National Institute for Health and Care Excellence

Draft

Cannabis-based medicinal products

[E] Evidence reviews for prescribing cannabis-based medicinal products

NICE guideline <number>

Evidence reviews underpinning recommendations 1.5.1 to 1.5.10 in the NICE guideline

[August 2019]

Draft for Consultation

These evidence reviews were developed by NICE Guideline Updates Team

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ISBN:

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Cannabis-based medicinal products: prescribing considerations

Introduction

In November 2018, The Misuse of Drugs (Amendments) (Cannabis and Licence Fees) (England, Wales and Scotland) Regulations 2018, ("the 2018 Regulations") came into force that allowed cannabis-based products for medicinal use to be prescribed when there is an unmet clinical need. Cannabis-based products for medicinal use are classed as schedule 2 controlled drugs under the Misuse of Drugs Regulations 2001 ("the 2001 Regulations"). The rescheduling of cannabis under the Misuse of Drugs legislation enables unlicensed cannabis-based products for medicinal use in humans to be available under the provisions for "special medicinal products'' ('specials') under Regulation 167 of the Human Medicines Regulations 2012. Unlicensed cannabis-based products for medicinal use can be prescribed on a named-patient basis only by doctors listed on the specialist register of the General Medical Council (see 16A of the 2001 Regulations).

The 2018 Regulations do not include Sativex (schedule 4 controlled drug) or nabilone (schedule 2 controlled drug), as these were available for medicinal use before the 2018 Regulations came into force, or cannabidiol (not classed as a controlled drug and unlicensed in the UK at the time of writing). For the purpose of this guideline, to capture Sativex, nabilone and cannabidiol as well as those cannabis-based products for medicinal use as defined by the 2018 Regulations (those rescheduled from schedule 1 to schedule 2 of the 2001 Regulations) all these products will be referred to collectively as cannabis-based medicinal products, unless stated otherwise.

Guidance from the MHRA provides information on supply, manufacture, importation and distribution of unlicensed cannabis-based medicinal products which have been specially manufactured or imported to the order of a registered doctor listed on the GMC's specialist register for the treatment of his/her individual patients. The MHRA guidance also includes a flow chart that summarises how to access these products.

The NICE guideline on controlled drugs provides recommendations for using and managing controlled drugs safely. This includes recommendations for prescribers to review prescriptions for controlled drugs, prescribe an appropriate quantity and to monitor use. NICE has also published a summary on the evidence base on shared decision making. A NICE guideline on shared decision making is in development.

At the time of developing this guideline, most cannabis-based medicinal products were unlicensed. The unlicensed status means there may be limited information about dosing and the products may not have been assessed by the relevant licensing authority against the criteria of safety, quality and efficacy. Prescribing unlicensed cannabis-based medicinal products may present a challenge to healthcare professionals, as the regulated use of these products is at an early stage. In line with the guidance from the General Medical Council (GMC), it is the responsibility of the prescriber to determine the clinical need of the patient and the appropriateness of using unlicensed cannabis-based medicinal products. Supporting information and advice is also available from the GMC.

The aim of the review questions in this chapter was to determine:

- what individual treatment factors need to be taken into account, including obtaining patient consent when prescribing cannabis-based medicinal products to reduce controlled drugs related incidents, including patient-safety incidents?
- what support is needed to help prescribers and patients (or their family members or carers) make decisions about cannabis-based medicinal products to ensure safe and effective use?
- who should prescribe and monitor cannabis-based medicinal products?

Review question 2.1

What individual treatment factors need to be taken into account when considering prescribing and obtaining patient consent for cannabis-based medicinal products?

The review protocol for this review question is in Appendix A. The summary table below formed part of the search to identify studies associated with the individual treatment factors that need to be considered by health care professionals when prescribing cannabis-based medicinal products.

Table 1: Review summary table

Population	Adults, young people, children and babies who are taking: 1. A cannabis-based product for medicinal use that is a preparation or other product, other than one to which paragraph 5 of part 1 of schedule 4 applies, which: • is or contains cannabis, cannabis resin, cannabinol or a cannabinol derivative (not being dronabinol or its stereoisomers) • is produced for medicinal use in humans; and • 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 (MDR 2018 regulations) 2. Synthetic compounds which are identical in structure to naturally occurring cannabinoids such as delta-9-tetrahydrocannabinol (THC) for example dronabinol 3. Licensed products Sativex and nabilone 4. Plant-derived cannabinoids such as pure cannabidiol For the purpose of this review protocol, all the interventions above will be classed as cannabis-based medicinal products. Health professionals who prescribe cannabis-based medicinal products as part of their practice. Specific considerations will be given to: • Young people, children and babies • Pregnant women and women who are breastfeeding • History of hepatic and renal failure • History of addiction or drug misuse
Factors	The following outlines factors for consideration, both by people taking cannabis-based medicinal products and by health professionals who prescribe them: Individual factors, including but not limited to: • Current treatments • Previous treatments • The use of other substances including cannabis-based products • Understanding of how to access of cannabis-based medicinal products • Age such as children and young people • Communication • Comorbidities • Misuse potential by the individual

	• Capacity to consent Treatment specific factors, including but not limited to: • Formulation of the cannabis-based medicinal product Route of administration of the cannabis-based medicinal product
Outcomes	• Prescriber, person and carer outcomes, including but not limited to: ○ Prescriber-specific outcomes: Prescriber, person and carer outcomes - Prescribing errors • Individual-specific outcomes: ○ Prevented addiction or drug misuse ○ Prevented misuse ○ Diversion ○ Satisfaction • Treatment-specific outcomes: ○ Adverse events (including psychosis) ○ Serious adverse events ○ Withdrawal due to adverse events ○ Quality of life

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual (2018). Methods specific to this review question are described in Appendix B.

Declarations of interest were recorded according to NICE's 2018 conflicts of interest policy.

A broad search strategy was used to identify all studies that examined the individual treatment factors that need to be taken into account when considering prescribing cannabis-based medicinal products, the support needed to help prescribers and patients make decisions about medicinal cannabis and who should prescribe and monitor the use of medicinal cannabis.

The review summary table highlighted in Table 1 and Appendix A was used to identify studies which highlighted the support needed for prescribers and patients (or their family members or carers) make decisions about cannabis-based medicinal products to ensure safe and effective use.

Both quantitative and qualitative studies were considered. National guidance for the UK, Europe and other countries with similar health care systems were also taken into consideration. Studies were excluded if they examined the use of:

- Synthetic cannabinoids in schedule 1 of the 2001 regulations,
- Smoked cannabis-based products

Evidence review

Clinical evidence

Included studies and guidelines

From a database of 5,346 quantitative and qualitative studies and systematic reviews, 117 studies were identified as being potentially relevant.

Following full text review of the 117 studies, 3 studies were included. One study was a prospective observational case-series study, 1 was a quasi- experimental study and 1 was a survey. Each study explored a different factor that may need to be considered when prescribing cannabis-based medicinal products:

- the effects of a history of marijuana use on a person's response to medicinal cannabis;
- the incidence of misuse of medicinal cannabis and the factors most associated with misuse;
- the incidence of diversion (removal of controlled drugs for unauthorised use) of medicinal cannabis.

A separate search also looked for guidelines. Out of 16 guidelines identified from the searches, 4 guidelines met the inclusion criteria for this review question. These are summarised in table 2. These guidelines included information that would be useful to consider during a consultation between a prescriber and a person who is considering the use of cannabis-based medicinal products. There were no outcome data to assess whether or not information in the guidelines had any impact on the outcomes of interest for this review question.

Excluded studies and guidelines

List of papers excluded at full text, with reasons, is given in Appendix J.

Guidelines looking at clinical effectiveness or based on regulation from countries other than the UK were excluded at first sift.

Summary of evidence

Table 2: Summary of studies/guidelines included in the evidence review

Reference	Evidence Type	Country	Population	Outcomes/findings
Ware 2018	Prospective case-series	Canada	People who recently initiated oral cannabinoid therapy	• Misuse of CBMP - based on psychiatric history and daily use of alcohol, tobacco or herbal cannabis
Kirk 1999	Quasi- experimental study	USA	Frequent and infrequent users of marijuana	• Adverse events (feeling high) • Adverse events (sedation) • Satisfaction (VAS scale of "like" effects)
Notcutt 2013	Survey	UK	Patients and carers of patients with long-term use of Sativex	• Diversion (medication sharing) • Diversion (losing medication)

Reference	Evidence Type	Country	Population	Outcomes/findings
Clinical guidance: for the use of medicinal cannabis products in Queensland, Australia (2018)	International guidance	Australia	Medical practitioners who choose to prescribe medicinal cannabis	Provides information about cautions, contraindications and considerations when prescribing cannabis-based medicinal products.
Information for healthcare practitioners - medical use of cannabis (2016) Access to cannabis for medical purposes regulations - daily amount fact sheet	International guidance/factsheet	Canada	Healthcare professionals and patients	Provides information about equivalency factor to take into account.
Information for Health Care Practitioners - Cannabis (marihuana, marijuana) and the cannabinoids. Government of Canada 2018	International guidance	Canada	Healthcare professionals	Provides information about cautions, contraindications and considerations when prescribing cannabis-based medicinal products.
An Roinn Siainte, Department of Health (2018). Clinical guidance on cannabis for medical use	International guidance	Ireland	Healthcare professionals using cannabis-based products (as defined in their guidance) for the treatment of patients under their care	Summarises treatment factors to take into considerations deciding to use cannabis-based medicinal products (this is based on the Queensland, Australian guideline)

See Appendix E for full evidence tables and Appendix F for evidence table on the guidance.

Table 3: Summary of key findings from prospective observational studies

Theme	Study	n	Factor	p value	Effect size (95%CI) (where applicable)
Factors associated with misuse of CBMP	Ware 2018	265	**Factors not significantly associated with problematic CBD use**		
			Demographic variables (age, sex, race, marital status, income, education)	p>0.05	
			Use of prescription drugs (opioids, antidepressants, anti-convulsants or sedatives)	p>0.05	
			Daily alcohol use	p>0.05	
			Factors significantly associated with problematic CBD use		
			Tobacco use	p<0.05 (ABC score)	*RR<1 favours daily smokers* RR 2.43 (1.15, 5.14)
			Psychiatric history	p<0.001 (COMM score) p<0.05 (ABC score)	
			Daily herbal cannabis use	p<0.05 (ABC score)	*RR<1 favours herbal cannabis users* RR 2.23 (1.01, 4.92)
			DAST-20 score	p<0.001 (ABC score)	
DAST: Drug Abuse Screening Test					

Table 4: Summary of key findings from cross-over studies

	Study	n	Rating	Dose	Results
Effect of history of marijuana use on responses to oral delta9-THC	Kirk 1999	21	**Adverse events**		
			Feeling 'high'	7.5 mg	Increased rating for feeling 'high' in frequent users but not infrequent users (DEQ score)
				15 mg	Increased rating for feeling 'high' in frequent and infrequent users (DEQ score)
			ARCI Marijuana scale	7.5 mg	Increased score in frequent users but not infrequent users
				15 mg	Increased score in frequent and infrequent users

	Study	n	Rating	Dose	Results
			Sedation	15 mg	Significantly more sedative-like effects for infrequent than frequent users (ARCI PCAG scale) Greater sedation effects for infrequent than frequent users but difference was non-significant (VAS)
			Satisfaction		
			'Like' effects	15 mg	Significantly lower 'like' effects for infrequent users but frequent users did not differ from placebo (VAS)
ARCI: Addiction Research Center Inventory; PCAG: DEQ: Depressive Experiences Questionnaire; Pentobarbital Chlorpromazine Alcohol Group; VAS: Visual Analogue Scale					

Table 5: Summary of key findings from cross-sectional surveys

Theme	Study	Population	Summary
Diversion of CBMP	Notcutt 2013	Patients and carers of patients with long-term use of Sativex	• Three of 124 patients (2.4%) reported sharing their medication • No patients reported losing their medication

Table 6: Summary of international guidelines

Title	Population	Summary of guidance
Clinical guidance: for the use of medicinal cannabis products in Queensland, Australia (2018)	Medical practitioners who choose to prescribe medicinal cannabis	The guidance includes the following treatment factors to consider: • Tetrahydrocannabinol is generally not appropriate for patients who: ○ have a personal history or strong family history of psychosis or have concurrent active mood or anxiety disorder ○ are pregnant, planning on becoming pregnant, or breastfeeding ○ have unstable cardiovascular disease. • When commencing treatment, in addition to usual presenting complaint and history taking during consultation, particular attention to be given to:

Title	Population	Summary of guidance
		○ current medical history: cardiovascular, liver and renal disease ○ psychological and psychiatric history such as mental illness, particularly schizophrenia ○ risk behaviours associated with drug dependence (nicotine/alcohol dependence, previous/current cannabis use, previous illicit drug use). • Contraindications are summarised in the guideline and include hypersensitivity to cannabis, pregnancy/breastfeeding, severe and unstable cardio-pulmonary disease, risk factors for cardiovascular disease and previous psychotic or concurrent active mood disorder or anxiety disorder. Other considerations include: tetrahydrocannabinol use in people under 25 years and paediatric and elderly patients.
Information for healthcare practitioners - medical use of cannabis (2016) Access to cannabis for medical purposes regulations - daily amount fact sheet	Healthcare professionals and patients	This guidance/information provides the following information about: • Doses for different formulations and how long it takes to work are summarised in this guidance. There is an important note about equivalency factor (the quantity of product other than dried marijuana [for example, fresh marijuana or cannabis oil] that is equivalent to one gram of dried marihuana) and how it depends on the production method, form of supply and the tetrahydrocannabinol/cannabidiol yield. The licensed producers will provide this information on the label. The information about the equivalency factor will also be available on the licensed producer's website.
Information for healthcare practitioners - cannabis (marihuana, marijuana) and the cannabinoids. Government of Canada 2018	Healthcare professionals	The guidance includes the following treatment factors to consider: • Contraindications that apply to those considering using prescription cannabinoid-based therapies (such as nabilone, nabiximols or dronabinol) also apply to those considering using cannabis, especially tetrahydrocannabinol-predominant cannabis. • The risk/benefit ratio of using cannabis (especially tetrahydrocannabinol-predominant cannabis) should be carefully evaluated in people with the following because of individual variation in response and tolerance to its effects, as well as the difficulty in dosing: ○ under the age of 25, unless the benefit/risk ratio is considered by the physician to be favourable. ○ with history of hypersensitivity to any cannabinoids or with severe cardiovascular or cerebrovascular disease, severe liver or renal disease or psychiatric disorders should not use cannabis ○ cautioned in people with a history of substance abuse, including alcohol abuse; in patients receiving concomitant therapy with sedative-hypnotics or other psychoactive drugs because of the potential for additive or synergistic central nervous system (CNS) depressant or psychoactive effects.

Title	Population	Summary of guidance
		○ cannabis is not recommended in women of childbearing age not on a reliable contraceptive, as well as those planning pregnancy, and those who are pregnant, or breastfeeding. • Supervision is advised when administration is initiated and should be monitored on a regular basis. • Tolerance, and psychological and physical dependence can occur with prolonged use of cannabis. Drug interactions involving cannabis and cannabinoids can be expected to vary considerably in their clinical significance given the wide variability in products, potencies, ratios of tetrahydrocannabinol and canabidiol, doses, routes of administration, populations using cannabinoids and other factors. However, some of the more clinically significant interactions may occur when cannabis is taken with other CNS depressant drugs such as sedative-hypnotics or alcohol.
An Roinn Sláinte, Department of Health, Ireland (2018). Clinical guidance on cannabis for medical use	Healthcare professionals using cannabis-based products (as defined in their guidance) for the treatment of patients under their care	The guidance includes the following treatment factors to consider: • medical history to include cardiovascular disease, liver disease and renal disease • psychological and psychiatric history that include: ○ risk behaviours associated with drug dependence — while previous cannabis use may not be a contraindication, care should be taken to manage the risk of dependence ○ child safety considerations ○ employment, especially where it involves driving or operating machinery ○ risk of falls (in older patients) ○ family responsibilities, such as caring for children. • Contraindications: ○ history of hypersensitivity to any cannabinoid ○ severe and unstable cardio-pulmonary disease or risk factors for cardiovascular disease ○ current, active drug dependence, including illicit drugs, alcohol, and prescription medications ○ breastfeeding. • Warnings and precautions are summarised in the guidance and include: ○ People aged 18 years old and under because of the potential effects of tetrahydrocannabinol on the developing brain ○ Personal or family history of schizophrenia or any psychotic disorder ○ Severe liver or renal disease ○ Previous drug dependence, including illicit drugs, nicotine, alcohol and prescription medications

Title	Population	Summary of guidance
		○ Pregnancy ○ Concomitant medications, especially sedatives such as opioids and benzodiazepines and medicines metabolised by cytochrome p450 isoenzymes ○ Whether the patient is elderly — as metabolism in the elderly is slower it is likely they will be more sensitive to the pharmacological effects of cannabis. Treatment should therefore be initiated at low doses and titrated slowly. ○ Drug-drug Interactions are listed in detail in the guideline. • Patients transferred from one cannabis-based medicine or product to another may require to be titrated again, depending on the composition of the medicine or product. • Gradual withdrawal of treatment is recommended, unless abrupt discontinuation is required for safety reasons.
Note the term cannabis-based product was mainly defined in the guidelines above as an unauthorised product (such as not having a marketing authorisation)		

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Quality assessment of clinical studies and guidelines included in the evidence review

The cross-sectional survey was critically appraised using the Centre for Evidence-Based Management (CEBMa) checklist. The overall quality of surveys was assessed based on potential selection bias, response rate achieved and validity and reliability of the questionnaire. This study was rated as directly applicable to the research question but at high risk of bias due to the use of unvalidated surveys and a low survey response rate.

The IHE Quality Appraisal Checklist was used for critical appraisal of the observational case-series study. This was rated as moderate risk of bias because of the use of patient-reported, subjective, outcomes. This was rated directly applicable to the research question.

The ROBINS-I tool was used for critical appraisal of the quasi- experimental study. This was rated as serious risk of bias because assignment to the frequent or infrequent user study arm was based on self-reported use of marijuana. This study was considered partially applicable as it examined the use of tetrahydrocannibinol in healthy people rather than people with a condition that may benefit from the use of cannabis-based medicinal product.

The quality of the guidelines were assessed using the international criteria of quality for guidance development, as outlined by the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument.

See Appendix E for full CEBMa critical appraisal checklist.

See Appendix I for full AGREE II checklist

Economic evidence

A global health economic search was conducted to identify economic evidence. No economic studies were identified which were applicable and no full-text copies of articles were requested.

Evidence statements

Effects of history of smoked cannabis use on responses to delta9-tetrahydrocannabinol (THC)

One non-randomised cross-over study at high risk of bias from the USA compared the effects of delta9-THC in people who reported frequent use of smoked cannabis (used at least 100 times for a minimum of 1 year and currently using at least 2 times per month) and people who reported infrequent use (used smoked cannabis less than 10 times and no use in the past 4 years).

- At a dose of 7.5 mg THC, frequent users reported increased ratings of feeling ‘high’ compared to placebo. No difference in feeling ‘high’ was found between 7.5 mg THC and placebo for infrequent users.
- At a dose of 15 mg THC, both frequent and infrequent users reported increased ratings of feeling ‘high’ compared to placebo. Infrequent users also reported more sedative-like effects and fewer ‘like’ effects. No difference was found between 15 mg THC and placebo for sedative-like effects or ‘like’ effects for frequent users.

Diversion for people using Sativex

One cross-sectional survey at high risk of bias from the UK asked people who had received at least 2 prescriptions of Sativex within the previous 16 weeks about their use of the medication including whether they had ever shared or lost their medication. This study found that 2.4% of people using Sativex for a range of medical conditions (MS, neuropathic pain, cancer, other) reported sharing their medication. No participants reported losing their medication.

Predictors of problematic medication use for people using Sativex or Nabilone

One prospective observational study at moderate risk of bias from Canada examined the use of CBMP in people who had started using either Sativex or nabilone within 14 days of the beginning of the study. The influence of a variety of factors were analysed to identify any markers for potential use of CBMP. The study found that:

- People who smoke tobacco or herbal cannabis each day are more likely to report problematic use of Sativex or nabilone
- People with a history of psychiatric problems are more likely to report problematic use of Sativex or nabilone
- The use of other prescription drugs or daily use of alcohol were not significantly associated with problematic use of Sativex or nabilone.

Treatment factors to take into account when prescribing cannabis-based medicinal products

Moderate quality Irish guidance and Australian, Queensland state guidance suggests that there are cannabis specific treatment factors that need to be taken into account when considering the use of cannabis-based medicinal products.

Moderate quality Canadian guidance and a low-quality Canadian factsheet also suggests that there are cannabis specific treatment factors that need to be taken into account when considering the use of cannabis-based medicinal products.

The committee's discussion of the evidence

The outcomes that matter most

The committee agreed that issues such as the potential for misuse, diversion and adverse events are important when deciding if a person should be prescribed cannabis-based medicinal products.

The quality of the evidence

Clinical studies examined factors that should be considered when prescribing cannabis-based medicinal products. Evidence was rated as moderate to high risk of bias due to issues such as the use of non-validated surveys, low response rates and assignment to study arms based on participant's self-reported use of marijuana. No research considered the use of cannabis-based medicinal products in children.

Guidance was low to moderate quality and did not have any outcome data. For all included guidelines, some of the AGREE II items were not applicable and so the scoring was limited to only those items that were relevant to the guideline under review. The committee highlighted that the sources of information for some of the guidance was unclear, with different guidelines often containing similar information and based on iterations of other international guidelines. Questions over the quality

of the guidance and sources of the information meant that the committee chose not to use them solely as the basis for their own recommendations. Instead they also incorporated the findings from the clinical studies and the reviews into the effectiveness and safety of cannabis-based medicinal products for nausea and vomiting, chronic pain, epilepsy and spasticity.

Each of the 3 clinical studies addressed a different factor to consider when prescribing cannabis-based medicinal products. One compared the effects of THC on frequent and infrequent users of smoked cannabis. However, this study examined the response to THC in healthy participants rather than a population who might be prescribed cannabis-based medicinal products. The committee also questioned the criteria for frequent marijuana use, stated as the use of cannabis at least twice per month. The committee considered this to be relatively infrequent use. As such, they were not confident that the findings would accurately reflect the effects of THC on a person who uses marijuana on a more regular basis. In addition, this study reported change as an increase or decrease in the score for a number of scales, but no additional statistical information was included. This meant the extent of the difference between frequent and infrequent users could not be determined.

One study investigated factors associated with problematic use of cannabis-based medicinal products (Sativex and nabilone) and included a 12-month follow-up period. This was the only evidence into longer-term use of cannabis-based medicinal products. However, the results of association tests were reported as a univariate analysis, which does not allow for assessment of potential mediating and modifying effects, with no further information and the only statistical information provided for the majority of outcomes were p values. This meant that the strength of the association between different factors could not be determined.

Another study investigated the use of Sativex as an unlicensed medication in the UK, including the potential for misuse or diversion. This study was the only UK study and therefore the most applicable to the NHS. However, patients only needed to have been prescribed Sativex twice within 16 weeks to be included and results were obtained used a survey which may not have been validated.

The committee were keen to highlight the low quality of current evidence which examines only a small number of cannabis-based medicinal products, mostly with short-term follow up. There are a wide range of cannabis-based medicinal products that are available, most currently unlicensed, and there was concern that the recommendations may be used to inform the use of these products in addition to those that have been used in existing research. Little is known about the use, effectiveness and potential harms of these other products and so future research is needed to increase the understanding of the effects of these products as they become available.

Benefits and harms

These recommendations will help to provide clinicians with guidance when determining who is likely to benefit from the use of cannabis-based medicinal products. Providing guidance on what factors to consider when prescribing these products will help to give both prescribers and patients more clarity when considering their effectiveness and potential adverse events.

The committee stated that there is currently confusion around the use of cannabis-based medicinal products, including the risk of adverse events and the potential for misuse. These recommendations may help clinicians to identify when a patient may be at higher risk of adverse events or have greater potential for misuse. However, the committee did not feel that they could provide more specific advice on which factors

should be considered, because evidence is currently limited and relatively low-quality, particularly for long-term effects. The committee agreed that more research is needed to identify the factors that indicate if someone will respond to cannabis-based medicinal products and the potential contraindications for their use.

None of the existing research has examined the effects of cannabis-based medicinal products in children. However, the committee decided that an additional recommendation for children was important as there may be potential harmful effects on brain development which may not hold the same concerns for adults. This recommendation was based on the committee's clinical knowledge and experience in relation to the concerns over the effects of these products.

A key concern when making the recommendations was that if they were too stringent then people who may benefit the most from these products may be excluded from their use. For instance, if previous use of cannabis was stated as an exclusion criterion then people who have used over-the-counter medications such as cannabis-based food supplements may also not be eligible for a prescription. This led the committee to state that factors such as current cannabis use should be considered but should not be a reason to exclude people from treatment.

Cost effectiveness and resource use

Cost effective analysis was not conducted as part of this review question.

Other factors the committee took into account

A concern of the committee was how little is currently known about the use of cannabis-based medicinal products. There is limited knowledge about the factors that determine whether a person will respond to these products and little research has examined the potential for adverse events, misuse or diversion. In particular, there is very little understanding of the long-term effects of using cannabis-based medicinal products. The committee agreed that the lack of research meant they could not make stronger recommendations on the factors to consider when prescribing. However, they decided that making some recommendations was important to provide clinicians with guidance given the current confusion over the use and potential effects of cannabis-based medicinal products.

The committee also highlighted that issues such as tolerance and the potential for addiction are likely to be key concerns for patients if they are prescribed cannabis-based medicinal products. However, the majority of current research examines these issues in relation to the use of illicit cannabis rather than products that would be available for prescription on the NHS. The committee agreed that while this information could be used to inform future research, the results could not be extrapolated to cannabis-based medicinal products.

This evidence review supports recommendations 1.5.5 , 1.5.6 and 1.5.7 .

Review question 2.2

What support is needed to help prescribers and patients (or their family members or carers) make decisions about cannabis-based medicinal products?

The review protocol for this review question is in Appendix A. The summary table below formed part of the search to identify studies associated with support needed to help prescribers and patients, including their families and carers, about cannabis-based medicinal products.

Table 7: Review summary table

Population	Adults, young people, children and babies who are taking: 1. A cannabis-based product for medicinal use that is a preparation or other product, other than one to which paragraph 5 of part 1 of schedule 4 applies, which: • is or contains cannabis, cannabis resin, cannabinol or a cannabinol derivative (not being dronabinol or its stereoisomers) • is produced for medicinal use in humans; and • 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 (MDR 2018 regulations) 2. Synthetic compounds which are identical in structure to naturally occurring cannabinoids such as delta-9-tetrahydrocannabinol (THC) for example dronabinol 3. Licensed products Sativex and nabilone 4. Plant-derived cannabinoids such as pure cannabidiol For the purpose of this review protocol, all the interventions above will be classed as cannabis-based medicinal products. Health professionals who prescribe cannabis-based medicinal products as part of their practice. Specific considerations will be given to: • Young people, children and babies • Pregnant women and women who are breastfeeding • History of hepatic and renal failure • History of addiction or drug misuse
Areas of Interest	Areas of interest, including but not limited to: • Patient information leaflets • Medicines quality assurance information • Provision of information regarding dose (including micro-dosing and tapering) • Education programmes (this includes understanding publicly available information) • Support around access • Shared decision aids and other decision support tools • The use of policies on prescribing and taking cannabis-based medicinal products • Multi-disciplinary team involvement • Monitoring tools

	• Safeguarding
Outcomes	• Prescriber, individual and carer outcomes, including but not limited to: ○ Adherence and compliance ○ Experience and satisfaction ○ Improvement in management, including: tailoring treatment or care to the individual's needs, patient empowerment, making an informed decision • Treatment-specific outcomes, including but not limited to: ○ Quality of life ○ Adverse events ○ Serious adverse events ○ Withdrawal due to adverse events

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual (2018). Methods specific to this review question are described in Appendix B.

Declarations of interest were recorded according to NICE's 2018 conflicts of interest policy.

A broad search strategy was used to identify all studies that examined the individual treatment factors that need to be taken into account when considering prescribing cannabis-based medicinal products (RQ2.1), the support needed to help prescribers and patients make decisions about medicinal cannabis (RQ2.2) and who should prescribe and monitor the use of medicinal cannabis (RQ3).

The review summary table highlighted in Table 1 and Appendix A was used to identify studies which highlighted the support needed for prescribers and patients (or their family members or carers) make decisions about cannabis-based medicinal products to ensure safe and effective use.

Both quantitative and qualitative studies were considered. National guidance for the UK, Europe and other countries with similar health care systems were also taken into consideration. Studies were excluded if they examined the use of:

- Synthetic cannabinoids in schedule 1 of the 2001 regulations
- Smoked cannabis-based products
- Smoked cannabis-based products
- Studies which do not report cannabinoid constituents.

Evidence review

Clinical evidence

Included studies and guidelines

From a database of 5,346 quantitative and qualitative studies and systematic reviews, 54 studies were identified as being potentially relevant. One additional study [Malouff 2013] was identified by examining the reference list for Malouff 2016.

Following full text review of the 55 studies, 6 studies were included. Five studies were cross-sectional surveys and 1 study was a qualitative study formed of a semi-structured interview. In terms of areas of interest explored in the studies:

- All 6 studies explored education/ training needs

A separate search also looked for guidelines. Out of 16 guidelines identified from the searches, 3 guidelines met the inclusion criteria for this review question. These are summarised in table 2. These guidelines included information that would be useful to consider during a consultation between a prescriber and a person considering the use of cannabis-based medicinal products.

Excluded studies and guidelines

List of papers excluded at full text, with reasons, is given in Appendix J.

Guidelines looking at clinical effectiveness or based on regulation from countries other than the UK were excluded at first sift.

Summary of evidence

Table 8: Summary of studies/guidelines included in the evidence review

Reference	Evidence Type	Country	Population	Outcomes/findings
Carlini 2017	Cross-sectional survey	USA	medical doctors (MDs), physician assistants (PAs), osteopathic physicians (DOs), osteopathic physician assistants (OAs), naturopathic physicians (NDs), advanced registered practitioners (ARNPs), registered nurses (RNs), licensed nurses (LNP) and pharmacists	Educational/ training needs
Ebert 2015	Cross-sectional survey	Israel	Physicians of the following specialities: oncology, pain medicine, rehabilitation, psychiatry and neurology	Educational/ training needs
Hwang 2016	Cross-sectional survey	USA	Pharmacists practicing in Minnesota	Educational/ training needs Source of education Method of education delivery

Reference	Evidence Type	Country	Population	Outcomes/findings
Isaac 2016	Semi-structured interviews Thematic analysis	Australia	Pharmacists, [practicing, academic and representatives of professional organisations (LRPO)]	Educational/ training needs
St-Amant 2015	Cross-sectional survey	Canada	Physicians (family physicians and specialists) practicing in south-western Quebec	Increasing comfort level with prescribing
Zylla 2018	Cross-sectional survey	USA	Medical oncologists, oncology nurse practitioners, oncology physician assistants	Method of education delivery
Clinical Guidance: for the use of medicinal cannabis products in Queensland, Australia (2018)	International guidance	Australia	Medical practitioners who choose to prescribe medicinal cannabis	Provides a framework that can be used during consultation when deciding to use cannabis-based medicinal products
Information for Health Care Practitioners - Medical Use of Cannabis (2016) Access to Cannabis for Medical Purposes Regulations - Daily Amount Fact Sheet (Dosage)	International guidance/factsheet	Canada	Healthcare professionals and patients	Provides dosing information when starting cannabis-based medicinal products with limited dosing information
An Roinn Siainte, Department of Health (2018). Clinical Guidance on Cannabis for Medical Use	International guidance	Ireland	Healthcare professionals using cannabis-based products for the treatment of patients under their care	Provides a framework that can be used during consultation when deciding to use cannabis-based medicinal products (this is based on the Queensland, Australia guideline below)

See Appendix E for full evidence tables and Appendix F for evidence table on the guidance.

Table 9: Summary of key themes from qualitative study

Review theme and subthemes	Studies contributing	Population	Summary	Supporting statements
Educational/ Training needs				
Professional training and public awareness	Isaac 2016	Pharmacists (practising, academic and representatives of professional organisations)	Pharmacists stated that there is a need for training and learning opportunities for pharmacists around medicinal cannabis. They also highlighted that pharmacists can play a role in public awareness as they can further educate the public about medicinal cannabis.	*"There will need to be education campaigns for pharmacists, consumers and probably all healthcare professionals around this issue when cannabis is legalised"* *"Pharmacists have a great capacity…to learn and then disseminate information...to educate the public."*

Table 10: Summary of key findings from cross-sectional surveys

Theme	Study	Population	Summary
Educational/ training needs	Hwang 2016	Pharmacists practising in Minnesota	Respondents were most interested in learning about the state-specific rules and regulations around medical cannabis (87%), the pharmacotherapy of medical cannabis (88%) and available types and forms of products on the market (82%).
Source of education	Hwang 2016	Pharmacists practising in Minnesota	Pharmacists who took part in the survey preferred information on medical cannabis to be delivered by the Minnesota Board of Pharmacy (62%)
Method of education delivery	Hwang 2016	Pharmacists practising in Minnesota	Pharmacists who took part in the survey preferred information to be delivered through email (56%) and online courses (48%)

Increasing comfort level with prescribing	St-Amant 2015	Physicians (family physicians and specialists) practising in south-western Quebec	When asked about factors that could increase the comfort level with prescribing cannabinoids for chronic non-cancer pain, physicians mentioned attending continual medical education (68.4%), having guidelines and algorithms that included cannabinoid prescribing (67.1%) and having more clinical data and new studies (50%).
Method of education delivery	Zylla 2018	Medical oncologists, oncology nurse practitioners, oncology physician assistants	When asked about what additional education participants wanted, respondents preferred written summaries, online learning programs and symposiums or conferences.
Educational/ training needs	Ebert 2015	Physicians of the following specialities: oncology, pain medicine, rehabilitation, psychiatry and neurology	Physicians agreed unanimously that more education on medical cannabis should be available to physicians (88.8%). They also agreed that physicians who are certified to recommend medical cannabis treatment should undergo specific training and broaden their knowledge on this subject before being certified (90.2%).
Educational/ training needs	Carlini 2017	Medical doctors (MDs), physician assistants (PAs), osteopathic physicians (DOs), osteopathic physician assistants (OAs), naturopathic physicians (NDs), advanced registered practitioners (ARNPs), registered nurses (RNs), licensed nurses (LNP) and pharmacists	All respondents agreed that continual medical education on medical cannabis should be available (96.1%), medical cannabis should be included in graduate medical curricula (87.2%), clinicians should receive training prior to recommending medical cannabis (86.4%) and medical cannabis should be included in undergraduate medical curricula (77.3%). Similar results were identified when data were stratified by respondents who had authorised medical cannabis, those who had not and those who were not eligible to authorise medical cannabis.

Table 11: Summary of international guidelines

Title	Population	Summary of guidance
Clinical Guidance: for the use of medicinal cannabis products	Medical practitioners who choose to	The guideline provides a framework to consider during consultation with a patient to support decision making: • Medical practitioners should ensure they access available literature to determine the efficacy and safety of the product they wish to prescribe

Title	Population	Summary of guidance

in Queensland, Australia (2018)	prescribe medicinal cannabis	• Initial treatment plan should include:
		  ○ treatment goals
		  ○ risk management processes
		  ○ monitoring arrangements
		  ○ exit strategy
		• Dosing is highly individualised and relies on titration of the product, regardless of the cannabinoid content ('starting low and going slow').
		• Patients with no prior experience of cannabis who are initiating therapy for the first time are cautioned to begin with a very low dose, such as 1mg daily THC or lower, and to immediately stop the product if they have any side effects.
		• Doses should be increased slowly, preferably weekly, until a satisfactory dose is reached.
		• When initiating therapy patients should be advised to have someone with them should they experience any adverse effects. All first doses should be given in the evening to assist with management of side effects.
		In the absence of studies using orally ingested oils, comparison with pharmaceutical products provides the best estimate of dosing levels.

Information for Health Care Practitioners - Medical Use of Cannabis, Canada, (2016) Access to Cannabis for Medical Purposes Regulations - Daily Amount Fact Sheet (Dosage)	Healthcare professionals and patients	This provides information about dosing that would be useful to a prescriber when starting cannabis-based products with limited dosing information: • Dosing remains highly individualised and relies to a great extent on titration. The suggested approach to dosing in the absence of evidence is to "start low and go slow." • Patients with no prior experience with cannabis and initiating such therapy for the first time are cautioned to begin at a very low dose and to immediately stop therapy if unacceptable or undesirable side effects occur. • When beginning therapy with cannabis it is best to try to have someone trusted with the person taking the cannabis product in case of an adverse effect and medical attention is needed.
An Roinn Sláinte, Department of Health, Ireland (2018). Clinical Guidance on Cannabis for Medical Use	Healthcare professionals using cannabis-based products (as	The guideline provides a framework to consider during consultation with a patient to support decision making: • Risks, benefits and alternative of the use of cannabis • Minor patient and parental/guardian consent • Initial treatment plan and what this includes: ○ treatment goals

Title	Population	Summary of guidance
	defined in their guidance) for the treatment of patients under their care	○ duration of treatment and when it should be stopped ○ dosing when starting treatment and titrating if continuing
Note: the term cannabis-based product was mainly defined in the guidelines above as an unauthorised product (such as not having a marketing authorisation)		

1

Quality assessment of clinical studies and guidelines included in the evidence review

Cross-sectional surveys were critically appraised using the Centre for Evidence-Based Management (CEBMa) checklist. GRADE approach was not utilised for survey data due to the nature of the evidence.

Five cross-sectional survey was included in this review. The overall quality of surveys was assessed based on potential selection bias, response rate achieved and validity and reliability of the questionnaire.

These cross-sectional surveys were also deemed as being partially direct as 3 studies did not explicitly state which cannabis-based products were being prescribed and the 1 study included medical marijuana.

With regard to the qualitative study, CASP qualitative checklist was used to quality assess individual studies. GRADE CerQual was used to assess the confidence we have in the summary findings of each of the identified themes. Moderate concerns were identified in terms of methodological limitations, primarily unclear reflexivity. The study also demonstrated serious concerns regarding adequacy of the data.

The quality of the guidelines were assessed using the international criteria of quality for guidance development, as outlined by the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument.

See Appendix E for full CEBMa critical appraisal checklist.

See Appendix H for full GRADE CERQual tables.

See Appendix I for full AGREE II checklist

Economic evidence

A global health economic search was conducted to identify economic evidence. No economic studies were identified which were applicable and no full-text copies of articles were requested.

Evidence statements

The evidence statement in this section reflect the evidence on the support needed to help prescribers and patients make decisions about cannabis-based medicinal products.

Clinical evidence

Educational/ training needs

One cross-sectional study of low-quality surveyed physicians who specialised in oncology, pain medicine, rehabilitation, psychiatry and neurology in Israel. Evidence showed that physicians agreed that more education on medical cannabis should be available to physicians. Evidence also showed that physicians agreed that physicians who are certified to recommend medical cannabis treatment should undergo specific training and broaden their knowledge on this subject before being certified.

One qualitative study from Australia conducted semi-structured interviews among pharmacists. Evidence of low confidence highlighted that pharmacists believed that

there was a need for training and learning opportunities around medicinal cannabis. The respondents also highlighted that pharmacists could play a role in public awareness as they could further educate the public on medicinal cannabis.

One cross-sectional study of low-quality surveyed pharmacists practicing in Minnesota to determine potential gaps in knowledge and concerns among Minnesota pharmacists. Evidence showed that respondents were most interested in learning about the state-specific rules and regulations around medical cannabis, the pharmacotherapy of medical cannabis and available types and forms of products on the market.

One cross-sectional study of low-quality surveyed healthcare professionals (medical doctors, physician assistants, osteopathic physicians, osteopathic physician assistants, naturopathic physicians, advanced registered practitioners, registered nurses, licensed nurses and pharmacists in Washington state. Respondents agreed that continual medical education on medical cannabis should be available, medical cannabis should be included in graduate medical curricula, clinicians should receive training prior to recommending medical cannabis and medical cannabis should be included in undergraduate medical curricula.

Source of education

One cross-sectional study of low-quality surveyed pharmacists practicing in Minnesota. Evidence showed that pharmacists who took part in the survey preferred information on medical cannabis to be delivered by the Minnesota Board of Pharmacy.

Method of education delivery

One cross-sectional study of low-quality surveyed pharmacists practicing in Minnesota. Evidence showed that pharmacists who took part in the survey preferred information on medical cannabis to be delivered through email and online courses.

One cross-sectional study of low-quality surveyed medical oncologists, oncology nurse practitioners and oncology physician assistants in Minnesota to explore interest in future research and educational opportunities. When asked about what additional education participants wanted regarding medical cannabis, respondents preferred written summaries, online learning programs and symposiums or conferences.

Increasing comfort level with prescribing

One cross-sectional study (conducted in Canada) of low-quality surveyed physicians (family physicians and specialists) practicing in south-western Quebec. When asked about factors that could increase the comfort level with prescribing cannabinoids for chronic non-cancer pain, physicians mentioned attending continual medical education, having guidelines and algorithms that included cannabinoid prescribing and having more clinical data and new studies.

Considerations to take into account during prescriber-patient consultation

Moderate quality Irish guidance and moderate quality Australian, Queensland state guidance provided a framework that can be used during the consultation process when making decisions to use cannabis-based medicinal products.

Low quality Canadian guidance provided information around the dosing of cannabis-based medicinal products that can be used where there is limited dosing information available for some products.

Interpreting the evidence

The outcomes that matter most

The committee identified training needs as well as support needed by people as outcomes that matter most.

The quality of the evidence

In this review, 5 cross-sectional surveys, 1 qualitative study comprised of semi structured interviews and 3 international guidelines were included. The international guidelines included in this review were of moderate to low quality and did not include any outcome data. Additionally, the guidelines were quality assessed using the AGREE II tool, however for all the included guidelines, some of the AGREE II items were not applicable. Therefore, the scoring was limited to only those items that were relevant to the guideline under review. The committee also noted that the included international guidelines had similar information as these were based on the iterations of other internationals guidelines. This was identified as a further limitation.

The cross-sectional studies that were included were of low quality. The majority of the cross-sectional studies demonstrated potential selection bias and it was unclear if the questionnaires that were used were valid and reliable. Some studies also had a very low response rate. Additionally, the evidence from the qualitative study was also of low confidence due to methodological limitations and a small sample size.

A major limitation of the evidence included in the review was directness of the evidence. Five of the included studies [Carlini 2017, Ebert 2015, Hwang 2016, Isaac 2016 and Zylla 2016] did not explicitly specify the medicinal cannabis products under questions. Additionally, the St-Amant 2015 study looked at the use of nabilone and nabiximols and also the use of medical marijuana, defined as dried cannabis. This was identified as not being applicable to the protocol as smoked cannabis- based products were excluded. Due to these limitations the committee noted that, while these studies offer some insight, it was unclear if these products matched the current UK definition of cannabis-based products for medicinal use.

As well as questioning the directness of the evidence, the committee raised concerns with the applicability of the data to the UK. One study was conducted in Israel [Ebert 2015] where licences are issued to certain patients and physicians cannot prescribe medical cannabis to patients but can sign a medical recommendation that is then processed by the Israeli Ministry of Health. One study was conducted in Canada [St-Amant 2015] where patients can obtain cannabis for medical purposes via a healthcare professional, who completes a medical document which is similar to a prescription. Patients can then send this to a licensed producer who provides the products.

One study was conducted in Australia [Isaac 2016] where doctors wishing to prescribe medicinal cannabis products must either apply to become authorised prescribers for a class of patients, or apply for access for individual patients under the ‘Special Access Scheme Category B (SAS-B) via the Therapeutic Goods Administration (TGA). Three additional studies were identified which were conducted in the USA. However, 2 studies [Zylla 2018 and Hwang 2016] were conducted in

Minnesota and 1 study [Carlini 2017] was conducted in Washington, which meant that regulations around cannabis-based products varied.

With each country having different regulations, healthcare professionals who can prescribe and patient access to cannabis-based products also varied. This meant that the support needed by health care professionals and people may have varied considerably within these studies. This raised additional questions around the applicability of these studies as the regulations described in these studies were not reflective of current UK legislation.

Benefits and harms

One theme identified from the international guidelines stated that healthcare professionals should discuss the risks, benefits and alternatives for the use of cannabis with the patients. This should also include an explanation of the authorisation status of the product being prescribed and consent should be obtained and documented. The committee identified this as a key area of support for patients because while cannabis-based medicinal products may have some benefits, there are a number of adverse events associated with the use of the product, the most common of which include dizziness, feeling 'high', sedation, somnolence and fatigue.

Additionally, there is the potential for licensed and unlicensed products to be prescribed therefore an open and clear discussion about products needs to take place between the prescriber and patient. Based on this, the committee recommended for healthcare professionals to advise people on the benefits, harms and licence status of products when prescribing cannabis based medicinal products.

The committee also noted that prescribers may need guidance when it comes to supporting patients through shared decision making. The committee identified the NICE guideline on patient experience in adult NHS services (CG138) as providing relevant guidance. The guidance aims to provide the NHS with clear guidance on the components of a good patient experience and provide patient-centred service. Therefore, the committee recommended healthcare professionals follow the recommendations for shared decision making within this guideline. The committee highlighted that such discussions would allow people to make informed decisions about their care.

In terms of the support prescribers may need, the clinical evidence highlighted that there was a need for education and further training on cannabis based medicinal products. Some evidence demonstrated that training should be provided to healthcare professionals prior to becoming certified to recommend medical cannabis while some studies highlighted the need for continual medical education.

While the committee agreed that with the recent change in scheduling of cannabis based medicinal products, healthcare professionals would benefit from training prior to prescribing, there were some limitations to this approach. Firstly, the studies and guidelines included in the review did not provide robust information on specific areas in which further education and training were needed and it was difficult to ascertain how such training would be delivered. The committee were also concerned about who would deliver the training as it important that information provided to healthcare professionals is not biased. The committee expected that information related to the prescribing of cannabis-based medicinal products would form part of a healthcare professional's general training.

Furthermore, the current legislation states that only doctors on the General Medical Council's Specialist Register can prescribe cannabis based medicinal products. With prescribing already being limited, further limiting prescribing to those who have

received training on cannabis-based products would restrict access to these products.

Cost effectiveness and resource use

Cost effective analysis was not conducted as part of this review question. The committee noted that a shared decision-making approach has been promoted through the recommendations, and this may involve a multidisciplinary team especially when dealing with babies, children, young people or when decisions need to be made that are in the patient's best interest. Shared care could also lead to fewer prescribing errors and therefore potentially fewer adverse events and their associated costs. It may also reduce the number of outpatient attendances for reviews which could lead to cost savings. However, this may not be feasible in all specialist care settings as staffing and structure of care provision varies.

Other factors the committee took into account

Based on the evidence presented in the international guidance and their own clinical expertise, the committee recommended that prescribers advise people on the benefits, harms and licence status of products. In order to further promote shared decision making, the committee made a further recommendation for prescribers to follow the recommendations in NICE guidance on patient experience in adult NHS services. However, the committee noted that in certain populations such as in people who lack capacity, it was important that further support is provided in the decision-making process.

While the committee noted that most trusts have protocols in place in order to efficiently manage care of people who may currently lack capacity or in the future, there are further guidance available, particularly NICE guidance on decision making and mental capacity (NG108) that can aid decision making. This guidance aims to help health and social care practitioners support people to make their own decision where they have the capacity to do so and making them central to the decision-making process.

The evidence indicated that medical cannabis should be included in undergraduate and graduate medical curricula, which would be out of the remit of this committee.

This evidence review supports recommendations 1.5.8 and 1.5.9.

Review question 3

Who should prescribe and monitor use of cannabis-based medicinal products in line with legislation?

The review protocol for this review question is in Appendix A. The summary table below formed part of the search strategy to identify studies associated with prescribing and monitoring of cannabis-based medicinal products.

Table 12: Review summary table

Population	Adults, young people, children and babies who are taking: 1. A cannabis-based product for medicinal use that is a preparation or other product, other than one to which paragraph 5 of part 1 of schedule 4 applies, which: • is or contains cannabis, cannabis resin, cannabinol or a cannabinol derivative (not being dronabinol or its stereoisomers) • is produced for medicinal use in humans; and • 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 (MDR 2018 regulations) 2. Synthetic compounds which are identical in structure to naturally occurring cannabinoids such as delta-9-tetrahydrocannabinol (THC) for example dronabinol 3. Licensed products Sativex and nabilone 4. Plant-derived cannabinoids such as pure cannabidiol For the purpose of this review protocol, all the interventions above will be classed as cannabis-based medicinal products. Health professionals who prescribe cannabis-based medicinal products as part of their practice. Specific considerations will be given to: • Young people, children and babies • Pregnant women and women who are breastfeeding • History of hepatic and renal failure • History of addiction or drug misuse
Areas of Interest	Areas of interest, including but not limited to: • Prescribing in different care settings, including primary and specialist care. • Prescribing models for cannabis-based medicinal products. • Monitoring arrangements for people who are prescribed cannabis-based medicinal products. • Shared care management

Outcomes	Outcomes, including but not limited to:
	• Prescriber-specific outcomes:
	  ○ Prescribing errors
	• Individual-specific outcomes:
	  ○ Prevented addiction or drug misuse
	  ○ Prevented misuse
	  ○ Prevented diversion

	• Individual, carer and prescriber-specific outcomes:
	  ○ Access
	  ○ Adherence
	  ○ Compliance to legislation
	  ○ Improvement in management, including: tailoring treatment or care to the individual's needs, patient empowerment, making an informed decision
	• Treatment-specific outcomes:
	  ○ Adverse events
	  ○ Serious adverse events
	  ○ Withdrawal due to adverse events
	  ○ Quality of life

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual (2018). Methods specific to this review question are described in the review protocol in Appendix A.

Declarations of interest were recorded according to NICE's 2018 conflicts of interest policy.

A broad search strategy was used to identify all studies that examined the individual treatment factors that need to be taken into account when considering prescribing cannabis-based medicinal products, the support needed to help prescribers and patients make decisions about medicinal cannabis and who should prescribe and monitor the use of medicinal cannabis.

The review protocol highlighted in Table 1 and Appendix A was used to identify studies which highlighted who should prescribe and monitor the use of medicinal cannabis.

Both quantitative and qualitative studies were considered. National guidance for the UK, Europe and other countries with similar health care systems were also taken into consideration. Studies were excluded if they examined the use of:

- Synthetic cannabinoids in schedule 1 of the 2001 regulations,
- Smoked cannabis-based products
- Studies which do not report cannabinoid constituents.

Evidence review

Clinical evidence

Included studies, legislation and guidelines

From a database of 5,346 quantitative and qualitative studies and systematic reviews, 67 studies were identified as being potentially relevant. Following full text review of the 67 studies, 4 studies were included. One study was a qualitative study formed of a semi structured interview and 3 studies were cross-sectional surveys. In terms of areas of interest explored in these studies:

- One study examined access of cannabis-based medicinal products, nationalisation and role of the pharmacists

- One study examined the views of GPs on models of access to cannabis-based products
- One study examined the prevalence of cannabinoid prescribing stratified by medical specialty
- One study examined use of CBD products in different settings for the treatment of childhood epilepsy.

A separate search also looked for guidelines. Out of 16 guidelines identified from the searches, 3 guidelines met the inclusion criteria for this review question. These are summarised in table 2. These guidelines included information about who should prescribe the medicines and monitoring arrangements. The 2018 regulations were also referred to as part of this evidence review. There were no outcome data to assess whether or not information in the guidelines had any impact on the outcomes of interest for this review question.

Excluded studies and guidelines

See Appendix J for excluded studies list.

Guidelines looking at clinical effectiveness or based on regulation from countries other than the UK were excluded at first sift.

Summary of clinical studies included in the evidence review

Table 13: Summary of studies/guidelines included in the evidence review

Reference	Evidence Type	Country	Population	Outcomes/findings
Isaac 2016	Semi-structured interviews Thematic analysis	Australia	Pharmacists, [practicing, academic and representatives of professional organisations (LRPO)]	Role of the pharmacist Access Nationalisation
Karanges 2018	Cross-sectional survey	Australia	General practitioners (GPs) and GP registrars	Views of GPs on models of access to cannabis
Klotz 2018	Cross-sectional survey	Various European countries (Germany, Spain, Austria, Switzerland, Netherlands, Belgium, France and Italy)	Board certified paediatric neurologists, neurologists or general paediatricians	Cannabidiol use in different settings
St- Amant 2015	Cross-sectional survey	Canada	Physicians (family physicians and specialists) practicing in south-western Quebec	Prevalence of prescribing
British Paediatric Neurology	Professional guidance	UK	Clinicians treating children and young people with	Prescribing framework

Reference	Evidence Type	Country	Population	Outcomes/findings
Association (2018) Guidance on the use of cannabis-based products for medicinal use in children and young people with epilepsy			epilepsy with cannabis-based medicinal products	
Clinical Guidance: for the use of medicinal cannabis products in Queensland (2018)	International guidance	Australia	Medical practitioners who choose to prescribe medicinal cannabis	Summarises a prescribing framework and how to monitor use
Department of Health (An Roinn Sláinte), Ireland (2018) - Clinical Guidance on cannabis for medical use	International guidance	Ireland	Healthcare professionals using cannabis-based products for the treatment of patients under their care	Summarises a prescribing framework and how to monitor use (this is based on the Queensland, Australian guideline below)

See Appendix E for full evidence tables and Appendix F for evidence table on the guidance.

Table 14: Summary of key themes from qualitative study

Review theme and subthemes	Studies contributing	Population	Summary	Supporting statements
Access				
Nationalisation	Isaac 2016	Pharmacists (practising, academic and representatives of Professional Organisations)	Pharmacists stated a nationalised framework would be required for the successful implementation of legal medicinal cannabis supply as this would allow consistency and standardisation across the country.	*"Establishing a nationalised system and accompanying that with the current E-Health scripts… that would help manage this well"*
Access	Isaac 2016	Pharmacists (practising, academic and representatives of Professional Organisations)	There were different views on the ideal setting for the access of cannabis. While community pharmacy was identified as the most suitable setting, a staged implementation was also suggested with supply initially occurring in clinics or hospitals before being introduced to a community setting. Some also suggested at that a hospital environment may be more suitable as there is a more specialised team available to monitor cannabis use.	*"It should be within a community setting. I think that all palliative care should be... in terms of accessibility, within the community is best"* *"Initially in a clinic setting and then following good feedback and positive outcomes in a community setting…because it is more readily available."* Some participants preferred cannabis to be supplied in a hospital environment with the key reason cited being a more specialised team monitoring its use. A few participants making this suggested also proposed a clinic setting like that used for methadone initiation would minimise potential for cannabis abuse.

Review theme and subthemes	Studies contributing	Population	Summary	Supporting statements
				A number of participants were indifferent to the location of supply, suggesting that it could be successfully supplied in a multiple number of settings in order to make it accessible to all patients in various locations and with various needs. A few participants suggested a specialised cannabis supplier model similar to those existing overseas as means of cannabis supply.
Role of the pharmacist	Isaac 2016	Pharmacists (practising, academic and representatives of Professional Organisations)	Pharmacists identified their role as central to the drugs supply, use and safekeeping as they are most likely to dispense and supply the product. Pharmacists also identified that they are part of the of the healthcare professional team and shared care management is needed to help the patient.	*"We need to have our input into the matter, I think that is very important. You know we are the ones to most likely dispense and supply it"* *"We are all part of the healthcare professional team and in order for us to help the patient we need to actually work hand-in hand together and have all different types of opinions amalgamated into one"*

Table 15: Summary of key findings from cross-sectional surveys

Theme	Study	Population	Summary
Role of GP	Karanges 2018	General practitioners (GPs) and GP registrars	GPs were more likely to endorse an access model permitting prescribing by trained and accredited GPs, or by GPs in a 'share care' arrangement with a specialist than specialist-only prescribing
Prevalence of prescribing	St Amant 2016	Physicians (family physicians and specialists) practicing in south-western Quebec	27.3% (45/165) of respondents had prescribed cannabinoids for all potential indications. 23% (38/165) had prescribed cannabis specially for the management of chronic non-cancer pain. Analysis by specialty showed that 34.8% (32/92) of family physicians and 8.2% (6/73) of specialists had prescribed cannabinoids for chronic non cancer pain.
CBD use in different settings	Klotz 2018	Board certified paediatric neurologists, neurologists or general paediatricians	45% (69/155) of respondents reported a current or previous use of CBD for treating epilepsy in childhood. Analysis by setting showed that 50% of participants from specialised epilepsy centres, 44.2% of participants from neuropediatric/neurologic department and 50% of participants working in general paediatric department were using CBD for the treatment epilepsy in childhood. Additionally, 28.6% of participants working in private practise were using CBD for treating epilepsy in childhood.

Table 16: Summary of international guidelines

Title	Population	Summary of guidance
British Paediatric Neurology Association (2018) Guidance on the use of cannabis-based products for medicinal use in children and young people with epilepsy	Clinicians treating children and young people with epilepsy with cannabis-based medicinal products	• Prescribing will be restricted to doctors on the Specialist Register, prescribing only within their relevant specialist registration. • In terms of access it summarises 3 access routes: 1. Prescribing these products will treated as "specials" 2. As an investigational product in the context of a clinical trial 3. As a medicinal product with a marketing authorisation • Responsibility remains with the prescribing clinician. • All cannabis-based products for medicinal use should have a clear contents description, and specifically including doses and concentrations of cannabidiol and tetrahydrocannabinol.
Clinical Guidance: for the use of medicinal cannabis products in Queensland, Australia (2018)	Medical practitioners who choose to prescribe medicinal cannabis	• If being managed by a GP, patient-specific supportive documentation for use of a particular medicinal cannabis product from a specialist in the field of medicine for which the symptom is being treated should be documented. • While no monitoring regimes are available internationally, suggests using a similar monitoring program to opioids. • Frequent reviews for people commencing on medicinal cannabis products, daily if needed. Once established on a dose, at a minimum monthly review recommended in the guideline. • The review should cover symptom control; adverse events; aberrant behaviour (concerns that the patient may be diverting their product) and records.
An Roinn Sláinte, Department of Health, Ireland (2018). Clinical guidance on cannabis for medical use	Healthcare professionals using cannabis-based products (as defined in their guidance) for the treatment of patients	• Documentation should record that an appropriate doctor–patient relationship has been established before prescribing and/or endorsing cannabis for medical use for the patient (and between the patient and the GP [if the GP is prescribing cannabis endorsed by a consultant and/or monitoring its use]). • Prescribing consultants should have appropriate expertise in the treatment of the medical conditions. • The monitoring (to include repeat prescribing where appropriate) may be carried out by the consultant in conjunction with the patient's GP and other healthcare professionals, including clinical nurse and midwife specialists and pharmacists. • The treatment plan for each patient should include clear definition of the treatment goals/desired endpoints and should specify regular clinical monitoring required, including the monitoring intervals and the duration of the trial period.

Title	Population	Summary of guidance
	under their care	• Patients should be reviewed more frequently when commencing cannabis-based products, daily if required. Once established on a dose, regular review is suggested which may include telephone management, if appropriate.
Note: the term cannabis-based product was mainly defined in the guidelines above as an unauthorised product (such as not having a marketing authorisation)		

1

Quality assessment of clinical studies and guidelines included in the evidence review

Cross-sectional surveys were critically appraised using the Centre for Evidence-Based Management (CEBMa) checklist. GRADE approach was not utilised for survey data due to the nature of the evidence.

Three cross-sectional survey were included in this review. The overall quality of surveys was assessed using the Centre for Evidence-Based Management (CEBMa) Critical Appraisal of a survey. All 3 cross-sectional surveys were of low quality due to unclear validity and reliability of the questionnaires, low response rates and potential introduction of selection bias.

The directness of the evidence was also assessed. Only 1 cross-sectional survey provided direct evidence as it explicitly stated the products which were under question. Two cross-sectional surveys were deemed as being partially direct as one study did not explicitly state which cannabis-based products were prescribed and the other study included medical marijuana.

With regard to the qualitative study, CASP qualitative checklist was used to quality assess individual studies. GRADE CerQual was used to assess the confidence we have in the summary findings of each of the identified themes Moderate concerns were identified in terms of methodological limitations, primarily unclear reflexivity. The study also demonstrated serious concerns regarding adequacy of the data.

An additional professional guidance produced by the British Paediatric Neurology Association (BPNA) was also included. This guidance was not assessed for quality as this was based on legislation and national policy.

The quality of the 2 guidelines were assessed using the international criteria of quality for guidance development, as outlined by the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument.

See Appendix E for full CEBMa critical appraisal checklist.

See Appendix H for full GRADE CERQual tables.

See Appendix I for full AGREE II checklist

Economic evidence

A global health economic search was conducted to identify economic evidence. No economic studies were identified which were applicable and no full-text copies of articles were requested.

Evidence statements

The evidence statement in this section reflect the evidence on who should prescribe and monitor the use of cannabis based medicinal products.

Clinical evidence

Access

Evidence of low confidence from 1 study (Australia) used semi-structured interviews to explore the views of pharmacists about medicinal cannabis, its legalisation and

supply. In this study there were different views on the ideal setting for cannabis supply. Community pharmacy was identified as a suitable setting; a staged implementation was also suggested, where supply of medicinal cannabis initially occurred in hospitals and clinics before being continued in a community setting. Some participants were indifferent to the location of supply as it was identified that patients may be in various locations with various needs. It was also suggested that hospitals may be a suitable environment to supply medicinal cannabis, due to the presence of specialised teams who can monitor its use.

The study also highlighted that pharmacists identify their role as being central in the access to cannabis-based products as they are responsible for the supply of the product. Different models were suggested for access, including hospital-based supply and monitoring, community-based supply, and shared -care arrangements.

Models of access to cannabis

One cross-sectional study of low quality surveyed general practitioners (GPs) and GP registrars to examine the knowledge and attitudes of Australian GPs towards medicinal cannabis. Evidence showed that respondents were more likely to endorse an access model permitting 'prescribing by trained and accredited GPs', followed by 'GPs in a 'shared care' arrangement with a specialist'.

When asked to choose one model, 'trained GPs as the preferred prescriber' was the preferred model, followed by 'shared care'.

Prevalence of prescribing

One cross-sectional study (Canada) of low-quality surveyed physicians (family physicians and specialists) practicing in south-western Quebec. Evidence showed that more family physicians were prescribing cannabinoids for chronic non-cancer pain compared to specialists.

Use in different settings

One cross-sectional study of a low-quality surveyed board-certified paediatric neurologists, neurologists or general paediatricians from 8 different European countries. Evidence showed that half of the participants from specialised epilepsy centres and general paediatric department were using CBD for treating childhood epilepsy.

Prescribing and monitoring considerations documented in guidelines

Professional guidance issued by the British Paediatric Neurology Association states that prescribing cannabis-based products for medicinal use in children and young people with epilepsy will be restricted to doctors on the specialist register, prescribing only within their relevant specialist registration and that responsibility remains with the prescribing clinician.

Moderate quality Irish guidance and moderate quality Australian, (Queensland state) guidance suggests that for unlicensed cannabis-based products for medicinal use, prescribing consultants should have appropriate expertise in the treatment of the medical conditions. A specialist clinician who has originally initiated treatment can endorse a GP to prescribe these medicines and to monitor treatment based on a case-by-case basis. The guidelines also suggest that patients should be reviewed more frequently when commencing cannabis-based products, for example daily. Once established on a dose, regular review is recommended (for example monthly).

Interpreting the evidence

The outcomes that matter most

The committee identified views on access of cannabis-based products and prescribing framework as outcomes of interest. The committee were also interested in the current legislation on CBMPs.

The quality of the evidence

In this review, 3 cross-sectional surveys,1 qualitative study comprised of semi-structured interviews and 1 guidance were included. The committee noted that the cross-sectional studies were of low quality due to potential selection bias and unclear validity and reliability of the questionnaires used in the studies. It was also further noted that the evidence from the qualitative study was of low confidence. This was due to methodological limitations and a small sample size. An additional professional guidance produced by the British Paediatric Neurology Association was also included. This guidance was not assessed for quality as this was based on legislation and national policy.

A major limitation of the evidence included in this review was the directness of the evidence. Two of the studies included [Karanges 2018 and Isaac 2016] did not explicitly specify the medicinal cannabis products under question. Additionally, St-Amant (2015) looked at the use of nabilone and nabiximols (Sativex) but also focused on medical marijuana, defined as dried cannabis. This is was identified as not being applicable to the protocol as smoked cannabis-based products were excluded. Due to this the committee highlighted that, while the studies offered an insight into the views of different healthcare professionals on the prescribing of cannabis-based products, it was unclear if these products matched the current definition of cannabis based medicinal products.

In this review, two studies were included which were conducted in Australia [Karanges 2018 and Isaac 2016], one study which was conducted in Canada [St-Amant 2015] and one professional guidance that was produced by the British Paediatric Neurology Association (BPNA). A cross-sectional survey [Klotz 2018] was also included which included participants from 8 different European countries (Germany, Spain, Austria, Switzerland, Netherlands, Belgium, France and Italy).

Karanges (2018) highlighted that patient access of medicinal cannabis is complex and highly restricted. Doctors wishing to prescribe medicinal cannabis products must either apply to become authorised prescribers for a class of patients or apply for access for individual patients under the ‘Special Access Scheme Category B (SAS-B), via the Therapeutic Goods Administration (TGA). The study also further stated that, under the scheme, Australian general practitioners are typically only permitted to prescribe medicinal cannabis if supported by a specialist.

The committee further highlighted that in Canada, patients can obtain cannabis for medical purposes via a healthcare professional, who completes a medical document which is similar to a prescription. Patients can then send this to a licensed producer who provides the products. Klotz (2018) also highlighted that in countries such as Spain, Germany, Switzerland and the Netherlands, the cost of CBD is covered by health care insurance providers.

As previously noted, some these studies had been downgraded for indirectness. However additional questions about the applicability of these studies were raised as these did not fully reflect the current UK legislation. Additionally, funding of CBMPs

was not clear in these studies, which the committee identified as an important factor for consideration.

Benefits and harms

The committee noted that people who may require CBMPs, may present with complex medical conditions. To further consider who should be prescribing, the committee referred to the guidance produced by the BPNA, which was aimed at clinicians for the use and prescription of CBMPs in children and young people with epilepsy. While it was noted that this guidance is targeted to a specific population, which is a potential limitation, it was the only evidence that took into consideration the current legislation and recommended prescribing to be restricted to doctors on the Specialist Register.

The guidance also stated that such specialists should only be prescribing within their relevant specialist registration, which the committee found to be a key part of the recommendation and highlighted that it should be followed for all conditions in which CBMPs are being considered for use. Also, when considering complex conditions, restricting prescribing to a specialist with expertise of that condition would be needed. Therefore, the committee recommended that the initial prescription for cannabis based medicinal products must be initiated by a specialist on the specialist register with an interest in the condition.

Further to the discussion around initial prescribing, the committee highlighted that special considerations need to be given when considering the use of CBMPs in children. The BPNA guideline, which referred to the NICE CG137 guidance on epilepsies: diagnosis and management, stated that for a child with intractable epilepsy, the prescription should be made by a Consultant Paediatric Neurologist. The committee noted that, this is crucial for any child or young person requiring CBMPs for the management of their condition. Therefore, the committee recommended that for children and young people, the initial prescriber should be on the relevant specialist register, have expertise in the condition and be a tertiary paediatric specialist.

The committee identified that people who need CBMPs for the management of their conditions may require repeat prescriptions and regular monitoring with regards to adverse events and efficacy. Furthermore, doses of products may need to be adjusted based on the monitoring. Currently, prescribing and monitoring is conducted in tertiary care centres which means that some people may have to travel considerable distances to visit their specialist which could be burdensome on the patient, their families or carers.

Taking this into consideration, the committee emphasised a need for shared care to help reduce the burden on people taking CBMPs and their families and carers by making access to prescriptions for agreed and effective CBMPs easier. Therefore, the committee recommended that subsequent prescriptions may be issued by a prescriber under the direction of the specialist.

The committee also agreed that the specialist initiating treatment should also be involved in monitoring and evaluation as many patients have complex treatment plans and may require dose adjustments. But there should be clear division of responsibilities with the other prescriber. Therefore, the committee recommended that efficacy should be monitored and evaluated, and doses adjusted by the specialist initiating treatment as part of shared care.

Furthermore, the committee also made a further recommendation to highlight that a shared care agreement would need to be put into place before the initiation of

treatment in order to highlight the responsibilities of all parties involved. Therefore, the committee recommended that a shared care agreement should be in place that details the responsibilities of the specialist, other prescriber, the patient and the families and carers involved. The committee also highlighted that fundamental aspects of care would need to be detailed in this agreement which should include, drug indication, how communication between parties would be managed, how funding would be obtained for the intervention, the frequency of and nature monitoring and when treatment may be stopped.

With some patients requiring long term use of the intervention, circumstances such as when patient or specialist moves locations would also need to be considered in the agreement especially in terms of the handover of responsibilities to other specialists or prescribers. The committee further identified this agreement as being best for care as it protects care and benefits patients, families and carers involved.

Cost effectiveness and resource use

Cost effective analysis was not conducted as part of this review question. However, during discussions, the committee highlighted that introduction of the recommendations may have a cost saving effect not only for the NHS but also for the individuals. This is because currently prescribing occurs in tertiary centres. With the recommendations allowing subsequent prescribing to occur in other care settings, such as primary care, this may reduce costs associated with tertiary care.

Additionally, the new recommendations would mean that people would no longer have to make monthly visits to tertiary care settings to obtain their prescriptions and could obtain them more locally. Therefore, this would reduce costs such as those associated with transportation.

Other factors the committee took into account

The committee took into consideration the Misuse of Drugs Regulations (2018) when making recommendations. This regulation currently states that the order, supply and use of cannabis-based products for medicinal use should be in accordance with a prescription or direction of a specialist medical practitioner. The committee also evaluated the evidence included to determine if it was in line with this regulation. The committee also took into consideration, the scheduling of CBPMs. Some products fall under Schedule 2 with some falling under Schedule 4.The NICE NG46 guideline on controlled drugs: safe use and management, which covers controlled drugs falling under Schedule 2 and 4, recommends prescribing enough of a controlled drug to meet the person's clinical needs for no more than 30 days. This means that repeat prescriptions would be required. In order to promote a holistic approach the committee recommended that subsequent prescriptions may be issued by a prescriber under the direction of the specialist.

This evidence review supports recommendations 1.5.1, 1.5.2, 1.5.3 and 1.5.4].

Glossary

Cannabis-based products for medicinal use

These are medicinal products containing cannabis or cannabinoids derived from the cannabis plant and is further defined in the 2018 Regulations

Cannabis-based medicinal products
In this guideline cannabis-based medicinal products include:

- cannabis-based products for medicinal use as set out by the UK Government in the 2018 Regulations
- the licensed products delta-9-tetrahydrocannibinol and cannabidiol (Sativex) and nabilone
- plant-derived cannabinoids such as pure cannabidiol (CBD)
- synthetic compounds which are identical in structure to naturally occurring cannabinoids such as delta-9-tetrahydrocannabinol (THC), for example, dronabinol.

Diversion

Removal of controlled drugs for unauthorised use.

Unlicensed medicine

Medicines that do not have a UK marketing authorisation.

Appendix A – Review protocols

Review question 2.1

Review protocol for individual treatment factors to take into account when considering prescribing and obtaining patient consent for cannabis-based medicinal products

Field (based on PRISMA-P	Content
Review question	What individual treatment factors need to be taken into account when considering prescribing and obtaining patient consent for cannabis-based medicinal products?
Type of review question	Qualitative and quantitative review
Objective of the review	To determine what individual treatment factors need to be taken into account (including obtaining patient consent) when prescribing cannabis-based medicinal products to reduce controlled drugs related incidents, including patient-safety incidents.
Eligibility criteria – population/disease/condition/issue/domain	Adults, young people, children and babies who are taking: 1. A cannabis-based product for medicinal use that is a preparation or other product, other than one to which paragraph 5 of part 1 of schedule 4 applies, which: • is or contains cannabis, cannabis resin, cannabinol or a cannabinol derivative (not being dronabinol or its stereoisomers) • is produced for medicinal use in humans; and • is a medicinal product, or

Field (based on PRISMA-P	Content
	• a substance or preparation for use as an ingredient of, or in the production of an ingredient of, a medicinal product (MDR 2018 regulations)' 2. Synthetic compounds which are identical in structure to naturally occurring cannabinoids such as delta-9-tetrahydrocannabinol (THC) for example dronabinol 3. Licensed products Sativex and nabilone 4. Plant-derived cannabinoids such as pure cannabidiol For the purpose of this review protocol, all the interventions above will be classed as cannabis-based medicinal products. Health professionals who prescribe cannabis-based medicinal products as part of their practice. Specific considerations will be given to: Young people, children and babies Pregnant women and women who are breastfeeding History of hepatic and renal failure History of addiction or drug misuse
Eligibility criteria – factors	The following outlines factors for consideration, both by people taking cannabis-based medicinal products and by health professionals who prescribe them: Individual factors, including but not limited to: Current treatments

Field (based on PRISMA-P	Content
	Previous treatments The use of other substances including cannabis-based products Understanding of how to access of cannabis-based medicinal products Age such as children and young people Communication Comorbidities Misuse potential by the individual Capacity to consent Treatment specific factors, including but not limited to: Formulation of the cannabis-based medicinal product Route of administration of the cannabis-based medicinal product
Eligibility criteria – outcomes	Prescriber, person and carer outcomes, including but not limited to: Prescriber-specific outcomes: Prescriber, person and carer outcomes Prescribing errors

Field (based on PRISMA-P	Content
	Individual-specific outcomes: Prevented addiction or drug misuse Prevented misuse Diversion Satisfaction Treatment-specific outcomes: Adverse events (including psychosis) Serious adverse events Withdrawal due to adverse events Quality of life
Eligibility criteria – study design	For adults: RCTs Systematic reviews of RCTs If less than five RCTs identified, prospective cohort studies will be used. For children:

Field (based on PRISMA-P	Content
	RCTs Systematic reviews of RCTs If less than five RCTs identified, prospective and retrospective cohort studies will be used. Additional information on safety concerns and contraindications will be obtained from the Summary of Product Characteristics and other relevant sources, such as the U.S Food and Drugs Administration.
Other inclusion/exclusion criteria	Inclusion Cannabis-based medicinal products (as defined under population). Exclusion Synthetic cannabinoids in schedule 1 of the MDR 2001 Regulations, Smoked cannabis-based products
Selection process – duplicate screening/selection/ analysis	10% of the abstracts will be reviewed by two reviewers, with any disagreements will be resolved by discussion or, if necessary, a third independent reviewer. If meaningful disagreements are found between the different reviewers, a further 10% of the abstracts will be reviewed by two reviewers, with this process continuing until agreement is achieved between the two reviewers. From this point, the remaining abstracts will be screened by a single reviewer.
Data management (software)	See Appendix B.
Information sources – databases and dates	Sources to be searched

Field (based on PRISMA-P	Content
	Clinical searches - Medline, Medline in Process, Medline EPub Ahead of Print, Embase, Cochrane CDSR, CENTRAL, DARE (legacy records), HTA, MHRA. Economic searches - Medline, Medline in Process, Medline EPub Ahead of Print, Embase, Econlit, NHS EED (legacy records) and HTA, with economic evaluations and quality of life filters applied. Supplementary search techniques None identified Limits Studies reported in English Study design RCT, SR and Observational filter will be applied (as agreed) Animal studies will be excluded from the search results Conference abstracts will be excluded from the search results No date limit will be set.
Identify if an update	N/A
Author contacts	Guideline updates team
Highlight if amendment to previous protocol	This is a new protocol.

Field (based on PRISMA-P	Content
Search strategy – for one database	For details please see Appendix C of relevant chapter.
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as Appendix D (clinical evidence tables) or H (economic evidence tables).
Data items – define all variables to be collected	For details please see evidence tables in Appendix D (clinical evidence tables) or H (economic evidence tables).
Methods for assessing bias at outcome/study level	Standard study checklists were used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis	For details please see section 6.4 of Developing NICE guidelines: the manual
Methods for quantitative analysis – combining studies and exploring (in)consistency	For details please see the methods and process section of the main file.

Field (based on PRISMA-P	Content
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual.
Confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual
Rationale/context – what is known	For details please see the introduction to the evidence review in the main file.
Describe contributions of authors and guarantor	A multidisciplinary committee [add link to history page of the guideline] developed the evidence review. The committee was convened by [add name of developer] and chaired by [add name of Chair] in line with section 3 of Developing NICE guidelines: the manual. Staff from NICE undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the evidence review in collaboration with the committee. For details please see Developing NICE guidelines: the manual.
Sources of funding/support	The NICE Guideline Updates Team is an internal team within NICE.
Name of sponsor	The NICE Guideline Updates Team is an internal team within NICE.
Roles of sponsor	The NICE Guideline Updates Team is an internal team within NICE.
PROSPERO registration number	

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Review question 2.2

Review protocol for support needed to help prescribers and patients make decisions about cannabis-based medicinal products

Field (based on PRISMA-P	Content
Review question	What support is needed to help prescribers and patients (or their family members or carers) make decisions about cannabis-based medicinal products?
Type of review question	Qualitative and quantitative review
Objective of the review	To determine what support is needed to help prescribers and patients (or their family members or carers) make decisions about cannabis-based medicinal products to ensure safe and effective use.
Eligibility criteria – population/disease/condition/issue/domain	Adults, young people, children, babies who are taking, or their family members or carers: 1. A cannabis-based product for medicinal use that is a preparation or other product, other than one to which paragraph 5 of part 1 of schedule 4 applies, which: is or contains cannabis, cannabis resin, cannabinol or a cannabinol derivative (not being dronabinol or its stereoisomers) is produced for medicinal use in humans; and 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 (MDR 2018 regulations)' 2. Synthetic compounds which are identical in structure to naturally occurring cannabinoids such as delta-9-tetrahydrocannabinol (THC) for example dronabinol 3. Licensed products Sativex and nabilone 4. Plant-derived cannabinoids such as pure cannabidiol For the purpose of this review protocol, all the interventions above will be classed as cannabis-based medicinal products. Health professionals who prescribe cannabis-based medicinal products as part of their practice. Specific considerations will be given to: Young people, children and babies Pregnant women and women who are breastfeeding

Field (based on PRISMA-P	Content
	People with existing substance misuse People with hepatic and renal failure
Eligibility criteria – Areas of interest	Areas of interest, including but not limited to: Patient information leaflets Medicines quality assurance information Provision of information regarding dose (including micro-dosing and tapering) Education programmes (this includes understanding publicly available information) Support around access Shared decision aids and other decision support tools The use of policies on prescribing and taking cannabis-based medicinal products Multi-disciplinary team involvement Monitoring tools Safeguarding
Outcomes	Prescriber, individual and carer outcomes, including but not limited to: Adherence and compliance Experience and satisfaction Improvement in management, including: tailoring treatment or care to the individual's needs, patient empowerment, making an informed decision Treatment-specific outcomes, including but not limited to: Quality of life Adverse events Serious adverse events Withdrawal due to adverse events Any available quantitative evidence which reports outcomes on areas of interest from questions on clinical effectiveness, safety and stopping criteria will be included.
Eligibility criteria – study design	Qualitative and quantitative studies Other national guidance from the UK, Europe and other countries with similar developed health systems, for example Australia, Canada and New Zealand.

Field (based on PRISMA-P	Content
	Relevant legislation and regulation: Misuse of Drugs (Supply to Addicts) Regulations 1997, and subsequent amendments). Misuse of Drugs Regulations 2001 and subsequent amendments ('MDR 2001 Regulations'). The Controlled Drugs (Supervision of Management and Use) Regulations 2013. The Misuse of Drugs [Amendments] [Cannabis and Licence Fees] [England, Wales and Scotland] Regulations 2018 ('MDR 2018 Regulations') Professional guidance such as guidance from the General Medical Council (GMC) on prescribing unlicensed medicines.
Other inclusion/exclusion criteria	Inclusion Cannabis-based products for the medicinal use when other treatments haven't helped or have been discounted. Exclusion Synthetic cannabinoids in schedule 1 of the 2001 regulations, Smoked cannabis-based products Studies which do not report cannabinoid constituents.
sub-group analysis	Subgroups, where possible, will include: Young people, children and babies Pregnant women and women who are breastfeeding People with existing substance misuse People with hepatic and renal failure
Selection process – duplicate screening/selection/analysis	10% of the abstracts will be reviewed by two reviewers, with any disagreements will be resolved by discussion or, if necessary, a third independent reviewer. If meaningful disagreements are found between the different reviewers, a further 10% of the abstracts will be reviewed by two reviewers, with this process continuing until agreement is achieved between the two reviewers. From this point, the remaining abstracts will be screened by a single reviewer.
Data management (software)	See Appendix B.
Information sources – databases and dates	Databases to be searched for qualitative evidence (all via the Ovid platform:

Field (based on PRISMA-P	Content
	MEDLINE MEDLINE in Process, MEDLINE e pub Ahead of print, Embase PSYCINFO The NICE inhouse qualitative filter will be attached where appropriate Databases to be searched for economic evidence (all via Ovid except where specified): MEDLINE MEDLINE in Process MEDLINE e pub ahead of Print Econlit Embase NHS EED (legacy database, CRD platform) Health Technology Assessment (legacy databases, CRD platform) The NICE inhouse economic evaluation and Quality of Life filters will be attached where appropriate A search of the MHRA will be undertaken to look for safety updates, alerts and recalls A search for national and international guidance, legislation and regulation will be undertaken on the following websites: NICE Evidence TRIP Google Health Departments of similar health systems which have licensed cannabis based medicines
Identify if an update	N/A

Field (based on PRISMA-P	Content
Author contacts	Guideline updates team
Highlight if amendment to previous protocol	This is a new protocol.
Search strategy – for one database	For details please see Appendix C of relevant chapter.
Data collection process – forms/duplicate	A standardised evidence table format will be used and published as Appendix D (clinical evidence tables).
Data items – define all variables to be collected	For details please see evidence tables in Appendix D (clinical evidence tables).
Methods for assessing bias at outcome/study level	Study checklists were used to critically appraise individual studies. For details please see Appendix Hof Developing NICE guidelines: the manual The following checklists will be used: Risk of bias of intervention studies - systematic reviews and meta-analyses will be assessed using the Risk of Bias in Systematic Reviews (ROBIS) checklist Risk of bias of intervention studies – randomised controlled trials (individual or cluster) will be assessed using the Cochrane risk of bias (RoB) 2.0 tool Risk of bias of cohort studies will be assessed using Cochrane ROBINS-I Risk of bias of case-series studies will be assessed using Institute of Health Economics (IHE) checklist Risk of bias of qualitative studies will be assessed using CASP qualitative checklist. Risk of bias of cross-sectional surveys and survey questionnaire studies will be assessed using CEBM checklist. Risk of bias of national guidance and factsheets from national guidance will be assessed using AGREE II reporting checklist. Factsheets from non-UK national legislation and policy will be summarised narratively. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/

Field (based on PRISMA-P	Content
	For qualitative studies, information from the studies was combined using a thematic synthesis. GRADE-CERQual was used to assess the confidence in the summary findings of each of the identified themes.
Criteria for quantitative synthesis	For details please see section 6 of Developing NICE guidelines: the manual
Methods for quantitative analysis – combining studies and exploring (in)consistency	For details please see the methods and process section of the main file.
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual.
Confidence in cumulative evidence	For details please see sections 6 Developing NICE guidelines: the manual
Rationale/context – what is known	For details please see the introduction to the evidence review in the main file.
Describe contributions of authors and guarantor	A multidisciplinary committee [add link to history page of the guideline] developed the evidence review. The committee was convened by NICE Guideline Updates Team and chaired by Stephen Pilling in line with section 3 of Developing NICE guidelines: the manual. Staff from NICE undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the evidence review in collaboration with the committee. For details please see Developing NICE guidelines: the manual.
Sources of funding/support	The NICE Guideline Updates Team is an internal team within NICE.
Name of sponsor	The NICE Guideline Updates Team is an internal team within NICE.

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Review question 3

Review protocol for who should prescribe and monitor use of cannabis-based medicinal products

Field (based on PRISMA-P	Content
Review question	Who should prescribe and monitor use of cannabis-based medicinal products in line with legislation?'
Type of review question	Qualitative and quantitative review
Objective of the review	To determine who is the most suitable prescriber to prescribe cannabis-based medicinal products in line with legislation and professional guidance. To determine how prescribing can be continued, monitored and stopped.
Eligibility criteria – population/disease/condition/issue/domain	Healthcare professionals who can prescribe cannabis=based products for medicinal use in line with legislation: 1. A cannabis-based product for medicinal use that is a preparation or other product, other than one to which paragraph 5 of part 1 of schedule 4 applies, which: is or contains cannabis, cannabis resin, cannabinol or a cannabinol derivative (not being dronabinol or its stereoisomers) is produced for medicinal use in humans; and 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 (MDR 2018 regulations)' 2. Synthetic compounds which are identical in structure to naturally occurring cannabinoids such as delta-9-tetrahydrocannabinol (THC) for example dronabinol 3. Licensed products Sativex and nabilone 4. Plant-derived cannabinoids such as pure cannabidiol For the purpose of this review protocol, all the interventions above will be classed as cannabis-based medicinal products. Health professionals who prescribe cannabis-based medicinal products as part of their practice. Specific considerations will be given to: Prescribers in all care settings

Field (based on PRISMA-P	Content
	Young people, children and babies Pregnant women and women who are breastfeeding People with existing substance misuse People with hepatic and renal failure
Eligibility criteria – Areas of interest	The following outlines areas of interest for consideration, both by people taking cannabis-based medicinal products and by health professionals who prescribe them: Prescribing in different care settings, including primary and specialist care. Prescribing models for cannabis-based medicinal products. Monitoring arrangements for people who are prescribed cannabis-based medicinal products. Shared care management
Outcomes	Prescriber, person and carer outcomes, including but not limited to: Outcomes, including but not limited to: Prescriber-specific outcomes: Prescribing errors Individual-specific outcomes: Prevented addiction or drug misuse Prevented misuse Prevented diversion Individual, family or carer and prescriber-specific outcomes: Access Adherence Compliance to legislation Improvement in management, including: tailoring treatment or care to the individual's needs, patient empowerment, making an informed decision Treatment-specific outcomes: Adverse events Serious adverse events Withdrawal due to adverse events or lack or efficacy Quality of life

Field (based on PRISMA-P	Content
	Any available quantitative evidence which reports outcomes on factors of interest from questions on clinical effectiveness, safety and stopping criteria will be included.
Eligibility criteria – study design	Qualitative and quantitative studies Other national guidance from the UK, Europe and other countries with similar developed health systems, for example Australia, Canada and New Zealand. Relevant legislation and regulation: Misuse of Drugs (Supply to Addicts) Regulations 1997, and subsequent amendments). Misuse of Drugs Regulations 2001 and subsequent amendments ('MDR 2001 Regulations'). The Controlled Drugs (Supervision of Management and Use) Regulations 2013. The Misuse of Drugs [Amendments] [Cannabis and Licence Fees] [England, Wales and Scotland] Regulations 2018 ('MDR 2018 Regulations') Professional guidance such as guidance from the General Medical Council (GMC) on prescribing unlicensed medicines
Other inclusion/exclusion criteria	Inclusion Cannabis-based products for the medicinal use when other treatments haven't helped or have been discounted. Exclusion Synthetic cannabinoids in schedule 1 of the 2001 regulations, Smoked cannabis-based products Studies which do not report the doses or the concentration of cannabinoid constituents.
sub-group analysis	 Subgroups, where possible, will include: Prescribers in different settings Young people, children and babies Pregnant women and women who are breastfeeding People with existing substance misuse People with hepatic and renal failure

Field (based on PRISMA-P	Content
Selection process – duplicate screening/selection/analysis	10% of the abstracts will be reviewed by two reviewers, with any disagreements will be resolved by discussion or, if necessary, a third independent reviewer. If meaningful disagreements are found between the different reviewers, a further 10% of the abstracts will be reviewed by two reviewers, with this process continuing until agreement is achieved between the two reviewers. From this point, the remaining abstracts will be screened by a single reviewer.
Data management (software)	See Appendix B.
Information sources – databases and dates	Databases to be searched for qualitative evidence: MEDLINE MEDLINE in Process, MEDLINE e pub Ahead of print, Embase PSYCINFO (all via the Ovid platform) The NICE inhouse qualitative filter will be attached where appropriate Databases to be searched for economic evidence (all via Ovid except where specified): MEDLINE MEDLINE in Process MEDLINE e pub ahead of Print Econlit Embase NHS EED (legacy database, CRD platform) Health Technology Assessment (legacy databases, CRD platform) The NICE inhouse economic evaluation and Quality of Life filters will be attached where appropriate

Field (based on PRISMA-P	Content
	A search of the MHRA will be undertaken to look for safety updates, alerts and recalls A search for national and international guidance, legislation and regulation will be undertaken on the following websites: NICE Evidence TRIP Google Health Departments of similar health systems which have licensed cannabis based medicines
Identify if an update	N/A
Author contacts	Guideline updates team
Highlight if amendment to previous protocol	This is a new protocol.
Search strategy – for one database	For details please see Appendix C of relevant chapter.
Data collection process – forms/duplicate	A standardised evidence table format will be used and published as appendix D (clinical evidence tables) or H (economic evidence tables).
Data items – define all variables to be collected	For details please see evidence tables in Appendix D (clinical evidence tables).
Methods for assessing bias at outcome/study level	Study checklists were used to critically appraise individual studies. For details please see AppendixHof Developing NICE guidelines: the manual The following checklists will be used: Risk of bias of intervention studies - systematic reviews and meta-analyses will be assessed using the Risk of Bias in Systematic Reviews (ROBIS) checklist Risk of bias of intervention studies – randomised controlled trials (individual or cluster) will be assessed using the Cochrane risk of bias (RoB) 2.0 tool Risk of bias of cohort studies will be assessed using Cochrane ROBINS-I Risk of bias of case-series studies will be assessed using Institute of Health Economics (IHE) checklist

Field (based on PRISMA-P	Content
	Risk of bias of qualitative studies will be assessed using CASP qualitative checklist. Risk of bias of cross-sectional surveys and survey questionnaire studies will be assessed using CEBM checklist. Risk of bias of national guidance and factsheets from national guidance will be assessed using AGREE II reporting checklist. Factsheets based on both national guidance and non-UK national legislation and policy will be assessed using a combination of the AGREE II reporting checklist and a narrative summary. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/ For qualitative studies, information from the studies was combined using a thematic synthesis. GRADE-CERQual was used to assess the confidence in the summary findings of each of the identified themes.
Criteria for quantitative synthesis	For details please see section 6 of Developing NICE guidelines: the manual
Methods for quantitative analysis – combining studies and exploring (in)consistency	For details please see the methods and process section of the main file.
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual.
Confidence in cumulative evidence	For details please see sections 6 Developing NICE guidelines: the manual
Rationale/context – what is known	For details please see the introduction to the evidence review in the main file.
Describe contributions of authors and guarantor	A multidisciplinary committee [add link to history page of the guideline] developed the evidence review. The committee was convened by NICE Guideline Updates Team and chaired by Stephen Pilling in line with section 3 of Developing NICE guidelines: the manual. Staff from NICE undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the evidence review in collaboration with the committee. For details please see Developing NICE guidelines: the manual.
Sources of funding/support	The NICE Guideline Updates Team is an internal team within NICE.

Field (based on PRISMA-P	Content
Name of sponsor	The NICE Guideline Updates Team is an internal team within NICE.
Roles of sponsor	The NICE Guideline Updates Team is an internal team within NICE.

1

Appendix B – Methods

Priority screening

The reviews undertaken for this guideline all made use of the priority screening functionality with the EPPI-reviewer systematic reviewing software. This uses a machine learning algorithm (specifically, an SGD classifier) to take information on features (1, 2 and 3 word blocks) in the titles and abstract of papers marked as being 'includes' or 'excludes' during the title and abstract screening process, and re-orders the remaining records from most likely to least likely to be an include, based on that algorithm. This re-ordering of the remaining records occurs every time 25 additional records have been screened.

As an additional check to ensure this approach did not miss relevant studies, the included studies lists of included systematic reviews were searched to identify any papers not identified through the primary search.

Incorporating published systematic reviews

For all review questions where a literature search was undertaken looking for a particular study design, systematic reviews containing studies of that design were also included. All included studies from those systematic reviews were screened to identify any additional relevant primary studies not found as part of the initial search.

Single-arm studies

Quality assessment of single-arm studies

Single-arm observational studies were quality assessed using the Institute of Health Economics (IHE) Quality Appraisal Checklist for Case Series Studies. Each of these studies were classified into one of the following three groups:

- Low risk of bias – The true result for the study is likely to be close to the estimated result
- Moderate risk of bias – There is a possibility the true result for the study is substantially different to the estimated result.
- High risk of bias – It is likely the true result for the study is substantially different to the estimated result.

Each individual study was also classified into one of three groups for directness, based on if there were concerns about the population, intervention, comparator and/or outcomes in the study and how directly these variables could address the specified review question. Studies were rated as follows:

- Direct – No important deviations from the protocol in population, intervention, comparator and/or outcomes.
- Partially indirect – Important deviations from the protocol in one of the population, intervention, comparator and/or outcomes.
- Indirect – Important deviations from the protocol in at least two of the following areas: population, intervention, comparator and/or outcomes.

GRADE approach was not utilised due to the nature of the evidence.

Cross-sectional surveys

Quality assessment of Cross-sectional surveys

Cross-sectional surveys were critically appraised using the Centre for Evidence-Based Management (CEBMa) checklist.

Each individual study was also classified into one of three groups for directness, based on if there were concerns about the population, intervention and/or outcomes in the study and how directly these variables could address the specified review question. Studies were rated as follows:

- Direct – No important deviations from the protocol in population, intervention and/or outcomes.
- Partially indirect – Important deviations from the protocol in one of the population, intervention and/or outcomes.
- Indirect – Important deviations from the protocol in at least two of the following areas: population, intervention and/or outcomes.

GRADE approach was not utilised for survey data due to the nature of the evidence.

Qualitative studies

Quality assessment of qualitative studies

Individual qualitative studies were quality assessed using the CASP qualitative checklist. Each individual study was classified into one of the following three groups:

- Low risk of bias – The findings and themes identified in the study are likely to accurately capture the true picture.
- Moderate risk of bias – There is a possibility the findings and themes identified in the study are not a complete representation of the true picture.
- High risk of bias – It is likely the findings and themes identified in the study are not a complete representation of the true picture

Each individual study was also classified into one of three groups for relevance, based on if there were concerns about the perspective, population, phenomenon of interest and/or setting in the included studies and how directly these variables could address the specified review question. Studies were rated as follows:

- Highly relevant – No important deviations from the protocol in perspective, population, phenomenon of interest and/or setting.
- Relevant – Important deviations from the protocol in one of the perspective, population, phenomenon of interest and/or setting.
- Partially relevant – Important deviations from the protocol in at least two of the perspective, population, phenomenon of interest and/or setting.

Methods for synthesising qualitative evidence

Where multiple qualitative studies were identified for a single question, information from the studies was combined using a thematic synthesis. By examining the findings of each included study, descriptive themes were independently identified and coded. Once all of the included studies had been examined and coded, the resulting themes and sub-

themes were evaluated to examine their relevance to the review question, the importance given to each theme, and the extent to which each theme recurred across the different studies. The qualitative synthesis then proceeded by using these 'descriptive themes' to develop 'analytical themes', which were interpreted by the reviewer in light of the overarching review questions.

CERQual for qualitative studies

CERQual was used to assess the confidence we have in the summary findings of each of the identified themes. Evidence from all qualitative study designs (interviews, focus groups etc.) was initially rated as high confidence and the confidence in the evidence for each theme was then downgraded from this initial point as detailed in Table 18below.

Table 18 Rationale for downgrading confidence in evidence for qualitative questions

CERQual criteria	Reasons for downgrading confidence
Methodological limitations	Not serious: If the theme was identified in studies at low risk of bias, the outcome was not downgraded Serious: If the theme was identified only in studies at moderate or high risk of bias, the outcome was downgraded one level. Very serious: If the theme was identified only in studies at high risk of bias, the outcome was downgraded two levels.
Relevance	High: If the theme was identified in highly relevant studies, the outcome was not downgraded Moderate: If the theme was identified only in relevant and partially relevant studies, the outcome was downgraded one level. Low: If the theme was identified only in partially relevant studies, the outcome was downgraded two levels.
Coherence	Coherence was addressed based on two factors: • Between study – does the theme consistently emerge from all relevant studies • Theoretical – does the theme provide a convincing theoretical explanation for the patterns found in the data The outcome was downgraded once if there were concerns about one of these elements of coherence, and twice if there were concerns about both elements.
Adequacy of data	The outcome was downgraded if there was insufficient data to develop an understanding of the phenomenon of interest, either due to insufficient studies, participants or observations.

Guidelines

Quality assessment of guidelines

The quality of the guidelines were assessed using the international criteria of quality for guidance development, as outlined by the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument.

When some AGREE II items were not applicable to the particular guideline under review, these items were not answered and were skipped. The domain scores were calculated and a quality threshold was agreed (by the appraisers) which was guided by the context in which the guideline was to be used and by evaluating the different domains and items in that context. See Appendix I.

Publication bias

If evidence of conducted but unpublished studies was identified during the review (e.g. conference abstracts or protocols without accompanying published results), available information on these unpublished studies was reported as part of the review.

Appendix C- Literature search strategies

A single systematic search was conducted for all the questions within this review on 1st March 2019. The following databases were searched MEDLINE, MEDLINE in Process, MEDLINE e pub Ahead of print, Embase, and PSYCINFO (all via the Ovid platform). The NICE inhouse qualitative filter was attached where appropriate.

The MEDLINE strategy is presented below. This was translated for other databases

1 Medical Marijuana/

2 cannabinoids/ or cannabidiol/ or cannabinol/ or cannabis/

3 ((cannabi* or hemp or marijuana or marihuana) adj4 (medicine* or medicinal or medical or oil or oils or product* or extract* or therap* or CBD or vap* or spray* or inhal* or compound* or resin* or derivative*)).tw.

4 (epidiolex* or cannabidiol* or cannabinoid*).tw.

5 (sativex or nabiximols or tetrabinex or nabidiolex).tw.

6 (nabilone or cesamet).tw.

7 (tilray* or bedrocan* or bedrobinol* or bedica* or bediol* or bedrolite*).tw.

8 Dronabinol/

9 (dronabinol* or marinol* or syndros*).tw.

10 (9-ene-tetrahydrocannabinol* or 9enetetrahydrocannabinol*).tw.

11 (THC or tetrahydrocannabinol*).tw.

12 ("delta(1)-thc*" or "delta(1)-tetrahydrocannabinol*" or "delta(9)-thc*" or "delta(9)-tetrahydrocannabinol*").tw.

13 (9-delta-tetra-hydrocannabinol* or "9-delta-THC*" or "9 delta tetra hydrocannabinol*" or "9 delta THC*").tw.

14 (1-delta-tetra-hydrocannabinol* or "1-delta-THC*" or "1 delta tetra hydrocannabinol" or "1 delta thc*").tw.

15 THCa.tw.

16 CBDa.tw.

17 cannabinol*.tw.

18 cannabigerol*.tw.

19 cannabichromene*.tw.

20 (tetrahydrocannabivarin* or THCV).tw.

21 (cannabidivarin* or CBDV).tw.

22 or/1-21

23 animals/ not humans/

24 22 not 23

25 limit 24 to english language

26 Qualitative Research/

27 Nursing Methodology Research/

28 Interview.pt.

29 exp Interviews as Topic/

30 Questionnaires/

31 Narration/

32 Health Care Surveys/

33 (qualitative$ or interview$ or focus group$ or questionnaire$ or narrative$ or narration$ or survey$).tw.

34 (ethno$ or emic or etic or phenomenolog$ or grounded theory or constant compar$ or (thematic$ adj4 analys$) or theoretical sampl$ or purposive sampl$).tw.

35 (hermeneutic$ or heidegger$ or husser$ or colaizzi$ or van kaam$ or van manen$ or giorgi$ or glaser$ or strauss$ or ricoeur$ or spiegelberg$ or merleau$).tw.

36 (metasynthes$ or meta-synthes$ or metasummar$ or meta-summar$ or metastud$ or meta-stud$ or metathem$ or meta-them$).tw.

37 "critical interpretive synthes*".tw.

38 (realist adj (review* or synthes*)).tw.

39 (noblit and hare).tw.

40 (meta adj (method or triangulation)).tw.

41 (CERQUAL or CONQUAL).tw.

42 ((thematic or framework) adj synthes*).tw.

43 or/26-42

44 25 and 43

Searches to identify economic evidence were run on 20th December 2018 in MEDLINE, MEDLINE in Process, MEDLINE e pub Ahead of print, Econlit and Embase (all via the Ovid platform), NHS EED and the Health Technology Assessment Database (via the CRD platform). NICE inhouse economic evaluation and Quality of Life filters were attached to lines 1 to 25 of the core strategy (lines 1 to 25 of the MEDLINE version shown above) in the MEDLINE and Embase databases. The MEDLINE version of the filters is displayed below.

Economic evaluations

1 Economics/

2 exp "Costs and Cost Analysis"/

3 Economics, Dental/

4 exp Economics, Hospital/

5 exp Economics, Medical/

6 Economics, Nursing/

7 Economics, Pharmaceutical/

8 Budgets/

9 exp Models, Economic/

10 Markov Chains/

11 Monte Carlo Method/

12 Decision Trees/

13 econom$.tw.

14 cba.tw.

15 cea.tw.

16 cua.tw.

17 markov$.tw.

18 (monte adj carlo).tw.

19 (decision adj3 (tree$ or analys$)).tw.

20 (cost or costs or costing$ or costly or costed).tw.

21 (price$ or pricing$).tw.

22 budget$.tw.

23 expenditure$.tw.

24 (value adj3 (money or monetary)).tw.

25 (pharmacoeconomic$ or (pharmaco adj economic$)).tw.

26 or/1-25

A search of the MHRA website was undertaken on the 24th January 2019 to look for safety updates, alerts and recalls. The search terms are displayed below.

Sativex

Dronabinol

Epidiolex

Nabiximols

Nabilone

Tetrabinex

Nabidiolex

Cesamet

Tilray

Bedrocan

Bedrobinol

Bedica

Bediol

Bedrolite

Marinol

Syndros

THC

Tetrahydrocannabinol

Cannabinol

Cannibigerol

Cannabichromene

Tetrahydrocannabivarin

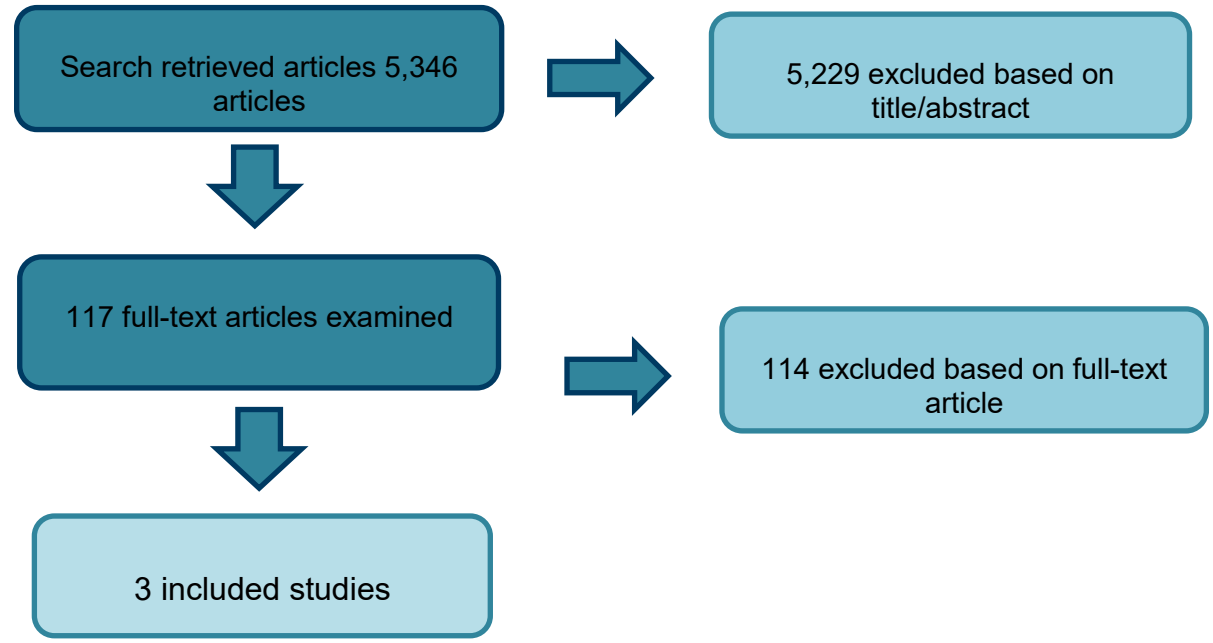
Cannabidivarin

A search for national and international guidance, regulation and policy was undertaken between 5th March 2019 and 28th March 2019. The NICE Evidence, TRIP, Health Departments of similar health systems which have licensed cannabis based medicines and Google websites were searched

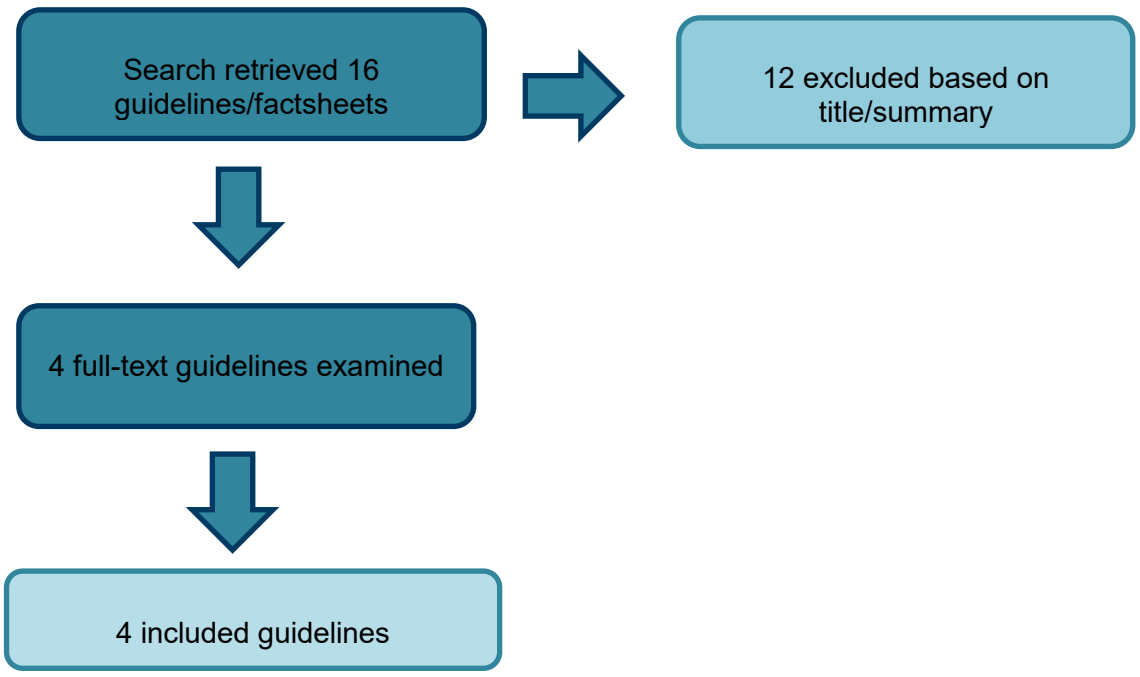
Appendix D – Clinical evidence study selection

Review question 2.1

Study selection

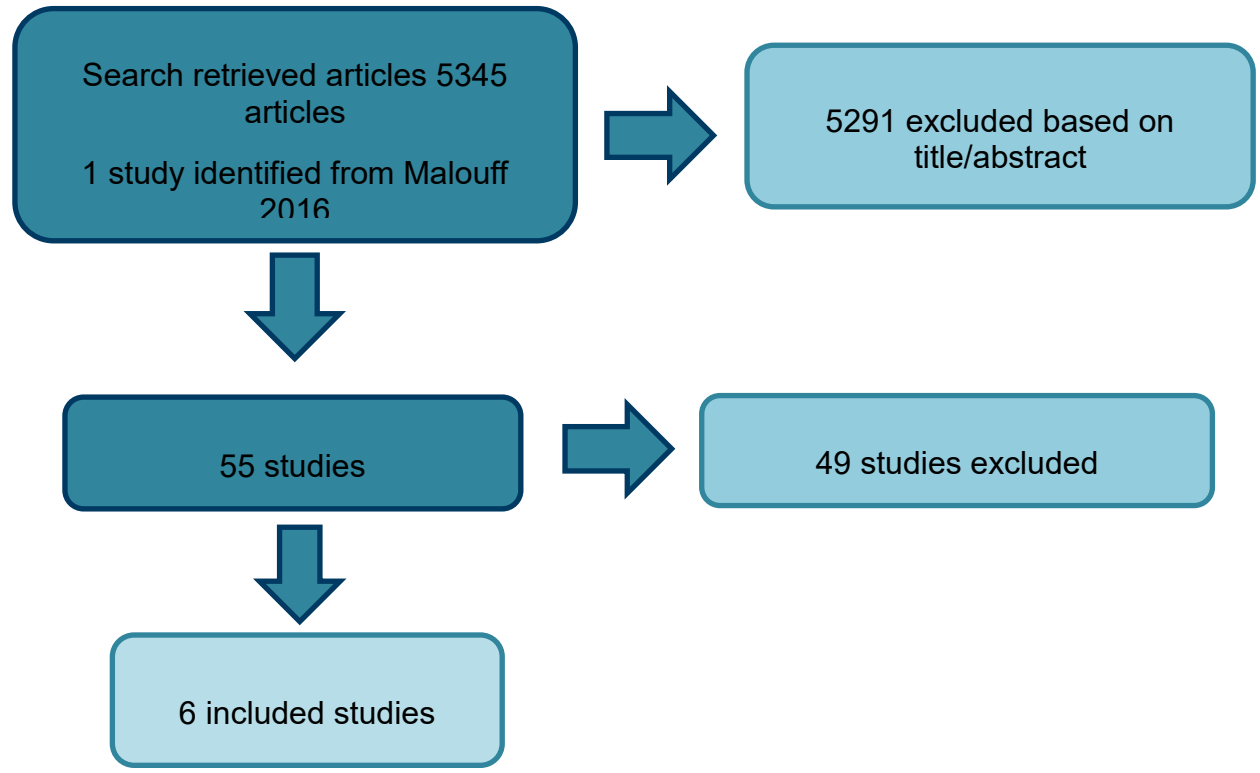


Guideline selection

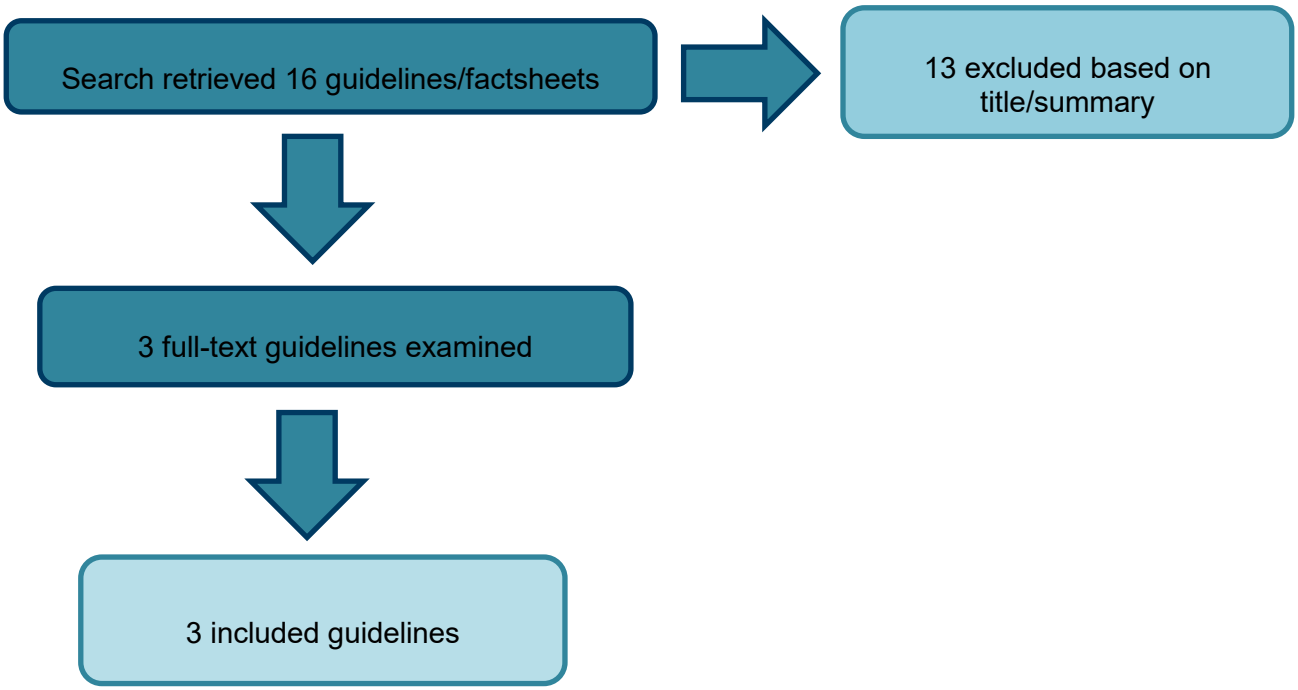


Review Question 2.2

Study selection

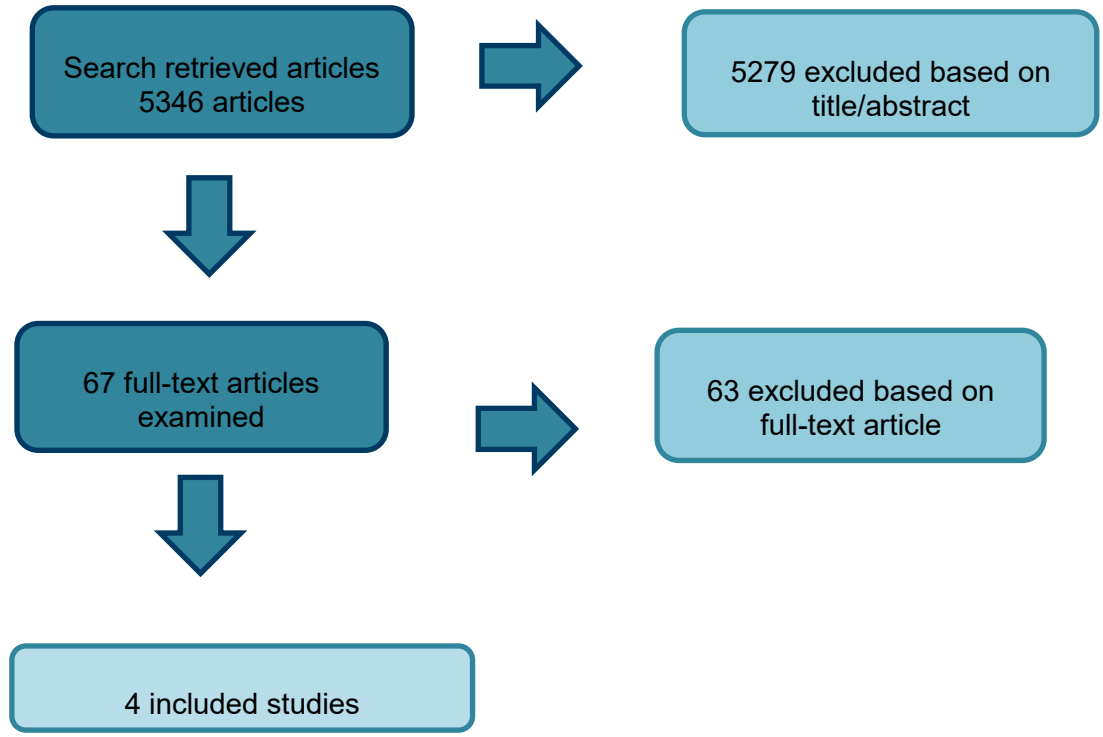


Guideline selection

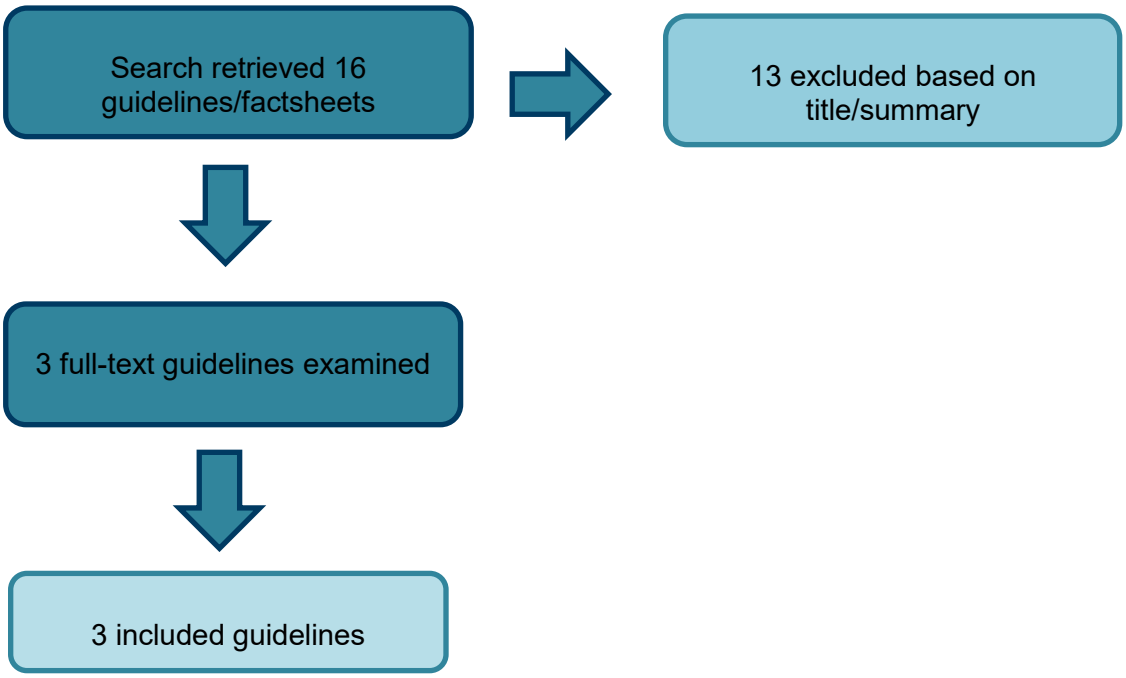


Review question 3

Study selection



Guideline selection



Appendix E – Clinical evidence table

Review question 2.1

E.1 Ware 2018

Ware, 2018	
Bibliographic Reference	Ware, Mark A.; Martel, Marc O.; Jovey, Roman; Lynch, Mary E.; Singer, Joel; A prospective observational study of problematic oral cannabinoid use; Psychopharmacology; 2018; vol. 235 (no. 2); 409-417

Study details

Study type	Prospective observational study
Study location	Canada
Study setting	12 out-patient clinics
Study dates	July 2009 - 2011
Duration of follow-up	12 months
Sources of funding	Valeant Pharmaceuticals
Inclusion criteria	Aged 18 years or over Started cannabinoid therapy in previous 14 days Prescribed cannabinoid medication during the course of normal practice at a pain, MS, HIV, physical rehabilitation or other clinic
Exclusion criteria	Previously prescribed cannabinoids People with a medical condition or reason that could interfere with study participation or protocol adherence Substance abuse history not grounds for exclusion
Sample size	265
% Female	69.7%
Mean age (SD)	49.2 (11.9)
Interventions	Sativex 9.2% of participants

Study type	Prospective observational study
	Nabilone 89.7% of participants Sativex in addition to nabilone 1.1% of participants
Outcome measures	Misuse (Current Opioid Misuse Measure) Comparisons made for psychiatric history and daily use of alcohol, tobacco or herbal cannabis Misuse (Addiction Behavior Checklist) Comparisons made for psychiatric history and daily use of alcohol, tobacco or herbal cannabis Misuse (Chadal Prescription Opioid Abuse Checklist) Comparisons made for psychiatric history and daily use of alcohol, tobacco or herbal cannabis

1

Risk of bias
Study objective Was the hypothesis/aim/objective of the study clearly stated? Yes Study design Was the study conducted prospectively? Yes Were the cases collected in more than one centre? Yes Were patients recruited consecutively? Unclear Study population Were the characteristics of the patients included in the study described? Yes Were the eligibility criteria (i.e. inclusion and exclusion criteria) for entry into the study clearly stated? Yes Did patients enter the study at a similar point in the disease?

Risk of bias
Unclear
Intervention and co-intervention
Was the intervention of interest clearly described?
Yes
Outcome measure
Were relevant outcome measures established a priori?
Yes
Were outcome assessors blinded to the intervention that patients received?
No
Were the relevant outcomes measured using appropriate objective/subjective methods?
Yes
Were the relevant outcome measures made before and after the intervention?
No
(Patients had already started CBD treatment within 14 days of the beginning of the study)
Statistical analysis
Were the statistical tests used to assess the relevant outcomes appropriate?
Yes
Results and conclusions
Was follow-up long enough for important events and outcomes to occur?
Yes
Were losses to follow-up reported?
No
Were the adverse events reported?
Yes
Were the conclusions of the study supported by results?
Yes
Competing interests and sources of support
Were both competing interests and sources of support for the study reported?
Yes

Risk of bias
Overall Risk of Bias Risk of Bias Moderate (Patient-reported subjective outcomes. Outcomes were only assessed after the beginning of the intervention) Applicability Directly applicable

1

2 E.2 Kirk 1999

Kirk, 1999	
Bibliographic Reference	Kirk, J. M.; de Wit, H.; Responses to oral delta9-tetrahydrocannabinol in frequent and infrequent marijuana users; Pharmacology, biochemistry, and behavior; 1999; vol. 63 (no. 1); 137-42

3 **Study details**

Study location	USA
Study setting	Laboratory
Study dates	Not reported
Duration of follow-up	N/A
Sources of funding	DA03517
Inclusion criteria	Frequent group - use of marijuana at least 100 times in their lifetime Frequent group - marijuana use for at least 1 year and current use at least twice per month Infrequent group - reported using marijuana 10 or fewer times in their lifetime and no use in previous 4 years
Exclusion criteria	None reported
Sample size	21
Outcome measures	Adverse events (feeling "high") Adverse events (sedation) Satisfaction (VAS scale of "like" effects)

Study arms

Frequent marijuana users (N = 11)	
Split between study groups	11
% Female	36%
Mean age (SD)	27.6 (5.18)
Interventions	Δ9-THC Marinol 7.5 or 15 mg
Infrequent marijuana users (N = 10)	
Split between study groups	10
% Female	50%
Mean age (SD)	25.1 (3.57)
Interventions	Placebo

Risk of bias
1. Bias due to confounding
1.1 Is there potential for confounding of the effect of intervention in this study?

Risk of bias
Probably no
Risk of bias judgement for confounding
Low
2. Bias in selection of participants into the study
2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4
No
2.4. Do start of follow-up and start of intervention coincide for most participants?
Yes
Risk of bias judgement for selection of participants into the study
Low
3. Bias in classification of interventions
3.1 Were intervention groups clearly defined?
Yes
3.2 Was the information used to define intervention groups recorded at the start of the intervention?
Probably no
3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?
Probably no
Risk of bias judgement for classification of interventions
Low
4. Bias due to deviations from intended interventions
4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?
No
Risk of bias judgement for deviations from intended interventions
Low
5. Bias due to missing data
5.1 Were outcome data available for all, or nearly all, participants?
Probably yes
5.2 Were participants excluded due to missing data on intervention status?

Risk of bias
No
(All participants completed every intervention)
Risk of bias judgement for missing data
Low
6. Bias in measurement of outcomes
6.1 Could the outcome measure have been influenced by knowledge of the intervention received?
Yes
6.2 Were outcome assessors aware of the intervention received by study participants?
No information
(No information about outcome assessors)
6.3 Were the methods of outcome assessment comparable across intervention groups?
Yes
6.4 Were any systematic errors in measurement of the outcome related to intervention received?
Probably no
Risk of bias judgement for measurement of outcomes
Low
7. Bias in selection of the reported result
7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?
Probably no
7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?
Probably no
7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?
Probably no
Risk of bias judgement for selection of the reported result
Low
Overall bias
Risk of bias judgement
Serious
(Assignment to study arm based solely on participant's self-reported use of marijuana)

Risk of bias
Directness Partially Applicable (Investigates use of THC in healthy people rather than those who may be prescribed cannabis-based products)

1

2 **Notcutt 2013**

Notcutt, 2013	
Bibliographic Reference	Notcutt, William G.; A questionnaire survey of patients and carers of patients prescribed Sativex as an unlicensed medicine; Primary health care research & development; 2013; vol. 14 (no. 2); 192-9

3 **Study details**

Study type	**Survey**
Study location	UK
Study setting	Sent to patients of GPs who had prescribed Sativex
Study dates	Not reported
Duration of follow-up	N/A
Sources of funding	GW Pharmaceuticals
Inclusion criteria	Received at least 2 prescriptions of Sativex within 16 weeks prior to study entry
Exclusion criteria	None reported
Sample size	124
% Female	62%
Mean age (SD)	Median (range): 56 (28-83)
Condition specific characteristics	Taking Sativex for spasticity 49% Taking Sativex to relieve pain 44% Taking Sativex to improve sleep

Study type	Survey
	6% Taking Sativex for other reasons 2%
Interventions	Sativex Median dose 6 sprays per day. 22% used over 8 sprays per day
Outcome measures	Diversion (Have patients ever shared their medication?) Diversion (Have patients ever lost their medication?)

1

1. Did the study address a clearly focused question / issue? Yes 2. Is the research method (study design) appropriate for answering the research question? Yes 3. Is the method of selection of the subjects (employees, teams, divisions, organisations) clearly described? Yes 4. Could the way the sample was obtained introduce (selection) bias? Yes Only GPs who had prescribed Sativex in the previous 16 weeks. No minimum time for taking Sativex so might miss long-term effects 5. Was the sample of subjects representative with regard to the population to which the findings will be referred? Can't tell 6. Was the sample size based on pre-study considerations of statistical power? No 7. Was a satisfactory response rate achieved? No (57%) 8. Are the measurements (questionnaires) likely to be valid and reliable? Can't tell 9. Was the statistical significance assessed? No

10. Are confidence intervals given for the main results? No 11. Could there be confounding factors that haven't been accounted for? Yes 12. Can the results be applied to your organisation N/A Overall bias Risk of bias judgement High (Unvalidated surveys and low response rate for people returning questionnaires) Directness Directly Applicable

Review question 2.2

Carlini 2017

Carlini, 2017

Bibliographic Reference	Carlini, Beatriz H.; Garrett, Sharon B.; Carter, Gregory T.; Medicinal Cannabis: A Survey Among Health Care Providers in Washington State; The American journal of hospice & palliative care; 2017; vol. 34 (no. 1); 85-91

Study details

Study type	**Cross-sectional survey**
Study location	USA
Study setting	Online survey
Study dates	March 1st 2014 to May 30th 2014
Duration of follow-up	3 months
Sources of funding	Funding for the survey was granted to the first author through a Cy Pres grant from the Washington State Attorney Genral's Office.
Inclusion criteria	Participants were practicing healthcare professionals in Washington State, including medical doctors (MDs), physician assistants (PAs), osteopathic physicians (DOs), osteopathic physician assistants (OAs), naturopathic physicians (NDs), advanced registered practitioners (ARNPs), registered nurses (RNs), licensed nurses (LNP) and pharmacists.
Exclusion criteria	Participants reporting not being a healthcare professional or not practicing in the state of Washington.
Sample size	494 respondents Included 132 ARNPs, 73 NPs, 53 MDs, 21 PAs and 3 OPs Respondents not legally allowed to write medical cannabis authorisations were mostly pharmacists (n=118) and RNs or LNPs (n=72).
% Female	68.7%
Mean age (SD)	Aged between 30 and 60 years
Interventions	Medical Cannabis

Study type	Cross-sectional survey
	Study states that the law (in Washington state) specifies the types of clinicians allowed to write a medicinal cannabis recommendation include medical doctors, physician assistants, osteopathic physicians, osteopathic physician assistants, naturopathic physicians and advanced registered nurse practitioners.
Outcome measures	Education/ Training needs In 2013, the Washington Attorney General's Office awarded the authors a grant to develop and deliver a comprehensive training program for Washington State healthcare providers regarding the scientific basis, clinical implications and legal ramifications for using medical cannabis to treat/manage chronic pain.

1

Centre for Evidence-Based Management (CEBMa) Critical Appraisal of a Survey	
Did the study address a clearly focused question/ issue?	Yes
Is the research method (study design) appropriate for answering the research question?	Yes
Is the method of selection of the subjects (employees, teams, divisions, organisations) clearly described?	Yes - Recruitment was done via professional organisation and social media. 25 Washington State based professional associations and healthcare organisations were contacted with a request to disseminate the survey. Online survey was also disseminated via numerous web site and blogs managed by the University of Washing Alcohol and Drug Abuse Institute Library (ADAI) and the Health Evidence Resource for Washington State (HEAL-WA).
Could the way sample was obtained introduce (selection) bias?	Yes- may have been introduced due to participants' self-selected participation. Also, authors stated that data was obtained anonymously, and its dissemination depended on the willingness of health professional organisational to support the study therefore it was not possible to prevent someone from responding to the survey more than once.
Was the sample of subjects representative with regard to the population to which the findings will be referred?	No- Authors state that the results cannot be generalised to healthcare providers in Washington state as a whole.
Was the sample size based on pre-study considerations of statistical power?	Can't tell – no information provided
Was a satisfactory response rate achieved?	Can't tell- however authors stated that dissemination depended on the willingness of health professional organisational to support the study

Centre for Evidence-Based Management (CEBMa) Critical Appraisal of a Survey	
	therefore it was not possible to prevent someone from responding to the survey more than once.
Are the measurements (questionnaires) likely to be valid and reliable?	Can't tell – no information provided
Was the statistical significance assessed?	Yes
Are confidence intervals given for the main results?	No
Could there be confounding factors that haven't been accounted for?	Can't tell – no information provided
Can the results be applied to your organization?	Yes
Overall Quality	**Low –** Selection bias may have been introduced. It is also unclear if questionnaire was valid and reliable. Response rate not reported and there was a potential for participants to respond more than once. Additionally, sample of subjects were not representative with regard to population to which the findings were referred to.
Directness	**Partially Direct-** Study does not explicitly state which cannabis-based products were being prescribed.

1 **Ebert 2015**

Ebert, 2015

2

Bibliographic Reference	Ebert, Tanya; Zolotov, Yuval; Eliav, Shani; Ginzburg, Orit; Shapira, Irena; Magnezi, Racheli; Assessment of Israeli Physicians' Knowledge, Experience and Attitudes towards Medical Cannabis: A Pilot Study; The Israel Medical Association journal : IMAJ; 2015; vol. 17 (no. 7); 437-41

3 **Study details**

Study type	Cross-sectional survey
Study location	Israel
Study setting	Not specified
Study dates	October 2013 (exact dates are not specified)
Duration of follow-up	2 weeks

Study type	Cross-sectional survey
Sources of funding	Not specified
Inclusion criteria	Israeli physicians of different specialties
Exclusion criteria	Not specified
Sample size	100 physicians This included physicians of the following specialities: - oncology - pain medicine - rehabilitation - psychiatry -neurology
% Female	34.7%
Mean age (SD)	50.5 ± 9.4 years (range 35–67)
Interventions	Medical Cannabis Study states the Israeli Ministry of Health issues licences to certain patients after approving a specialist physician's recommendation. Thus, physicians in Israel cannot directly prescribe medical cannabis to patients but can sign a medical recommendation that is then processed by the Health Ministry
Outcome measures	Education/ Training needs

1

Centre for Evidence-Based Management (CEBMa) Critical Appraisal of a Survey	
Did the study address a clearly focused question/ issue?	Yes
Is the research method (study design) appropriate for answering the research question?	Yes
Is the method of selection of the subjects (employees, teams, divisions, organisations) clearly described?	No- no information provided
Could the way sample was obtained introduce (selection) bias?	Can't tell – no information provided as to how subjects were selected
Was the sample of subjects representative with regard to the population to which the findings will be referred?	No- Authors state that the sample was small and not necessarily representative of the physician population in Israel since most of the

Centre for Evidence-Based Management (CEBMa) Critical Appraisal of a Survey	
	participants were from one area and the spectrum of specialities was limited.
Was the sample size based on pre-study considerations of statistical power?	Can't tell – no information provided
Was a satisfactory response rate achieved?	Yes- response rate was 72%
Are the measurements (questionnaires) likely to be valid and reliable?	Can't tell – no information provided
Was the statistical significance assessed?	Yes
Are confidence intervals given for the main results?	No
Could there be confounding factors that haven't been accounted for?	Can't tell – no information provided
Can the results be applied to your organization?	Yes
Overall Quality	**Low –** Method of participant selection not specified, unclear if selection bias was introduced. It is also unclear if questionnaire was valid and reliable. Additionally, sample of subjects were not representative with regard to population to which the findings were referred to.
Directness	**Partially Direct-** Study does not explicitly state which cannabis-based products were being prescribed.

1 **Hwang 2016**

Hwang, 2016	
Bibliographic Reference	Hwang, Joy; Arneson, Tom; St Peter, Wendy; Minnesota Pharmacists and Medical Cannabis: A Survey of Knowledge, Concerns, and Interest Prior to Program Launch; P & T : a peer-reviewed journal for formulary management; 2016; vol. 41 (no. 11); 716-722

2 **Study details**

Study type	Cross-sectional survey
Study location	Minnesota, USA
Study setting	No setting. This was an online survey conducted 2 months before the implementation of the state-wide medical cannabis program.
Study dates	End of March 2015- May 1st 2015
Sources of funding	Not reported

Study type	Cross-sectional survey
Inclusion criteria	All pharmacists whose email addresses were registered with the Minnesota Board of Pharmacy's database.
Exclusion criteria	Not specified
Sample size	738 pharmacists
Mean age (SD)	Age ranges: <34 years: 35% 35-44 years: 26% 45-54 years: 14% 55-64 years: 19% 65-74 years: 5% 75+ years: 1%
Interventions	Medical Cannabis Study states in the Minnesota Medical Cannabis Program, only non-smoked forms of medical cannabis are permitted. These include oral liquids (including oils), tablets, capsules, and vaporised cannabis extracts (liquids or oils).
Outcome measures	Education/ Training needs Study states that in Minnesota, pharmacists provide registered patients with consultations at one of the state-approved cannabis distribution centres. They are the only healthcare professionals who are permitted to dispense cannabis products. Four questions were developed to explore education needs and preferred method of delivery among pharmacists

1

Centre for Evidence-Based Management (CEBMa) Critical Appraisal of a Survey	
Did the study address a clearly focused question/ issue?	Yes
Is the research method (study design) appropriate for answering the research question?	Yes
Is the method of selection of the subjects (employees, teams, divisions, organisations) clearly described?	Yes
Could the way sample was obtained introduce (selection) bias?	Yes- Authors state that selection bias may have been introduced by participants' self-selected participation.
Was the sample of subjects representative with regard to the population to which the findings will be referred?	No- Authors state that in comparison with Minnesota's statistics on the state's pharmacists, survey respondents were younger, more likely to

Centre for Evidence-Based Management (CEBMa) Critical Appraisal of a Survey	
	be from nonrural areas and more likely to practice in clinical and hospital settings rather than in community dispensing pharmacies.
Was the sample size based on pre-study considerations of statistical power?	Can't tell – no information provided
Was a satisfactory response rate achieved?	No- response rate was 10%
Are the measurements (questionnaires) likely to be valid and reliable?	Can't tell – no information provided
Was the statistical significance assessed?	Can't tell – no information provided
Are confidence intervals given for the main results?	No
Could there be confounding factors that haven't been accounted for?	Can't tell – no information provided
Can the results be applied to your organization?	Yes
Overall Quality	**Low –** Selection bias may have been introduced. It is also unclear if questionnaire was valid and reliable. Additionally, sample of subjects were not representative with regard to population to which the findings were referred to and response rate was very low.
Directness	**Partially Direct-** Study does not explicitly state which cannabis-based products were being prescribed.

1 **Isaac 2016**

Isaac, 2016	
Bibliographic Reference	Isaac, Sami; Saini, Bandana; Chaar, Betty B.; The Role of Medicinal Cannabis in Clinical Therapy: Pharmacists' Perspectives; PloS one; 2016; vol. 11 (no. 5); e0155113

2 **Study Characteristics**

Study type	Semi structured interviews
Study details	Study location Australia Study setting Not specified. Study methods

Study type	Semi structured interviews
	The sample strategy involved a convenience sampling of Australian pharmacists (including practising pharmacists, academics and . Leading Representatives of Professional Organisations (LRPO)) followed by a passive snowballing as a result of individual requests to participate. An interview protocol was developed based on research literature on medicinal cannabis and practice experience of the researching team. The semi-structured interviews incorporated open-ended questions to enable the exploration of new ideas with prompts to allow deeper probing and expansion of key issues relating to medicinal cannabis. For uniformity, the interviews were conducted by one interviewer and were between 10-20 minutes in length each. They were audio recorded following participants consent, transcribed ad verbatim and de-identified. Study dates July- November 2015 Sources of funding Authors had no support or funding
Inclusion Criteria	Interviewees were currently registered with the Australian Health Practitioner Regulation Agency as pharmacists, and willing to express their views on the legalisation of medicinal cannabis
Exclusion criteria	Not specified
Sample characteristics	Sample size 34 registered pharmacists Reason for stopping recruitment Not specified. Mean age (SD) 20 to 29: 50%, 30 to 39: 23%, 40 to 49:12%, 50 to 59: 9%, 60+: 6% Number of years in practice ≤ 1 year: 12%, 1 to 5 years: 32%, 6 to 10 years: 18%, 11 to 15 years: 12%, 16 to 20 years: 3%, ≥21 years: 23% Primary Roles Practicing Pharmacists: 73%, Academia: 9%, Leading representatives of professional organisations (LRPO): 18%
Thematic Analysis	Professional training and public awareness Finding 1: The majority of the participants suggested the need for development of new training courses and learning opportunities, in order to ensure a greater understanding of the effects of medicinal cannabis: “There will need to be education campaigns for pharmacists, consumers and probably all healthcare professionals around this issue when cannabis is legalised” “Pharmacists have a great capacity…to learn and then disseminate information...to educate the public.”

1

CASP checklist
Aims of the research
Overall, based on the above, was there a clear statement of the aims of the research?
Yes
Appropriateness of methodology
Overall, based on the above, is a qualitative methodology appropriate?
Yes
Research Design
Overall, based on the above, was the research design appropriate to address the aims of the research?
Yes
Recruitment Strategy
Overall, based on the above, was the recruitment strategy appropriate to the aims of the research?
Yes
Data collection
Overall, based on the above, was the data collected in a way that addressed the research issue?
Yes
Researcher and participant relationship
Overall, based on the above, has the relationship between researcher and participants been adequately considered?
No
Ethical Issues
Overall, based on the above, have ethical issues been taken into consideration?
Yes
Data analysis
Overall, based on the above, was the data analysis sufficiently rigorous?
Yes
Findings
Overall, based on the above, is there a clear statement of findings?
Yes
Research value

CASP checklist
Overall, based on the above, how valuable is the research? Valuable **Overall risk of bias and directness** **Overall risk of bias** Moderate **Directness** Partially directly applicable Unclear mode of administration of cannabis based medicinal products.

1 **St-Amant 2015**

St-Amant, 2015	
Bibliographic Reference	St-Amant, Huguette; Ware, Mark A.; Julien, Nancy; Lacasse, Anais; Prevalence and determinants of cannabinoid prescription for the management of chronic noncancer pain: a postal survey of physicians in the Abitibi-Temiscamingue region of Quebec; CMAJ open; 2015; vol. 3 (no. 2); E251-7

2 **Study details**

Study type	Cross-sectional survey
Study location	Quebec, Canada
Study setting	No setting. Postal survey
Study dates	Not specifed
Sources of funding	This study was funded by the Fonds institutionnel de developpement de la recherche et de la creation of Université du Québec en Abitibi- Témiscamingue.
Inclusion criteria	Physicians practicing in south-western Quebec
Exclusion criteria	Not specified
Sample size	166 respondents Of the 166, 127 did not prescribe cannabinoids and 38 prescribed cannabinoids.
% Female	53.8%
Interventions	Cannabinoids

Study type	Cross-sectional survey
	Study defines cannabinoids as pharmaceutical product s of a therapeutic class that include psychoactive constituents of the Cannabis sativa plant (THC) or synthetic analogues that can be prescribed to produce analgesia via the endocannabinoid system.
Outcome measures	Education/ Training needs Respondents were asked about factors that could increase their comfort level with prescribing cannabinoids for chronic non cancer pain

1

Centre for Evidence-Based Management (CEBMa) Critical Appraisal of a Survey	
Did the study address a clearly focused question/ issue?	Yes
Is the research method (study design) appropriate for answering the research question?	Yes
Is the method of selection of the subjects (employees, teams, divisions, organisations) clearly described?	Yes
Could the way sample was obtained introduce (selection) bias?	Yes- selection bias may have been introduced by participants' self-selected participation.
Was the sample of subjects representative with regard to the population to which the findings will be referred?	No
Was the sample size based on pre-study considerations of statistical power?	Can't tell – no information provided
Was a satisfactory response rate achieved?	Yes- response rate was 52.2%
Are the measurements (questionnaires) likely to be valid and reliable?	Can't tell – no information provided
Was the statistical significance assessed?	Yes
Are confidence intervals given for the main results?	No
Could there be confounding factors that haven't been accounted for?	Can't tell – no information provided
Can the results be applied to your organization?	Yes
Overall Quality	**Low –** Selection bias may have been introduced. It is also unclear if questionnaire was valid and reliable. Additionally, sample of subjects were not representative with regard to population to which the findings were referred to.
Directness	**Partially Direct-** Study looked at the prescribing of nabilone and nabiximols as well as medical marijuana.

1 Zylla 2018

Zylla, 2018	
Bibliographic Reference	Zylla, Dylan; Steele, Grant; Eklund, Justin; Mettner, Jeanne; Arneson, Tom; Oncology Clinicians and the Minnesota Medical Cannabis Program: A Survey on Medical Cannabis Practice Patterns, Barriers to Enrollment, and Educational Needs; Cannabis and cannabinoid research; 2018; vol. 3 (no. 1); 195-202

2 **Study details**

Study type	Cross-sectional survey
Study location	Minnesota, USA
Study setting	No setting. Study included an online survey. Those who did not respond to the email were sent a paper version of the survey.
Study dates	June to August 2017
Sources of funding	Not specified.
Inclusion criteria	Oncology providers practicing in Minnesota
Exclusion criteria	Not specified
Sample size	153 medical oncologists/ oncology nurse practitioners/ oncology physician assistants In the 153 respondents, 68 were identified as registered respondents. Registered respondents were providers who stated that they had registered with Minnesota Board of Medical Practice (MMCP) and were thus eligible to certify for medicinal cannabis.
Interventions	Medical Cannabis Authors note that in Minnesota, medical cannabis has been available since July 2015 through the Minnesota Medical Cannabis Program (MMCP). Paper does not state specific cannabis based products.
Outcome measures	Education/ Training needs Authors note that any clinician (physician, advanced practice registered nurse or physician assistant) may register with MMCP and can then certify patients with cannabis-eligible diagnoses for which they actively manage. Eligible diagnoses currently include epilepsy, cancer, intractable pain, HIV/AIDS and many others. In the questionnaire, one question asked about what additional education the providers wanted regarding medical cannabis.

3

4

Centre for Evidence-Based Management (CEBMa) Critical Appraisal of a Survey	
Did the study address a clearly focused question/ issue?	Yes
Is the research method (study design) appropriate for answering the research question?	Yes
Is the method of selection of the subjects (employees, teams, divisions, organisations) clearly described?	Yes
Could the way sample was obtained introduce (selection) bias?	Yes- selection bias may have been introduced by participants' self-selected participation.
Was the sample of subjects representative with regard to the population to which the findings will be referred?	No – Authors state that sample was not generalisable to other states
Was the sample size based on pre-study considerations of statistical power?	Can't tell – no information provided
Was a satisfactory response rate achieved?	No- response rate was 29%
Are the measurements (questionnaires) likely to be valid and reliable?	Can't tell – no information provided
Was the statistical significance assessed?	Can't tell – no information provided
Are confidence intervals given for the main results?	No
Could there be confounding factors that haven't been accounted for?	Can't tell – no information provided
Can the results be applied to your organization?	Yes
Overall Quality	**Low –** Selection bias may have been introduced. It is also unclear if questionnaire was valid and reliable. Additionally, sample of subjects were not representative with regard to population to which the findings were referred to and response rate was very low.
Directness	**Partially Direct-** Study does not explicitly state which cannabis-based products were being prescribed.

Review question 3

Karanges 2018

Karanges, 2018	
Bibliographic Reference	Karanges, Emily A.; Suraev, Anastasia; Elias, Natalie; Manocha, Ramesh; McGregor, Iain S.; Knowledge and attitudes of Australian general practitioners towards medicinal cannabis: a cross-sectional survey; BMJ open; 2018; vol. 8 (no. 7); e022101

1 **Study details**

Study type	Cross-sectional survey
Study location	Australia
Study setting	Printed surveys distributed at one-day general practice educational seminars in five major Australian cities (Sydney, Melbourne, Brisbane, Adelaide and Perth)
Study dates	August and November 2017
Sources of funding	This work was supported by the Lambert initiative for Cannabinoid Therapeutics at the University of Sydney.
Inclusion criteria	All GPs and GP registrars were eligible to participate
Exclusion criteria	Not specified
Sample size	640 participants
% Female	67.3%
Mean age (SD)	Age ranges: <35: 8.9% 35-44: 20.9% 45-54: 27.2% 55-64: 28.9% 65+: 13.6%
Interventions	Medicinal cannabis Study details that in Australia, doctors wishing to prescribe medicinal cannabis products must either apply to become authorised prescribers for a class of patients, or apply for access for individual patients under the 'Special Access Scheme Category B (SAS-B)' via the Therapeutic Goods Administration (TGA), a regulatory body for therapeutic goods in Australia. Study does not detail specific cannabis-based products.
Outcome measures	Views of GPs on cannabis access models Authors stated that Australian general practitioners (GPs) are typically only permitted to prescribe medicinal cannabis if supported by a specialist. Nonetheless, GPs are generally the first point of contact for patients enquiring about, or seeking access to, medicinal cannabis. Survey included questions on access models and preferred prescriber.

1

Centre for Evidence-Based Management (CEBMa) Critical Appraisal of a Survey	
Did the study address a clearly focused question/ issue?	Yes
Is the research method (study design) appropriate for answering the research question?	Yes
Is the method of selection of the subjects (employees, teams, divisions, organisations) clearly described?	Yes
Could the way sample was obtained introduce (selection) bias?	No
Was the sample of subjects representative with regard to the population to which the findings will be referred?	No – Authors state that the survey respondents differed on a number of demographic and practice characteristics to the general population of GPs in Australia, suggestive of a non-representative sample.
Was the sample size based on pre-study considerations of statistical power?	Can't tell – no information provided
Was a satisfactory response rate achieved?	No- response rate was 37%
Are the measurements (questionnaires) likely to be valid and reliable?	Can't tell – no information provided
Was the statistical significance assessed?	Can't tell – no information provided
Are confidence intervals given for the main results?	No
Could there be confounding factors that haven't been accounted for?	Can't tell – no information provided
Can the results be applied to your organization?	Yes
Overall Quality	**Low –** Selection bias may have been introduced. It is also unclear if questionnaire was valid and reliable. Additionally, sample of subjects were not representative with regard to population to which the findings were referred to and response rate was low.
Directness	**Partially Direct-** Study does not explicitly state which cannabis-based products were being prescribed.

2 **Klotz 2018**

Klotz, 2018	
Bibliographic Reference	Klotz, Kerstin A.; Schulze-Bonhage, Andreas; Antonio-Arce, Victoria San; Jacobs, Julia; Cannabidiol for Treatment of Childhood Epilepsy-A Cross-Sectional Survey; Frontiers in neurology; 2018; vol. 9; 731

1 **Study details**

Study type	Cross-sectional survey
Study location	Germany
Study setting	Various. Study included participants from Germany, Spain, Austria, Switzerland, Netherlands, Belgium, France and Italy.
Study dates	December 2017 to March 2018
Sources of funding	Not reported
Inclusion criteria	European practitioners treating children and adolescents for epilepsy 8 different European countries
Exclusion criteria	Not specified
Sample size	155 physicians treating children and adolescents with epilepsy form 8 different European countries
Interventions	Cannabinoids Study examined the use of CBD amongst European practitioners treating children and adolescents for epilepsy. This included preparations which included THC.
Outcome measures	Prevalence of prescribing

2

Centre for Evidence-Based Management (CEBMa) Critical Appraisal of a Survey	
Did the study address a clearly focused question/ issue?	Yes
Is the research method (study design) appropriate for answering the research question?	Yes
Is the method of selection of the subjects (employees, teams, divisions, organisations) clearly described?	Yes
Could the way sample was obtained introduce (selection) bias?	Yes- selection bias may have been introduced by participants' self-selected participation.
Was the sample of subjects representative with regard to the population to which the findings will be referred?	No – Authors noted that number and percentages of CBD prescribers may have been overestimated as this was indicated by a substantial variation of responses between countries. These numbers could not be related to the total number of physicians that were treating children and adolescents with CBD in participating countries.
Was the sample size based on pre-study considerations of statistical power?	Can't tell – no information provided

Centre for Evidence-Based Management (CEBMa) Critical Appraisal of a Survey	
Was a satisfactory response rate achieved?	Can't tell – Authors stated that as the survey was open access, they could not generate a response rate
Are the measurements (questionnaires) likely to be valid and reliable?	Can't tell – no information provided
Was the statistical significance assessed?	No
Are confidence intervals given for the main results?	No
Could there be confounding factors that haven't been accounted for?	Can't tell – no information provided
Can the results be applied to your organization?	Yes
Overall Quality	**Low –** Selection bias may have been introduced. It is also unclear if questionnaire was valid and reliable. Additionally, sample of subjects were not representative with regard to population to which the findings were referred to and response rate could not be calculated.
Directness	**Direct**

1 **Isaac 2016**

Isaac, 2016	
Bibliographic Reference	Isaac, Sami; Saini, Bandana; Chaar, Betty B.; The Role of Medicinal Cannabis in Clinical Therapy: Pharmacists' Perspectives; PloS one; 2016; vol. 11 (no. 5); e0155113

2 **Study Characteristics**

Study type	Semi structured interviews
Study details	Study location Australia Study setting Not specified. Study methods The sample strategy involved a convenience sampling of Australian pharmacists. Leading Representatives of Professional Organisations (LRPO) were also sampled and was followed by a passive snowballing as a result of individual requests to participate. An interview protocol was developed based on research literature on medicinal cannabis and practice experience of the researching

Study type	Semi structured interviews
	team. The semi-structured interviews incorporated open-ended questions to enable the exploration of new ideas with prompts to allow deeper probing and expansion of key issues relating to medicinal cannabis. For uniformity, the interviews were conducted by one interviewer and were between 10-20 minutes in length each. They were audio recorded following participants consent, transcribed ad verbatim and de-identified. Study dates July- November 2015 Sources of funding Authors had no support or funding
Inclusion Criteria	Interviewees were currently registered with the Australian Health Practitioner Regulation Agency as pharmacists, and willing to express their views on the legalisation of medicinal cannabis
Exclusion criteria	Not specified
Sample characteristics	Sample size 34 registered pharmacists Reason for stopping recruitment Not specified. Mean age (SD) 20 to 29: 50%, 30 to 39: 23%, 40 to 49:12%, 50 to 59: 9%, 60+: 6% Number of years in practice ≤ 1 year: 12%, 1 to 5 years: 32%, 6 to 10 years: 18%, 11 to 15 years: 12%, 16 to 20 years: 3%, ≥21 years: 23% Primary Roles Practicing Pharmacists: 73%, Academia: 9%, Leading representatives of professional organisations (LRPO): 18%
Thematic Analysis	**Role of the pharmacist** Finding 1: As drug specialists, participating pharmacists identified their role as central to the drugs supply, use and safekeeping: “We need to have our input into the matter, I think that is very important. You know we are the ones to most likely dispense and supply it” Finding 2: The also acknowledged, successful implementation of medicinal cannabis programs require input from the profession in this contemporary debate and discussions amongst all involved: “We are all part of the healthcare professional team and in order for us to help the patient we need to actually work hand-in hand together and have all different types of opinions amalgamated into one” **Nationalisation** Finding 1: Some participants stated that the success of implementation of legal medicinal cannabis supply would depend on a nationalised framework. Pharmacists’ support for a nationalised framework was to ensure a level of consistency, uniformity and

Study type	Semi structured interviews
	standardisation cross the country: “Establishing a nationalised system and accompanying that with the current E-Health scripts… that would help manage this well” **Access** Finding 1: The majority of the participants felt that the most suitable setting would be via a community pharmacy setting due to the importance of accessibility for chronic and palliative patients: “It should be within a community setting. I think that all palliative care should be... in terms of accessibility, within the community is best” Finding 2: A staged implementation was suggested, with supply initiating at clinics or hospitals before being introduced to a community setting: “Initially in a clinic setting and then following good feedback and positive outcomes in a community setting…because it is more readily available.” Some participants preferred cannabis to be supplied in a hospital environment with the key reason cited being a more specialised team monitoring its use. A few participants making this suggested also proposed a clinic setting like that used for methadone initiation would minimise potential for cannabis abuse. A number of participants were indifferent to the location of supply, suggesting that it could be successfully supplied in a multiple number of settings in order to make it accessible to all patients in various locations and with various needs. A few participants suggested a specialised cannabis supplier model similar to those existing overseas as means of cannabis supply.

1

CASP checklist
Aims of the research Overall, based on the above, was there a clear statement of the aims of the research? Yes **Appropriateness of methodology** Overall, based on the above, is a qualitative methodology appropriate? Yes **Research Design** Overall, based on the above, was the research design appropriate to address the aims of the research? Yes **Recruitment Strategy** Overall, based on the above, was the recruitment strategy appropriate to the aims of the research? Yes **Data collection** Overall, based on the above, was the data collected in a way that addressed the research issue? Yes

CASP checklist
Researcher and participant relationship
Overall, based on the above, has the relationship between researcher and participants been adequately considered?
No
Ethical Issues
Overall, based on the above, have ethical issues been taken into consideration?
Yes
Data analysis
Overall, based on the above, was the data analysis sufficiently rigorous?
Yes
Findings
Overall, based on the above, is there a clear statement of findings?
Yes
Research value
Overall, based on the above, how valuable is the research?
Valuable
Overall risk of bias and directness
Overall risk of bias
Moderate
Directness
Partially directly applicable
Unclear mode of administration of cannabis based medicinal products.

1

2 **St- Amant 2015**

St-Amant, 2015	
Bibliographic Reference	St-Amant, Huguette; Ware, Mark A.; Julien, Nancy; Lacasse, Anais; Prevalence and determinants of cannabinoid prescription for the management of chronic noncancer pain: a postal survey of physicians in the Abitibi-Temiscamingue region of Quebec; CMAJ open; 2015; vol. 3 (no. 2); E251-7

1 **Study details**

Study type	Cross-sectional survey
Study location	Quebec, Canada
Study setting	No setting. Postal survey
Study dates	Not specified
Sources of funding	This study was funded by the Fonds institutionnel de developpement de la recherche et de la creation of Université du Québec en Abitibi- Témiscamingue.
Inclusion criteria	Physicians practicing in south-western Quebec
Exclusion criteria	Not specified
Sample size	165 respondents Of the 165, 120 did not prescribe cannabinoids and 45 prescribed cannabinoids for all potential indications.
% Female	53.8%
Interventions	Cannabinoids Study defines cannabinoids as pharmaceutical product s of a therapeutic class that include psychoactive constituents of the Cannabis sativa plant (THC) or synthetic analogues that can be prescribed to produce analgesia via the endocannabinoid system.
Outcome measures	Prevalence of prescribing Prevalence of cannabinoid prescribing stratified by medical specialty.

2

Centre for Evidence-Based Management (CEBMa) Critical Appraisal of a Survey	
Did the study address a clearly focused question/ issue?	Yes
Is the research method (study design) appropriate for answering the research question?	Yes
Is the method of selection of the subjects (employees, teams, divisions, organisations) clearly described?	Yes
Could the way sample was obtained introduce (selection) bias?	Yes- selection bias may have been introduced by participants' self-selected participation.
Was the sample of subjects representative with regard to the population to which the findings will be referred?	No

Centre for Evidence-Based Management (CEBMa) Critical Appraisal of a Survey	
Was the sample size based on pre-study considerations of statistical power?	Can't tell – no information provided
Was a satisfactory response rate achieved?	Yes- response rate was 52.2%
Are the measurements (questionnaires) likely to be valid and reliable?	Can't tell – no information provided
Was the statistical significance assessed?	Yes
Are confidence intervals given for the main results?	No
Could there be confounding factors that haven't been accounted for?	Can't tell – no information provided
Can the results be applied to your organization?	Yes
Overall Quality	**Low –** Selection bias may have been introduced. It is also unclear if questionnaire was valid and reliable. Additionally, sample of subjects were not representative with regard to population to which the findings were referred to.
Directness	**Partially Direct-** Study looked at the prescribing of nabilone and nabiximols as well as medical marijuana.

1

Appendix F - Guidance

Review question 2.1

Reference	Quality	Research parameters	Population	Guideline summary	Limitations	Source of funding
Clinical Guidance: for the use of medicinal cannabis products in Queensland, Australia (2018)	Overall AGREE II score of 4/7 (moderate)	The guideline provides a review of the available evidence for the use of medicinal cannabis for named conditions and also provides medical practitioners who may choose to prescribe medicinal cannabis, under current access schemes in Queensland, with some guidance as to the research available.	Healthcare professionals	The following treatment factors are listed in the guideline: • Tetrahydrocannabinol) is generally not appropriate for patients who: ○ have a personal history or strong family history of psychosis or have concurrent active mood or anxiety disorder ○ are pregnant, planning on becoming pregnant, or breastfeeding ○ have unstable cardiovascular disease. • When commencing treatment, in addition to usual presenting complaint and history taking during consultation, particular attention to be given to: ○ current medical history: cardiovascular, liver and renal disease ○ psychological and psychiatric history such as mental illness, particularly schizophrenia ○ risk behaviours associated with drug dependence (nicotine/alcohol dependence, previous/current cannabis use, previous illicit drug use) • Contraindications are summarised in the guideline see relevant section for details, and include hypersensitivity to cannabis, pregnancy/breastfeeding, severe and unstable cardio-pulmonary disease, risk factors for cardiovascular disease and previous psychotic or concurrent active mood disorder or anxiety disorder.	International guidance No outcomes data reported as this is guidance.	Unknown

Reference	Quality	Research parameters	Population	Guideline summary	Limitations	Source of funding
				Other considerations include: tetrahydrocannabinol use in people under 25 years and paediatric and elderly patients.		
Information for Health Care Practitioners - Medical Use of Cannabis, Canada (2016) Access to Cannabis for Medical Purposes Regulations - Daily Amount Fact Sheet (Dosage)	Overall AGREE II score of 3/7 (low)	This information has been prepared to provide patients and healthcare practitioners with information related to daily amounts and dosing for cannabis for medical purposes (as defined by the guidance).	Healthcare practitioners and patients	This guidance/information provides the following information about: • Doses for different formulations and how long it takes to work are summarised in this guidance. There is an important note about equivalency factor (the quantity of product other than dried marijuana [for example, fresh marijuana or cannabis oil] that is equivalent to one gram of dried marihuana) and how it depends on the production method, form of supply and the tetrahydrocannabinol/cannabidiol yield. The licensed producers will provide this information on the label. The information about the equivalency factor will also be available on the licensed producer's website.	International guidance No outcomes data reported as this is guidance.	Unknown
Information for Health Care Practitioners - Cannabis (marihuana, marijuana) and the cannabinoids. Government of Canada 2018	Overall AGREE II score of 4/7 (moderate)	This document has been prepared by the Cannabis Legalisation and Regulation Branch at Health Canada to provide information on the use of cannabis (marihuana) and cannabinoids for	Healthcare professionals	The following treatment factors are listed in the guideline: • Contraindications that apply to those considering using prescription cannabinoid-based therapies (such as nabilone, nabiximols or dronabinol) also apply to those considering using cannabis, especially tetrahydrocannabinol-predominant cannabis. • The risk/benefit ratio of using cannabis (especially THC-predominant cannabis) should be carefully evaluated in people with the following because of individual variation in response and tolerance to its effects, as well as the difficulty in dosing: ○ under the age of 25, unless the benefit/risk ratio is considered by the physician to be favourable.	International guidance No outcomes data reported as this is guidance.	Unknown

Reference	Quality	Research parameters	Population	Guideline summary	Limitations	Source of funding
		medical purposes. This document is a summary of peer-reviewed literature and international reviews concerning potential therapeutic uses and harmful effects of cannabis and cannabinoids. It is to be used in addition with other national (Canadian) documents		○ with history of hypersensitivity to any cannabinoids or with severe cardiovascular or cerebrovascular disease, severe liver or renal disease or psychiatric disorders should not use cannabis - Cannabis should be used with caution in patients: - with a history of substance abuse, including alcohol abuse - receiving concomitant therapy with sedative-hypnotics or other psychoactive drugs because of the potential for additive or synergistic CNS depressant or psychoactive effects ○ Cannabis is not recommended in women of childbearing age not on a reliable contraceptive, as well as those planning pregnancy, and those who are pregnant, or breastfeeding • Patients should be supervised when administration is initiated and should be monitored on a regular basis. • Tolerance, and psychological and physical dependence can occur with prolonged use of cannabis Drug interactions involving cannabis and cannabinoids can be expected to vary considerably in their clinical significance given the wide variability in products, potencies, ratios of tetrahydrocannabinol and cannabidiol, doses, routes of administration, populations using cannabinoids and other factors. However, some of the more clinically significant interactions may occur when cannabis is taken with other CNS depressant drugs such as sedative-hypnotics or alcohol (details of interactions provided in the information document).		

Reference	Quality	Research parameters	Population	Guideline summary	Limitations	Source of funding
An Roinn Sláinte, Department of Health (Ireland) 2018. Clinical Guidance on Cannabis for Medical Use	Overall AGREE II score of 4/7 (moderate)	This guidance aims to provide practical clinical information to healthcare professionals who are prescribing, dispensing and monitoring cannabis-based products (as defined by the guidance)	Healthcare professionals	The following treatment factors are listed in the guideline: • Before the initiation of cannabis treatment an accurate and thorough history should be confirmed by the medical practitioner. Particulars include: ○ medical history: cardiovascular disease, liver disease and renal disease ○ medical treatments that have been tried and have failed, ○ the duration of treatments and the reasons for discontinuation ○ psychological and psychiatric history, including: - history of mental illness, including any psychotic disorders - risk behaviours associated with drug dependence, while previous cannabis use may not be a contraindication, care should be taken to manage the risk of dependence - nicotine dependence (may contribute to patient smoking a cannabis-based product) - alcohol dependence/abuse ○ current and previous illicit drug use, family health history, including: - mental health, particularly a family history of psychotic disorders - paranoia - family history of addiction ○ social history, including: social support and family support - child safety considerations	International guidance No outcomes data reported as this is guidance.	Unknown

Reference	Quality	Research parameters	Population	Guideline summary	Limitations	Source of funding
				- employment, especially where it involves driving or operating machinery - risk of falls (in older patients) - family responsibilities, such as caring for children • medication review • Contraindications: ○ history of hypersensitivity to any cannabinoid ○ severe and unstable cardio-pulmonary disease or risk factors for cardiovascular disease: tetrahydrocannabinol acts through the cannabinoid-1 receptors to decrease blood pressure, increase cardiac demand and causes vasodilation ○ current, active drug dependence, including illicit drugs, alcohol, and prescription medications ○ breastfeeding: considerable levels of cannabinoids are likely to be present in maternal breast milk and there are potential impacts on an infant • Warnings and precautions are summarised in the guidance and include: ○ People aged 18 years old and under because of the potential effects of tetrahydrocannabinol on the developing brain ○ Personal or family history of schizophrenia or any psychotic disorder ○ Severe liver or renal disease ○ Previous drug dependence, including illicit drugs, nicotine, alcohol and prescription medications ○ Pregnancy		

Reference	Quality	Research parameters	Population	Guideline summary	Limitations	Source of funding
				• Concomitant medications, especially sedatives such as opioids and benzodiazepines and medicines metabolised by cytochrome p450 isoenzymes • Whether the patient is elderly — as metabolism in the elderly is slower it is likely they will be more sensitive to the pharmacological effects of cannabis. Treatment should therefore be initiated at low doses and titrated slowly. • Drug-drug Interactions (see also Table 2 in the Irish guideline: A list of possible interactions with cannabis in the guideline) • Patients transferred from one cannabis-based medicine or product to another may require to be titrated again, depending on the composition of the medicine or product. The impact of any differences in composition should be considered in terms of the potential for side effects and interactions. • The symptoms associated with the withdrawal of treatment include irritability, difficulty sleeping, decreased appetite and anxiety. Gradual withdrawal of treatment is recommended, unless abrupt discontinuation is required for safety reasons.		

Review question 2.2

Reference	Quality	Research parameters	Population	Guideline summary	Limitations	Source of funding
Clinical Guidance: for the use of medicinal cannabis products in Queensland, Australia (2018)	Overall AGREE II score of 4/7 (moderate)	The guideline provides a review of the available evidence for the use of medicinal cannabis for named conditions and also provides medical practitioners who may choose to prescribe medicinal cannabis, under current access schemes in Queensland, with some guidance as to the research available.	Medical practitioners who choose to prescribe medicinal cannabis	• Medical practitioners should ensure they access available literature to determine the efficacy and safety of the product they wish to prescribe, to ensure they are comfortable with prescribing it. • Initial treatment plan should include: ○ treatment goals ○ risk management processes, such as frequency of dispensing. ○ monitoring arrangements—weekly/fortnightly/monthly reviews, any blood tests, specialist reviews, other investigations (as needed) for the particular medical condition and/or symptoms being treated. ○ an exit strategy for situations where the medication is not helping manage the symptoms or the goals of treatment are not reached. ○ that informed consent has been obtained and the patient provided with information about the medicinal cannabis product, possible side effects and treatment goals, and that treatment will be discontinued if benefit has not been demonstrated. ○ that the patient has been advised that they are not able to drive while on medicinal cannabis. • Dosing is highly individualised and relies on titration of the product, regardless of the cannabinoid content, using the premise ‘starting low and going slow’. Finding the right dose, where therapeutic effect is maximised and adverse effects are minimised, requires patients and doctors to work together to determine the efficacy	International guideline No outcomes data reported as this is guidance.	

Reference	Quality	Research parameters	Population	Guideline summary	Limitations	Source of funding
				of the product for that patient and their medical condition. • Patients with no prior experience of cannabis who are initiating therapy for the first time are cautioned to begin with a very low dose, such as 1mg daily THC or lower, and to immediately cease the product if they have any side effects. • Doses should be increased slowly, preferably weekly, until a satisfactory dose is reached. • When initiating, therapy patients should be advised to have someone with them should they experience any adverse effects. All first doses should be given in the evening to assist with management of side effects. In the absence of studies using orally ingested oils, comparison with pharmaceutical products provides the best estimate of dosing levels.		
Information for Health Care Practitioners - Medical Use of Cannabis, Canada (2016) Access to Cannabis for Medical Purposes Regulations - Daily Amount Fact Sheet (Dosage)	Overall AGREE II score of 3/7 (low)	This information has been prepared to provide patients and healthcare practitioners with information related to daily amounts and dosing for cannabis for medical purposes (as defined by the guidance).	Healthcare professionals (and patients)	This guidance/information provides the following information about dosing that would be useful to a prescriber when starting cannabis-based products for which there is limited dosing information: • Dosing remains highly individualized and relies to a great extent on titration (i.e. finding the right dose where potential therapeutic effects are maximized while adverse or harmful effects are minimized). The most prudent approach to dosing in the absence of evidence is to "start low and go slow." Patients with no prior experience with cannabis and initiating such therapy for the first time are cautioned to begin at a very low dose (e.g. 1 mg THC) and to immediately stop therapy if unacceptable or undesirable side effects occur. When beginning therapy with cannabis it is best to try to have someone trusted with the person	International guidance No outcomes data reported as this is guidance.	Unknown

Reference	Quality	Research parameters	Population	Guideline summary	Limitations	Source of funding
				taking the cannabis product in case of an adverse effect and medical attention is needed.		
An Roinn Sláinte, Department of Health (Ireland) 2018. Clinical Guidance on Cannabis for Medical Use	Overall AGREE II score of 4/7 (moderate)	This guidance aims to provide practical clinical information to healthcare professionals who are prescribing, dispensing and monitoring cannabis-based products (as defined by the guidance)	This guidance is intended for use by healthcare professionals .	The guidance has the following that may help with support: • Doctors should use their professional judgment to decide if prescribing cannabis-based products is appropriate treatment and informed decision should be made by the patient to accept treatment or not. • The doctor should discuss the risks, benefits and alternatives of the use of cannabis with the patient. This should also include an explanation of the authorisation status of the product being prescribed • If the patient is a minor then the patient's parent or guardian will need to consent to the treatment. Once a patient reaches the age of 16 years then the patient should be re-consented. If the patient lacks capacity to consent then the options outlined in the Assisted Decision-Making (Capacity) Act 2015 should be taken into consideration. • An initial treatment plan should be discussed with the patient and address the following: ○ treatment goals for cannabis use — these should be discussed with the patient and should be related to the symptoms and measurable, where possible. ○ specify the duration of treatment: for example, 3-6 months, depending on the response, and, in the case of chemotherapy-induced nausea and vomiting, for the duration of the SACT causing intractable nausea and vomiting ○ risk management processes, such as frequency of dispensing. For example, weekly dispensing if there	International guidance No outcomes data reported as this is guidance.	Unknown

Reference	Quality	Research parameters	Population	Guideline summary	Limitations	Source of funding
				are concerns that a patient may self-escalate their dose ○ regular review of interactions with concomitant medications ○ a treatment cessation plan for situations where the medication is not helping manage the symptoms or the goals of treatment are not reached ○ upon agreement of the treatment plan informed consent should be obtained. The patient should be provided with information about cannabis for medical use and advised not to drive or operate heavy machinery while starting cannabis treatment ○ written consent should be obtained for data gathering purposes • In the absence of dosage information, the general recommendation is to 'start low and go slow'. This is the pragmatic approach taken in guidance issued by Queensland Health, Australia (2017). • Specific recommendations are: ○ commence treatment at the lowest possible dose ○ first doses should be given in the evening to assist with management of side effects, and the patient should be advised to have someone with them ○ the dose should be titrated up slowly, at intervals of between 1 and 4 weeks, until a satisfactory dose is reached ○ monitor carefully for side effects upon initiation and on an ongoing basis. • Doses depend on the type of product used, individual variation, the development of tolerance, interaction with		

Reference	Quality	Research parameters	Population	Guideline summary	Limitations	Source of funding
				other drugs and previous exposure to cannabis, either recreationally or medically. Lower doses are less likely to be associated with side effects.		

Review question 3

Reference	Quality	Research parameters	Population	Guideline summary Guideline summary	Limitations	Source of funding
British Paediatric Neurology Association (2018) Guidance on the use of cannabis-based products for medicinal use in children and young people with epilepsy	Professional guidance has not been assessed for quality as this is based on legislation and national policy.	Interim clinical guidance for clinicians in the use and prescription of cannabis-based products for medicinal use in children and young people with epilepsy To highlight the key questions specialist clinicians should address before considering prescribing and also provide guidance on appropriate dosage and	Clinicians treating children and young people with epilepsy with cannabis-based medicinal products	A prescribing framework proposed by the UK government is summarised: - Prescribing will be restricted to doctors on the Specialist Register, prescribing only within their relevant specialist registration. - In terms of access it summarises 3 access routes: 1. Prescribing these products will treated as “Specials”; in other words, in the same way as an unlicensed medication. 2. As an investigational product in the context of a clinical trial 3. As a medicinal product with a marketing authorisation - It states that "the assumption is that such prescribing is a last resort and used only when no other drug with MHRA marketing authorisation meets the clinical need." - Responsibility remains with the prescribing clinician. - This government guidance applies to both public and private sectors. - All cannabis-based products for medicinal uses should have a clear contents description, and specifically including	Professional guidance only, mainly directed to clinicians treating epilepsy in children and young people. No outcomes data reported as this is guidance.	N/A

Reference	Quality	Research parameters	Population	Guideline summary Guideline summary	Limitations	Source of funding
		treatment regimes		doses and concentrations of cannabidiol and tetrahydrocannabinol.		
Clinical Guidance: for the use of medicinal cannabis products in Queensland, Australia (2018)	Overall AGREE II score of 4/7 (moderate)	The guideline provides a review of the available evidence for the use of medicinal cannabis for named conditions and also provides medical practitioners who may choose to prescribe medicinal cannabis, under current access schemes in Queensland, with some guidance as to the research available.	Healthcare professionals	The guideline states the following: • If being managed by a GP, patient-specific supportive documentation for use of a particular medicinal cannabis product from a specialist in the field of medicine for which the symptom is being treated (for example. palliative care) should be documented. • While no monitoring regimes are available internationally, it would seem appropriate that using a similar monitoring program to opioids would be clinically useful. • Patients should be reviewed more frequently when commencing on medicinal cannabis products, daily if needed. Once established on a dose, at a minimum monthly review is recommended. At each review the medical practitioner should ensure the following areas are covered: symptom control; adverse events; aberrant behaviour (concerns that the patient may be on-selling their product); records.	International guideline No outcomes data reported as this is guidance.	Unknown
An Roinn Sláinte, Department of Health (Ireland) 2018. Clinical Guidance on Cannabis for Medical Use	Overall AGREE II score of 4/7 (moderate)	This guidance aims to provide practical clinical information to healthcare professionals who are prescribing, dispensing and monitoring	Healthcare professionals	The guideline states the following: • Doctors must document that an appropriate doctor–patient relationship has been established prior to prescribing and/or endorsing cannabis for medical use for the patient (and between the patient and the GP [if the GP is prescribing cannabis endorsed by a consultant and/or monitoring its use]).	International guideline No outcomes data reported as this is guidance.	Unknown

Reference	Quality	Research parameters	Population	Guideline summary Guideline summary	Limitations	Source of funding
		cannabis-based products (as defined by the guidance)		• Prescribing consultants should have appropriate expertise in the treatment of the medical conditions. The term endorsed by consultant describes the system where the consultant who has initially prescribed the cannabis-based product supports the course of treatment and outlines the monitoring requirements on a case-by-case basis. The monitoring (to include repeat prescribing where appropriate) may be carried out by the consultant in conjunction with the patient's GP and other healthcare professionals, including clinical nurse and midwife specialists and pharmacists. • Authorised cannabis-based medicines should be used in the first instance. However, if an authorised medicine is not available or is not suitable for the patient, unauthorised cannabis-based products may be considered as a treatment option. • Patients transferred from one cannabis-based medicine or product to another may require to be titrated again, depending on the composition of the medicine or product. The impact of any differences in composition should be considered in terms of the potential for side effects and interactions. • The symptoms associated with the withdrawal of treatment include irritability, difficulty sleeping, decreased appetite and anxiety. Gradual withdrawal of treatment is		

Reference	Quality	Research parameters	Population	Guideline summary Guideline summary	Limitations	Source of funding
				recommended, unless abrupt discontinuation is required for safety reasons. • The treatment plan for each patient should include clear definition of the treatment goals/desired endpoints and should specify regular clinical monitoring required, including the monitoring intervals and the duration of the trial period. • Patients should be reviewed regularly to monitor effectiveness and manage any side effects and potential drug interactions. Patients should be advised to record their experience of use, including any side effects observed, or views regarding the impact of treatment and to share this at the time of review. Patients should be reviewed more frequently when commencing cannabis-based products, daily if required. Once established on a dose, regular review is recommended. This may include telephone management, as deemed appropriate.		

Appendix G- Survey data

Review question 2.2

G.1 Educational/ Training needs

Ebert 2015	
Physicians agreed unanimously that:	More education on medical cannabis should be available to physicians (88.8%) Physicians who are certified to recommend medical cannabis treatment should undergo specific training and broaden their knowledge on this subject before being certified (90.2%)

Hwang 2016	
Respondents were very interested in learning more about medical cannabis in the following areas:	State-specific rules and regulations (87%) Pharmacotherapy (88%) Available types and forms of products on the market (82%) Federal laws related to marijuana (53%) No interest in learning more about any of these topics (7%)
Preferred source and delivery method for information on the Minnesota Medical Cannabis Program:	The Minnesota Board of Pharmacy was ranked as the most preferred source (62%), followed by the Minnesota Department of Health (23%), and the Minnesota Pharmacists Association (11%).
The preferred routes of delivery were:	Email (56%) Online courses (48%) Mail (12%) Conferences (11%)

Zylla 2018	
Authors asked participants what additional education they wanted regarding medical cannabis	All respondents: Written summary: 98 (64%) Online learning program: 66 (48%) Symposia/conference: 41 (27%) Newsletter: 24 (16%) Other: 4 (3%) Not interested in more information: 23 (15%) Registered respondents: Written summary: 46 (68%) Online learning program: 31 (46%) Symposia/conference: 21 (31%) Newsletter: 13 (19%) Other: 4 (6%) Not interested in more information: 5 (7%)

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Carlini 2017	
Opinions about medical cannabis training:	<u>All respondents (n=484)</u> Medical cannabis should be included in undergraduate medical curricula: 77.3% Medical cannabis should be included in graduate medical curricula: 87.2% Continual medical education (CME) on medical cannabis should be available: 96.1% Clinician should receive training prior to recommending medical cannabis: 86.4% <u>Respondents that had authorised medical cannabis (n=75)</u> Medical cannabis should be included in undergraduate medical curricula: 80% Medical cannabis should be included in graduate medical curricula: 92% Continual medical education (CME) on medical cannabis should be available: 92% Clinician should receive training prior to recommending medical cannabis: 73.3%

Carlini 2017	
	Respondents that had not authorised medical cannabis (n=201) Medical cannabis should be included in undergraduate medical curricula: 75.7% Medical cannabis should be included in graduate medical curricula: 88.1% Continual medical education (CME) on medical cannabis should be available: 94% Clinician should receive training prior to recommending medical cannabis: 86.1% Respondents that were not eligible to authorise medical cannabis (n=208) Medical cannabis should be included in undergraduate medical curricula: 77.9% Medical cannabis should be included in graduate medical curricula: 84.6% Continual medical education (CME) on medical cannabis should be available: 97.6% Clinician should receive training prior to recommending medical cannabis: 91.4%

G.2 Increasing comfort level with prescribing

St- Amant	
When asked about what factors could increase their comfort level with prescribing cannabinoids for chronic non-cancer pain, the majority of the respondents (cannabinoid prescribers and non-prescribers alike) mentioned:	Attending continual medical education (CME) (68.4%) Having guideline and algorithms that included cannabinoid prescribing (67.1%) Having more clinical data and new studies (50%)

Review question 3

G.1 Access Model

Karanges 2018	
Respondents were more likely to endorse an access model permitting:	Prescribing by trained and accredited GPs (78.6%) GPs in a 'shared care' arrangement with a specialist (63.2%) Specialist-only prescribing (44.6%)
When asked to choose one model:	Trained GPs as their preferred prescriber (41.2%) Shared care (29.6%) Specialist only prescribing (14.6%) All GPs have the right to prescribe, regardless of training (12.1%)

G.2 Prevalence of prescribing

St- Amant 2015	
27.3% (45/165) of respondents had prescribed cannabinoids for all potential indications. The prevalence of cannabinoid prescription specifically for the management of chronic pain was 23.0% (38/165). Cannabinoid prescribing for chronic noncancer pain, stratified by medical specialty:	
Family physicians	34.8% (32/92)
Specialists	8.2% (6/73)

Klotz 2018	
Participants were qualified as board certified paediatric neurologists (110/155) neurologists (n = 36) or general paediatricians (n = 9). 45% (69/155) of respondents reported a current or previous use of CBD for treating epilepsy in childhood. CBD use, stratified by setting:	
Participants from specialised epilepsy centres	50% (19/38)
Participants working in neuropediatric/neurologic department	44.2% (46/104)
Participants working in private practice	28.6% (2/7)
Participants working in a general paediatric department	50% (3/6)

Appendix H – GRADE CERQual

Review question 2.2

Summary of review finding	Studies contributing to the review finding	Methodological limitations	Coherence	Adequacy	Relevance	CERQual assessment of confidence in the evidence
Educational/ Training needs						
Pharmacists stated that there is a need for training and learning opportunities for pharmacists around medicinal cannabis. They also highlighted that pharmacists can play a role in public awareness as they can further educate the public about medicinal cannabis.	Isaac 2016	Moderate concerns (Unclear reflexivity)	No concerns	Serious concerns (Small participant number)	No concerns	Low confidence

Review question 3

Summary of review finding	Studies contributing to the review finding	Methodological limitations	Coherence	Adequacy	Relevance	CERQual assessment of confidence in the evidence
Access						
There were different views on the ideal setting for the access cannabis. While community pharmacy was identified as the most suitable setting, a staged implementation was also suggested with supply initially occurring in clinics or hospitals	Isaac 2016	Moderate concerns (Unclear reflexivity)	No concerns	Serious concerns (Small participant number)	No concerns	Low confidence

Summary of review finding	Studies contributing to the review finding	Methodological limitations	Coherence	Adequacy	Relevance	CERQual assessment of confidence in the evidence
before being introduced to a community setting. Some also suggested at that a hospital environment may be more suitable as there is a more specialised team available to monitor cannabis use. Pharmacists stated a nationalised framework would be required for the successful implementation of legal medicinal cannabis supply. Pharmacists also identified their role as central to the drugs supply, use and safekeeping as they are most likely to dispense and supply the product. Additionally, they identified themselves as being part of the of the healthcare professional team and shared care management is needed to help the patient.						

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Appendix I – Guideline appraisal with AGREE II criteria

	An Roinn Siainte, Department of Health (2018). Clinical Guidance on Cannabis for Medical Use		Information for Health Care Practitioners - Medical Use of Cannabis (2016) Access to Cannabis for Medical Purposes Regulations - Daily Amount Fact Sheet (Dosage)		Information for Health Care Practitioners - Cannabis (marihuana, marijuana) and the cannabinoids. Government of Canada 2018		Clinical Guidance: for the use of medicinal cannabis products in Queensland, Australia (2018)	
	Appraiser 1	Appraiser 2	Appraiser 1	Appraiser 2	Appraiser 1	Appraiser 2	Appraiser 1	Appraiser 2
DOMAIN 1. SCOPE AND PURPOSE								
1. The overall objective(s) of the guideline is (are) specifically described.	7	5	5	4	3	1	7	6
2. The health question(s) covered by the guideline is (are) specifically described.	5	5	n/a	n/a	n/a	n/a	5	5

	An Roinn Siainte, Department of Health (2018). Clinical Guidance on Cannabis for Medical Use		Information for Health Care Practitioners - Medical Use of Cannabis (2016) Access to Cannabis for Medical Purposes Regulations - Daily Amount Fact Sheet (Dosage)		Information for Health Care Practitioners - Cannabis (marihuana, marijuana) and the cannabinoids. Government of Canada 2018		Clinical Guidance: for the use of medicinal cannabis products in Queensland, Australia (2018)	
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	7	5	n/a	n/a	n/a	n/a	7	5
DOMAIN 2. STAKEHOLDER INVOLVEMENT								
4. The guideline development group includes individuals from all relevant professional groups	3	2	n/a	n/a	n/a	n/a	2	1
5. The views and preferences	2	2	n/a	n/a	n/a	n/a	1	1

	An Roinn Siainte, Department of Health (2018). Clinical Guidance on Cannabis for Medical Use		Information for Health Care Practitioners - Medical Use of Cannabis (2016) Access to Cannabis for Medical Purposes Regulations - Daily Amount Fact Sheet (Dosage)		Information for Health Care Practitioners - Cannabis (marihuana, marijuana) and the cannabinoids. Government of Canada 2018		Clinical Guidance: for the use of medicinal cannabis products in Queensland, Australia (2018)	
of the target population (patients, public, etc.) have been sought.								
6. The target users of the guideline are clearly defined.	6	5	n/a	n/a	7	6	6	5
DOMAIN 3. RIGOUR OF DEVELOPMENT								
7. Systematic methods were used to search for evidence.	2	1	n/a	n/a	n/a	n/a	n/a	n/a
8. The criteria for selecting the evidence	1	1	n/a	n/a	n/a	n/a	n/a	n/a

	An Roinn Siainte, Department of Health (2018). Clinical Guidance on Cannabis for Medical Use		Information for Health Care Practitioners - Medical Use of Cannabis (2016) Access to Cannabis for Medical Purposes Regulations - Daily Amount Fact Sheet (Dosage)		Information for Health Care Practitioners - Cannabis (marihuana, marijuana) and the cannabinoids. Government of Canada 2018		Clinical Guidance: for the use of medicinal cannabis products in Queensland, Australia (2018)	
are clearly described.								
9. The strengths and limitations of the body of evidence are clearly described.	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
10. The methods for formulating the recommendations are clearly described.	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
11. The health benefits, side effects, and risks have been considered	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a

	An Roinn Siainte, Department of Health (2018). Clinical Guidance on Cannabis for Medical Use		Information for Health Care Practitioners - Medical Use of Cannabis (2016) Access to Cannabis for Medical Purposes Regulations - Daily Amount Fact Sheet (Dosage)		Information for Health Care Practitioners - Cannabis (marihuana, marijuana) and the cannabinoids. Government of Canada 2018		Clinical Guidance: for the use of medicinal cannabis products in Queensland, Australia (2018)	
in formulating the recommendations.								
12. There is an explicit link between the recommendations and the supporting evidence.	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
13. The guideline has been externally reviewed by experts prior to its publication.	n/a	n/a	n/a	n/a	7	3	n/a	n/a
14. A procedure	n/a	n/a	n/a	n/a	n/a	n/a	1	1

	An Roinn Siainte, Department of Health (2018). Clinical Guidance on Cannabis for Medical Use		Information for Health Care Practitioners - Medical Use of Cannabis (2016) Access to Cannabis for Medical Purposes Regulations - Daily Amount Fact Sheet (Dosage)		Information for Health Care Practitioners - Cannabis (marihuana, marijuana) and the cannabinoids. Government of Canada 2018		Clinical Guidance: for the use of medicinal cannabis products in Queensland, Australia (2018)	
for updating the guideline is provided.								
DOMAIN 4. CLARITY OF PRESENTATION								
15. The recommendations are specific and unambiguous.	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
16. The different options for management of the condition or health issue are clearly presented.	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
17. Key recommendations are easily identifiable.	7	7	n/a	n/a	n/a	n/a	n/a	n/a

	An Roinn Siainte, Department of Health (2018). Clinical Guidance on Cannabis for Medical Use		Information for Health Care Practitioners - Medical Use of Cannabis (2016) Access to Cannabis for Medical Purposes Regulations - Daily Amount Fact Sheet (Dosage)		Information for Health Care Practitioners - Cannabis (marihuana, marijuana) and the cannabinoids. Government of Canada 2018		Clinical Guidance: for the use of medicinal cannabis products in Queensland, Australia (2018)	
DOMAIN 5. APPLICABILITY								
18. The guideline describes facilitators and barriers to its application.	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
20. The potential resource implications of applying the recommend	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a

	An Roinn Siainte, Department of Health (2018). Clinical Guidance on Cannabis for Medical Use		Information for Health Care Practitioners - Medical Use of Cannabis (2016) Access to Cannabis for Medical Purposes Regulations - Daily Amount Fact Sheet (Dosage)		Information for Health Care Practitioners - Cannabis (marihuana, marijuana) and the cannabinoids. Government of Canada 2018		Clinical Guidance: for the use of medicinal cannabis products in Queensland, Australia (2018)	
ations have been considered.								
21. The guideline presents monitoring and/or auditing criteria.	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
DOMAIN 6. EDITORIAL INDEPENDENCE								
22. The views of the funding body have not influenced the content of the guideline.	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
23. Competing interests of guideline developme	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a

	An Roinn Siainte, Department of Health (2018). Clinical Guidance on Cannabis for Medical Use		Information for Health Care Practitioners - Medical Use of Cannabis (2016) Access to Cannabis for Medical Purposes Regulations - Daily Amount Fact Sheet (Dosage)		Information for Health Care Practitioners - Cannabis (marihuana, marijuana) and the cannabinoids. Government of Canada 2018		Clinical Guidance: for the use of medicinal cannabis products in Queensland, Australia (2018)	
nt group members have been recorded and addressed.								
OVERALL GUIDELINE ASSESSMENT								
1. Rate the overall quality of this guideline.	4	4	3	3	4	4	4	4
2. I would recommend this guideline for use.	yes	yes	yes	yes	yes	yes	yes	yes
Scaled domain scores[a]								
Domain 1	77.8%		58.3%		16.7%		80.5%	
Domain 2	38.9%		n/a		91.7%		27.8%	
Domain 3	4.2%		n/a		66.7%		0%	
Domain 4	100%		n/a		n/a		n/a	

	An Roinn Siainte, Department of Health (2018). Clinical Guidance on Cannabis for Medical Use	Information for Health Care Practitioners - Medical Use of Cannabis (2016) Access to Cannabis for Medical Purposes Regulations - Daily Amount Fact Sheet (Dosage)	Information for Health Care Practitioners - Cannabis (marihuana, marijuana) and the cannabinoids. Government of Canada 2018	Clinical Guidance: for the use of medicinal cannabis products in Queensland, Australia (2018)
Note: cells with n/a recorded indicate the item in question being skipped due to it not being applicable to the guideline under review [a] The domain scores were calculated using the methodology in the AGREE II tool and the appraisers agreed to set thresholds for 4 of the 6 domains (1, 2, 3 and 4) as these were the only domains relevant to the guidelines reviewed. Domains 5 and 6 were not applicable. High quality guidelines were those with the domain scores (domains 1, 2, 3 and 4) that were all >80%. A high threshold was agreed as domains 1, 2, 3 and 4 were considered to be important for usability of the guideline. Other options in the AGREE II tool for setting thresholds were considered. We discussed the options of prioritising 1 domain over another and valuing 1 domain over another before appraising (staged appraisal), however we agreed that all domains carried that same weight and so prioritising 1 over another would not be suitable and the scores across the domains varied.				

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Appendix J – Excluded studies

Review question 2.1

Clinical studies

Study	Reason for exclusion
Abuhasira, Ran, Schleider, Lihi Bar-Lev, Mechoulam, Raphael et al. (2018) Epidemiological characteristics, safety and efficacy of medical cannabis in the elderly. European journal of internal medicine 49: 44-50	Includes smoked cannabis-based products
Aggarwal, Sunil Kumar (2009) The medical geography of cannabinoid botanicals in Washington State: Access, delivery, and distress. Dissertation Abstracts International Section A: Humanities and Social Sciences 70(1a): 294	Dissertation
Aggarwal, Sunil Kumar, Carter, Gregory, Sullivan, Mark et al. (2013) Distress, coping, and drug law enforcement in a series of patients using medical cannabis. The Journal of nervous and mental disease 201(4): 292-303	Includes smoked cannabis-based products
Aguirre-Velazquez, Carlos G. (2017) Report from a Survey of Parents Regarding the Use of Cannabidiol (Medicinal cannabis) in Mexican Children with Refractory Epilepsy. Neurology research international 2017: 2985729	Study does not contain factors of interest
Arroyo, Rafael; Vila, Carlos; Dechant, Kerry L. (2014) Impact of Sativex on quality of life and activities of daily living in patients with multiple sclerosis spasticity. Journal of comparative effectiveness research 3(4): 435-44	Study does not contain factors of interest
Attal, N., Brasseur, L., Guirimand, D. et al. (2004) Are oral cannabinoids safe and effective in refractory neuropathic pain? European journal of pain (London, England) 8(2): 173-7	Study does not contain factors of interest

Study	Reason for exclusion
Baron, Eric P., Lucas, Philippe, Eades, Joshua et al. (2018) Patterns of medicinal cannabis use, strain analysis, and substitution effect among patients with migraine, headache, arthritis, and chronic pain in a medicinal cannabis cohort. The journal of headache and pain 19(1): 37	Study does not contain factors of interest
Belackova, Vendula; Shanahan, Marian; Ritter, Alison (2017) Mapping regulatory models for medicinal cannabis: a matrix of options. Australian health review: a publication of the Australian Hospital Association	Study does not contain factors of interest
Bellnier, Terrance; Brown, Geoffrey W.; Ortega, Tulio R. (2018) Preliminary evaluation of the efficacy, safety, and costs associated with the treatment of chronic pain with medical cannabis. The mental health clinician 8(3): 110-115	Study does not contain factors of interest
Bestard, Jennifer A. and Toth, Cory C. (2011) An open-label comparison of nabilone and gabapentin as adjuvant therapy or monotherapy in the management of neuropathic pain in patients with peripheral neuropathy. Pain practice: the official journal of World Institute of Pain 11(4): 353-68	Study does not contain factors of interest
Boden, Matthew Tyler, Gross, James J., Babson, Kimberly A. et al. (2013) The interactive effects of emotional clarity and cognitive reappraisal on problematic cannabis use among medical cannabis users. Addictive behaviors 38(3): 1663-8	Includes smoked cannabis-based products
Boehnke, Kevin F.; Litinas, Evangelos; Clauw, Daniel J. (2016) Medical Cannabis Use Is Associated with Decreased Opiate Medication Use in a Retrospective Cross-Sectional Survey of Patients with Chronic Pain. The journal of pain: official journal of the American Pain Society 17(6): 739-44	Includes smoked cannabis-based products
Boehnke, Kevin F., Scott, J. Ryan, Litinas, Evangelos et al. (2019) Pills to Pot: Observational Analyses of Cannabis Substitution Among Medical Cannabis Users with Chronic Pain. The journal of Pain: official journal of the American Pain Society	Includes smoked cannabis-based products
Bogdanoski, Tony (2010) Accommodating the medical use of marijuana: surveying the differing legal approaches in Australia, the United States and Canada. Journal of law and medicine 17(4): 508-31	Study does not contain relevant information

Study	Reason for exclusion
Bramness, Jorgen G., Dom, Geert, Gual, Antoni et al. (2018) A Survey on the Medical Use of Cannabis in Europe: A Position Paper. European addiction research 24(4): 201-205	Study does not contain outcomes of interest
Brooks, Elizabeth, Gundersen, Doris C., Flynn, Erin et al. (2017) The clinical implications of legalizing marijuana: Are physician and non-physician providers prepared? Addictive behaviors 72: 1-7	Types of cannabis used not stated
Bruce, Douglas, Brady, John P., Foster, Elissa et al. (2018) Preferences for Medical Marijuana over Prescription Medications Among Persons Living with Chronic Conditions: Alternative, Complementary, and Tapering Uses. Journal of alternative and complementary medicine (New York, N.Y.) 24(2): 146-153	Includes smoked cannabis-based products
Brunt, Tibor M., van Genugten, Marianne, Honer-Snoeken, Kathrin et al. (2014) Therapeutic satisfaction and subjective effects of different strains of pharmaceutical-grade cannabis. Journal of clinical psychopharmacology 34(3): 344-9	Study does not contain factors of interest
Budney, Alan J., Hughes, John R., Moore, Brent A. et al. (2004) Review of the validity and significance of cannabis withdrawal syndrome. The American journal of psychiatry 161(11): 1967-77	Systematic review does not contain factors of interest
Calhoun, S. R.; Galloway, G. P.; Smith, D. E. (1998) Abuse potential of dronabinol (Marinol). Journal of psychoactive drugs 30(2): 187-96	Systematic review does not contain factors of interest
Campbell, F. A., Tramer, M. R., Carroll, D. et al. (2001) Are cannabinoids an effective and safe treatment option in the management of pain? A qualitative systematic review. BMJ (Clinical research ed.) 323(7303): 13-6	Systematic review does not contain factors of interest
Campbell, Gabrielle, Hall, Wayne D., Peacock, Amy et al. (2018) Effect of cannabis use in people with chronic non-cancer pain prescribed opioids: findings from a 4-year prospective cohort study. The Lancet. Public health 3(7): e341-e350	Types of cannabis used not stated
Caputi, Theodore L. and Humphreys, Keith (2018) Medical Marijuana Users are More Likely to Use Prescription Drugs Medically and Nonmedically. Journal of addiction medicine 12(4): 295-299	Includes smoked cannabis-based products

Study	Reason for exclusion
Carlini, Beatriz H.; Garrett, Sharon B.; Carter, Gregory T. (2017) Medicinal Cannabis: A Survey Among Health Care Providers in Washington State. The American journal of hospice & palliative care 34(1): 85-91	Study does not contain outcomes of interest
Chapman, Susan A., Spetz, Joanne, Lin, Jessica et al. (2016) Capturing Heterogeneity in Medical Marijuana Policies: A Taxonomy of Regulatory Regimes Across the United States. Substance use & misuse 51(9): 1174-84	Includes smoked cannabis-based products
Charuvastra, Anthony; Friedmann, Peter D.; Stein, Michael D. (2005) Physician attitudes regarding the prescription of medical marijuana. Journal of addictive diseases 24(3): 87-93	Study does not contain outcomes of interest
Chen, Chuan-Yu; O'Brien, Megan S.; Anthony, James C. (2005) Who becomes cannabis dependent soon after onset of use? Epidemiological evidence from the United States: 2000-2001. Drug and Alcohol Dependence 79(1): 11-22	Study on recreational cannabis use
Colangelo, Tracy L. (2016) Clinicians' experiences and cognitive processes treating medicinal marijuana users: A qualitative inquiry. Dissertation Abstracts International Section A: Humanities and Social Sciences 76(12ae): No-Specified	Full text paper not available
Cooke, Alexis C.; Knight, Kelly R.; Miaskowski, Christine (2019) Patients' and clinicians' perspectives of co-use of cannabis and opioids for chronic non-cancer pain management in primary care. The International journal on drug policy 63: 23-28	Includes smoked cannabis-based products
Coomber, R.; Oliver, M.; Morris, C. (2003) Using cannabis therapeutically in the UK: A qualitative analysis. Journal of Drug Issues 33(2): 325-356	Includes smoked cannabis-based products
Corey, Susan (2005) Recent developments in the therapeutic potential of cannabinoids. Puerto Rico health sciences journal 24(1): 19-26	Review article but not a systematic review
Corroon, James M., Jr.; Mischley, Laurie K.; Sexton, Michelle (2017) Cannabis as a substitute for prescription drugs - a cross-sectional study. Journal of pain research 10: 989-998	Includes smoked cannabis-based products

Study	Reason for exclusion
Crowell, Tara L. (2016) Understanding Patients' Process to Use Medical Marijuana: A Southern New Jersey Community Engagement Project. Journal of patient experience 3(3): 81-87	Study does not contain outcomes of interest
Davis, Alan K., Walton, Maureen A., Bohnert, Kipling M. et al. (2018) Factors associated with alcohol consumption among medical cannabis patients with chronic pain. Addictive behaviors 77: 166-171	Types of cannabis used not stated
Feingold, Daniel, Brill, Silviu, Goor-Aryeh, Itay et al. (2017) Depression and anxiety among chronic pain patients receiving prescription opioids and medical marijuana. Journal of affective disorders 218: 1-7	Types of cannabis used not stated
Feingold, Daniel, Goor-Aryeh, Itay, Bril, Silviu et al. (2017) Problematic Use of Prescription Opioids and Medicinal Cannabis Among Patients Suffering from Chronic Pain. Pain medicine (Malden, Mass.) 18(2): 294-306	Includes smoked cannabis-based products
Fishman, S. M. (2007) Carpel tunnel syndrome, diabetic neuropathy, fibromyalgia, glucosamine and chondroitin, hypnosis in pain management, marijuana for pain. Journal of Pain and Palliative Care Pharmacotherapy 21(2): 61-67	Not a relevant study design
Fiz, Jimena, Duran, Marta, Capella, Dolors et al. (2011) Cannabis use in patients with fibromyalgia: effect on symptoms relief and health-related quality of life. PloS one 6(4): e18440	Includes smoked cannabis-based products
Fogel, Jessica S., Kelly, Thomas H., Westgate, Philip M. et al. (2017) Sex differences in the subjective effects of oral DELTA9-THC in cannabis users. Pharmacology, biochemistry, and behavior 152: 44-51	Study does not contain outcomes of interest
Frank, B., Serpell, M. G., Hughes, J. et al. (2008) Comparison of analgesic effects and patient tolerability of nabilone and dihydrocodeine for chronic neuropathic pain: randomised, crossover, double blind study. BMJ (Clinical research ed.) 336(7637): 199-201	Study does not contain factors of interest
Gill, A. and Williams, A. C. (2001) Preliminary study of chronic pain patients' concerns about cannabinoids as analgesics. The Clinical journal of pain 17(3): 245-8	Study does not contain outcomes of interest

Study	Reason for exclusion
Habib, George and Artul, Suheil (2018) Medical Cannabis for the Treatment of Fibromyalgia. Journal of clinical rheumatology: practical reports on rheumatic & musculoskeletal diseases 24(5): 255-258	Study does not contain factors of interest
Habib, George and Avisar, Irit (2018) The Consumption of Cannabis by Fibromyalgia Patients in Israel. Pain research and treatment 2018: 7829427	Includes smoked cannabis-based products
Haney, M., Ward, A. S., Comer, S. D. et al. (1999) Abstinence symptoms following oral THC administration to humans. Psychopharmacology 141(4): 385-94	Product not being taken for medicinal use
Haney, Margaret (2007) Opioid antagonism of cannabinoid effects: differences between marijuana smokers and nonmarijuana smokers. Neuropsychopharmacology: official publication of the American College of Neuropsychopharmacology 32(6): 1391-403	Study does not contain outcomes of interest
Haroutiunian, Simon, Rosen, Gila, Shouval, Rivka et al. (2008) Open-label, add-on study of tetrahydrocannabinol for chronic nonmalignant pain. Journal of pain & palliative care pharmacotherapy 22(3): 213-7	Study does not contain outcomes of interest
Haroutounian, Simon, Ratz, Yael, Ginosar, Yehuda et al. (2016) The Effect of Medicinal Cannabis on Pain and Quality-of-Life Outcomes in Chronic Pain: A Prospective Open-label Study. The Clinical journal of pain 32(12): 1036-1043	Study does not contain outcomes of interest
Harris, D., Jones, R. T., Shank, R. et al. (2000) Self-reported marijuana effects and characteristics of 100 San Francisco medical marijuana club members. Journal of addictive diseases 19(3): 89-103	Includes smoked cannabis-based products
Hauser, W.; Petzke, F.; Fitzcharles, M. A. (2018) Efficacy, tolerability and safety of cannabis-based medicines for chronic pain management - An overview of systematic reviews. European journal of pain (London, England) 22(3): 455-470	Systematic review does not contain factors of interest
Hazekamp, Arno, Ware, Mark A., Muller-Vahl, Kirsten R. et al. (2013) The medicinal use of cannabis and cannabinoids--an international cross-sectional survey on administration forms. Journal of psychoactive drugs 45(3): 199-210	Includes smoked cannabis-based products

Study	Reason for exclusion
Heng, Marilyn, McTague, Michael F., Lucas, Robert C. et al. (2018) Patient Perceptions of the Use of Medical Marijuana in the Treatment of Pain After Musculoskeletal Trauma: A Survey of Patients at 2 Trauma Centers in Massachusetts. Journal of orthopaedic trauma 32(1): e25-e30	Study does not contain factors of interest
Hoffman, K. A., Ponce Terashima, J., McCarty, D. et al. (2017) Toward a Patient Registry for Cannabis Use: An Exploratory Study of Patient Use in an Outpatient Health-Care Clinic in Oregon. World Medical and Health Policy 9(3): 307-317	Includes smoked cannabis-based products
Hoggart, B., Ratcliffe, S., Ehler, E. et al. (2015) A multicentre, open-label, follow-on study to assess the long-term maintenance of effect, tolerance and safety of THC/CBD oromucosal spray in the management of neuropathic pain. Journal of neurology 262(1): 27-40	Study does not contain factors of interest
Hutcheon, A. W., Palmer, J. B., Soukop, M. et al. (1983) A randomised multicentre single blind comparison of a cannabinoid anti-emetic (levonantradol) with chlorpromazine in patients receiving their first cytotoxic chemotherapy. European journal of cancer & clinical oncology 19(8): 1087-90	Study does not contain factors of interest
Hwang, Joy; Arneson, Tom; St Peter, Wendy (2016) Minnesota Pharmacists and Medical Cannabis: A Survey of Knowledge, Concerns, and Interest Prior to Program Launch. P & T: a peer-reviewed journal for formulary management 41(11): 716-722	Study does not contain outcomes of interest
Jaffe, Steven L. and Klein, Matthew (2010) Medical marijuana and adolescent treatment. The American journal on addictions 19(5): 460-1	Study does not contain outcomes of interest
Janichek, Jennifer L. and Reiman, Amanda (2012) Clinical service desires of medical cannabis patients. Harm reduction journal 9: 12	Includes smoked cannabis-based products
Johnson, Jeremy R., Lossignol, Dominique, Burnell-Nugent, Mary et al. (2013) An open-label extension study to investigate the long-term safety and tolerability of THC/CBD oromucosal spray and oromucosal THC spray in patients with terminal cancer-related pain refractory to strong opioid analgesics. Journal of pain and symptom management 46(2): 207-18	Study does not contain factors of interest

Study	Reason for exclusion
Karanges, Emily A., Suraev, Anastasia, Elias, Natalie et al. (2018) Knowledge and attitudes of Australian general practitioners towards medicinal cannabis: a cross-sectional survey. BMJ open 8(7): e022101	Study does not contain outcomes of interest
Kirk, J. M.; Doty, P.; De Wit, H. (1998) Effects of expectancies on subjective responses to oral delta9-tetrahydrocannabinol. Pharmacology, biochemistry, and behavior 59(2): 287-93	Study does not contain outcomes of interest
Kondrad, Elin C., Reed, Alex J., Simpson, Matthew J. et al. (2018) Lack of Communication about Medical Marijuana Use between Doctors and Their Patients. Journal of the American Board of Family Medicine: JABFM 31(5): 805-808	Study does not contain outcomes of interest
Krcevski-Skvarc, N.; Wells, C.; Hauser, W. (2018) Availability and approval of cannabis-based medicines for chronic pain management and palliative/supportive care in Europe: A survey of the status in the chapters of the European Pain Federation. European journal of pain (London, England) 22(3): 440-454	Study does not contain outcomes of interest
Kruger, Daniel J. and Kruger, Jessica S. (2019) Medical Cannabis Users' Comparisons between Medical Cannabis and Mainstream Medicine. Journal of psychoactive drugs 51(1): 31-36	Includes smoked cannabis-based products
Lamonica, Aukje K.; Boeri, Miriam; Anderson, Timothy (2016) Gaps in medical marijuana policy implementation: Real-time perspectives from marijuana dispensary entrepreneurs, health care professionals and medical marijuana patients. Drugs: Education, Prevention & Policy 23(5): 422-434	Includes smoked cannabis-based products
Lenoue, Sean R.; Wongngamnit, Narin; Thurstone, Christian (2016) Practical Aspects of Discussing Marijuana in a New Era. Journal of psychiatric practice 22(6): 471-477	Systematic review does not contain factors of interest
Leos-Toro, Cesar; Shiplo, Samantha; Hammond, David (2018) Perceived support for medical cannabis use among approved medical cannabis users in Canada. Drug and alcohol review 37(5): 627-636	Study does not contain outcomes of interest

Study	Reason for exclusion
Linares, Roberto, Choi-Nurvitadhi, Jo, Cooper, Svetlana et al. (2016) Personnel training and patient education in medical marijuana dispensaries in Oregon. Journal of the American Pharmacists Association, JAPhA 56(3): 270-273.e2	Study does not contain outcomes of interest
Lucas, Philippe (2012) It can't hurt to ask; a patient-centered quality of service assessment of health canada's medical cannabis policy and program. Harm reduction journal 9: 2	Includes smoked cannabis-based products
Lucas, Philippe; Baron, Eric P.; Jikomes, Nick (2019) Medical cannabis patterns of use and substitution for opioids & other pharmaceutical drugs, alcohol, tobacco, and illicit substances; results from a cross-sectional survey of authorized patients. Harm reduction journal 16(1): 9	Includes smoked cannabis-based products
Lucas, Philippe and Walsh, Zach (2017) Medical cannabis access, use, and substitution for prescription opioids and other substances: A survey of authorized medical cannabis patients. The International journal on drug policy 42: 30-35	Includes smoked cannabis-based products
Lynch, Mary E.; Young, Judee; Clark, Alexander J. (2006) A case series of patients using medicinal marihuana for management of chronic pain under the Canadian Marihuana Medical Access Regulations. Journal of pain and symptom management 32(5): 497-501	Includes smoked cannabis-based products
Malouff, J. M.; Johnson, C. E.; Rooke, S. E. (2016) Cannabis Users' Recommended Warnings for Packages of Legally Sold Cannabis: An Australia-Centered Study. Cannabis and Cannabinoid Research 1(1): 239-243	Study does not contain outcomes of interest
McGriff, Deepa; Anderson, Susan; Arneson, Tom (2016) Early Survey Results from the Minnesota Medical Cannabis Program. Minnesota medicine 99(4): 18-22	Types of cannabis used not stated
Narang, S., Wasan, A. D., Ross, E. L. et al. (2008) Patients with chronic pain on opioid therapy taking dronabinol: Incidence of false negatives using radioimmunoassay. Journal of Opioid Management 4(1): 21-26	Study does not contain outcomes of interest
Neavyn, Mark J., Blohm, Eike, Babu, Kavita M. et al. (2014) Medical marijuana and driving: a review. Journal of medical toxicology: official journal of the American College of Medical Toxicology 10(3): 269-79	Systematic review does not contain factors of interest

Study	Reason for exclusion
Notcutt, W., Price, M., Miller, R. et al. (2004) Initial experiences with medicinal extracts of cannabis for chronic pain: Results from 34 'N of 1' studies. Anaesthesia 59(5): 440-452	Study does not contain factors of interest
Noyes, Russell, Brunk, S. Fred, Avery, David H. et al. (1976) Psychologic effects of oral delta-9-tetrahydrocannabinol in advanced cancer patients. Comprehensive Psychiatry 17(5): 641-646	Study does not contain factors of interest
Nussbaum, Abraham M., Thurstone, Christian, McGarry, Laurel et al. (2015) Use and diversion of medical marijuana among adults admitted to inpatient psychiatry. The American journal of drug and alcohol abuse 41(2): 166-72	Study does not contain outcomes of interest
O'Donnell, Rhonda (2006) Rx for medical marijuana? Interview by Susan Trossman. The American journal of nursing 106(4): 77-9	Not a peer-reviewed publication
Page, Stacey A. and Verhoef, Marja J. (2006) Medicinal marijuana use: experiences of people with multiple sclerosis. Canadian family physician Medecin de famille canadien 52: 64-5	Smoked cannabis-based products
Palmieri, Beniamino; Laurino, Carmen; Vadala, Maria (2019) Spontaneous, anecdotal, retrospective, open-label study on the efficacy, safety and tolerability of cannabis galenical preparation (Bedrocan). The International journal of pharmacy practice	Study does not contain outcomes of interest
Pergolizzi, Joseph V., Jr., Lequang, Jo A., Taylor, Robert, Jr. et al. (2018) The role of cannabinoids in pain control: the good, the bad, and the ugly. Minerva anestesiologica 84(8): 955-969	Systematic review does not contain factors of interest
Peters, David C., II (2013) Patients and caregivers report using medical marijuana to decrease prescription narcotics use. Humboldt Journal of Social Relations 35: 24-40	Includes smoked cannabis-based products
Piper, Brian J., Beals, Monica L., Abess, Alexander T. et al. (2017) Chronic pain patients' perspectives of medical cannabis. Pain 158(7): 1373-1379	Includes smoked cannabis-based products

Study	Reason for exclusion
Porter, Brenda E. and Jacobson, Catherine (2013) Report of a parent survey of cannabidiol-enriched cannabis use in pediatric treatment-resistant epilepsy. Epilepsy & behavior : E&B 29(3): 574-7	Study does not contain factors of interest
Pulido, J., Barrio, G., Lardelli, P. et al. (2011) Cannabis use and traffic injuries. Epidemiology 22(4): 609-610	Letter to the editor
Rapp, Laura A.; Michalec, Barret; Whittle, Tanya (2015) Delaware Physicians' Knowledge and Opinions on Medical Marijuana. Delaware medical journal 87(10): 304-9	Full text paper not available
Reiman, Amanda; Welty, Mark; Solomon, Perry (2017) Cannabis as a Substitute for Opioid-Based Pain Medication: Patient Self-Report. Cannabis and cannabinoid research 2(1): 160-166	Includes smoked cannabis-based products
Rochford, Ciaran, Edgeworth, Deirdre, Hashim, Mohammad et al. (2019) Attitudes of Irish patients with chronic pain towards medicinal cannabis. Irish journal of medical science 188(1): 267-272	Study does not contain outcomes of interest
Rolon, Nydia Jeannette (2019) Parents of children with chronic illness and the role of religion, stigma, and personal beliefs in the use of medical marijuana in treatment. Dissertation Abstracts International: Section B: The Sciences and Engineering 80(2be): No-Specified	Full text paper not available
Rong, Carola, Carmona, Nicole E., Lee, Yena L. et al. (2018) Drug-drug interactions as a result of co-administering DELTA9-THC and CBD with other psychotropic agents. Expert opinion on drug safety 17(1): 51-54	Systematic review does not contain factors of interest
Ryan, Jennie and Sharts-Hopko, Nancy (2017) The Experiences of Medical Marijuana Patients: A Scoping Review of the Qualitative Literature. The Journal of neuroscience nursing: journal of the American Association of Neuroscience Nurses 49(3): 185-190	Includes smoked cannabis-based products
Schley, Marcus, Legler, Andreas, Skopp, Gisela et al. (2006) Delta-9-THC based monotherapy in fibromyalgia patients on experimentally induced pain, axon reflex flare, and pain relief. Current medical research and opinion 22(7): 1269-76	Study does not contain outcomes of interest

Study	Reason for exclusion
Sexton, Michelle; Cuttler, Carrie; Mischley, Laurie K. (2018) A Survey of Cannabis Acute Effects and Withdrawal Symptoms: Differential Responses Across User Types and Age. Journal of alternative and complementary medicine (New York, N.Y.)	Includes smoked cannabis-based products
Sharon, Haggai, Goldway, Noam, Goor-Aryeh, Itay et al. (2018) Personal experience and attitudes of pain medicine specialists in Israel regarding the medical use of cannabis for chronic pain. Journal of pain research 11: 1411-1419	Study does not contain outcomes of interest
Smart, R. G.; Ogborne, A. C.; Birchmore-Timney, C. (1999) An exploratory study of physicians experiences with patients who use marijuana for medical reasons. Addiction (Abingdon, England) 94(3): 435-6	Letter to the editor
St-Amant, Huguette, Ware, Mark A., Julien, Nancy et al. (2015) Prevalence and determinants of cannabinoid prescription for the management of chronic noncancer pain: a postal survey of physicians in the Abitibi-Temiscamingue region of Quebec. CMAJ open 3(2): E251-7	Study does not contain outcomes of interest
Staud, Roland and Koo, Eubee B. (2008) Are cannabinoids a new treatment option for pain in patients with fibromyalgia? Nature clinical practice. Rheumatology 4(7): 348-9	Article commentary
Suraev, Anastasia S., Todd, Lisa, Bowen, Michael T. et al. (2017) An Australian nationwide survey on medicinal cannabis use for epilepsy: History of antiepileptic drug treatment predicts medicinal cannabis use. Epilepsy & behavior: E&B 70(ptb): 334-340	Study does not contain factors of interest
Swift, Wendy; Gates, Peter; Dillon, Paul (2005) Survey of Australians using cannabis for medical purposes. Harm reduction journal 2: 18	Includes smoked cannabis-based products
Sznitman, Sharon R., Goldberg, Victoria, Sheinman-Yuffe, Hedva et al. (2016) Storage and disposal of medical cannabis among patients with cancer: Assessing the risk of diversion and unintentional digestion. Cancer 122(21): 3363-3370	Includes smoked cannabis-based products

Study	Reason for exclusion
Szyliowicz, Dara and Hilsenrath, Peter (2019) Medical Marijuana Knowledge and Attitudes: A Survey of the California Pharmacists Association. Journal of primary care & community health 10: 2150132719831871	Study does not contain outcomes of interest
Thurstone, C., Tomcho, M., Salomonsen-Sautel, S. et al. (2013) Diversion of medical marijuana: When sharing is not a virtue. Journal of the American Academy of Child and Adolescent Psychiatry 52(6): 653-654	Article commentary
Thurstone, Christian; Lieberman, Shane A.; Schmiege, Sarah J. (2011) Medical marijuana diversion and associated problems in adolescent substance treatment. Drug and alcohol dependence 118(23): 489-92	Types of cannabis used not stated
Vigil, Jacob M., Stith, Sarah S., Adams, Ian M. et al. (2017) Associations between medical cannabis and prescription opioid use in chronic pain patients: A preliminary cohort study. PloS one 12(11): e0187795	Study does not contain outcomes of interest
Waissengrin, Barliz, Urban, Damien, Leshem, Yasmin et al. (2015) Patterns of use of medical cannabis among Israeli cancer patients: a single institution experience. Journal of pain and symptom management 49(2): 223-30	Includes smoked cannabis-based products
Ware, Mark A. and St Arnaud-Trempe, Emmanuelle (2010) The abuse potential of the synthetic cannabinoid nabilone. Addiction (Abingdon, England) 105(3): 494-503	Systematic review. Reference list checked for potential includes.
Webb, Charles W. and Webb, Sandra M. (2014) Therapeutic benefits of cannabis: a patient survey. Hawai'i journal of medicine & public health: a journal of Asia Pacific Medicine & Public Health 73(4): 109-11	Study does not contain outcomes of interest
Weber, Janet, Schley, Marcus, Casutt, Matthias et al. (2009) Tetrahydrocannabinol (Delta 9-THC) Treatment in Chronic Central Neuropathic Pain and Fibromyalgia Patients: Results of a Multicenter Survey. Anesthesiology research and practice 2009	Study does not contain factors of interest
Wong, Su-Wei and Lin, Hsien-Chang (2019) Medical marijuana legalization and associated illicit drug use and prescription medication misuse among adolescents in the U.S. Addictive behaviors 90: 48-54	Study does not contain outcomes of interest

Study	Reason for exclusion
Zaki, P., Blake, A., Wolt, A. et al. (2017) The use of medical cannabis in cancer patients. Journal of Pain Management 10(4): 353-362	Study does not contain factors of interest
Zaki, P., Ganesh, V., O'Hearn, S. et al. (2017) The use of medical cannabis in common medical conditions excluding cancer. Journal of Pain Management 10(4): 363-374	Study does not contain factors of interest
Zolotov, Yuval, Vulfsons, Simon, Zarhin, Dana et al. (2018) Medical cannabis: An oxymoron? Physicians' perceptions of medical cannabis. The International journal on drug policy 57: 4-10	Study does not contain outcomes of interest
Zylla, Dylan, Steele, Grant, Eklund, Justin et al. (2018) Oncology Clinicians and the Minnesota Medical Cannabis Program: A Survey on Medical Cannabis Practice Patterns, Barriers to Enrollment, and Educational Needs. Cannabis and cannabinoid research 3(1): 195-202	Study does not contain outcomes of interest

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2

3

Review question 2.2

Clinical studies

Study	Code [Reason]
Aggarwal, Sunil Kumar (2009) The medical geography of cannabinoid botanicals in Washington State: Access, delivery, and distress. Dissertation Abstracts International Section A: Humanities and Social Sciences 70(1a): 294	- Study does not contain relevant information
Aggarwal, Sunil Kumar, Carter, Gregory, Sullivan, Mark et al. (2013) Distress, coping, and drug law enforcement in a series of patients using medical cannabis. The Journal of nervous and mental disease 201(4): 292-303	- Study does not report any of the factors of interest specified in the protocol
Balneaves, Lynda G., Alraja, Abeer, Ziemianski, Daniel et al. (2018) A National Needs Assessment of Canadian Nurse Practitioners Regarding Cannabis for Therapeutic Purposes. Cannabis and cannabinoid research 3(1): 66-73	- Study does not look at cannabis based medicinal products as defined in protocol [Study conducted under old Canadian MMAR which is different to UK practice.]
Belackova, Vendula; Shanahan, Marian; Ritter, Alison (2017) Mapping regulatory models for medicinal cannabis: a matrix of options. Australian health review: a publication of the Australian Hospital Association	- Review article but not a systematic review
Bonar, Erin E., Cranford, James A., Arterberry, Brooke J. et al. (2019) Driving under the influence of cannabis among medical cannabis patients with chronic pain. Drug and alcohol dependence 195: 193-197	- Study does not report any of the factors of interest specified in the protocol
Bramness, Jorgen G., Dom, Geert, Gual, Antoni et al. (2018) A Survey on the Medical Use of Cannabis in Europe: A Position Paper. European addiction research 24(4): 201-205	- Study does not report any of the factors of interest specified in the protocol
Brezing, Christina A., Choi, C. Jean, Pavlicova, Martina et al. (2018) Abstinence and reduced frequency of use are associated with improvements in quality of life among treatment-seekers with cannabis use disorder. The American journal on addictions 27(2): 101-107	- Study does not report any of the factors of interest specified in the protocol
Colangelo, Tracy L. (2016) Clinicians' experiences and cognitive processes treating medicinal marijuana users: A qualitative inquiry. Dissertation	- Full text paper not available

Study	Code [Reason]
Abstracts International Section A: Humanities and Social Sciences 76(12ae): No-Specified	
Crowell, Tara L. (2016) Understanding Patients' Process to Use Medical Marijuana: A Southern New Jersey Community Engagement Project. Journal of patient experience 3(3): 81-87	- Study does not report any of the factors of interest specified in the protocol
Evanoff, Anastasia B., Quan, Tiffany, Dufault, Carolyn et al. (2017) Physicians-in-training are not prepared to prescribe medical marijuana. Drug and alcohol dependence 180: 151-155	- Study does not look at cannabis based medicinal products as defined in protocol
Feldman, H. W. and Mandel, J. (1998) Providing medical marijuana: the importance of cannabis clubs. Journal of psychoactive drugs 30(2): 179-86	- Study does not report any of the factors of interest specified in the protocol
Fishman, S. M. (2007) Carpel tunnel syndrome, diabetic neuropathy, fibromyalgia, glucosamine and chondroitin, hypnosis in pain management, marijuana for pain. Journal of Pain and Palliative Care Pharmacotherapy 21(2): 61-67	- Not a relevant study design
Gill, A. and Williams, A. C. (2001) Preliminary study of chronic pain patients' concerns about cannabinoids as analgesics. The Clinical journal of pain 17(3): 245-8	- Study does not report any of the factors of interest specified in the protocol
Haney, M., Ward, A. S., Comer, S. D. et al. (1999) Abstinence symptoms following oral THC administration to humans. Psychopharmacology 141(4): 385-94	- Study does not report any of the factors of interest specified in the protocol
Hazekamp, Arno, Ware, Mark A., Muller-Vahl, Kirsten R. et al. (2013) The medicinal use of cannabis and cannabinoids--an international cross-sectional survey on administration forms. Journal of psychoactive drugs 45(3): 199-210	- Study does not report any of the factors of interest specified in the protocol
Heng, Marilyn, McTague, Michael F., Lucas, Robert C. et al. (2018) Patient Perceptions of the Use of Medical Marijuana in the Treatment of Pain After Musculoskeletal Trauma: A Survey of Patients at 2 Trauma Centers in Massachusetts. Journal of orthopaedic trauma 32(1): e25-e30	- Study does not report any of the factors of interest specified in the protocol
Jaffe, Steven L. and Klein, Matthew (2010) Medical marijuana and adolescent treatment. The American journal on addictions 19(5): 460-1	- Study does not report any of the factors of interest specified in the protocol

Study	Code [Reason]
Janichek, Jennifer L. and Reiman, Amanda (2012) Clinical service desires of medical cannabis patients. Harm reduction journal 9: 12	- Study does not report any of the factors of interest specified in the protocol
Karanges, Emily A., Suraev, Anastasia, Elias, Natalie et al. (2018) Knowledge and attitudes of Australian general practitioners towards medicinal cannabis: a cross-sectional survey. BMJ open 8(7): e022101	- Study does not report any of the factors of interest specified in the protocol
Kondrad, Elin C., Reed, Alex J., Simpson, Matthew J. et al. (2018) Lack of Communication about Medical Marijuana Use between Doctors and Their Patients. Journal of the American Board of Family Medicine: JABFM 31(5): 805-808	- Study does not report any of the factors of interest specified in the protocol
Kondrad, Elin and Reid, Alfred (2013) Colorado family physicians' attitudes toward medical marijuana. Journal of the American Board of Family Medicine: JABFM 26(1): 52-60	- Study does not look at cannabis based medicinal products as defined in protocol
Kruger, Daniel J. and Kruger, Jessica S. (2019) Medical Cannabis Users' Comparisons between Medical Cannabis and Mainstream Medicine. Journal of psychoactive drugs 51(1): 31-36	- Study does not report any of the factors of interest specified in the protocol
Lamonica, Aukje K.; Boeri, Miriam; Anderson, Timothy (2016) Gaps in medical marijuana policy implementation: Real-time perspectives from marijuana dispensary entrepreneurs, health care professionals and medical marijuana patients. Drugs: Education, Prevention & Policy 23(5): 422-434	- Study does not look at cannabis based medicinal products as defined in protocol
Lenoue, Sean R.; Wongngamnit, Narin; Thurstone, Christian (2016) Practical Aspects of Discussing Marijuana in a New Era. Journal of psychiatric practice 22(6): 471-477	- Review article but not a systematic review
Leos-Toro, Cesar; Shiplo, Samantha; Hammond, David (2018) Perceived support for medical cannabis use among approved medical cannabis users in Canada. Drug and alcohol review 37(5): 627-636	- Study does not report any of the factors of interest specified in the protocol
Lewis, Nehama and Sznitman, Sharon R. (2017) You brought it on yourself: The joint effects of message type, stigma, and responsibility attribution on attitudes toward medical cannabis. Journal of Communication 67(2): 181-202	- Study does not report any of the factors of interest specified in the protocol
Linares, Roberto, Choi-Nurvitadhi, Jo, Cooper, Svetlana et al. (2016) Personnel training and patient education in medical marijuana dispensaries	- Study does not look at cannabis based medicinal products as defined in protocol

Study	Code [Reason]
in Oregon. Journal of the American Pharmacists Association: JAPhA 56(3): 270-273.e2	
Lucas, Philippe (2012) It can't hurt to ask; a patient-centered quality of service assessment of health canada's medical cannabis policy and program. Harm reduction journal 9: 2	- Study does not report any of the factors of interest specified in the protocol
Lucas, Philippe and Walsh, Zach (2017) Medical cannabis access, use, and substitution for prescription opioids and other substances: A survey of authorized medical cannabis patients. The International journal on drug policy 42: 30-35	- Study does not report any of the factors of interest specified in the protocol
Malouff JM and Rooke SE (2013) Expert-recommended warnings for medical marijuana. Substance abuse 34(2): 92-93	- Not a relevant study design
Malouff, J. M.; Johnson, C. E.; Rooke, S. E. (2016) Cannabis Users' Recommended Warnings for Packages of Legally Sold Cannabis: An Australia-Centered Study. Cannabis and Cannabinoid Research 1(1): 239-243	- Study does not include population of interest [Unclear if participants were using cannabis for medicinal use.]
McGriff, Deepa; Anderson, Susan; Arneson, Tom (2016) Early Survey Results from the Minnesota Medical Cannabis Program. Minnesota medicine 99(4): 18-22	- Study does not look at cannabis based medicinal products as defined in protocol
Neavyn, Mark J., Blohm, Eike, Babu, Kavita M. et al. (2014) Medical marijuana and driving: a review. Journal of medical toxicology: official journal of the American College of Medical Toxicology 10(3): 269-79	- Review article but not a systematic review
Peiper, Nicholas C., Gourdet, Camille, Meinhofer, Angelica et al. (2017) Medical Decision-Making Processes and Online Behaviors Among Cannabis Dispensary Staff. Substance abuse: research and treatment 11: 1178221817725515	- Study does not look at cannabis based medicinal products as defined in protocol
Pergam, Steven A., Woodfield, Maresa C., Lee, Christine M. et al. (2017) Cannabis use among patients at a comprehensive cancer center in a state with legalized medicinal and recreational use. Cancer 123(22): 4488-4497	- Study does not look at cannabis based medicinal products as defined in protocol
Philpot, Lindsey M.; Ebbert, Jon O.; Hurt, Ryan T. (2019) A survey of the attitudes, beliefs and knowledge about medical cannabis among primary care providers. BMC family practice 20(1): 17	- Study does not report any of the factors of interest specified in the protocol

Study	Code [Reason]
Piper, Brian J., Beals, Monica L., Abess, Alexander T. et al. (2017) Chronic pain patients' perspectives of medical cannabis. Pain 158(7): 1373-1379	- Study does not look at cannabis based medicinal products as defined in protocol
Reiman, Amanda E. (2008) Self-efficacy, social support and service integration at medical cannabis facilities in the San Francisco Bay area of California. Health & social care in the community 16(1): 31-41	- Study does not look at cannabis based medicinal products as defined in protocol
Rochford, Ciaran, Edgeworth, Deirdre, Hashim, Mohammad et al. (2019) Attitudes of Irish patients with chronic pain towards medicinal cannabis. Irish journal of medical science 188(1): 267-272	- Study does not report any of the factors of interest specified in the protocol
Ryan, Jennie and Sharts-Hopko, Nancy (2017) The Experiences of Medical Marijuana Patients: A Scoping Review of the Qualitative Literature. The Journal of neuroscience nursing: journal of the American Association of Neuroscience Nurses 49(3): 185-190	- Study does not report any of the factors of interest specified in the protocol
Satterlund, Travis D.; Lee, Juliet P.; Moore, Roland S. (2015) Stigma among California's Medical Marijuana Patients. Journal of psychoactive drugs 47(1): 10-7	- Study does not report any of the factors of interest specified in the protocol
Sharon, Haggai, Goldway, Noam, Goor-Aryeh, Itay et al. (2018) Personal experience and attitudes of pain medicine specialists in Israel regarding the medical use of cannabis for chronic pain. Journal of pain research 11: 1411-1419	- Study does not report any of the factors of interest specified in the protocol
Smart, R. G.; Ogborne, A. C.; Birchmore-Timney, C. (1999) An exploratory study of physicians' experiences with patients who use marijuana for medical reasons. Addiction (Abingdon, England) 94(3): 435-6	- Not a relevant study design [Letter to editor.]
Swift, Wendy; Gates, Peter; Dillon, Paul (2005) Survey of Australians using cannabis for medical purposes. Harm reduction journal 2: 18	- Study does not report any of the factors of interest specified in the protocol
Sznitman, Sharon R., Goldberg, Victoria, Sheinman-Yuffe, Hedva et al. (2016) Storage and disposal of medical cannabis among patients with cancer: Assessing the risk of diversion and unintentional digestion. Cancer 122(21): 3363-3370	- Study does not report any of the factors of interest specified in the protocol
Ware, Mark A., Martel, Marc O., Jovey, Roman et al. (2018) A prospective observational study of problematic oral cannabinoid use. Psychopharmacology 235(2): 409-417	- Study does not report any of the factors of interest specified in the protocol

Study	Code [Reason]
Wilsey, Barth, Atkinson, J. Hampton, Marcotte, Thomas D. et al. (2015) The Medicinal Cannabis Treatment Agreement: Providing Information to Chronic Pain Patients Through a Written Document. The Clinical journal of pain 31(12): 1087-96	- Study does not look at cannabis based medicinal products as defined in protocol
Wilson, Ian; Whiting, Matthew; Scammell, Amy (2007) Addressing cannabis use in primary care: GPs' knowledge of cannabis-related harm and current practice. Primary Health Care Research and Development 8(3): 216-225	- Study does not include population of interest
Ziemianski, Daniel, Capler, Rielle, Tekanoff, Rory et al. (2015) Cannabis in medicine: a national educational needs assessment among Canadian physicians. BMC medical education 15: 52	- Study does not look at cannabis based medicinal products as defined in protocol [Study conducted under old Canadian MMAR which is different to UK practice.]

Review question 3

Clinical studies

Study	Code [Reason]
Ablin, Jacob N.; Elkayam, Ori; Fitzcharles, Mary-Ann (2016) Attitudes of Israeli Rheumatologists to the Use of Medical Cannabis as Therapy for Rheumatic Disorders. Rambam Maimonides medical journal 7(2)	- Study does not contain relevant information
Aggarwal, Sunil K., Carter, Gregory T., Zumbrunnen, Craig et al. (2013) From 32 ounces to zero: a medical geographic study of dispensing a cultivated batch of "plum" cannabis flowers to medical marijuana patients in Washington State. Journal of psychoactive drugs 45(2): 141-55	- Study does not look at cannabis based medicinal products as defined in protocol
Aggarwal, Sunil Kumar (2009) The medical geography of cannabinoid botanicals in Washington State: Access, delivery, and distress. Dissertation	- Study does not contain relevant information

Study	Code [Reason]
Abstracts International Section A: Humanities and Social Sciences 70(1a): 294	
Balneaves, Lynda G., Alraja, Abeer, Ziemianski, Daniel et al. (2018) A National Needs Assessment of Canadian Nurse Practitioners Regarding Cannabis for Therapeutic Purposes. Cannabis and cannabinoid research 3(1): 66-73	- Study does not look at cannabis based medicinal products as defined in protocol [Study conducted under old Canadian MMAR which is different to UK practice.]
Belackova, Vendula; Shanahan, Marian; Ritter, Alison (2017) Mapping regulatory models for medicinal cannabis: a matrix of options. Australian health review: a publication of the Australian Hospital Association	- Review article but not a systematic review
Belle-Isle, Lynne, Walsh, Zach, Callaway, Robert et al. (2014) Barriers to access for Canadians who use cannabis for therapeutic purposes. The International journal on drug policy 25(4): 691-9	- Study does not look at cannabis based medicinal products as defined in protocol
Bogdanoski, Tony (2010) Accommodating the medical use of marijuana: surveying the differing legal approaches in Australia, the United States and Canada. Journal of law and medicine 17(4): 508-31	- Review article but not a systematic review
Bowling, Candice M. and Glantz, Stanton A. (2019) Conflict of Interest Provisions in State Laws Governing Medical and Adult Use Cannabis. American journal of public health 109(3): 423-426	- Study does not contain relevant information
Bramness, Jorgen G., Dom, Geert, Gual, Antoni et al. (2018) A Survey on the Medical Use of Cannabis in Europe: A Position Paper. European addiction research 24(4): 201-205	- Study does not report any of the factors of interest specified in the protocol
Brooks, Elizabeth, Gundersen, Doris C., Flynn, Erin et al. (2017) The clinical implications of legalizing marijuana: Are physician and non-physician providers prepared? Addictive behaviors 72: 1-7	- Study does not contain relevant information
Bruce, Douglas, Brady, John P., Foster, Elissa et al. (2018) Preferences for Medical Marijuana over Prescription Medications Among Persons Living with Chronic Conditions: Alternative, Complementary, and Tapering Uses. Journal of alternative and complementary medicine (New York, N.Y.) 24(2): 146-153	- Study does not contain relevant information

Study	Code [Reason]
Carlini, Beatriz H.; Garrett, Sharon B.; Carter, Gregory T. (2017) Medicinal Cannabis: A Survey Among Health Care Providers in Washington State. The American journal of hospice & palliative care 34(1): 85-91	- Study does not look at cannabis based medicinal products as defined in protocol
Chapman, Susan A., Spetz, Joanne, Lin, Jessica et al. (2016) Capturing Heterogeneity in Medical Marijuana Policies: A Taxonomy of Regulatory Regimes Across the United States. Substance use & misuse 51(9): 1174-84	- Study does not report any of the factors of interest specified in the protocol
Colangelo, Tracy L. (2016) Clinicians' experiences and cognitive processes treating medicinal marijuana users: A qualitative inquiry. Dissertation Abstracts International Section A: Humanities and Social Sciences 76(12ae): No-Specified	- Full text paper not available
Crowell, Tara L. (2016) Understanding Patients' Process to Use Medical Marijuana: A Southern New Jersey Community Engagement Project. Journal of patient experience 3(3): 81-87	- Study does not report any of the factors of interest specified in the protocol
Decorte, Tom (2015) Cannabis social clubs in Belgium: organizational strengths and weaknesses, and threats to the model. The International journal on drug policy 26(2): 122-30	- Study does not contain relevant information
Doblin, R. E. and Kleiman, M. A. (1991) Marijuana as antiemetic medicine: a survey of oncologists' experiences and attitudes. Journal of Clinical Oncology: official journal of the American Society of Clinical Oncology 9(7): 1314-9	- Study does not contain relevant information
Ebert, Tanya, Zolotov, Yuval, Eliav, Shani et al. (2015) Assessment of Israeli Physicians' Knowledge, Experience and Attitudes towards Medical Cannabis: A Pilot Study. The Israel Medical Association Journal: IMAJ 17(7): 437-41	- Study does not report any of the factors of interest specified in the protocol
Erkens, J. A.; Janse, A. F. C.; Herings, R. M. C. (2005) Limited use of medicinal cannabis but for labeled indications after legalization. Pharmacoepidemiology and drug safety 14(11): 821-2	- Study does not contain relevant information
Evanoff, Anastasia B., Quan, Tiffany, Dufault, Carolyn et al. (2017) Physicians-in-training are not prepared to prescribe medical marijuana. Drug and alcohol dependence 180: 151-155	- Study does not report any of the factors of interest specified in the protocol

Study	Code [Reason]
Freisthler, Bridget, Kepple, Nancy J., Sims, Revel et al. (2013) Evaluating medical marijuana dispensary policies: spatial methods for the study of environmentally based interventions. American journal of community psychology 51(12): 278-88	- Study does not look at cannabis based medicinal products as defined in protocol
Gill, H. K. and Young, S. D. (2019) Exploring cannabis use reasons and experiences among mobile cannabis delivery patients. Journal of Substance Use 24(1): 15-20	- Study does not look at cannabis based medicinal products as defined in protocol
Grotenhermen, F. and Schnelle, M. (2003) Survey on the medical use of Cannabis and THC in Germany. Journal of Cannabis Therapeutics 3(2): 17-40	- Study does not contain relevant information
Haug, Nancy A., Kieschnick, Dustin, Sottile, James E. et al. (2016) Training and Practices of Cannabis Dispensary Staff. Cannabis and cannabinoid research 1(1): 244-251	- Study does not include population of interest
Hwang, Joy; Arneson, Tom; St Peter, Wendy (2016) Minnesota Pharmacists and Medical Cannabis: A Survey of Knowledge, Concerns, and Interest Prior to Program Launch. P & T: a peer-reviewed journal for formulary management 41(11): 716-722	- Study does not report any of the factors of interest specified in the protocol
Kondrad, Elin C., Reed, Alex J., Simpson, Matthew J. et al. (2018) Lack of Communication about Medical Marijuana Use between Doctors and Their Patients. Journal of the American Board of Family Medicine: JABFM 31(5): 805-808	- Study does not report any of the factors of interest specified in the protocol
Kondrad, Elin and Reid, Alfred (2013) Colorado family physicians' attitudes toward medical marijuana. Journal of the American Board of Family Medicine: JABFM 26(1): 52-60	- Study does not report any of the factors of interest specified in the protocol
Krcevski-Skvarc, N.; Wells, C.; Hauser, W. (2018) Availability and approval of cannabis-based medicines for chronic pain management and palliative/supportive care in Europe: A survey of the status in the chapters of the European Pain Federation. European journal of pain (London, England) 22(3): 440-454	- Study does not report any of the factors of interest specified in the protocol

Study	Code [Reason]
Kruger, Daniel J. and Kruger, Jessica S. (2019) Medical Cannabis Users' Comparisons between Medical Cannabis and Mainstream Medicine. Journal of psychoactive drugs 51(1): 31-36	- Study does not report any of the factors of interest specified in the protocol
Lamonica, Aukje K.; Boeri, Miriam; Anderson, Timothy (2016) Gaps in medical marijuana policy implementation: Real-time perspectives from marijuana dispensary entrepreneurs, health care professionals and medical marijuana patients. Drugs: Education, Prevention & Policy 23(5): 422-434	- Study does not report any of the factors of interest specified in the protocol
Lenoue, Sean R.; Wongngamnit, Narin; Thurstone, Christian (2016) Practical Aspects of Discussing Marijuana in a New Era. Journal of psychiatric practice 22(6): 471-477	- Review article but not a systematic review
Leos-Toro, Cesar; Shiplo, Samantha; Hammond, David (2018) Perceived support for medical cannabis use among approved medical cannabis users in Canada. Drug and alcohol review 37(5): 627-636	- Study does not report any of the factors of interest specified in the protocol
Linares, Roberto, Choi-Nurvitadhi, Jo, Cooper, Svetlana et al. (2016) Personnel training and patient education in medical marijuana dispensaries in Oregon. Journal of the American Pharmacists Association: JAPhA 56(3): 270-273.e2	- Study does not look at cannabis based medicinal products as defined in protocol
Lucas, Philippe (2012) It can't hurt to ask; a patient-centered quality of service assessment of health canada's medical cannabis policy and program. Harm reduction journal 9: 2	- Study does not report any of the factors of interest specified in the protocol
Lucas, Philippe and Walsh, Zach (2017) Medical cannabis access, use, and substitution for prescription opioids and other substances: A survey of authorized medical cannabis patients. The International journal on drug policy 42: 30-35	- Study does not report any of the factors of interest specified in the protocol
McGriff, Deepa; Anderson, Susan; Arneson, Tom (2016) Early Survey Results from the Minnesota Medical Cannabis Program. Minnesota medicine 99(4): 18-22	- Study does not report any of the factors of interest specified in the protocol
Morrison, Chris, Gruenewald, Paul J., Freisthler, Bridget et al. (2014) The economic geography of medical cannabis dispensaries in California. The International journal on drug policy 25(3): 508-15	- Study does not look at cannabis based medicinal products as defined in protocol

Study	Code [Reason]
Narang, S., Wasan, A. D., Ross, E. L. et al. (2008) Patients with chronic pain on opioid therapy taking dronabinol: Incidence of false negatives using radioimmunoassay. Journal of Opioid Management 4(1): 21-26	- Study does not contain relevant information
Nelson, Regina (2018) The medical cannabis recommendation: An integral exploration of doctor-patient narrative. Dissertation Abstracts International Section A: Humanities and Social Sciences 79(1ae): No-Specified	- Full text paper not available
Notcutt, William G. (2013) A questionnaire survey of patients and carers of patients prescribed Sativex as an unlicensed medicine. Primary health care research & development 14(2): 192-9	- Study does not contain relevant information
O'Donnell, Rhonda (2006) Rx for medical marijuana? Interview by Susan Trossman. The American journal of nursing 106(4): 77-9	- Not a relevant study design
Pardal, Mafalda (2018) An analysis of Belgian Cannabis Social Clubs' supply practices: A shapeshifting model? International Journal of Drug Policy 57: 32-41	- Study does not include population of interest
Peiper, Nicholas C., Gourdet, Camille, Meinhofer, Angelica et al. (2017) Medical Decision-Making Processes and Online Behaviors Among Cannabis Dispensary Staff. Substance abuse: research and treatment 11: 1178221817725515	- Study does not look at cannabis based medicinal products as defined in protocol
Philpot, Lindsey M.; Ebbert, Jon O.; Hurt, Ryan T. (2019) A survey of the attitudes, beliefs and knowledge about medical cannabis among primary care providers. BMC family practice 20(1): 17	- Study does not report any of the factors of interest specified in the protocol
Piper, Brian J., Beals, Monica L., Abess, Alexander T. et al. (2017) Chronic pain patients' perspectives of medical cannabis. Pain 158(7): 1373-1379	- Study does not look at cannabis based medicinal products as defined in protocol
Rapp, Laura A.; Michalec, Barret; Whittle, Tanya (2015) Delaware Physicians' Knowledge and Opinions on Medical Marijuana. Delaware medical journal 87(10): 304-9	- Full text paper not available
Reiman, Amanda E. (2008) Self-efficacy, social support and service integration at medical cannabis facilities in the San Francisco Bay area of California. Health & social care in the community 16(1): 31-41	- Study does not look at cannabis based medicinal products as defined in protocol

Study	Code [Reason]
Rochford, Ciaran, Edgeworth, Deirdre, Hashim, Mohammad et al. (2019) Attitudes of Irish patients with chronic pain towards medicinal cannabis. Irish journal of medical science 188(1): 267-272	- Study does not report any of the factors of interest specified in the protocol
Ryan, Jennie and Sharts-Hopko, Nancy (2017) The Experiences of Medical Marijuana Patients: A Scoping Review of the Qualitative Literature. The Journal of neuroscience nursing: journal of the American Association of Neuroscience Nurses 49(3): 185-190	- Study does not report any of the factors of interest specified in the protocol
Schwartz, R. H. and Beveridge, R. A. (1994) Marijuana as an antiemetic drug: how useful is it today? Opinions from clinical oncologists. Journal of addictive diseases 13(1): 53-65	- Study does not contain relevant information
Sharon, Haggai, Goldway, Noam, Goor-Aryeh, Itay et al. (2018) Personal experience and attitudes of pain medicine specialists in Israel regarding the medical use of cannabis for chronic pain. Journal of pain research 11: 1411-1419	- Study does not report any of the factors of interest specified in the protocol
Sideris, Alexandra, Khan, Fahad, Boltunova, Alina et al. (2018) New York Physicians' Perspectives and Knowledge of the State Medical Marijuana Program. Cannabis and cannabinoid research 3(1): 74-84	- Study does not report any of the factors of interest specified in the protocol
Smart, R. G.; Ogborne, A. C.; Birchmore-Timney, C. (1999) An exploratory study of physicians experiences with patients who use marijuana for medical reasons. Addiction (Abingdon, England) 94(3): 435-6	- Not a relevant study design [Letter to editor.]
Swift, Wendy; Gates, Peter; Dillon, Paul (2005) Survey of Australians using cannabis for medical purposes. Harm reduction journal 2: 18	- Study does not report any of the factors of interest specified in the protocol
Szyliowicz, Dara and Hilsenrath, Peter (2019) Medical Marijuana Knowledge and Attitudes: A Survey of the California Pharmacists Association. Journal of primary care & community health 10: 2150132719831871	- Study does not look at cannabis based medicinal products as defined in protocol
Thurstone, C., Tomcho, M., Salomonsen-Sautel, S. et al. (2013) Diversion of medical marijuana: When sharing is not a virtue. Journal of the American Academy of Child and Adolescent Psychiatry 52(6): 653-654	- Not a relevant study design [Letter to editor]
Thurstone, Christian; Lieberman, Shane A.; Schmiege, Sarah J. (2011) Medical marijuana diversion and associated problems in adolescent substance treatment. Drug and alcohol dependence 118(23): 489-92	- Study does not include population of interest

Study	Code [Reason]
Waissengrin, Barliz, Urban, Damien, Leshem, Yasmin et al. (2015) Patterns of use of medical cannabis among Israeli cancer patients: a single institution experience. Journal of pain and symptom management 49(2): 223-30	- Study does not contain relevant information
Wilson, Ian; Whiting, Matthew; Scammell, Amy (2007) Addressing cannabis use in primary care: GPs' knowledge of cannabis-related harm and current practice. Primary Health Care Research and Development 8(3): 216-225	- Study does not include population of interest
Zarhin, Dana, Negev, Maya, Vulfsons, Simon et al. (2018) Rhetorical and regulatory boundary-work: The case of medical cannabis policymaking in Israel. Social science & medicine (1982) 217: 1-9	- Study does not report any of the factors of interest specified in the protocol
Ziemianski, Daniel, Capler, Rielle, Tekanoff, Rory et al. (2015) Cannabis in medicine: a national educational needs assessment among Canadian physicians. BMC medical education 15: 52	- Study does not look at cannabis based medicinal products as defined in protocol [Study conducted under old Canadian MMAR which is different to UK practice.]
Zolotov, Yuval, Vulfsons, Simon, Zarhin, Dana et al. (2018) Medical cannabis: An oxymoron? Physicians' perceptions of medical cannabis. The International journal on drug policy 57: 4-10	- Study does not report any of the factors of interest specified in the protocol
Zylla, Dylan, Steele, Grant, Eklund, Justin et al. (2018) Oncology Clinicians and the Minnesota Medical Cannabis Program: A Survey on Medical Cannabis Practice Patterns, Barriers to Enrollment, and Educational Needs. Cannabis and cannabinoid research 3(1): 195-202	- Study does not report any of the factors of interest specified in the protocol

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2

Appendix K- References

Review question 2.1

Included studies

Kirk, J. M. and de Wit, H. (1999) Responses to oral delta9-tetrahydrocannabinol in frequent and infrequent marijuana users. Pharmacology, biochemistry, and behavior 63(1): 137-42

Notcutt, William G. (2013) A questionnaire survey of patients and carers of patients prescribed Sativex as an unlicensed medicine. Primary health care research & development 14(2): 192-9

Ware, Mark A., Martel, Marc O., Jovey, Roman et al. (2018) A prospective observational study of problematic oral cannabinoid use. Psychopharmacology 235(2): 409-417

Excluded studies

Abuhasira, Ran, Schleider, Lihi Bar-Lev, Mechoulam, Raphael et al. (2018) Epidemiological characteristics, safety and efficacy of medical cannabis in the elderly. European journal of internal medicine 49: 44-50

Aggarwal, Sunil Kumar (2009) The medical geography of cannabinoid botanicals in Washington State: Access, delivery, and distress. Dissertation Abstracts International Section A: Humanities and Social Sciences 70(1a): 294

Aggarwal, Sunil Kumar, Carter, Gregory, Sullivan, Mark et al. (2013) Distress, coping, and drug law enforcement in a series of patients using medical cannabis. The Journal of nervous and mental disease 201(4): 292-303

Aguirre-Velazquez, Carlos G. (2017) Report from a Survey of Parents Regarding the Use of Cannabidiol (Medicinal cannabis) in Mexican Children with Refractory Epilepsy. Neurology research international 2017: 2985729

Arroyo, Rafael; Vila, Carlos; Dechant, Kerry L. (2014) Impact of Sativex on quality of life and activities of daily living in patients with multiple sclerosis spasticity. Journal of comparative effectiveness research 3(4): 435-44

Attal, N., Brasseur, L., Guirimand, D. et al. (2004) Are oral cannabinoids safe and effective in refractory neuropathic pain? European journal of pain (London, England) 8(2): 173-7

Baron, Eric P., Lucas, Philippe, Eades, Joshua et al. (2018) Patterns of medicinal cannabis use, strain analysis, and substitution effect among patients with migraine, headache, arthritis, and chronic pain in a medicinal cannabis cohort. The journal of headache and pain 19(1): 37

Belackova, Vendula; Shanahan, Marian; Ritter, Alison (2017) Mapping regulatory models for medicinal cannabis: a matrix of options. Australian health review: a publication of the Australian Hospital Association

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Review question 2.2

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Review question 3

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