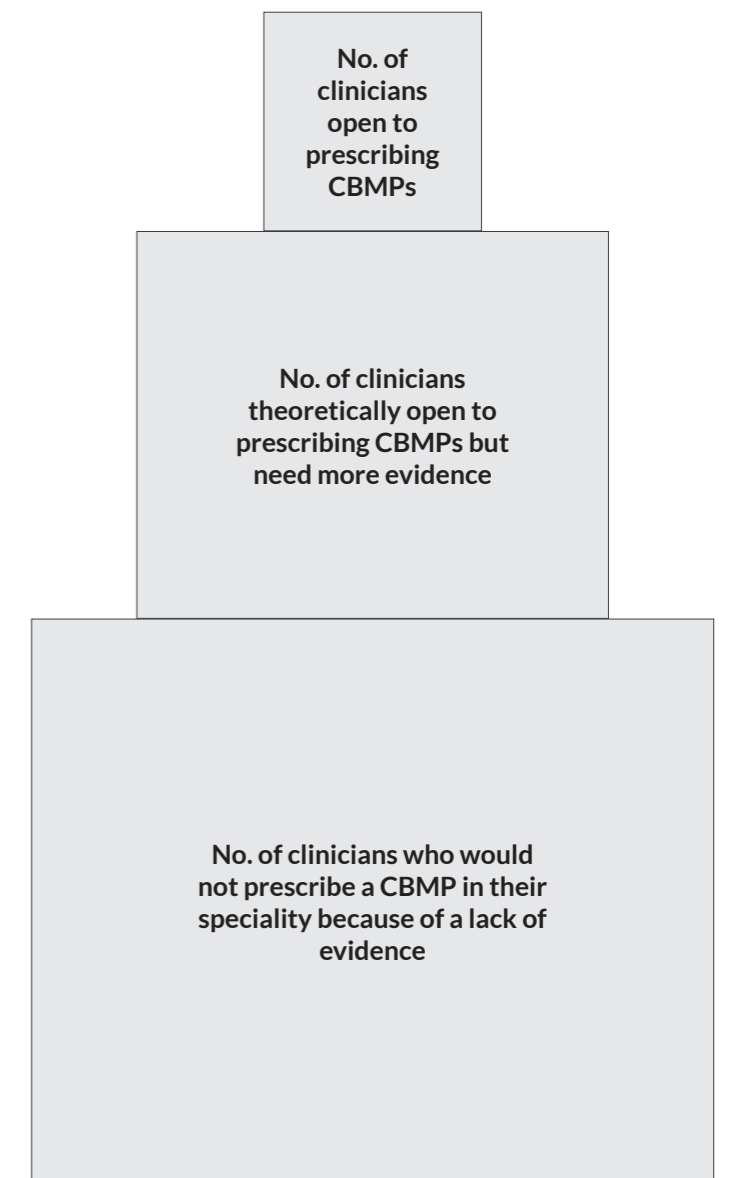


Figure 2. The proportion of consultant currently willing to prescribe a CBMP is limited by the small numbers of specialities in which there is sufficient high quality evidence of benefit to their patient populations.

8.6.1 The Three 'E's

This question is now, how do we turn this pyramid the other way around to increase the familiarity and confidence of clinicians to prescribe in this space? To enable this, we recommend the three Es; Education, Evidence and Experience. Strategies of how this could be enabled are detailed below as well as other relevant recommendations throughout this report.

The 3 Es

The 3 Es	
EDUCATION	<ul style="list-style-type: none"> • Introduction of cannabinoid pharmacology to medical school curriculums • Continuous professional development courses for healthcare professionals • Clear definition and education about each of the different types of CBMP (including routes of administration) and their likely therapeutic effects • Increase guidance from local speciality groups, relevant societies/associations and NICE • Support from local Trusts and NHS England • UK conferences specialising on cannabis-based medicines and prescribing CBMPs
EVIDENCE	<ul style="list-style-type: none"> • Online resources publicising the evidence that currently exists • High quality, dose-ranging phase 3 trials • Data collection on all patients prescribed a CBMP under the new law change and guidelines to monitor for efficacy, safety and long-term effects • Increased government funding of preclinical and clinical research • Increased industrial sponsorship of clinical research • Health economics analysis
EXPERIENCE	<ul style="list-style-type: none"> • Collaborations and networks with CBMP-prescribing clinicians from across the world with experience • UK network of CBMP-prescribing clinicians for peer support and sharing of good practice and experience • Open disclosure from patients about CBMP use • Talking to patients about their experiences with CBMPs

Table 7. Education, evidence and experience are the key factors that will create the right support system for clinicians to feel confident prescribing CBMPs.

Recommendation 27: CBMP-friendly clinicians within the NHS should lobby at a local level within their speciality and within professional societies and ultimately NICE, to modify guidelines to make prescribing easier.

demand is likely to build, and barriers to access cause anxiety and aggravation, leading to antagonism. In policy terms the effects of this can be predicted. Some patients who then struggle to access a legal supply of cannabis for their healthcare needs, will feel as if they are out of options and may be forced back into the clutches of an emboldened black market. This is counter to the policy goals of the reform and unnecessary.

It is therefore imperative that any changes that are made are not unduly delayed and new measures are introduced in 2019-20 that will avoid some of the consequences of an immature system that has not yet become institutionalised throughout the NHS.

9: Roadmap for Reform

The recommendations throughout this report are designed for government and regulators as they plan the next phases of this new healthcare development. Experience of other systems shows that patient

9.1 What needs to happen in 2019-20

The most important changes that could be made in the short-term are:

- Expanding the number of iterations that the NICE guidelines (due by October 2019) encompass;
- Publishing an approved list of CBMPs to aid clinicians and issuing new guidance for pharmacists to support efficient ordering;
- Permitting GPs to manage follow-on prescriptions for CBMPs after a specialist has initiated the treatment;
- Streamlining the importation process to make the supply less cumbersome for the NHS, quicker and cheaper for patients, and more efficient for clinicians and pharmacists;
- Creating a compassionate use scheme for terminally-ill patients as an interim programme

9.2 Medium-term changes to provide solid foundations

9.2.1 Training packages for clinicians

There are many ways that clinicians get educated 'on the job' now and there are several ways these could be applicable to cannabinoid science and research. In addition to the training offered by the Royal Colleges, there is a role for specialist private training providers utilising those with years of practitioner experience from other jurisdictions. The newly-created Academy of Medical Cannabis¹⁰¹, founded by Professor Mike Barnes, is one such offering. In addition, there should exist an NHS training package for clinicians which summarises the current state of the law and the permissible products, as well as the process for prescribing CBMPs where supplies are not available in the UK.

Recommendation 28: Create a DHSC-funded training package on CBMPs for NHS clinicians, in partnership with the Royal Colleges and medical professional bodies and associations.

9.2.2 Data collection and a patient registry

For CBMPs, the MHRA has specified that it requires reporting of all suspected adverse reactions (serious and non-serious, whether the product is licensed or unlicensed), including reports of failure of efficacy. Given the limited safety data that is

currently available on the products, the MHRA will be conducting enhanced vigilance activities to support their safe use¹⁰².

We also would suggest that a single patient registry tracks and records all treatments with a CBMP will serve to provide further reassurance for clinicians to prescribe. Giving them confidence that their patients are enrolled in a national effort to better monitor and understand the impact of these medicines. For researchers the advantages are clear, and if created quickly, such a registry would avoid the missed opportunity that Canada experienced, where patient data was not collected systematically from the outset.

Recommendation 29: Create a single patient registry for all those who are prescribed CBMPs – either on the NHS or privately – and use the data as a resource for studying efficacy and side effects, and for designing future studies and novel trial designs.

9.3 Long-term changes to grow an innovative medical cannabis sector

Importation is the most likely route for patients to be supplied with cannabis medicines in the UK for at least the next two years and potentially longer. However as Australia has found, relying on imports alone is not good for patients if it makes the cost of medicines prohibitive. In that system, there is no public health insurance coverage for cannabis products, so registered patients paying privately are forced to pay high prices.

Patients have a right to quality CBMPs that are available to them at a fair price, but that requires an efficient market where there is production at scale and adequate competition. In the long term, it is not in the interests of patients to have access only via the private healthcare route but neither is it realistic that future public supplies for the NHS will be met solely by imported products.

The Government must therefore plan for an economic development agenda to help stimulate the growth of a domestic medical cannabis industry that includes local cultivation, processing and product development. The Department for Health & Social Care should begin now to collaborate with other Whitehall departments on what steps need to be taken to foster a successful domestic industry that can service UK patient demand, and make any legal or regulatory changes to ensure new companies can begin to invest in medical cannabis production in the UK.

9.3.1 Medical Cannabis as part of an Industrial Strategy

The UK Government unveiled their Modern Industrial Strategy in 2017¹⁰³ and as part of the implementation, they are progressing a series of sector deals to form partnerships between government and key industry sectors. The parallel Life Sciences Strategy, authored by Sir John Bell, shows why the health life sciences industry is ripe to embrace medical cannabis. As an industry it is geographically dispersed across the UK and has high productivity.

Among many recommendations, was the ambition to create 2-3 entirely new industries over the next ten years, and cannabis could be one of those industries. Alongside this strategic goal, was a call for increasing the number and speed of clinical trials, and that: “Government should improve the UK’s clinical trial capabilities so that the UK can best compete globally in our support for industry and academic studies at all phases.”

The Health Advanced Research Programme (HARP) sees the NHS as a key pillar to support a more successful life science industry, with the public health system as a unique advantage to the UK that other social insurance systems cannot match. In future, the HARP approach envisages innovation through scientific ventures, clinical trials and new commercial partnerships with the NHS to deliver benefits to patients. The cannabis sector could be a natural fit for such an agenda, providing new drugs and treatment options and potentially cost savings to the NHS in the long-term. And finally, the Government’s Modern Industrial Strategy identifies some macro policy challenges that need addressing, including an ageing society. The potential for cannabis-based medicinal products to alleviate pain and provide new treatment options for cancer and terminal illnesses common in elderly patients, make this sector important to helping the UK meet the challenges of an ageing society.

Legalisation of medicinal cannabis alone creates an opportunity for the private sector that was not there previously. Canada shows how much additional investment and innovation flows in once non-medical legalisation is adopted, alongside significant conventional job creation as labour is attracted into the new legal sector. Even though that path is not one the UK is following, the countries that have legalised medical access have instantly created economic development opportunities in the agriculture and life sciences sectors that the UK should be emulating.

From the industrial hemp sector to supply the CBD market, to cultivation and plant science, new medical

R&D ventures, and the ancillary medtech businesses associated with cannabis extraction, processing and patient care, the government should be actively encouraging all such avenues to help catalyse a domestic cannabis market, bringing jobs and investment to the UK. After all, a sustainable medical cannabis system in the UK cannot rely on imported products indefinitely or patients will be significantly disadvantaged in the long-term.

Recommendation 30: To address affordability and ensure a diverse supply of good quality CBMPs in the next decade, the government should start work on an economic development plan for encouraging and supporting the medical cannabis industry to establish itself in the UK, consistent with the modern industrial strategy and the life sciences sector deal. This should include an economic analysis by HM Treasury of the domestic benefits of a medicinal cannabis market in the UK and what this could support, including the levels of investment, job creation, and tax receipts that such an industry could generate.

9.4 Stages of Maturation for a Medicinal Market in the UK

If the recommendations contained in this blueprint are adopted, there is greater chance that widespread benefits for patients, science, and the economy will be achieved most quickly. Maturation of a medicinal market for cannabis in the UK will take many years, but the stages that define its development are predictable:

1. Familiarisation and Knowledge Investments

- Small number of specialist doctors prescribing
- New clinical trials commissioned – research consortia form
- Education efforts to disseminate existing research knowledge
- Clinician awareness grows

2. Access Liberalised and Private Market Emerges

- More consultants prescribing and becoming confident in CBMPs
- Compassionate use scheme developed and rolled out
- Private clinic growth gives patients new access options
- GP follow-on prescribing helps expand NHS access
- Patient testimony from private clinics encourages wider uptake by NHS clinicians

3. Developing Expertise, Sharing Results

- New Centres of Excellence provide hubs of expertise
- Universities invest and degree courses created
- Cannabinoid pharmacology on healthcare professionals curricula
- Release of new trial data from all the currently registered trials
- Professional networks form, share results among their members

4. Consolidation and Sector-wide Growth

- Mainstream NHS use occurs, helps drive down drug costs
- Vibrant private clinic sector helps deliver innovation
- New industry investments in new medicines and new indications
- Major pharmaceutical ventures launch, and R&D spin-offs occur
- Supply from domestic cultivation/processing by UK companies

9.5 Warning signs - what does failure look like?

Even before a comprehensive strategy is outlined by government, we can identify those scenarios that we need to avoid and which would manifest themselves unless changes of the kind outlined in this report are made. These are the signs that any medicinal cannabis market was not meeting the needs of patients. Given the urgent demands of patients and the high expectations that their needs will be met, the resulting political pressure could lead to demands for more radical action, whether that is general decriminalisation, (as in Portugal), or fully-fledged recreational legalisation, following the recent example of Canada¹⁰⁴.

The UK government remains adamant that the changes to permit medicinal cannabis are not a forerunner to wider legalisation¹⁰⁵ and they are right to see the two issues as qualitatively distinct. However, the following is what failure of a medicinal cannabis market in the UK would look like, and it is highly likely that if the following scenarios were to occur, pressure for wider liberalisation of cannabis laws would peak.

Future Signs that the UK Medicinal Cannabis Market is Failing

Ongoing self-medication by patients unable to access unlicensed products, and/or continued cases of patients travelling abroad to obtain treatments;

Studies will continue to be conducted into patient attitudes and self-report surveys will indicate how people are using cannabis and where they are obtaining it. If they continue to source it from the black market at home, or feel compelled to travel themselves to source it legally from abroad, it will be clear that policies for legal access via health channels are inadequate;

Growing reliance on paid-for prescriptions supplied by private clinics, excluding those of modest means who must rely on the NHS;

As the private clinic market expands to cater for CBMP referrals from private doctors it will pick up some of the slack from patients unable to receive an NHS prescription, however this will generate a two-tier system where access is only possible if a patient can afford to pay (as Australia is demonstrating) - and that would be a failure of policy in causing inequity and going against the principles of the NHS.

Ongoing use of imported products at high prices which prevent the development of a domestic industry;

Even if it is imported unlicensed CBMPs that meet a GMP standard that are the primary products supplied in the first 1-2 years, the consequences will mean inflated prices that reduce uptake by NHS drug purchasers and make costs too prohibitive for many patients, and over-dependence on imported products will retard the growth of a domestic industry that could suppress costs through competition (and the avoidance of import fees on orders).

Persistent low rates of prescribing and no major investments in clinical trials;

Unless prescribing becomes more common, and involves more clinicians across all parts of the UK, patients will not have the access they need where they need it, but clinicians who seek more evidence from clinical trials will only get that if new trials are funded and there are patients enrolled, and if those do not happen, a cycle of poor access and low clinician confidence will persist.

10. Conclusion

In 2018 quickly and quite unexpectedly, the UK joined the ranks of dozens of other developed countries around the world in creating a legal regime for access to cannabis for medical purposes for the first time, and in so doing, officially recognised that the cannabis plant and products derived from it could have therapeutic benefits. It was a landmark movement.

In 2019, it should become the explicit goal of the UK government to create a world class medicinal cannabis system, and to agree the policies and set out the regulations and other steps necessary to achieve that. This world-class system will have distinctly British contours, but it should be defined as one that meets the needs of patients whilst simultaneously catalysing the development of an innovative new medical and science sector for the twenty-first century. Patient demand should drive the creation and expansion of the latter, and not the other way round.

A Vision for the UK

The United Kingdom, drawing on the inherent strengths of its publicly-funded National Health System, top-tier research universities, and world-class life sciences sector, should be the home to the safest, most innovative, and best regulated medical cannabis market anywhere in the world. One that not only improves patient health and reduces suffering, but contributes substantially to scientific progress and the evidence base globally for this new frontier in medicine.

The UK's current system, even in its earliest days and with a lot of potential still unrealised, does not contain the ingredients to deliver that vision. Admittedly this vision is too ambitious to be achieved without a formal strategy and a cross-departmental and multi-sector plan encompassing medicine, academia, industry and the third sector.

And it is not the case that this vision is either disputed, or that it is taken for granted. It is simply that Government ministers have not yet articulated it. Now is the time for them to do so.

Given the barriers to an effective patient access model and a fully-functioning medicinal cannabis market identified in this report, it leaves only two options. Either the vision is not how the law change is seen by Government and it has to be rejected, or alternatively, if rescheduling is accepted as a pivotal start on this journey and the vision is embraced, then changes to the system must be made. The best opportunity to make those changes is in the early years where stakeholders can work together to co-design the right model. An influential White Paper in Australia, published by the University of Sydney predicted where Australia after legalisation, and now the UK, would find itself, and set out the ingredients that are now needed here in the UK:

It is likely that any initial regulation will need to be adjusted as patients' needs change and as scientific and industrial knowledge progresses. This means that crafting regulatory processes and institutions which can accommodate change is important. But frequent and significant regulatory changes can place a heavy burden on any industry. Having policy makers work collaboratively with patients, the medical community and medicinal cannabis producers can help reduce these burdens. This could be achieved through supporting the formation of an industry peak body, and by including industry representatives in the policy development process alongside patient, law enforcement and medical science groups.

The UK needs the same engagement from government and the collaboration across sectors to help reach agreement about the reforms that are needed to improve the system. The goal throughout must be to work on behalf of patients to make good on the promises made by politicians when the law change was first announced. Many groups are already working hard to this end, and new organisations have emerged to address particular barriers, for example clinician education¹⁰⁶.

To its credit, the UK Government has never argued that the final and proper destination has been reached. We await a clearer statement of what the Government hopes to achieve by this reform. However, those like the CMC who are seeking to improve on the current system so that patient needs can be met should take note of the clear signal sent by the Home Secretary when he told Parliament:

These regulations are not an end in themselves..... The Government will monitor the impact of the policy closely as the evidence-base develops and review when the ACMD provides its final advice.

Between now and October 2019, the Government must monitor how the system is operating and be open to all the ways that it could be improved. Patient expectations are high and another year of being

unable to gain legal access will leave thousands angry and exasperated. We hope that this Blueprint provides the necessary recommendations for policy-makers in government to act upon.

Glossary

ABPI	Association of the British Pharmaceutical Industry	ISB	Information Standards Board for Health and Social Care
ACMD	Advisory Council on the Misuse of Drugs	MEE	Medical Education England
ACMPR	Access to Cannabis for Medical Purposes Regulations	MHRA	Medicines & Healthcare products Regulatory Agency
AHCS	Academy for Healthcare Science	MRC	Medical Research Council
AHP	Allied Health Professional	MS	Multiple Sclerosis
ALD	Adrenoleukodystrophy	NAPC	National Association of Primary Care
APPG	All Party Parliamentary Groups	NHS	National Health Service
AQA	Advancing Quality Alliance	NHSI	NHS Institute for Innovation and Improvement
BEIS	Department for Business, Energy and Industrial Strategy	NIC	(NHS) National Innovation Centre
BMA	British Medical Association	NICE	The National Institute for Health & Care Excellence
BMJ	British Medical Journal	NIHR	National Institute for Health Research
BOPA	British Oncology Pharmacy Association	OHE	Office of Health Economics
BPS	British Psychological Society	OSCHR	Office for Strategic Coordination of Health Research
CBD	Cannabidiol	PSA	Professional Standards Authority for Health and Social Care
CICRA	Crohns in Childhood Research Association	PTSD	Post-traumatic Stress Disorder
CMC	Centre for Medicinal Cannabis	RCGP	Royal College of General Practitioners
DCP	Division of Clinical Psychology	RCM	Royal College of Midwives
DHSC	Department of Health & Social Care	RCN	Royal College of Nursing
EHPF	European Health Policy Forum	RCP	Royal College of Physicians
EAA	European Economic Area	RCOA	Royal College of Anaesthetists
EU	European Union	RCP	Royal College of Physicians
FDA	Food & Drug Administration	RCS	Royal College of Surgeons
FPH	Faculty of Public Health	RPS	Royal Pharmaceutical Society
F4A	Families for Access	SAM	Society for Acute Medicine
GMC	General Medical Council	SCIE	Social Care Institute for Excellence
GOSH	Great Ormond Street Hospital	SMAC	Standing Medical Advisory Committee
GPC	General Practitioners Committee	TARN	Trauma Audit and Research Network
GPhC	General Pharmaceutical Council	THC	Tetrahydrocannabinol
HCPC	Health and Care Professions Council	TGA	Therapeutic Goods Administration
HPA	Health Protection Agency	UKCRC	UK Clinical Research Collaboration
HRA	Health Research Authority	UPA	United Patients Alliance
HSCIC	Health and Social Care Information Centre	WHO	World Health Organisation
IHI	Institute for Healthcare Improvement		

End notes

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104 The current Liberal Government made Canada the first country in the G7 to legalise cannabis for non-medical use for adults with the passage into law of the Cannabis Act 2018 (C-45). Legal sales commenced across the country on 17 October. The fully-regulated medical system - ACMPR - remains in place for registered patients, alongside these new recreational laws that permit the sale, purchase and consumption of cannabis by adults and limited home-grow: <https://justice.gc.ca/eng/csj-sjc/pl/charter-charte/c45.html>

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106 One example being the recently founded Academy for Medical Cannabis which is offering an e-learning platform for doctors: <https://taomc.org/>

Support the CMC

The Centre for Medicinal Cannabis (CMC) is a not-for-profit, registered as a company limited by guarantee. Our objective is to advance patients access to medicinal cannabis in the UK. We rely on our members to help support our research and advocacy.

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Following the rescheduling of cannabis-based medicines in November 2018, the UK has joined dozens of other countries in permitting certain doctors to prescribe the drug for the first time. In the UK, it was public and media pressure that made this reform possible but the biggest challenges for patients lay ahead.

As in other countries, medical legalisation is a process and not an event, and education about and support for this new healthcare development needs to be fostered in many areas, including the medical community itself. We need to learn the right lessons from overseas systems, address the knowledge gaps that exist and be prepared to adapt the system to overcome barriers to access.

It is vital that the interests of patients are fully respected and embraced as this reform is implemented, as their experience will dictate whether this reform is successful. In the long-term the UK needs a comprehensive strategy for medicinal cannabis that reflects the importance of this new frontier in healthcare both for patients and clinicians, and to allow the UK to seize the opportunity to build a world-class industry.

This report outlines and evaluates the current medicinal cannabis system, examines the state of the research into cannabinoids as medical treatments, and draws on experience from Canada and Australia to guide policy-makers. It recommends a raft of changes that are needed to guarantee fair and sustainable access, to create a robust and evidence-led regime, and to ensure the political pledges made to patients are met.



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