Public Consultation Paper on Medicinal Cannabis

On 1 November 2018, the law in the United Kingdom changed to allow medicinal cannabis to be used in very limited circumstances. Because of the way that the Isle of Man's drug legislation works, this change affected our law too. Other countries have gone further in allowing the use of medicinal cannabis. In the Isle of Man, we have an opportunity to consider whether we want our approach to medicinal cannabis to remain in line with the UK, or whether we would like an alternative approach. The Isle of Man Government is undertaking a consultation with the public to develop a framework for medicinal cannabis use here.

This document sets out:

- what is meant by medicinal cannabis;
- the current legal framework and the reasons for it;
- current knowledge of the efficacy and safety of medicinal cannabis;
- broader frameworks for medicinal cannabis use from other countries; and,
- links between medicinal cannabis use and illegal supply and the implications of this.

The main options for an approach to medicinal cannabis use here will be described and you will be asked for your views on these. You will also have an opportunity to propose additional or modified options if you so wish.

What is medicinal cannabis?

Medicinal cannabis is cannabis consumed with the objective of reducing the symptoms of a medical condition. This differs from recreational use where the purpose is to achieve a sensation of euphoria or relaxation – often referred to as a 'high'.

Cannabis has been advocated as an alternative or adjunct to conventional medicines in a range of conditions. Cannabis plants contain around 80 – 100 chemical components known as cannabinoids. Two main cannabinoids have been associated with possible therapeutic benefits. These are delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). THC has strong psychoactive effects (it is responsible for the 'high' from cannabis) and may also have analgesic, anti-inflammatory, anti-nausea and anti-emetic properties. CBD does not have psychoactive effects and its therapeutic use is being explored in a range of conditions including epilepsy, inflammatory bowel disease and other conditions.

Current legal framework

1. On 1 November 2018, the scheduling of cannabis-based medicinal products under the Misuse of Drugs legislation changed. As a result of the application of earlier legislation in the Isle of Man, the Statutory Instrument that made this change in England, Wales and Scotland also applies in the Isle of Man.
2. Since 1 November 2018, it has been legal for any doctor on the Specialist Register of the General Medical Council (GMC)[1] to prescribe cannabis-based medicinal products. As these do not have a marketing authorisation from the Medicines and Healthcare Regulatory Agency, it is the responsibility of the prescribing doctor to seek reassurance on the efficacy, safety and quality of the product and to assess the best interests of the patient.

[1] Doctors on the Specialist Register have specialist training in a particular branch of medicine and are mainly consultants working in hospitals or other services, e.g. Mental Health.

3. From 1 November 2018, it has been legal to use cannabis-based medicinal products in clinical trials in the same way as any other Schedule 2 drug. Use would be subject to compliance with the clinical trial governance arrangements followed by the Department of Health and Social Care (DHSC).

4. Doctors on the General Practice Register of the GMC (i.e. GPs) are not able to prescribe cannabis-based medicinal products.

5. Interim guidance from NHS England, the Royal College of Physicians and the British Paediatric Neurology Association (BPNA) has been published.

The guidance limits the use of cannabis-based medicinal products to the following indications:

a) Chemotherapy induced nausea and vomiting,

b) Intractable epilepsy in children, provided the child meets the clinical criteria specified by the BPNA, the type of medicinal cannabis is Epidiolex (a medicine which is already undergoing clinical trials) and it is prescribed by a consultant paediatric neurologist.

There is one cannabis-based medicine which already has a marketing authorisation in the UK and the Isle of Man. This is Sativex, which is licensed for use in spasticity associated with multiple sclerosis. It is not available on NHS prescription here or in England as it is not considered cost-effective. It can be obtained on private prescription. The changes to the legislation do not make any difference to the prescribing of Sativex.

The National Institute for Health and Care Excellence (NICE) will produce a clinical guideline, which is expected to be published in October 2019. This may cover more indications for medicinal cannabis than those included in the interim guidance above.

The reasons for the change in the law were:

1. The UK Home Secretary's desire to respond to concerns raised by families with children with severe, intractable epilepsy who had responded to medicinal cannabis used legally in other countries but who could not access the treatment in the UK; and

2. The desire to make investigating the efficacy of medicinal cannabis through high quality clinical trials easier by moving medicinal cannabis to Schedule 2. This means that trials can be carried out without the need to apply for a license from the UK Home Office – a process that had been perceived as a barrier to trials.

What is the evidence for efficacy and safety of medicinal cannabis?

The most recent comprehensive review, appraisal and evaluation of safety and efficacy in the main indications for medicinal cannabis which we identified, was that undertaken to inform the Australian medicinal cannabis access programme. This work was a systematic 'review of reviews' drawing on previously published systematic reviews and synthesising the findings of the individual studies as well as the conclusions of the original reviews.

The review methodology conformed to international standards regarding identification of papers for inclusion, assessing for bias and evaluating the quality of the evidence. The review included studies published between 1980 and early 2017. Priority was given to randomised controlled trials (RCTs) conducted since 1980, but observational studies (e.g. case reports, retrospective reviews and self-report surveys) were also included. The review was commissioned by the Australian Government Department of Health and was carried out by teams at the Universities of Sydney, New South Wales and Queensland under the coordination of the National Drug and Alcohol Council. The review included five indications for medicinal cannabis: epilepsy in paediatric and young adult patients, multiple sclerosis, nausea and vomiting, palliative care, and chronic non-cancer pain. The review chapters were then used as the basis for the development of evidence-based guidance by working groups which included representatives of all state and territory health departments, clinical staff, consumer groups, healthcare professional organisations and out-patient or primary care networks. The resulting guidelines have been endorsed by the Australian Advisory Council on Medicinal Cannabis.

Three of the review chapters (epilepsy, multiple sclerosis and palliative care) have been published in peer reviewed journals. All the reviews have been published in full on the Therapeutic Goods Administration (the Australian medicines regulatory body) website.[2]

Overall, **across all conditions and indications**, the review concluded that there is only limited evidence for the effectiveness of medicinal cannabis. There is inadequate evidence to determine the appropriate doses of individual cannabis products.

For epilepsy in children and young people, the review found no high quality evidence for the use of medicinal cannabis as an add-on to existing anti-epileptic drugs and no evidence for its use as sole therapy. The identified studies looked at the effectiveness of medicinal cannabis (CBD, oral cannabis extracts, CBD:THC, herbal cannabis, and THC) in reducing seizure frequency/achieving complete seizure freedom, quality of life, tolerability/persistence with treatment and adverse effects. The quality of evidence was graded as low to very low. Data from two RCTs suggested that CBD increased the likelihood of parents self-reporting that their child was 'much or very much improved' on a global rating scale, compared to placebo. Open label trials and observational studies reported just under half of participants achieving a 50% or greater reduction in seizures. The evidence for efficacy of other cannabis products in reducing seizure frequency was much weaker. Three RCTs suggested that CBD may increase the likelihood of complete seizure freedom. In addition, 8.5% of participants in open label trials and observational studies reported complete seizure freedom. CBD was also associated with improved quality of life, as reported by parents, compared to placebo. CBD was associated with a small but statistically significant risk of adverse events compared to placebo – these ranged from diarrhoea, somnolence, change in appetite, change in weight and other relatively minor events through to worsening of seizures, convulsion and status epilepticus. CBD was generally well tolerated with no difference in withdrawals from treatment compared to placebo.[3]

The review of **medicinal cannabis in treating symptoms of multiple sclerosis** concluded that the identified evidence would support a trial of cannabinoids for pain or spasticity in multiple sclerosis (and the use of cannabinoids in the form of Sativex has marketing authorisation for use in spasticity in MS).

2 http://www.tga.gov.au/medicinal-cannabis-guidance-documents

3 Stockings D, et al, 'Evidence for cannabis and cannabinoids for epilepsy: a systematic review of controlled and observational evidence', Journal of Neurology, Neurosurgery and Psychiatry (BMJ Journals), published On-line First, 6 March 2018 (available on-line at: http://jnnp.bmj.com/content/early/2018/02/05/jnnp-2017-317168, accessed 31 May 2018).

The effect sizes were generally small suggesting only modest clinical effects are expected. Adverse events were mild to moderate.[4]

The review of **medicinal cannabis in palliative care** considered its clinical effectiveness in patients with cancer, HIV-AIDS or dementia. The evidence found was inadequate, due to poor quality, to demonstrate effectiveness in cachexia, nausea and vomiting, pain reduction, sleep, mental health symptoms or quality of life in any patient group or for any type of medicinal cannabis. Tolerability and safety appeared similar between medicinal cannabis and placebo although the quality of evidence was too low to draw firm conclusions. The review authors were unable to make recommendations on the clinical utility of medicinal cannabis in palliative care.[5]

For chronic non-cancer pain (CNCP)[6], the review authors and the clinical guideline working group concluded that the available studies were of variable quality, with many being at high risk of bias. Overall, there was evidence of limited efficacy of plant-based and synthetic cannabinoids in some patients with CNCP.
The review authors concluded that they were able to have moderate confidence that CNCP patients receiving medicinal cannabis were more likely to report 30 or 50% reductions in pain compared to those receiving placebo. However, based on analysis of patient outcomes reported in one systematic review, only one person out of every 22-26 treated with medicinal cannabis would get significant pain relief.

The evidence was strongest for nabiximols (Sativex). The majority of studies looked at medicinal cannabis as an add on to existing treatments and the review concluded that medicinal cannabis should not replace current approved first-line treatments for pain. The review identified concerns about common adverse events including nausea, dizziness, drowsiness, effects on mood, cognition and attention and the lack of data on long term use of medicinal cannabis.[7]

Evidence for effectiveness of medicinal cannabis in preventing the onset of nausea and vomiting (including chemotherapy or radiotherapy induced nausea and vomiting in cancer patients, post-operative patients or any other patient group) is limited in quantity and is of moderate quality at best. There is no high quality evidence to support the use of medicinal cannabis in the management of established nausea and vomiting in adults in any clinical situation.

The guidance development working group concluded that high-THC medicinal cannabis products may sometimes be effective for nausea and vomiting but should only be prescribed after the newer standard treatments have failed and where there are no contraindications.

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4 Nielsen S, et al, 'The use of cannabis and cannabinoids in treating symptoms of multiple sclerosis: a systematic review of reviews', Current Neurology and Neuroscience Reports (2018), 18:8 (available on line at: https://link.springer.com/epdf/10.1007/s11910-018-0814-x?author_access_token=ZeOqgmdQ9fo46HTiSRUqvfe4RwlQNchNByi7wbcMAY5dNhl7RxwQKmCh5c-2Htr2LDtbK_2mCECgGpx3_chij2vZ3kL-s01CJW2PNvhNyKWbLvuSJzFrq1dCeXpxm298Jw0gD9aps3jxdeTKbsmNpQ%3D%3D, accessed 31 May 2018).

5 Mucke M, et al, 'Systematic review and meta-analysis of cannabinoids in palliative medicine', *Journal of Cachexia, Sarcopenia and Muscle*, February 2018, Volume 9, Issue 2 (available on-line at: https://onlinelibrary.wiley.com/doi/full/10.1002/jcsm.12273, accessed 31 May 2018).

6 The report included systematic reviews on specific pain conditions: neuropathic pain, fibromyalgia, arthritis, rheumatoid arthritis and reviews that included patients with pain from a variety of causes.

7 The review of cannabis and cannabinoids in chronic non-cancer pain is available on-line here: http://www.tga.gov.au/publication/guidance-use-medicinal-cannabis-treatment-chronic-non-cancer-pain-australia (accessed 31 May 2018).

Adverse effects included dysphoria or depression (13% of patients), hallucinations (6%), paranoid delusions (5%), and drowsiness and dry mouth (proportions not reported).[8]

Other recent reviews: 'Cannabis for Medical Use – A Scientific Review' was published by the Irish Health Products Regulatory Authority in January 2017. The conclusions of this review are in line with those from the Australian one. The HPRA authors noted 'the decision to allow cannabis for medical use is as much a societal and policy decision as a scientific one due to the paucity of robust clinical evidence, the [already established] recreational use of the product and the strong public and patient led demand.'[9]

Further information on adverse effects associated with cannabis is available from studies of recreational use. A recent review has attempted to rank the current evidence for adverse effects and this is reproduced in **Table 1**[10], below:

Table 1: Level of Confidence in the Evidence for Adverse Effects of Marijuana on Health and Well-Being.

Effect	Overall Level of Confidence*
Addiction to marijuana and other substances	High
Abnormal brain development	Medium
Progression to use of other drugs	Medium
Schizophrenia	Medium
Depression or anxiety	Medium
Diminished lifetime achievement	High
Motor vehicle accidents	High
Symptoms of chronic bronchitis (smoked cannabis)	High
Lung cancer (smoked cannabis)	Low

* *The indicated overall level of confidence in the association between marijuana use and the listed effects represents an attempt to rank the strength of the current evidence, especially with regard to heavy or long-term use and use that starts in adolescence.*

The authors of this review note that the association observed between adverse effects and cannabis use does not, of itself, prove causation. With respect to the mental health effects of cannabis use, it is possible that the association may be due to other factors that predispose a person to both cannabis use and mental ill health. However, the finding of similar adverse effects within the clinical studies discussed above tends to support a causal link.

8 The review of cannabis and cannabinoids in nausea and vomiting is available on-line here: http://www.tga.gov.au/publication/guidance-use-medicinal-cannabis-prevention-or-management-nausea-and-vomiting-australia (accessed 31 May 2018).

9 Cannabis for Medical Use – A Scientific Review, Health Products Regulator Authority (Ireland), 31 January 2017, p.4 (available on-line at: https://www.hpra.ie/docs/default-source/publications-forms/newsletters/cannabis-for-medical-use---a-scientific-review.pdf?sfvrsn=7, accessed 31 May 2018).

10 Volkow N, et al, 'Adverse effects of marijuana use', New England Journal of Medicine, 2014, June 5, 370 (23): 2219-2227 (available on-line at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4827335/, accessed 4 June 2018).

THC is the component of cannabis responsible for its psychoactive effects and is also thought to be the component responsible of mental health adverse effects. The THC content of illegal cannabis has been increasing over recent years. A recent study based on sampling of cannabis seized by the UK police during 2015 and 2016 indicated that 94% was the high potency 'skunk' variety which is specifically bred to have high THC levels. The average THC content of the 'skunk' samples was 14.2% although the range varied from 1.9% to 22.5%.[11]

Offering medicinal cannabis within a well-regulated access scheme would offer the opportunity to specify and quality assure the THC and CBD content, set criteria to avoid use in people with a history of psychosis or concurrent mood disorder and ensure consistent advice not to drive whilst on treatment.[12]

Medicinal Cannabis Frameworks from Other Countries

The Australian working groups identified the tension between respecting patient autonomy and maintaining the principle of 'doing no harm'. They have made the clear statement that 'medicinal cannabis is not considered a first-line therapy for any indication' – this means that it should not be considered to be the first treatment given for a disease or condition. They go on to suggest that 'medicinal cannabis may be considered only when registered medicines have been tried and proven unsuccessful in managing the patient's condition.'[13] This principle has been accepted within the Australian medicinal cannabis access scheme which envisages access to a pharmaceutically controlled, locally produced supply, on a doctor's prescription following guidance for the initiation, dosage, monitoring and stopping of treatment. Arrangements for access are subject to both Commonwealth and individual state regulations and, as such, there is some variation between states. In general, prescription is expected to be based on the five indications covered by the evidence review (multiple sclerosis, severe intractable epilepsy in children and young adults, chronic pain, nausea and vomiting and palliative care) and to be by specialist medical practitioners. States may also make arrangements for access beyond these indications and/or by non-specialist practitioners on the basis of individual applications for approval from the relevant state or the Therapeutic Goods Agency.[14] Medicinal cannabis products are not included in the Australian Pharmaceutical Benefits Scheme and the costs must be met by the patient or a third party.[15]

HPRA (Ireland) has made similar recommendations but restricted to a smaller number of indications: spasticity associated with multiple sclerosis resistant to standard therapies (note that Sativex already has a marketing authorisation for this indication); intractable nausea and vomiting associated with chemotherapy, despite use of standard anti-emetic regimes; and severe, refractory epilepsy that has failed to respond to standard anti-convulsant medications. The HPRA envisage that medicinal cannabis in these conditions would only be given under expert medical supervision.[16]

The HPRA approach is similar to the current approach in the UK and Isle of Man.

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11 https://www.nhs.uk/news/mental-health/high-strength-skunk-now-dominates-uk-cannabis-market/, accessed 4 June 2018.

12 https://www.tga.gov.au/publication/guidance-use-medicinal-cannabis-australia-overview, accessed 4 June 2018.

13 Guidance for the use of medicinal cannabis in Australia: Overview, version 1, December 2017: Caveats (available on-line at: https://www.tga.gov.au/publication/guidance-use-medicinal-cannabis-australia-overview, accessed 31 May 2018).

14 For an example of state level guidance, see: Queensland Health, Clinical Guidance for the use of medicinal cannabis products in Queensland, August 2018, available on-line at: www.health.quld.gov.au (accessed 30 November 2018)

15 https://www.tga.gov.au/publication/guidance-use-medicinal-cannabis-australia-overview#cost (accessed 31 May 2018).

16 Cannabis for Medical Use, HPRA, p.4.

The Dutch Office of Medicinal Cannabis acknowledges the levels of evidence available for the major indications (as included within the Australian and Irish reviews, with the addition of tics in Tourette's syndrome and glaucoma) but states that doctors may use their own judgement in deciding with patients on indications for medicinal cannabis and that these are not limited to the major indications alone. Dutch health insurers have discretion to decide which treatments will be reimbursed for patients and different insurers take different approaches to reimbursement for medicinal cannabis.[17]

Other states including Germany and Israel are proceeding along similar lines with cannabis access schemes based on standardised quality assurance and state regulation for all components of the supply chain.

Of the states in the US that have 'legalised' medicinal cannabis, a number have a more inclusive view of what constitutes 'medical marijuana', including protection from prosecution for using marijuana for a 'medical purpose', allowing access to medical marijuana through home cultivation, dispensaries or other methods, allowing access to a variety of strains with less tightly defined or regulated THC:CBD ratios, and allowing smoking or vaporisation of a marijuana product, plant material or extract.[18] (Australia and European access schemes generally exclude smoking as a route of administration due to concerns over the negative health impacts of smoke inhalation).

Links between medicinal cannabis use and the illegal cannabis market

Arguments have been put forward for widening access to medicinal cannabis to reduce demand for illegal supplies.[19]

Potential demand for medicinal cannabis in the UK is considered to be large and we may have similar levels of demand here. As described above, the evidence for the efficacy of medicinal cannabis is weak and the evidence for safety is also limited. Despite this, many patients may wish to access medicinal cannabis for indications for which there is currently less than clear evidence of safety and efficacy. Patients may wish to make their own judgements while better evidence from clinical trials is collected.

The advantages of having a clear framework for prescribing medicinal cannabis, like that in Australia, include ensuring that patients are given, and understand, the current evidence for benefits and harms, and the ability to monitor and evaluate outcomes. The cannabis products used would be quality assured and of defined strength and composition. However, the clinical criteria used in these schemes may mean that patients who want to use medicinal cannabis will not be eligible under the scheme. Some people may, therefore, buy cannabis for self-medication from the illegal market. This means they will continue to fund the harms of organised crime, they will have no guarantee of content or quality and they may risk prosecution for illegal possession. Having a broad framework for accessing medicinal cannabis could reduce demand for and harms from illegal supplies.

17 https://english.cannabisbureau.nl/medicinal-cannabis (accessed 31 May 2018).

18 http://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx#3

19 Stevens, A, 'Medical cannabis in the UK – Patients should not be criminalised for seeking the drug's benefits', British Medical Journal, 2018; 363:k4844 (available on line at: http://dx.doi/org/10.1136/bmj.k4844, accessed 30 November 2018).

Options for the Isle of Man

There are four main options we could consider here:

a) Continue to follow the approach taken in the UK.

At present, that means limiting access to medicinal cannabis to nausea and vomiting caused by chemotherapy and severe, intractable epilepsy in children. Only medical consultants could prescribe.[20] The indications and arrangements for prescription may be widened by the NICE guidance expected in October 2019 but at present we don't know what this might look like. The UK approach also makes it easier to do clinical trials which could mean that more medicinal cannabis products will eventually receive marketing authorisation to make them available on prescription. But we do not know how long this will take. In the short to medium term, very few patients would be likely to get access to medicinal cannabis with this approach.

b) Develop a framework that would support doctors and patients in using medicinal cannabis in line with current best evidence for efficacy and safety.

This could look like the Australian scheme which includes access to medicinal cannabis for chronic pain and palliative care (both currently excluded from the UK approach), as well as chemotherapy-induced nausea and vomiting and severe, intractable epilepsy.[21] Medicinal cannabis would only be permitted for the agreed indications when all existing treatments have been tried and have failed to control the condition. Clear guidance would be provided to doctors (and patients) on dosage and duration of treatment and treatment outcomes would be monitored and evaluated. Prescribing would be by the appropriate specialist consultant. The medicinal cannabis products prescribed through the scheme would be quality assured and manufactured to Good Manufacturing Practice (GMP) standards.

c) Develop a much broader framework in which guidance would be provided to doctors and patients about current evidence but with the decision about when/how to use medicinal cannabis being left with the doctor and patient.

This would mean that medicinal cannabis could be used for any condition when the prescribing doctor and patient, after discussion, consider it appropriate. Specialist doctors and general practitioners could prescribe. This approach is broadly similar to that followed in the Netherlands. It could also include arrangements for reporting outcomes in order to extend our understanding of what works. The medicinal cannabis products prescribed through the scheme would be quality assured and manufactured to Good Manufacturing Practice standards.

d) Remove the need for medicinal cannabis to be prescribed by a doctor.

Quality assured products manufactured to GMP standards could be sold directly to the public through accredited dispensaries.

This scheme could be further extended to allow home cultivation of a specified number of cannabis plants (and potentially also limited to specified seed varieties) for self-medication.

20 Sativex for multiple sclerosis continues to be available on private prescription as was the case before 1 November.

21 Note that Sativex for multiple sclerosis already has a marketing authorisation making it available on prescription. No additional arrangements are therefore required as part of the framework to be developed.

Growing Medicinal Cannabis in the Isle of Man

Options 2, 3 and 4 above are likely to lead to a significant demand for medicinal cannabis and the Isle of Man government will need to develop a regulatory framework to secure sufficient supplies of quality assured product. The Isle of Man could seek to acquire medicinal cannabis products from established manufacturers using cannabis grown in other jurisdictions. However, currently, established manufacturers are finding it difficult to meet the demand resulting from the changes to legislation in a number of jurisdictions. This means that if the government were to introduce a wider framework for access to medicinal cannabis, it may not be possible to secure supplies to meet the demand.

One approach to securing an adequate supply of medicinal cannabis products would be to allow cannabis to be grown on the Island for the production of medicinal cannabis products. A separate regulatory framework could be established to cover the processing of the cannabis into GMP standard medicinal cannabis. Alternatively, herbal cannabis grown in the Isle of Man could be transported to a manufacturer elsewhere for final processing to medicinal cannabis products.

Regulatory frameworks for growing cannabis for the production of medicinal products set standards for cultivation, harvesting and primary processing to produce herbal cannabis suitable for processing into medicinal cannabis products. Good Agricultural Practice (GAP) standards for growing cannabis for medicinal products are intended to ensure that the cannabis:

- is produced hygienically to keep microbiological contamination to a minimum;
- is produced such that negative effects on the plants during cultivation, processing and storage are kept to a minimum; and,
- is produced under conditions that ensure that the therapeutic properties of the end product are constant and reproducible.

GMP guidelines are generic and cover the manufacturing of all pharmaceutically active drugs. There is a European Union guideline which could form the basis of manufacturing regulations here. GAP guidelines could be based on the general rules developed by the Working Group on Herbal Medicines of the European Medicines Evaluation Agency.[22]

Growing quality assured cannabis and processing it into quality assured medicinal products could:

a) secure a supply of medicinal cannabis for Isle of Man use (in line with whatever framework for medicinal cannabis is agreed); and/or

b) create an economic opportunity for growers and manufacturers to supply external markets for medicinal cannabis.

[22] Now the Committee on Herbal Medicinal Products of the European Medicines Agency