Schweizerische Eidgenossenschaft
Confédération suisse
Confederazione Svizzera
Confederaziun svizra

Federal Department of Home Affairs
Federal Office of Public Health FOPH
Health and Accident Insurance Directorate
Section Health Technology Assessment

Health Technology Assessment (HTA)

Scoping Report

Title	Medical cannabis for treating various symptoms in Switzerland
Author/Affiliation	Anouk Oordt, Jennifer Eeuwijk, Eveline Bunge From Pallas Health Research and Consultancy Valérie Wester, Philip Klein, Tim Kanters, Carin Uyl-de Groot From institute for Medical Technology Assessment, Erasmus University of Rotterdam

Bundesamt für Gesundheit
Sektion Health Technology Assessment
Schwarzenburgstrasse 157
CH-3003 Bern
Schweiz
Tel.: +41 58 462 92 30
E-mail: hta@bag.admin.ch

Technology	Medical cannabis
Date	26-08-2020
Type of Technology	Pharmaceuticals and natural products

Executive Summary:

Medical cannabis encompasses all cannabis-based products which are used for medical treatment. Since 2012, Switzerland allows patients to get access to medical cannabis through a timely limited exceptional license. To date, general reimbursement by the compulsory health insurance for medical cannabis does not exist in Switzerland. Medical cannabis can be used to treat various symptoms and is predominantly used as add-on therapy or after other therapeutic options were unsuccessful. The aim of this scoping report was to investigate the evidence for the efficacy, effectiveness, safety, and cost-effectiveness of medical cannabis for treating the following symptoms: chronic pain, spasticity, unintentional weight loss, and nausea and vomiting related to cancer treatment. The selection of these symptoms was guided by a preliminary literature search.

For this scoping report, systematic literature searches were performed in PubMed (MEDLINE), Embase, and other complementary databases to identify relevant published efficacy, effectiveness, safety, and cost-effectiveness evidence. The applied search filters were time period (1980-22 January 2020) and the language of publications (i.e. English, French, German, and Dutch). Furthermore, only randomised controlled trials (RCTs) and economic evaluations were included. Additional literature was searched for information on social, legal, ethical, and organisational aspects related to medical cannabis.

For the symptom chronic pain, nineteen RCTs were included. The RCTs studied the efficacy of

medical cannabis use for chronic pain in patient populations with eleven divergent causes and different underlying mechanisms of chronic pain. In addition, there is large heterogeneity in the definitions and outcome measures of the reported outcomes. Most RCTs on chronic pain were included for the diagnosis multiple sclerosis (MS).

In total, fourteen RCTs were included for medical cannabis use for the symptom spasticity in patients with various diseases. The effect of medical cannabis on spasticity caused by MS is most often studied. The most frequently used outcomes are the Ashworth scale score, modified Ashworth scale score, and the spasticity 0-10 numerical rating scale.

Five RCTs were found on the efficacy of medical cannabis use for the symptom unintentional weight loss. Varying outcome measures were used across studies, which complicates comparison between studies and pooling of the data.

Twenty-two RCTs were included for the symptoms nausea and vomiting related to cancer treatment. The RCTs are however dated; nineteen of the RCTs were published before 1990. The methodological and reporting quality of older RCTs may be more often inadequate than in modern RCTs. Also, the treatment circumstances may have changed over time (including the comparator treatment), which limits the applicability of the study results to the current clinical practice. Again, a large variety of outcomes is used to measure the frequency or severity of nausea or vomiting. The heterogeneity of the outcomes has implications for synthesis of the reported data.

Two economic evaluations were identified for medical cannabis in chronic pain, and six for the symptom spasticity, however, these economic evaluations did not provide evidence on the cost-effectiveness of medical cannabis in Switzerland. No economic evaluations were identified for unintentional weight loss and nausea and vomiting related to cancer treatment.

Based on the findings in this scoping report, it was concluded that conducting a health technology assessment (HTA) for medical cannabis in Switzerland is feasible. For the symptoms chronic pain and spasticity, cost-effectiveness models can be built inspired by the models developed by the National Institute for Health and Care Excellence (NICE) in the United Kingdom. The models can be adapted to the Swiss context, using the input from the identified literature and by performing additional searches for Swiss costs and quality of life data. For the symptoms unintentional weight loss and nausea and vomiting related to cancer treatment it was concluded that, due to methodological limitations of the studies found in the systematic review, data of sufficient quality is too scarce to

analyse individual study outcomes or to develop a sufficiently robust cost-effectiveness model. The HTA report will include a discussion on why the evidence is insufficient to draw conclusions on medical cannabis for these two symptoms. The HTA will include a description of the social, legal, ethical and organisational aspects that were discussed in grey literature (i.e. guidelines and documents from HTA agencies).

Zusammenfassung:

Als Cannabis zur medizinischen Anwendung gelten alle Produkte auf Cannabisbasis, die für ärztliche Behandlungen eingesetzt werden. Seit 2012 erhalten Patientinnen und Patienten in der Schweiz mit einer zeitlich befristeten Ausnahmebewilligung Zugang zur medizinischen Anwendung von Cannabis. Bisher wird zur medizinischen Anwendung bestimmtes Cannabis in der Schweiz nicht generell von der obligatorischen Krankenpflegeversicherung übernommen. Cannabis zur medizinischen Anwendung kann zur Behandlung verschiedener Symptome eingesetzt werden. Es wird vorwiegend als Begleittherapie oder bei Nichtansprechen auf andere Behandlungsmöglichkeiten verwendet. In diesem Scoping-Bericht sollen die evidenzbasierten Daten für die Wirksamkeit unter idealen Bedingungen und unter Alltagsbedingungen, die Unbedenklichkeit und die Kosten-Wirksamkeit der medizinischen Anwendung von Cannabis zur Behandlung der folgenden Symptome untersucht werden: chronische Schmerzen, Spastik, ungewollte Gewichtsabnahme sowie Übelkeit und Erbrechen im Zusammenhang mit Krebstherapien. Die Auswahl dieser Symptome beruhte auf einer vorgängigen Literaturrecherche.

Für diesen Scoping-Bericht wurde die Fachliteratur in PubMed (MEDLINE), Embase und in weiteren ergänzenden Datenbanken systematisch durchsucht, um relevante, publizierte evidenzbasierte Daten zur Wirksamkeit unter idealen Bedingungen und unter Alltagsbedingungen, zur Unbedenklichkeit und zur Kosten-Wirksamkeit zu ermitteln. Dabei wurde nach Zeitraum (1980 bis 22. Januar 2020) und Sprache der Publikationen (d. h. Englisch, Französisch, Deutsch und Holländisch) gefiltert. Einbezogen wurden zudem nur randomisierte kontrollierte Studien (RKS) und ökonomische Bewertungen. Zusätzliche Literatur wurde nach Informationen zu sozialen, rechtlichen, ethischen und organisatorischen Aspekten im Zusammenhang mit der medizinischen Anwendung von Cannabis durchsucht.

Für das Symptom chronische Schmerzen wurden 19 RKS einbezogen. In diesen Studien wurde die

Wirksamkeit der medizinischen Anwendung von Cannabis bei chronischen Schmerzen bei Patientengruppen mit elf verschiedenen Ursachen und unterschiedlichen zugrundeliegenden Schmerzmechanismen untersucht. Auch die Definitionen und die Messgrössen für die Therapieergebnisse sind sehr heterogen. Die meisten berücksichtigten RKS zu chronischen Schmerzen betrafen die Diagnose Multiple Sklerose (MS).

Für das Symptom Spastik wurden insgesamt 14 RKS zur medizinischen Anwendung von Cannabis bei Patientinnen und Patienten mit verschiedenen Erkrankungen berücksichtigt. Am häufigsten wurde in diesen Studien die Wirkung der medizinischen Anwendung von Cannabis auf eine durch MS verursachte Spastik untersucht. Zur Messung der Therapieergebnisse wurden in erster Linie die Ashworth-Skala, die modifizierte Ashworth-Skala sowie die numerische Skala zur Beurteilung von Spastik mit einem Wertebereich von 0 bis 10 herangezogen.

Es wurden fünf RKS zur Wirksamkeit der medizinischen Anwendung von Cannabis bei ungewollter Gewichtsabnahme ermittelt. In diesen Studien wurden unterschiedliche Messgrössen für das Therapieergebnis verwendet, was den Vergleich zwischen den Studien und das Poolen der Daten erschwert.

Zu den Symptomen Übelkeit und Erbrechen im Zusammenhang mit Krebstherapien wurden 22 Studien einbezogen. Allerdings sind diese RKS schon älter: 19 von ihnen wurden vor 1990 publiziert. Bei älteren RKS besteht eine höhere Wahrscheinlichkeit als bei neueren Studien, dass die Qualität der Methodik und der Berichterstattung unzulänglich ist. Da sich zudem die Umstände der Behandlung im Verlauf der Zeit verändert haben können (einschliesslich der Vergleichstherapie), sind die Studienresultate nur begrenzt auf die gegenwärtige klinische Praxis anwendbar. Um die Häufigkeit und den Schweregrad der Übelkeit oder des Erbrechens zu messen, wird ebenfalls eine grosse Bandbreite von Therapieergebnissen herangezogen. Die Heterogenität der Therapieergebnisse wirkt sich auf die Zusammenführung der gemeldeten Daten aus.

Es wurden zwei ökonomische Bewertungen für die medizinische Anwendung von Cannabis bei chronischen Schmerzen und sechs für das Symptom Spastik ermittelt. Diese Evaluationen boten jedoch keine evidenzbasierten Erkenntnisse zur Kosten-Wirksamkeit der medizinischen Anwendung von Cannabis in der Schweiz. Für die Symptome ungewollte Gewichtsabnahme sowie Übelkeit und Erbrechen im Zusammenhang mit Krebstherapien liessen sich keine ökonomischen Bewertungen finden.

Aufgrund der Erkenntnisse in diesem Scoping-Bericht wurde der Schluss gezogen, dass die Durchführung einer Bewertung von Gesundheitstechnologien (Health Technology Assessment, HTA) zur

medizinischen Anwendung von Cannabis in der Schweiz möglich ist. Für die Symptome chronische Schmerzen und Spastik lassen sich Kosten-Wirksamkeits-Modelle ausgehend von den Modellen erarbeiten, die das National Institute for Health and Care Excellence (NICE) im Vereinigten Königreich entwickelt hat. Diese Modelle lassen sich an den Schweizer Kontext anpassen, indem die Angaben aus der eruierten Literatur benutzt und zusätzliche Suchen nach Schweizer Daten zu den Kosten und zur Lebensqualität durchgeführt werden. Bei den Symptomen ungewollte Gewichtsabnahme sowie Übelkeit und Erbrechen im Zusammenhang mit Krebstherapien wurde im Rahmen der systematischen Übersicht festgestellt, dass die aufgefundenen Studien methodische Mängel aufweisen. Daher wurde der Schluss gezogen, dass zu wenige Daten von ausreichender Qualität vorliegen, um die Therapieergebnisse in den einzelnen Studien zu analysieren und um ein ausreichend solides Kosten-Wirksamkeits-Modell zu entwickeln. Der HTA-Bericht wird eine Diskussion zur Frage umfassen, weshalb die evidenzbasierten Daten nicht ausreichen, um bei diesen beiden Symptomen Schlussfolgerungen zur medizinischen Anwendung von Cannabis zu ziehen. Zudem wird das HTA eine Beschreibung der sozialen, rechtlichen, ethischen und organisatorischen Aspekte enthalten, die in der grauen Literatur (z. B. Leitlinien und Dokumente von HTA-Agenturen) diskutiert werden.

Résumé :

Le cannabis médical comprend tous les produits à base de cannabis utilisés à des fins thérapeutiques. Depuis 2012, les patients en Suisse y ont accès par le biais d'autorisations exceptionnelles temporaires. À ce jour, l'assurance obligatoire des soins ne rembourse pas le cannabis médical de manière générale en Suisse. Le cannabis médical peut être utilisé pour traiter divers symptômes, principalement en tant que traitement d'appoint ou si d'autres options thérapeutiques se sont avérées inefficaces. Le présent rapport vise à évaluer les preuves de l'efficacité, de l'innocuité et de l'économicité du cannabis médical pour le traitement des douleurs chroniques, de la spasticité, de la perte de poids involontaire ainsi que des nausées et vomissements dus à une thérapie oncologique. Ces symptômes ont été choisis suite à une recherche préliminaire dans la littérature.

Ce rapport se fonde sur des recherches systématiques dans PubMed (MEDLINE), Embase et d'autres bases de données complémentaires pour identifier des publications attestant l'efficacité, l'innocuité et l'économicité du cannabis médical. Des filtres de période (1980 - 22 janvier 2020) et de langue (anglais, français, allemand et néerlandais) ont été appliqués. De plus, seuls des essais contrôlés randomisés (RCT pour *randomised controlled trials*) et des évaluations économiques ont été inclus. Les aspects sociaux, légaux, éthiques et organisationnels liés au cannabis médical ont fait l'objet de recherches supplémentaires dans la littérature.

Concernant les douleurs chroniques, 19 RCT ont été pris en compte. Ils étudient l'efficacité du cannabis médical pour traiter les douleurs chroniques chez des patients présentant onze causes divergentes et différents mécanismes latents à l'origine de ces douleurs. De plus, les définitions et les mesures des résultats rapportés sont très hétérogènes. La plupart des RCT sur les douleurs chroniques ont été inclus pour leurs analyses sur la sclérose en plaques (SEP).

Au total, 14 RCT étudiant l'usage du cannabis médical pour traiter la spasticité chez des patients atteints de plusieurs maladies ont été pris en considération. L'effet du cannabis médical sur la spasticité due à la SEP est le plus souvent analysé. Les méthodes les plus utilisées pour présenter les résultats en la matière sont l'échelle d'Ashworth, l'échelle d'Ashworth modifiée et une échelle numérique 0-10.

Cinq RCT mesurant l'efficacité du cannabis médical pour traiter la perte de poids involontaire ont été trouvés. Les études ont eu recours à différentes méthodes pour mesurer les résultats, rendant difficile la comparaison entre elles et la mise en commun des données.

Concernant les nausées et vomissements dus à une thérapie oncologique, 22 RCT ont été intégrés. Ils remontent cependant à un certain temps : 19 d'entre eux ont été publiés avant 1990. Les anciens RCT présentent davantage de problèmes concernant la qualité méthodologique et informative des résultats que les récents. De plus, les circonstances thérapeutiques ont pu changer au fil des ans (y compris le traitement de comparaison), ce qui limite l'applicabilité des résultats obtenus à la pratique clinique actuelle. À nouveau, la fréquence ou la sévérité des nausées ou vomissements est mesurée à l'aide d'un large éventail de méthodes. Cette hétérogénéité impacte la synthèse des données rapportées.

Deux évaluations économiques s'intéressent à l'emploi du cannabis médical dans le traitement des douleurs chroniques, et six à la spasticité. Elles ne présentaient cependant pas de preuves sur l'économicité du cannabis médical en Suisse. Aucune évaluation économique n'a été identifiée à propos de la perte de poids involontaire et des nausées et vomissements dus à une thérapie oncologique.

Le présent rapport conclut des résultats mentionnés qu'il est possible de procéder à une évaluation des technologies de la santé (ETS, en anglais *Health Technology Assessment*) pour le cannabis médical en Suisse. Pour ce qui est des douleurs chroniques et de la spasticité, des modèles d'économicité peuvent être élaborés en s'inspirant des modèles développés par le *National Institute for Health and Care Excellence* (NICE) au Royaume-Uni. Ils peuvent être adaptés au contexte suisse à l'aide des éléments fournis par la littérature et de recherches additionnelles sur les coûts et la qualité

de vie en Suisse. En ce qui concerne la perte de poids involontaire et les nausées et vomissements dus à une thérapie oncologique, le rapport énonce que, en raison des limites méthodologiques des études mentionnées, les données de bonne qualité manquent pour analyser les résultats individuels des études ou pour développer un modèle d'économicité suffisamment valide. Le rapport d'ETS expliquera pourquoi il faut considérer les preuves comme insuffisantes pour tirer des conclusions sur l'usage du cannabis médical dans le traitement de ces deux symptômes. Il inclura également une description des aspects sociaux, légaux, éthiques et organisationnels abordés dans la littérature parallèle (c'est-à-dire les lignes directrices et les documents d'agences d'ETS).

Table of contents

List of tables

Abbreviations and acronyms

AIDS	Acquired immune deficiency syndrome
ART	Anti-retroviral therapy
CADTH	Canadian Agency for Drugs and Technologies in Health
CB1	Cannabinoid Receptor 1
CB2	Cannabinoid Receptor 2
CBD	Cannabidiol
CDC	Centers for Disease Control and Prevention
CHEC	Consensus Health Economic Criteria
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CUA/CUAs	Cost-Utility Analysis/ Cost-Utility Analyses
DRG	Diagnosis-related group
EDSS	Expanded Disability Status Scale
ESPEN	European Society for Clinical Nutrition and Metabolism
EQ-5D	EuroQol 5 dimensions instrument (for quality of life)
EU	European Union
FOPH	Federal Office of Public Health
GP	General Practitioner
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
HAART	Highly active antiretroviral therapy
HIV	Human Immune-Deficiency Virus
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
ICER	Incremental Cost-Effectiveness Ratio
LMP	Licensed medical product
MS	Multiple Sclerosis
NA	Not applicable

NHS	National Health Service
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NIP	Narcotic individual prescription
NRS	Numeric Rating Scale
OMC	Office of Medical Cannabis
OR	Odds Ratio
PICO	Population-Intervention-Comparison-Outcome
QALY	Quality-Adjusted Life Years
QoL	Quality of life
RCT	Randomised Controlled Trial
SCI	Spinal cord injury
SoC	Standard of Care
SR	Systematic Review
THC	Tetrahydrocannabinol
TLEL	Timely Limited Exceptional License
UK	United Kingdom
USA	United States of America

Objective of the HTA scoping report

The objective of the scoping report is to conduct a systematic literature search and to synthesise the available evidence base addressing the main health technology assessment (HTA) domains, i.e., efficacy/effectiveness/safety, costs/budget, impact/cost-effectiveness, legal/social/ethical, and organisational issues. This report describes the analytical methods to pursue or omit an HTA. Based on quantity and quality of the extracted evidence the feasibility of pursuing an HTA is judged. Analysis of the individual study outcomes is not the objective of the scoping report.

1 Policy question and context

Medical cannabis is available in Switzerland for patients upon narcotic individual prescription (NIP). The physicians obtain for each specific patient a timely limited exceptional license (TLEL) from the Federal Office of Public Health (FOPH) for preparations that contain more than 1% (-)-trans-delta-9-Tetrahydrocannabinol (THC). Currently, patients need to pay for medical cannabis themselves or they may get exceptional reimbursement in special cases. General reimbursement by the compulsory health insurance for medical cannabis does not exist at the moment.

In response to the political calls for better access, possible reimbursement of medical cannabis, and the increasing number of TLEL, the FOPH investigates the evidence for efficacy, effectiveness, safety, and cost-effectiveness of medical cannabis for the treatment of the most common symptoms where medical cannabis may be indicated.

2 Research question

In this Chapter, the central research questions on which the systematic literature search is based are detailed. The central research question is divided into two sub questions.

Central research question of systematic literature search

What is the efficacy[a], effectiveness[b], and safety[c], as well as the cost-effectiveness and budget impact of medical cannabis compared to placebo, no treatment, or standard of care (depending on the symptom), in patients of all ages with one of the four pre-specified symptoms that may be treated with medical cannabis?

- Chronic pain
- Spasticity

[a] Efficacy is the extent to which a specific health technology produces a beneficial, reproducible result under study conditions compared with alternative technologies (i.e. internal validity).
[b] Effectiveness is the extent to which a specific health technology, when applied in real world circumstances in the target group, does what it is intended to do for a diagnostic or therapeutic purpose regarding the benefits compared with alternative technologies (i.e. external validity).
[c] Safety is a judgement of the harmful effects and their severity using the health technology. Relevant adverse events are those that result in death, are life-threatening, require inpatient hospitalisation or cause prolongation of existing hospitalisation (i.e. serious adverse events) and those that occur repetitively and the most frequent (highest rate).

- Unintentional weight loss
- Nausea and vomiting related to cancer treatment

Research sub question of the efficacy, effectiveness, and safety systematic literature search

- What is the efficacy, effectiveness, and safety of medical cannabis compared to placebo, no treatment or standard of care (depending on the symptom), in patients of all ages with one of the four pre-specified symptoms that may be treated with medical cannabis?

Research sub question of the cost-effectiveness systematic literature search

- What is the cost-effectiveness and budget impact of medical cannabis compared to placebo, no treatment, or standard of care (depending on the symptom), in patients of all ages with one of the four pre-specified symptoms that may be treated with medical cannabis?

A non-systematic search for grey literature will be conducted to identify information on legal, social, ethical, and organisational issues related to medical cannabis.

3 Medical background

The use of cannabis or cannabis-based products for medical purposes has a long history and its applications have been influenced by multiple factors, such as the development of standardised drugs to treat specific symptoms and the inclusion of cannabis in laws regarding narcotics.[1, 2] After discovery of the human cannabinoid system in the early 1990s, developments in the legalisation of medical cannabis, and an increasing number of clinical trials, there has been a resurgence of interest in medical cannabis use for a variety of symptoms and diseases.[1, 2] Nowadays, most European Union (EU) countries allow or are considering allowing the medical use of cannabis. However, the approaches vary widely in the products allowed, as well as the regulatory frameworks governing their provision.[1] Medical cannabis includes a wide variety of plant-derived and synthetic products that may contain different active ingredients and use different routes of administration.[1] The rising interest in the medical use of cannabis also raises safety concerns. A systematic review (SR) of safety studies of medical cannabis found that the rate of nonserious adverse events was 1.86 times higher among people using medical cannabis for short-term versus controls.[3] Dizziness was the most commonly reported nonserious adverse event among medical cannabis users. There was no evidence of a higher incidence of serious adverse events following medical cannabis use compared with control. The most common serious adverse events were

relapse of multiple sclerosis (MS), vomiting, and urinary tract infection. The difference in mortality between the two groups was not statistically significant. The authors highlight that the risks associated with long-term medical cannabis use were poorly characterised in published randomised controlled trials (RCTs) and observational studies. Chapter 4 provides a more detailed description of medical cannabis products and their mechanism of action.

A first appreciation of the available evidence on medical cannabis revealed a wide variety of symptoms on which medical cannabis can potentially have a positive effect. For a detailed investigation into the efficacy, effectiveness, and safety, as well as the cost-effectiveness and budget impact of medical cannabis, the focus of the scoping report had to be narrowed down to a pre-specified selection of symptoms. During the process of writing the protocol for this scoping report, a preliminary literature search was conducted to gain more insight into the various symptoms which may be treated with medical cannabis (see Appendix 1). The findings of the preliminary literature search were used to help decide on the selection of symptoms to be included in the scope of this report. The final selection of symptoms was based on the availability of literature and HTA documents on the use of medical cannabis for treating the symptom, as well as well as information on the main symptoms for which medical cannabis has been previously prescribed in Switzerland.

3.1 Preliminary literature search on the symptoms that may be treated with medical cannabis

The preliminary literature search included a search for English-language SRs published in the last five years on the efficacy, effectiveness, safety, and cost-effectiveness of medical cannabis, a search for cost-effectiveness studies, and a grey literature search for HTA documents. The methods of this preliminary search are enclosed in Appendix I. The search had a broad approach in which all potential medical cannabis indications were included. The preliminary literature was aimed to provide insight into the various symptoms which may be treated with medical cannabis, as well as a first estimation of the available evidence for a specific symptom.

For the clinical effectiveness of medical cannabis 37 SRs and a Swiss evaluation study were included.[4-38] Most frequently studied medical cannabis symptoms in these SRs were pain, chemotherapy induced nausea and vomiting, spasticity, and epileptic seizures. The evaluation study, conducted by Kilcher et al. (2017), examined almost 1,200 TLELs for medical cannabis (i.e. permit issued typically for 6 months with possible extensions) in Switzerland in 2013-2014; chronic pain (53%) and spasticity (40%) were the most common symptoms for medical cannabis use, followed by a lack of appetite (4%), nausea (2%), and tremor (1%).[21] Two SRs with cost-effectiveness data were found, one on the effect of medical

cannabis on MS symptoms[39] and the other on paediatric drug-resistant epilepsy.[40] In addition, and partly overlapping with the included SR on MS, 8 cost-effectiveness studies were found with the preliminary search: 6 on the use of medical cannabis in MS[41-46], 1 on chronic neuropathic pain[47], and 1 study on substance abuse[48]. Furthermore, reports from 11 different institutes in Europe, Australia, Canada, and the United States of America (USA) were found with the grey literature search. The most frequently reviewed symptoms that may be treated with medical cannabis were spasticity, nausea and vomiting, chronic pain, and epileptic seizures.

After discussion of these preliminary results with the FOPH, it was decided which symptoms were deemed most relevant to the current Swiss context and should be the focus of the scoping report. The relevance of the symptoms was based upon a combination of the availability of evidence found in the peer-reviewed and grey literature to support the (cost-)effectiveness of the use of medical cannabis to treat the symptom, and the demand in Switzerland for the use of medical cannabis for treating the symptom based on the registry of Kilcher et al. 2017.[21] From this exploratory search, it can be concluded that chronic pain, spasticity, nausea and vomiting, and epileptic seizures are the symptoms which received most interest in the literature. Chronic pain, spasticity, and nausea and vomiting were therefore selected to be included within the scope of this report. The registry of Kilcher et al. 2017[21] showed that a lack of appetite belonged to the main symptoms for which medical cannabis has been prescribed in Switzerland. The ability of medical cannabis to stimulate appetite, and thereby potentially decrease unintentional weight loss, was considered a clinically important topic to be included within the scope of this report, since severe diseases such as cancer and human immunodeficiency virus (HIV) result in considerable weight loss with negative consequences for the disease course. In dialogue with the FOPH the decision was made to include unintentional weight loss as well.

In conclusion, the following symptoms that may be treated with medical cannabis were ultimately selected as the focus of the scoping report: chronic pain, spasticity, unintentional weight loss, and nausea and vomiting related to cancer treatment. The input from the preliminary search on which this selection was based is summarised in Table 1. Other symptoms which may be treated with medical cannabis (including epilepsy, mental illness, and Gilles de la Tourette syndrome) may be considered to be the subject of a future HTA.

Table 1 Results of the preliminary literature search for the 4 symptoms of interest for medical cannabis

	Effectiveness (number of SRs)	Cost-effectiveness (number of SRs)	Cost-effectiveness (number of economic evaluations)	HTA/guidelines (number of reports)	Symptoms in patients for medical cannabis use in Switzerland (Kilcher et al., 2017)*
Chronic pain	- Neuropathic pain: n=11[4, 6, 13, 15, 18, 25, 27-29, 32, 49] - Nociceptive pain: n=1[29] - Cancer pain: n=9[4, 6, 10, 12, 27, 29, 30, 49, 50] - Non-cancer pain: n=2[4, 32] - HIV pain: n=2[5, 13] - MS pain: n=2[4, 27] - Rheumatic pain: n=3[4, 28, 49] - Fibromyalgia pain: n=2[4, 32] - Post-operative pain: n=1[6] - Pain in advanced diseases in general: n=1[4] - No diagnosis for pain symptoms: n=5[4, 5, 11, 27, 36]	n=0	n=1[47]	n=11[51-61]	53.0%
Spasticity	Spasticity in MS: n=4[4, 15, 28, 36]	Spasticity in MS: n=1[39]	n=6[41-46]	n=15[2, 51, 54-56, 58, 61-69]	39.9%
Unintentional weight loss	Weight-loss in patients with cancer or HIV/AIDS: n=3[10, 28, 49]	n=0	n=0	n=6 (i.e. lack of appetite)[2, 51, 54-56, 70]	3.5% (i.e. lack of appetite)
Nausea and vomiting related to cancer treatment	Chemotherapy induced nausea and vomiting: n=7[4, 10, 28, 31, 33, 36, 37]	n=0	n=0	n=12[2, 51, 54-56, 58, 61, 62, 64, 70-72]	2.2%

Keys: AIDS = acquired immunodeficiency syndrome, HIV = human immune-deficiency virus, n = number of studies, MS = multiple sclerosis, SR = systematic review; * Symptoms in patients granted timely limited exceptional licenses for therapeutic use of medical cannabis

3.2 Symptoms selected for inclusion in the scoping report

Chronic pain

Chronic pain is defined as persistent or recurrent pain lasting longer than 3 months.[73] Chronic pain is a prevalent condition, affecting about 20% of the people worldwide and is associated with a significant personal, social, medical, and economic burden.[25] The distribution of type and pattern of chronic pain symptoms varies between people and can be a result of various underlying causes, such as cancer, spinal cord injury (SCI), diabetes, MS, HIV, and postoperative or traumatic peripheral nerve lesions.[25, 74] The treatment of chronic pain is multimodal but mostly contains a pharmacological agent.[75] Existing medications for the treatment of chronic pain, such as opioids, have limited efficacy and come with considerable side effects. In addition, the increase in the prescription of opioids is associated with an increase in opioid use disorders and opioid-related mortality.[76] Since chronic pain is difficult to treat, other treatment options such as medical cannabis or combinations of treatments, are explored with different mechanisms of action for treatment of chronic pain or the various conditions underlying chronic pain.[25, 76] This scoping report will explore the available literature on the efficacy of medical cannabis on all types of chronic pain, not limited to a specific underlying disease.

Spasticity

Spasticity is often inconsistently defined in scientific studies and also the applied outcome measures do not always correspond to the reported spasticity definition.[77] The most commonly used definition of spasticity was formulated by Lance in 1980 as a motor disorder characterised by a velocity-dependent increase in muscle tone with exaggerated tendon jerks, resulting from hyper-excitability of the stretch reflex as one component of the upper motor neurone syndrome.[78] This definition changed during the years by adding other features of spasticity such as spasm and clonus.[78] Spasticity results from a lesion of the descending motor pathways due to pathologies such as stroke, SCI, or MS, and is a common and distressing symptom in these diseases.[79] MS is a progressive disease and eventually up to 90% of people with MS will suffer from the symptom muscle spasticity.[80] Also in SCI the epidemiology of spasticity affirms the significance of this medical problem.[81] Spasticity may be mild as the feeling of tightness of muscles or more severe and be associated with spasms, sleep disturbance, and pain, which contributes to reduced mobility and increases the burden of disease for both the patients and their caregivers.[82-84] Furthermore, these symptoms may cause severe complications such as fibrous contractures and pressure sores, and eventually disability resulting from spasticity can lead to patients requiring extensive healthcare.[82]

Medicinal treatment is prescribed to reduce spasticity, but may be insufficiently effective, difficult to obtain, or associated with intolerable side effects.[79] As a consequence, people with MS or SCI have experimented with alternative therapies, including cannabis, to ease their physical problems.[80, 81] Medical cannabis is suggested as an effective and tolerable alternative treatment for patients with residual spasticity not adequately controlled using existing treatments.[79]

Unintentional weight loss

Unintentional weight loss is the involuntary decline in total body weight of persons over time and indicates acute changes in the protein-energy status.[85] Unintentional weight loss in studies is often defined as the absence of self-reported action to try to lose weight, which may include diet, physical activity, use of medications, or by medical recommendation.[86] According to The European Society for Clinical Nutrition and Metabolism (ESPEN) thresholds for alarming unintentional weight loss are more than 5% weight loss in the last 3 months or more than 10% weight loss with indefinite time.[87] Unintentional weight loss has serious consequences; it affects outcomes of surgery and chemotherapy[85] and hospital patients with critical weight loss have a higher one-year mortality compared to inpatients with no critical weight loss.[88]

Unintentional weight loss suggests the presence of disease. It can be caused by various conditions, such as malignant diseases, chronic organ diseases, drug-induced weight loss, or psychological disorders.[85, 86] Despite extensive investigations, up to one quarter of all cases of unintentional weight loss have no identifiable cause, since its pathophysiology is poorly understood.[86] In cancer patients unintentional weight loss is common. High percentages of weight loss were seen in patients with tumours of oesophagus (57%), stomach (50%), larynx (47%)[89], and in patient with different types of lung cancer: small cell lung cancer (59%), non-small cell lung cancer (58%), and mesothelioma (76%).[90] Another disease with frequent unintentional weight loss is HIV. The HIV wasting syndrome and other HIV-associated weight loss is a major problem in HIV-infected patients. The available data strongly suggest that wasting is associated with decreased survival.[91] The incidence of HIV-associated wasting may have declined since the introduction of highly active antiretroviral therapy (HAART), it continues to be a concern in this patient population.[92] In 2015, the Centers for Disease Control and Prevention (CDC) estimated 1.2 million people were infected with HIV in the United States and 36.9 million people globally.[93] Anti-retroviral therapy (ART) is the primary therapy for HIV patients in many countries. While effective, ART therapy can also induce nausea and reduced appetite. Furthermore, HIV infection, even when properly controlled by ART, is associated with physical wasting.[93] In a prospective cohort with HIV patients receiving HAART, 58% of the cohort lost more than 1.5 kg of weight in a 6-month period.[94]

Medical cannabis has been prescribed to symptomatically treat loss of appetite and unintentional weight loss caused by different underlying diseases (such as patients with cancer, HIV, or Alzheimer-type dementia) and the effectiveness and safety is investigated in multiple studies. The psychiatric eating disorder anorexia nervosa is out of scope for this project.

Nausea and vomiting related to cancer treatment

Although often used together, nausea and vomiting should be considered separately. Nausea describes the feeling of being sick and is a subjective measure which could only be rated by the patient. While vomiting is an objective measure and the number of vomiting episodes can be counted.

Nausea and vomiting are considered the most stressful adverse effects by people under treatment for cancer (i.e. treatment with radiotherapy, chemotherapy, immune therapy, and targeted therapy) and the amount of nausea and vomiting symptoms depends on the emetic potential of the therapy agents.[31, 33] Up to 75% of all people with cancer experience chemotherapy-related nausea and vomiting.[95] Chemotherapy-induced nausea and vomiting can be divided in four categories: acute, delayed, anticipatory, and breakthrough nausea and vomiting.[33] Despite advances in anti-emetic therapy (i.e. anti-sickness drugs), nausea and a feeling of helplessness decrease the quality of life (QoL) and may eventually affect chemotherapy adherence.[31, 33]

Depending on the experienced adverse events of cannabis, medical cannabis might be an alternative therapeutic option for people with chemotherapy-induced nausea and vomiting related to cancer treatment that respond poorly to commonly prescribed anti-emetic drugs. Currently, there are two synthetic cannabinoid agents that have been evaluated in RCTs and are approved for the treatment of nausea and vomiting related to cancer treatment: nabilone and dronabinol.[31]

4 Technology

4.1 Technology description

Medical cannabis includes all cannabis-based products which are used for medical treatment. Medical cannabis can be taken in herbal form (e.g. dried cannabis flowers, cannabis resin (hashish)), extracted naturally from the plant (e.g. sativa oil), or manufactured synthetically (e.g. dronabinol). Cannabinoids are the main active ingredients in both the medicinal products derived from cannabis and cannabis preparations. The cannabis plant can produce over 100 cannabinoids.[96] The so far most studied cannabinoids, and thought to be the most important in terms of clinical effects, are THC and cannabidiol (CBD). [1, 2] Medical cannabis products are therefore often referred to by their composition of THC and

CBD, or by the ratio of these components. While the exact mechanism, interaction and magnitude of effects of THC and CBD are not yet fully understood, they are both known for binding to CB1 and CB2 receptors of the endocannabinoid system. The endocannabinoid system is a system of cannabinoid receptors, their endogenous ligands (endocannabinoids), and endocannabinoid-degrading enzymes as part of the central and peripheral nervous system that performs a large role in maintaining homeostasis in many physiological functions.[97] The effects of cannabinoids are primarily mediated by CB1 and CB2 cannabinoid receptors. CB1 receptors are predominantly located in the central nervous system, mainly in the cortex, basal ganglia, hippocampus, and cerebellum[97, 98] The distribution of these receptors within the central nervous system correlates to their roles in the control of physical functions, such as motor function, analgesia, cognition, and memory.[97, 98] CB2 receptors play a role in immune cell activation and inflammation and are mainly expressed in peripheral organs with immune function.[97, 98]

Since CB1 and CB2 receptors are widespread in the human body and their ligands trigger a variety of physiological actions, medical cannabis can potentially have an effect on divergent symptoms and underlying diseases. Short-term effects of THC include amongst others muscle relaxation, increased heart rate, reduction in intra-ocular pressure, increase in appetite, and it has antiemetic and analgesic properties.[1, 2, 99] THC is also the main psychoactive component of cannabis, producing the psychoactive effects sought by recreational users, such as euphoria, relaxation, and heightened sensory experiences.[57] CBD is a non-psychoactive constituent of cannabis, and may reduce the psychoactive and appetite stimulating effects caused by THC. CBD contains therapeutic (sedative and anticonvulsant) properties, and potential effects include seizure reduction, improvements in anxiety symptoms and improved mental health outcomes in schizophrenia.[24, 100] Synthetic cannabinoids for therapeutic use typically mimic the effects of natural cannabinoids such as THC and CBD. THC and CBD may have pharmacokinetic or pharmacodynamic interactions that influence their effects on physiological functions. This is a topic of ongoing research.

Medical cannabis products come with several different modes of administration, including oral, sublingual, topical, smoked, inhaled, mixed into food, or infused as tea. The mode of administration of cannabis can affect the onset, intensity, and duration of the therapeutic effects, the addictive potential, and negative consequences associated with its use.[57] As the harms associated with smoking are well known, and safer and more precise methods of administration are available, countries in the European Union (EU) do not recommend or reimburse smoking as a mode of consumption for medical cannabis preparations.[1] The appropriate dose of medical cannabis is generally found with the “start low, go slow” approach (start with a low dose and wait to see the effects before increasing the dose) and varies with the treated symptoms. Duration of the treatment depends on the symptom to be treated, its effectiveness, experienced side effects by the patient, and costs.[101]

Within medical cannabis, the distinction can be made between products that have a marketing authorisation for medical use and those that do not. Several (plant-derived and synthetic) cannabinoid-containing products have been authorised for marketing in EU countries. Having a marketing authorisation generally implies that the drug has been studied extensively in clinical trials and that the drug has been tested for safety, efficacy, and side effects.[102, 103] Table 2 contains the details of the most commonly referred to licensed medical products (LMPs).[1, 2]

Table 2. **Medical cannabis products with marketing authorisation in at least one EU country**

Brand name	Active ingredient	Administration	Composition	Authorised indication
Sativex®	Nabiximols	Oromucosal spray	Approximately equal quantities of THC and CBD from two cannabis plant varieties	Muscle spasticity resulting from MS
Cesamet® and Canemes®	Nabilone	Oral capsules	Synthetic cannabinoid similar to THC	Nausea and vomiting associated with chemotherapy
Marinol® and Syndros®	Dronabinol	Oral capsules or oral Solution	Synthetic THC	(1) Anorexia associated with weight loss in patients with acquired immune deficiency syndrome (AIDS) and (2) Nausea and vomiting associated with cancer chemotherapy

Epidiolex®	CBD	Oral solution (oil)	Plant-derived CBD	Epileptic seizures associated with Lennox-Gastaut syndrome or Dravet syndrome in patients aged ≥ 2 years

Keys: AIDS = acquired immune deficiency syndrome, CBD = cannabidiol, MS = multiple sclerosis, THC = tetrahydrocannabinol

Apart from these LMPs, the raw cannabis may be transformed by a pharmacist into a magistral preparation for consumption in accordance with a specified medical prescription for an individual patient, or the raw cannabis may already have been transformed by the manufacturer in larger batches (standardised preparation). Such products, which do not have a marketing authorisation for medical use may include the raw cannabis, such as the flowers, compressed resin or hash; oils extracted from the plant; concentrated cannabis extracts; and other cannabis preparations, such as soft gels, tinctures, or edibles. A variety of pharmacy-prepared, magistral preparations of medical cannabis is available in Switzerland, as shown in Table 3.[104]

Table 3. Description of Swiss Extemporaneous Preparations and Sativex®

	Sativa oil 1%	Dronabinol solution 2.5%	Standardised cannabis tincture	Standardised cannabis oil	Sativex®	Praescriptio magistralis Cannabis 1% THC	Praescriptio magistralis Cannabis 2.7% THC
THC content (mg/ml)	10	25	10	10	27	10	27
THC:CBD	1:0.3	1:1	1:2	1:2	1:1	1:2.2	1:0.9
Formulation	Oily solution	Oily solution	Ethanolic solution	Oily solution	Ethanolic solution	Oily solution	Oily solution

Costs per mg THC (CHF)	1.58	1.60-1.80	1.10	1.60	Approx. 0.96	1.60	1.57

Keys: CHF = Swiss Franc

Regulation in Switzerland

The cultivation, the trade, and the consumption of cannabis with more than 1% THC by patients is forbidden in Switzerland, although the possession of a small amount (10 grams of cannabis) for own consumption is only mildly punished.[105, 106] CBD is not considered a psychoactive compound. Hence, its consumption and use are not restricted by the Federal Act on Narcotics and Psychotropic Substances. Since 2011 the access to cannabis for medical use was allowed with an obtained TLEL from the FOPH. To obtain medical cannabis in Switzerland, the following criteria should be met,

- a patient must suffer from a non-curable disease
- their suffering is expected to diminish with the use of medical cannabis
- all therapeutic alternatives have not shown any improvement
- due to the use of medical cannabis the patient maintains or gains an independent life style.[107]

Between 2012 and 2019 approximately 15,000 patients received access to medical cannabis via TLEL.[108] However, the number of patients who use medical cannabis without TLEL and NIP (i.e. illicit users) is estimated to range from 66,000 to 110,000.[107, 109] Sativex® is currently the only LMP containing medical cannabis in Switzerland. It is indicated to improve symptoms in patients with moderate to severe spasticity due to MS who have not responded adequately to other anti-spastic drug therapy and who show a clinically significant improvement in spasticity-related symptoms during an initial trial therapy. Medical cannabis is generally not reimbursed by the Swiss compulsory health insurance, but individual patients may get reimbursement on a case-to-case basis.

Regulation in Other Countries

Regulation and reimbursement policies of medical cannabis differ substantially between countries. To date, the number of countries who fully or partially authorise the use of medical cannabis is growing.

Germany

In Germany the use of medical cannabis is legalised since March 2017. Besides the prescription, no special permit is required to obtain medical cannabis.[110] Reimbursement of medical cannabis is not restricted to a specific indication. Medical cannabis is reimbursed (a) if no therapeutic alternative is available or (b) if therapeutic alternatives are not effective.[111] The Deutscher Bundestag revealed the six most-reported diagnoses for which medical cannabis has been prescribed and covered by statutory health insurers as of September: pain (70.9%), spasticity (10.8%), anorexia (6.9%), epilepsy (1.6%), ADHD (1.5%) and Tourette Syndrome (1.0%).[112]

Denmark

Since January 2018, medical doctors can prescribe medical cannabis in Denmark. A 4-year pilot programme aims to offer patients a legal access to medical cannabis if they have not benefitted from authorised medicines. An assessment after the 4-year trial intends to provide better basis for the use of medical cannabis. As of January 2019, people in Denmark are reimbursed at the rate of 50% for cannabis products in the pilot programme.[113] The use of medical cannabis in Denmark is restricted to certain indications, namely painful spasms caused by MS or SCI, nausea after chemotherapy, or neuropathic pain.

France

The French Senate recently authorised an experiment that allows doctors to prescribe medical cannabis for the following indications: treatment-resistant epilepsy, neuropathic pain that does not respond to other treatment, involuntary muscle spasms and/or other nervous system conditions, side effects of chemotherapy, or palliative care.[114]

Belgium

In Belgium, a draft resolution was recently submitted which calls for approval of- and research into the use of Sativex® in indications beyond MS, namely in amyotrophic lateral sclerosis and epilepsy.[115]

The Netherlands

In the Netherlands patients are allowed to use cannabis for medical use. Since 2001 the government agency Office of Medicinal Cannabis (OMC) is responsible for overseeing the production of cannabis

for medicinal and scientific purposes. The OMC has a monopoly on supplying medical cannabis to pharmacies, and on its import and export. Medical cannabis provided by the OMC is of pharmaceutical quality and complies with strict requirements.[116] Pharmacies can supply medical cannabis on doctor's prescription only. While it is up to doctors to determine which conditions would benefit from treatment with medicinal cannabis, the OMC states that current data shows that medicinal cannabis can help relieve pain and muscle spasms associated with MS or SPI; nausea, reduced appetite, weight loss and debilitation associated with cancer and AIDS; nausea and vomiting caused by medication or radiotherapy for cancer and HIV/AIDS; long-term neurogenic pain (i.e. originating in the nervous system), phantom limb pain, facial neuralgia or chronic pain following an attack of shingles; and tics associated with Tourette Syndrome.[117] Medical cannabis is not generally reimbursed in the Netherlands, but health insurers may decide to cover (part of) the costs.

4.2 Alternative technologies

Medical cannabis is predominantly used as add-on therapy or after other therapeutic options were unsuccessful. Hence, alternative treatment are standard treatments of the pertaining symptoms.

5 PICO

Table 4. PICO (population - intervention - comparator – outcome) box

P:	1. Patients (all ages) with the symptom chronic pain with various underlying causes 2. Patients (all ages) with the symptom treatment-resistant residual spasticity with various underlying causes 3. Patients (all ages) with the symptom unintentional weight loss with various underlying causes 4. Cancer patients (all ages) with the symptom nausea and vomiting related to cancer treatment who poorly respond to regular anti-emetic drugs
I:	Medical cannabis, prescribed as standalone treatment or add-on treatment
C:	• Placebo • No treatment for the symptom of interest

	• Standard treatment according to the treatment guidelines (i.e. conventional drugs for the chronic pain condition, spasticity or nausea and vomiting related to cancer treatment, or conventional treatment for weight loss)
O (clinical):	**1. Efficacy of medical cannabis; chronic pain** a. Clinically relevant patient-reported pain relief b. Withdrawal due to lack of pain relief efficacy of medical cannabis c. Improvement in HRQoL **2. Efficacy of medical cannabis; spasticity** a. Clinically relevant improvement in a specific spasticity aspect b. Withdrawal due to lack of anti-spasticity efficacy of medical cannabis c. Improvement in HRQoL **3. Efficacy of medical cannabis; unintentional weight loss** a. Weight gain b. Increased daily caloric intake c. Withdrawal due to lack of appetite stimulating efficacy of medical cannabis d. Improvement in HRQoL **4. Efficacy of medical cannabis; nausea and vomiting related to cancer treatment** a. Absence of nausea, vomiting, or nausea and vomiting after cancer treatment b. Frequency of nausea, vomiting, or nausea and vomiting after cancer treatment c. Severity of nausea after cancer treatment d. Withdrawal due to lack of anti-emetic efficacy of medical cannabis e. Improvement in HRQoL **5. Safety of medical cannabis:** a. Occurrence of cannabis-associated adverse events b. Withdrawal of treatment due to adverse effects of medical cannabis
O (health economic):	1. Resource use due to medical cannabis adverse events 2. Health-care costs (total and incremental) from a healthcare perspective 3. Quality adjusted cost comparison after 6 months, 2 years, 5 years, (…), lifetime 4. ICERs, incremental/total costs, QALYs and life years gained, after 6 months, 2 years, 5 years,

(…), lifetime

Keys: HRQoL = health-related quality of life, ICERs = incremental cost-effectiveness ratios, QALYs = quality-adjusted-life-years

6 HTA key questions

For the evaluation of medical cannabis the following key questions covering the central HTA domains, as designated by the EUnetHTA Core Model[118] (efficacy, effectiveness, safety, costs, cost-effectiveness, budget impact, legal, social, ethical, and organisational aspects), are addressed for each of the four pre-specified symptoms:

- Chronic pain
- Spasticity
- Unintentional weight loss
- Nausea and vomiting related to cancer treatment

6.1 Key questions - efficacy, effectiveness, and safety

For the evaluation of the technology the following key questions covering the efficacy, effectiveness, and safety will be addressed (definitions provided by the FOPH):

1. What is the efficacy of medical cannabis compared to placebo, no treatment, or standard of care (depending on the symptom), in patients of all ages with one of the four pre-specified symptoms that may be treated with medical cannabis?
2. What is the effectiveness of medical cannabis compared to placebo, no treatment, or standard of care (depending on the symptom), in patients of all ages with one of the four pre-specified symptoms that may be treated with medical cannabis?
3. What is the safety of medical cannabis compared to placebo, no treatment, or standard of care (depending on the symptom), in patients of all ages with one of the four pre-specified symptoms that may be treated with medical cannabis?

6.2 Key questions - costs, budget impact, and cost-effectiveness

For the evaluation of the technology the following key questions covering the cost-effectiveness will be addressed:

1. What is the healthcare resource use patients of all ages with one of the four pre-specified symptoms, with and without medical cannabis (resource-use identification)?
2. What are the Swiss unit costs of the resources identified in question 1?
3. What are the utilities associated with the use of medical cannabis (including administration), adverse events, and the four pre-specified symptoms?
4. What are the estimated differences in costs and outcomes of medical cannabis use compared to no medical cannabis in patients of all ages with one of the four pre-specified symptoms?
5. What is the likely budget impact of the reimbursement of medical cannabis in patients of all ages with one of the four pre-specified symptoms?
6. What are the uncertainties surrounding the costs and outcomes of medical cannabis compared to no medical cannabis in patients of all ages with one of the four pre-specified symptoms?

6.3 Key questions - legal, social, and ethical issues

For the evaluation of the technology the following key questions covering the legal, social, and ethical issues will be addressed:

1. Are there specific legal issues associated with potential reimbursement of medical cannabis for patients of all ages with one of the four pre-specified symptoms?

2. What are the socially and ethically relevant consequences of potential reimbursement of medical cannabis for patients of all ages with one of the four pre-specified symptoms?

6.4 Key questions - organisational issues

For the evaluation of the technology the following key question covering the organisational question will be addressed:

1. What organisational issues are attached to the use of medical cannabis in patients of all ages with one of the four pre-specified symptoms?

7 Methodology literature search

In the scoping phase, a systematic literature search was done based on the methodology of SRs. An SR is a method to collect, critically appraise, and summarise the best available evidence in a transparent and systematic way using generally accepted evidence-based principles. The methodology of SRs follows international standards, such as the Cochrane Collaboration guidelines for performing SRs, and the reporting of this scoping review follows the recommendations of PRISMA.[119, 120]

The SR process consists of the following fundamental steps:

1. Formulation of the research questions
2. Comprehensive information search, including defining data sources and search strategy
3. Selection procedure, applying pre-determined clear inclusion and exclusion criteria
4. Critical appraisal (quality and risk of bias assessment)
5. Data extraction
6. Quality control

The applied systematic literature search follows the same fundamental steps described above. As the scoping phase comprised of a systematic literature search to inform the decision on whether a HTA can be conducted, a preliminary critical appraisal and preliminary data extraction of included literature was conducted in the scoping phase. In the Outlook (Chapter 10) the SR process that may be conducted for the HTA is further detailed.

In the following sections the search strategy for the applied systematic literature search of both the efficacy, effectiveness, and safety (Section 7.1.1) and the cost-effectiveness (Section 7.1.2) of medical cannabis is described in detail.

7.1 Databases and search strategy

7.1.1 Efficacy, effectiveness, and safety

Search strategy

PubMed (MEDLINE) and Embase databases were searched for RCTs published in the peer-reviewed scientific literature. Since there is considerable overlap in studies included in other literature databases (such as Cochrane Library), the decision was made to search in these two main databases. The

searches were built using the PICO-framework (see PICO box in Chapter 5). Given the various outcomes of interest, it was decided to keep the search broad. Only search strings on 'population' and 'intervention' were applied in combination with a search string for the study design RCTs. The applied search filters were time period (i.e. 1980-22 January 2020) and the language of publications (i.e. English, French, German, and Dutch). Furthermore, animal studies and SRs were excluded with additional search strings. Four separate search strategies were developed, one for each pre-specified symptom that may be treated with medical cannabis (Appendix 2). The literature database output, including all indexed fields per record (e.g. title, authors, and abstract), was exported to Endnote version X7.8. Duplicates in Endnote were automatically removed and further manually deleted.

Selection procedure

From the articles retrieved from PubMed (MEDLINE) and Embase the relevant references were selected by a two-step selection procedure, based on:

1. Screening of title and abstract: this step yielded the articles that were assessed in full-text. The major topics of the articles were assessed on relevancy for the objectives by the title and abstract. In this step, articles that seemed to contain relevant data for the objectives were selected for full-text screening, while articles that did not seem to contain relevant data were not selected for full-text assessment. In case of doubt, the study was assessed in full-text.
2. Screening of full article: the articles selected during the first phase were assessed in full-text. Articles were included if the reported information was relevant and of sufficient quality, based on the inclusion and exclusion criteria (see below).

The process of selection and inclusion and exclusion of articles was registered in an Endnote library by one of the researchers. The exclusion criteria applied during the full-text screening phase are reported in PRISMA flow charts (Section 8.1.1). The implemented quality control during the selection process is described in a next section.

Inclusion and exclusion criteria

The inclusion and exclusion criteria applied during the selection processes for the four pre-specified symptoms that may be treated with medical cannabis are presented in Table 5. The list of excluded studies can be found in Appendix 3.

Table 5. Inclusion and exclusion criteria for RCTs on medical cannabis use for the 4 symptoms of interest for medical cannabis

	Medical cannabis indication	Inclusion	Exclusion
Period of publication	All 4 symptoms	1980-January 2020	Publications before 1980
Language of publication	All 4 symptoms	English, French, German, Dutch	All other languages
Country of study	All 4 symptoms	All countries	-
Study design/type	All 4 symptoms	RCTs	• Reviews • Phase I RCTs (i.e. testing of drug on healthy volunteers) • (Irrelevant) post-hoc/subgroup analysis of an RCT included in the systematic literature search • Open-label extension study of an RCT • Observational studies • Case reports • Study protocol • Abstract only • Non-pertinent publication types (e.g. expert opinion, letter, editorial, comment)
	Chronic pain and spasticity	-	Experimental studies (e.g. with pain stimuli)
Study quality	All 4 symptoms	All sample sizes	• Insufficient methodological quality (both inherent methodology as well as insufficient description of methodology provided, e.g. incorrect flow of patient numbers without an explanation for loss to follow-up or studies without appropriate statistical testing)

			• Studies only presenting preliminary/interim results • No extractable data, e.g. Figures only
Study population	All 4 symptoms	Patients (all ages) with chronic pain, spasticity, unintentional weight loss, or nausea and vomiting related to cancer treatment with various underlying causes	No or lacking information on study population
	Chronic pain	-	• Patients without chronic pain • Patients in whom medical cannabis is not primarily prescribed for the symptom chronic pain
	Spasticity	-	• Patients in whom medical cannabis is not primarily prescribed for the symptom spasticity • No or lacking definition of spasticity
	Nausea and vomiting related to cancer treatment	Cancer patients (all ages) with nausea and vomiting related to cancer treatment who poorly respond to regular anti-emetic drugs	Nausea and vomiting caused by cancer and not by cancer treatment
Study intervention	All 4 symptoms	Medical cannabis, prescribed as standalone treatment or add-on treatment	Non-prescribed/recreational cannabis

	Chronic pain	Treatment duration: at least 2 weeks[121]	Treatment duration: <2 weeks
Study comparison	All 4 symptoms	• Placebo • No treatment for any of the 4 symptoms • Standard treatment according to the treatment guidelines (i.e. conventional drugs for the chronic pain condition, spasticity or nausea and vomiting related to cancer treatment, or conventional treatment for weight loss)	• Comparisons with other treatments than standard treatment • No comparison
Study outcomes	All 4 symptoms	See pre-specified outcomes in PICO table (Chapter 5)	No efficacy outcomes
	Spasticity	The outcome measures must be in line with the reported definition for spasticity	-

Keys: RCT= randomized-controlled trial, PICO = Patient Intervention Comparator Outcome

Quality control

The following quality control measures were applied during the selection process:

- The first 30% of titles and abstracts from the peer-reviewed literature were screened in duplicate by two independent researchers. The results were compared and discussed before the remaining references were assessed by one researcher. Both researchers categorised the titles as 'include for full-text assessment', 'exclude for full-text assessment', or 'doubt'. If there were differences between the two researchers regarding more than 2% of the articles selected as 'in-

clude for full-text assessment', another 10% of the articles would have been screened in duplicate. This would have been repeated if necessary. If there was still more than 2% discrepancy at 50% of the duplicate selection, the screening of title and abstracts would have been done fully in duplicate by two independent researchers. If the two reviewers disagreed on the relevance of a study, this was discussed. If the differences remained after discussion, the study was assessed in full text. During screening there was less than 2% discrepancy between the two researchers.

- The first 10% of the full-text articles from the peer-reviewed literature were assessed for relevancy and critically appraised in duplicate by two independent researchers. The results were compared and discussed early in the process. If there were differences between the two researchers with regard to more than 5% of the articles screened in duplicate, another 10% of the articles would have been screened in duplicate. This would have been repeated if necessary. If there was still more than 5% discrepancy at 50% of the duplicate selection, the screening of full-text articles would have been done fully in duplicate by two independent researchers. The remaining full-text selection was done by one researcher in close collaboration with a second reviewer; any doubts were discussed in detail. In case of discrepancy or disagreements during the selection phase, a third researcher was consulted. The study was discussed until consensus was reached.

7.1.2 Cost-effectiveness

In line with the principles outlined for the systematic literature search on efficacy, effectiveness, and safety, a systematic literature search was performed on the cost-effectiveness of medical cannabis in the four pre-specified symptoms. The methods of this systematic literature search will be discussed in this section.

Search strategy

PubMed (MEDLINE), Embase, and NHS Economic Evaluation Database (NHS EED) were searched for peer-reviewed scientific literature. The PICO method was used to specify the research questions. Table 4 (Chapter 5) outlines the utilised PICO for the cost-effectiveness review. Based on expert opinion, the time period of the search was not restricted. Due to this, it is important to be aware of the influence of inflation and discount rates on the cost-effectiveness outcomes of medical cannabis throughout the search period. Publications in English, Dutch, French, and German were included.

The search terms of the efficacy, effectiveness, and safety literature search were combined with search terms to find economic evaluations. The search terms for economic evaluations were developed together with an information specialist of the Erasmus University Medical Centre and validated extensively with other search terms for economic evaluations (e.g. search terms used in the NICE (National Institute for Health and Care Excellence) evidence reviews). Four separate search strategies were developed, one for each pre-specified symptom that may be treated with medical cannabis (Appendix 4).

The search for economic evaluations on medical cannabis for the four specified symptom groups was performed in January 2020. The literature database output, including all indexed fields per record (e.g. title, authors, and abstract) was exported to Endnote version X7.8. Duplicates in Endnote were automatically removed and/or manually deleted.

Selection procedure

The same two-step selection procedure was put in place in the cost-effectiveness literature search as for the effectiveness, efficacy, and safety literature search. From the articles retrieved from PubMed (MEDLINE), Embase and NHS EED the relevant references were selected based on:

1. Screening of title and abstract: this step yielded the articles that were assessed in full-text. The major topics of the articles were assessed on relevancy for the objectives by the title and abstract. In this step, articles that seemed to contain relevant data for the objectives were selected for full-text screening, while articles that did not seem to contain relevant data were not selected for full-text assessment. In case of doubt, the study was assessed in full-text.
2. Screening of full article: the articles selected during the first phase were assessed in full-text. Articles were included if the reported information was relevant and of sufficient quality, based on the inclusion and exclusion criteria (see below).

The process of selection and inclusion and exclusion of articles was registered in an Endnote library by one of the researchers. The exclusion criteria applied during the full-text screening phase are reported in PRISMA flow charts (Section 8.2.1). The implemented quality control during the selection process is described in a next section.

Inclusion and exclusion criteria

The inclusion and exclusion criteria applied during the selection processes for the four pre-specified symptoms that may be treated with medical cannabis are presented in Table 6. The list of excluded studies can be found in Appendix 5.

Table 6. Inclusion and exclusion criteria for economic evaluations of medical cannabis use for the 4 symptoms of interest for medical cannabis

	Medical cannabis indication	Inclusion	Exclusion
Period of publication	All 4 symptoms	Start database - January 2020	
Language of publication	All 4 symptoms	English, French, German, Dutch	All other languages
Country of study	All 4 symptoms	All countries	-
Study design/type	All 4 symptoms	Economic evaluations (CEA, CUA), Budget impact analyses	Other economic evaluations
Study quality	All 4 symptoms	All economic evaluations	
Study population	All 4 symptoms	Patients (all ages) with chronic pain, spasticity, unintentional weight loss, or nausea and vomiting related to cancer treatment with various underlying causes	No or lacking information on study population
	Chronic pain	-	• Patients without chronic pain • Patients in whom medical cannabis is not primarily prescribed for the symptom chronic pain
	Spasticity	-	• Patients in whom medical cannabis is not primarily prescribed for the symptom spasticity • No or lacking definition of spasticity
	Nausea and vomiting related	Cancer patients (all ages) with nausea and vomiting related to	Nausea and vomiting caused by cancer and not by cancer treatment

	to cancer treatment	cancer treatment who poorly respond to regular anti-emetic drugs	
Study intervention	All 4 symptoms	Medical cannabis, prescribed as standalone treatment or add-on treatment	Non-prescribed/recreational cannabis
Study comparison	All 4 symptoms	• Placebo • No treatment for chronic pain • Standard treatment according to the treatment guidelines (i.e. conventional drugs for the chronic pain condition, spasticity or nausea and vomiting related to cancer treatment, or conventional treatment for weight loss)	Comparisons with other treatments than standard treatment
Study outcomes	Incremental costs Incremental QALYs ICERs	No/other cost-effectiveness outcomes	Incremental costs Incremental QALYs ICERs

Keys: CEA = cost-effectiveness analysis, CUA = cost-utility analysis, ICER = incremental cost-effectiveness ratio, QALY = quality-adjusted life year

Quality control

The same quality control measures were put in place in the cost-effectiveness literature search as for the effectiveness, efficacy, and safety literature search:

- The first 30% of titles and abstracts from the peer-reviewed literature were screened in duplicate by two independent researchers. The results were compared and discussed before the remaining references were assessed by one researcher. During screening there was more than 5% discrepancy between the two researchers, therefore all titles and abstracts were screened in duplicate. Any conflicts were discussed and amended accordingly.

- The first 10% of the full-text articles from the peer-reviewed literature were assessed for relevancy and critically appraised in duplicate by two independent researchers. Again, during screening there was more than 5% discrepancy between the two researchers, therefore all full-text articles were screened in duplicate. Any conflicts were discussed and amended accordingly.

7.2 Other sources

Hand search of reference lists

During the full-text screening phase of both the efficacy, effectiveness, and safety systematic literature search and the cost-effectiveness systematic literature search, reference lists of the included studies in the scoping report were checked to find any other studies that were not captured with our literature search. For both systematic literature searches, no studies were included by this process and assessed in full-text in the scoping phase.

HTA agency websites

Clinical guidelines and technology assessments from the major national HTA agency websites (e.g. EUnetHTA[d] for Europe, NICE[e] from the United Kingdom (UK), IQWIG[f] from Germany, HAS[g] from France, ZiN[h] from the Netherlands, CADTH[i] from Canada, and PBAC[j] and TGA[k] from Australia) were

[d] www.eunethta.eu/
[e] www.nice.org.uk
[f] www.iqwig.de/
[g] https://www.has-sante.fr/
[h] https://www.zorginstituutnederland.nl/
[i] https://www.cadth.ca/
[j] www.pbs.gov.au/
[k] www.tga.gov.au

searched for documents addressing medical cannabis for the four pre-specified symptoms (i.e. search terms 'medical cannabis' in relevant language). The aim of this search was to check whether the published economic evaluations possibly missed relevant evidence on the cost-effectiveness of medical cannabis. The initial search yielded three NICE guidelines on the symptoms chronic pain[59], spasticity[67], and nausea and vomiting[71], three SRs on the CADTH webpage for the symptoms chronic pain[52], spasticity[63], and nausea and vomiting[70], three SRs on the TGA website for the symptoms chronic pain[60], spasticity[68], and nausea and vomiting[72], one evaluation on the IQWIG website for the symptom spasticity[66], and a stance document on medical cannabis in various symptoms from ZiN[61]. No missed studies/articles were identified in these guidelines/reviews. However, as the NICE guidelines for chronic pain and spasticity included de-novo cost-effectiveness models based on input from their own SR, these were included for the cost-effectiveness systematic literature search.

Other HTA Domains

For legal aspects, a search in the Swiss legislation database[l] (in English, French, German languages; for all legal product types; for both national and international law documents; for both in force and not in force legislations) was conducted to find any relevant legislation documents associated with medical cannabis, from 1848 until 2020. The terms "medical cannabis" and their French and German translations were entered.

For ethical and social aspects, information was retrieved from the economic evaluations identified in the cost-effectiveness search. For organisational aspects, a search in PubMed (MEDLINE) was conducted using the MeSH subheadings of "medical cannabis/organisation and administration" or "medical cannabis/supply and distribution".

7.3 Quality of evidence assessment

7.3.1 Efficacy, effectiveness, and safety

Based on the key risk of bias criteria used in the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) approach, a first estimation was made of the risk of bias of the RCTs included during the full-text selection.[122] During the HTA phase a more extensive critical appraisal will be applied.

[l] https://www.admin.ch/

For RCTs, the following study limitations or risk of bias were initially judged:

- Lack of allocation concealment (i.e. those enrolling patients are aware of the group or period to which the next enrolled patient will be allocated, e.g. based on birth date or chart number)
- Blinding (i.e. patient, caregivers, those recording outcomes, those adjudicating outcomes, or data analysts are aware of the arm to which patients are allocated)
- Incomplete accounting of patients and outcome events:
  - Loss to follow-up (i.e. the significance of particular rates of loss to follow-up varies widely and is dependent on the relation between loss to follow-up and number of events; the higher the proportion lost to follow-up in relation to intervention and control group event rates, and differences between intervention and control groups, the greater the threat of bias)
  - Intention to treat (i.e. failure to adhere to the intention-to-treat principle)
- Selective outcome reporting (i.e. incomplete or absent reporting of some outcomes and not others on the basis of the results)
- Other limitations (e.g. stopping trial early for benefit; use of unvalidated outcome measures (e.g. patient-reported outcomes); carryover effects in crossover trial; recruitment bias in cluster-randomised trials)

7.3.2 Cost-effectiveness

The Consensus Health Economics Checklist (CHEC) was used for the appraisal of the methodological quality of the economic evaluations.[123] The CHEC was preferred over the Drummond checklist, because of the decreasing use of the Drummond checklist in the field[33] and the experienced feasibility of completing the checklists. The CHEC is one of the two most often used checklists in recent studies, the other checklist is the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist.[124] The CHEC was chosen over the CHEERS as the CHEC can be used to assess the methodological quality of economic evaluations, while the CHEERS was primarily intended for use as a reporting checklist.

The CHEC is a 19-item checklist [123] with clear questions about the economic evaluation that will give us insight into the general quality of the study for a preliminary critical appraisal of the quality of the included studies. In addition to the CHEC, it was assessed whether medical cannabis-specific outcomes were included in the economic evaluations (e.g. treatment adherence and disutility for administering the product).

8 Synthesis of evidence base

8.1 Evidence base pertaining to efficacy, effectiveness and safety

The evaluation of the overall effectiveness of the technology encompasses its efficacy, its effectiveness, and its safety.

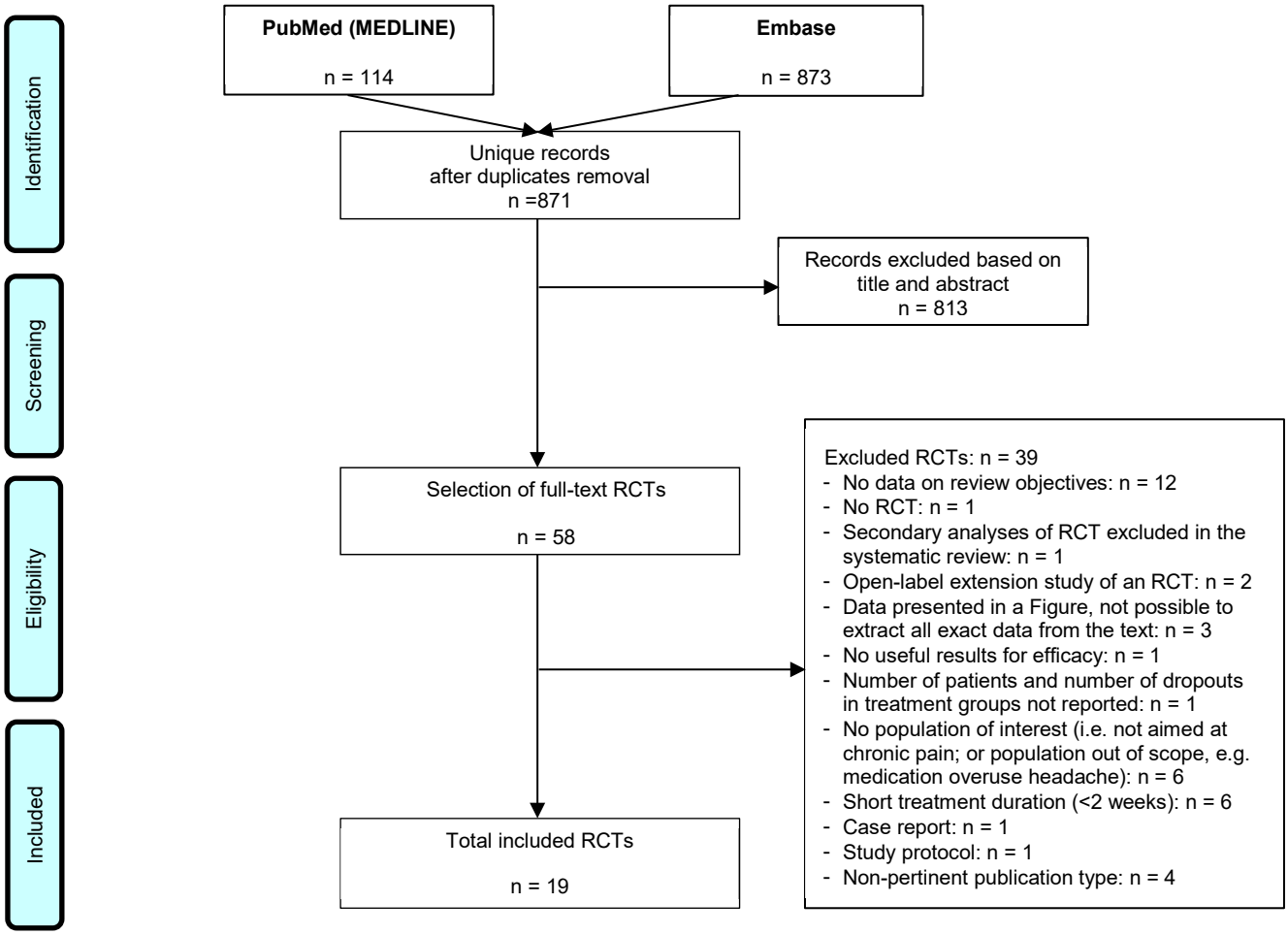
- Efficacy is the extent to which a specific health technology produces a beneficial, reproducible result under study conditions compared with alternative technologies (internal validity).
- Effectiveness is the extent to which a specific health technology, when applied in real world circumstances in the target group, does what it is intended to do for a diagnostic or therapeutic purpose regarding the benefits compared with alternative technologies (external validity).
- Safety is a judgement of the harmful effects and their severity using the health technology. Relevant adverse events are those that result in death, are life-threatening, require inpatient hospitalisation or cause prolongation of existing hospitalisation (serious adverse events) and those that occur repetitively and the most frequent (highest rate).

8.1.1 PRISMA flow charts

Chronic pain

In total, 871 unique records were identified in PubMed (MEDLINE) and Embase on the use of medical cannabis for the symptom chronic pain. Of those, 813 records were excluded based on their title and abstract, resulting in 58 RCTs selected to be screened in full-text. After applying the inclusion and exclusion criteria, 19 RCTs were finally included. The main reasons for exclusion were no data on review objectives (n=12 studies), no population of interest such as patients with pain without a chronic character (n=6 studies), and a short treatment duration with medical cannabis of less than 2 weeks (n=6 studies). A complete overview of the reasons for exclusion is enclosed in the PRISMA flow chart (Figure 1).

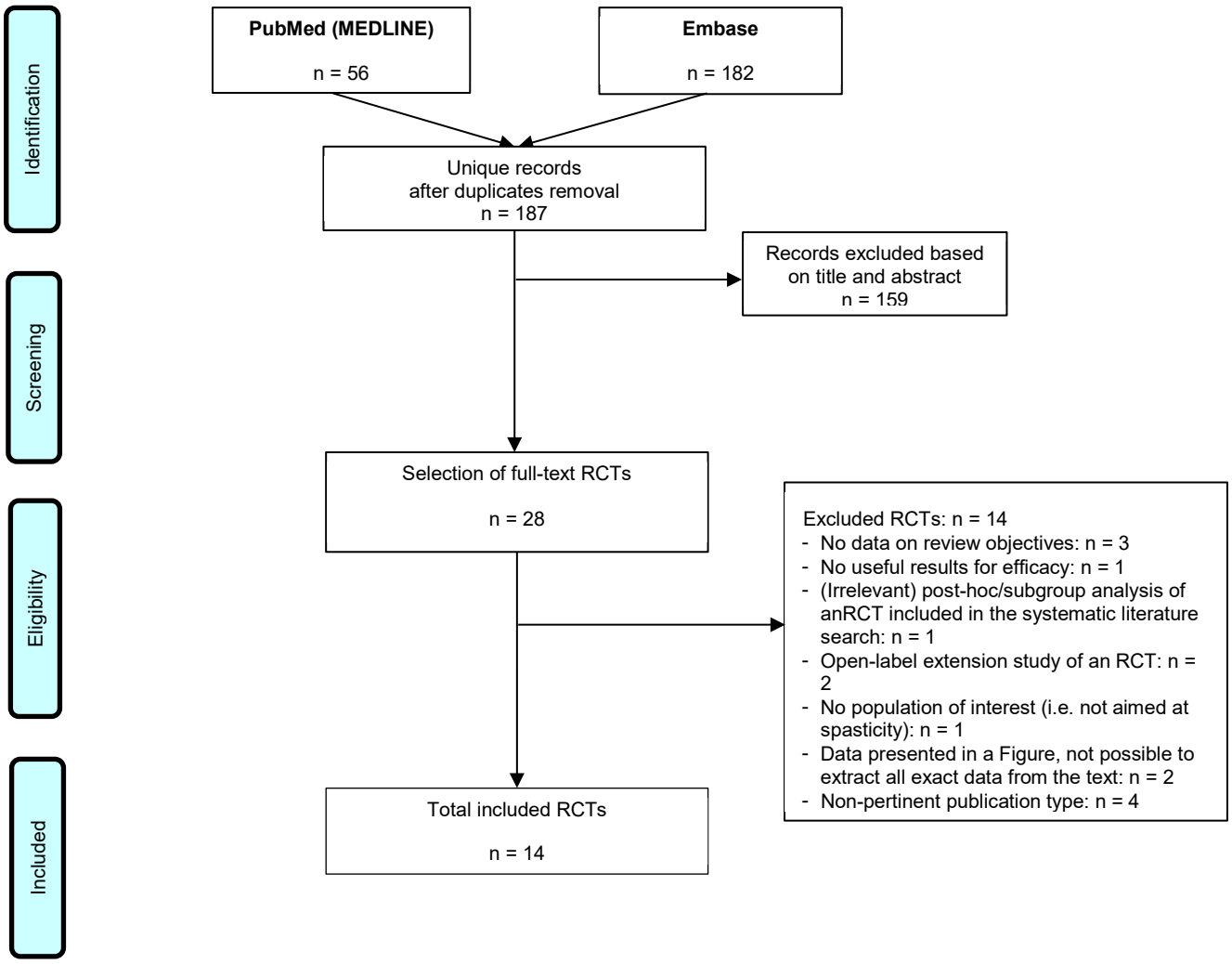
Figure 1. PRISMA flow chart of the efficacy, effectiveness, and safety systematic literature search on the use of medical cannabis for the symptom chronic pain



Spasticity

In the literature databases PubMed (MEDLINE) and Embase 187 unique records were found on medical cannabis use for the symptom spasticity. In total, 159 records were excluded based on their title and abstract and 14 studies based on the full-text article. The reasons for exclusion after full-text screening of the articles are listed in the PRISMA flow chart (Figure 2). Finally, 14 RCTs were included in this scoping report.

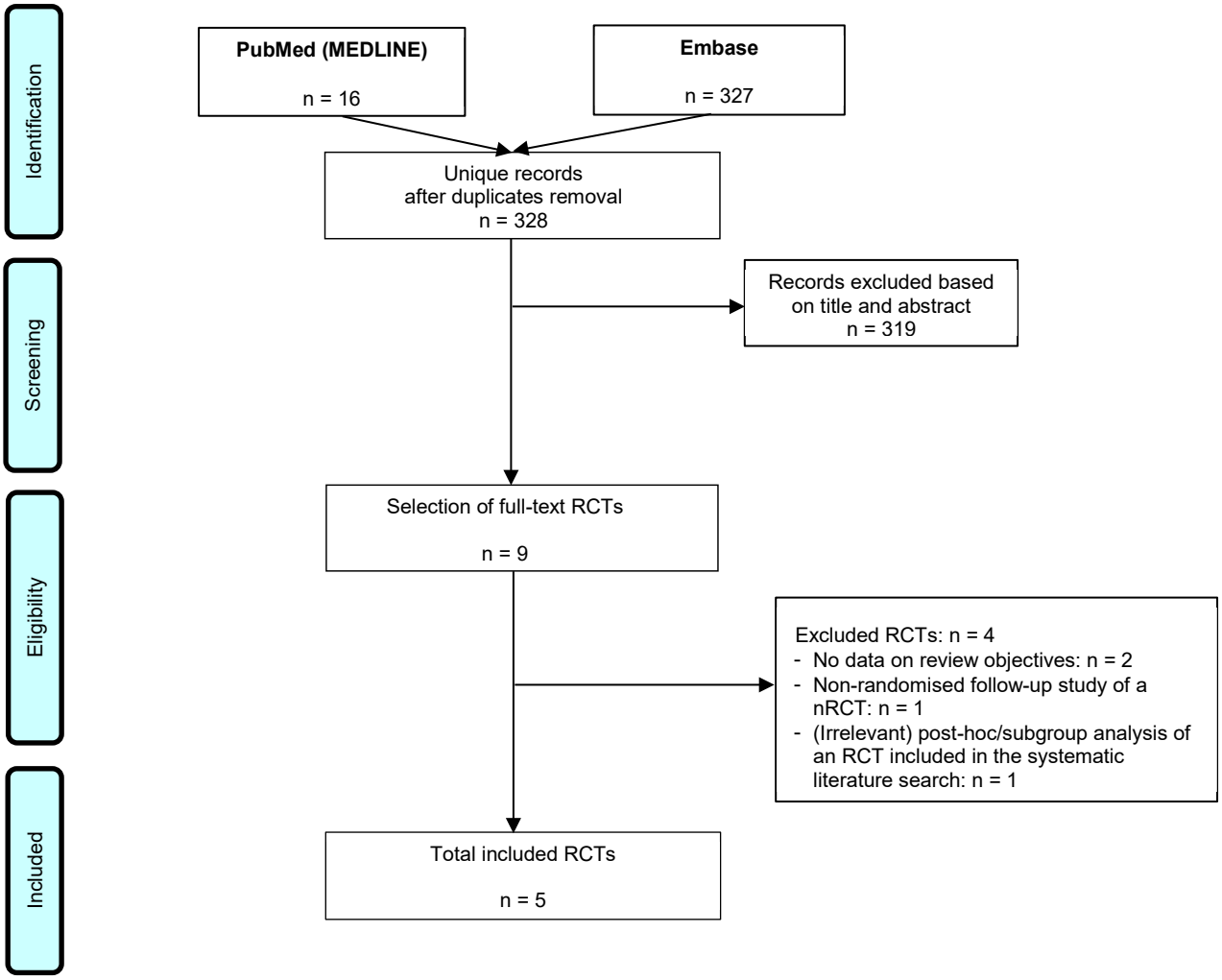
Figure 2. PRISMA flow chart of the efficacy, effectiveness, and safety systematic literature search on the use of medical cannabis for the symptom spasticity



Unintentional weight loss

For medical cannabis use for the symptom unintentional weight loss 328 unique records were identified in PubMed (MEDLINE) and Embase (Figure 3). Of those, 319 records were excluded based on their title and abstract, resulting in 9 RCTs selected to be screened in full-text. After applying the inclusion and exclusion criteria 4 RCTs were excluded, because of the following reasons: no data on review objectives (n=2 studies), non-randomised follow-up study of an RCT (n=1 study), and a post-hoc/sub-group analysis of an RCT already included in the systematic literature search (n=1 study).

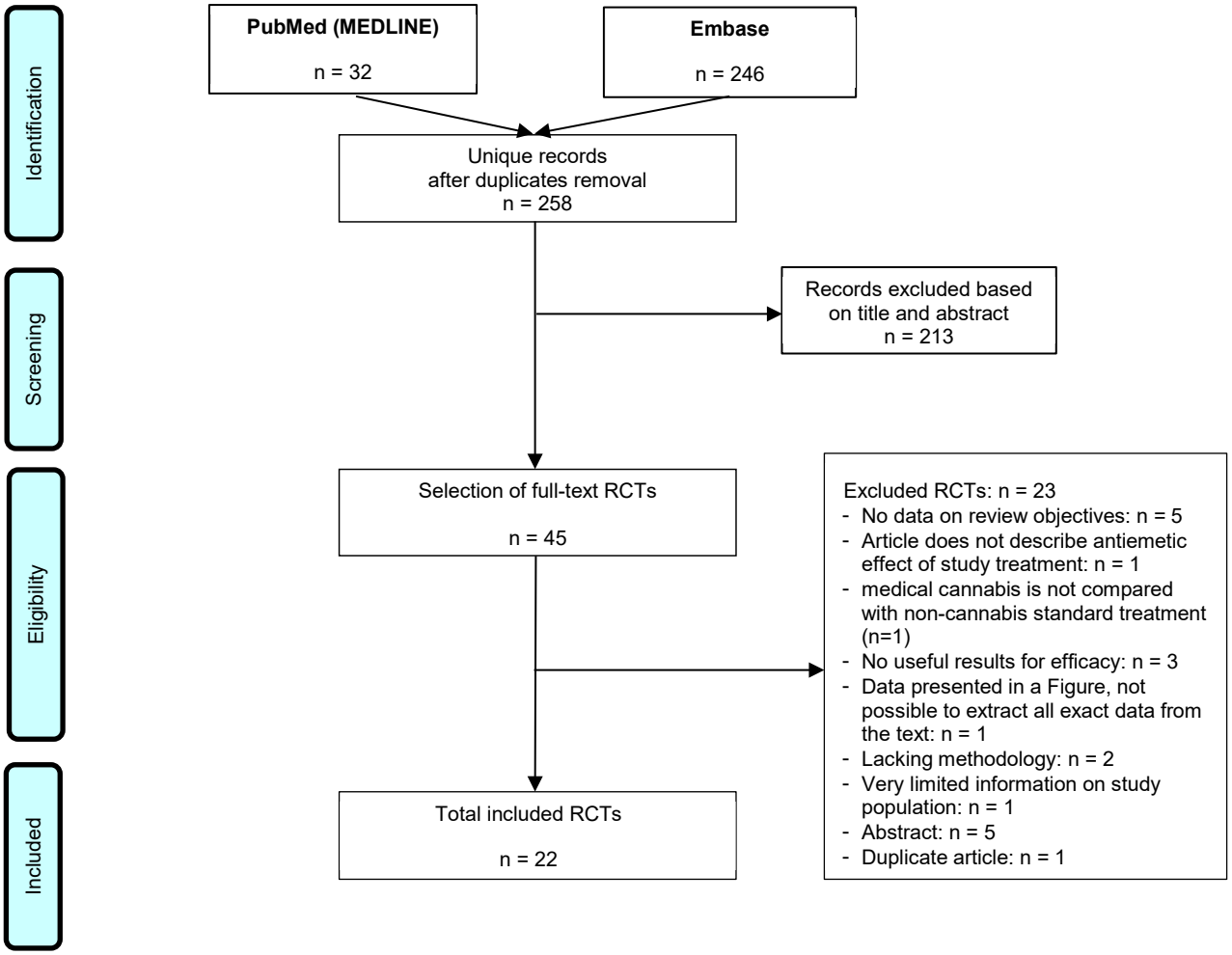
Figure 3. PRISMA flow chart of the efficacy, effectiveness, and safety systematic literature search on the use of medical cannabis for the symptom unintentional weight loss



Nausea and vomiting related to cancer treatment

The systematic literature search in PubMed (MEDLINE) and Embase on medical cannabis use for the symptom nausea and vomiting related to cancer treatment yielded 258 unique records. Titles and abstracts of these records were screened and 45 articles were selected for full-text reading. After exclusion of 23 studies, 22 RCTs were included in this scoping report. The reasons for exclusion were diverse and are listed in the PRISMA flow chart (Figure 4).

Figure 4. PRISMA flow chart of the efficacy, effectiveness, and safety systematic literature search on the use of medical cannabis for the symptom nausea and vomiting related to cancer treatment



8.1.2 Evidence tables

In this section the preliminary extracted data from the RCTs included on medical cannabis use in populations with one of the four pre-specified symptoms chronic pain, spasticity, unintentional weight loss, or nausea and vomiting related to cancer treatment is presented in summary tables (Table 7, Table 8, Table 9, and Table 10). The complete evidence tables are enclosed in Appendix 6; separate evidence tables are compiled for the study characteristics, preliminary pre-specified outcomes reported, and other not pre-specified outcomes reported in the RCTs. The findings are described in more detail in Section 8.1.3.

Table 7. Summary of the study characteristics of the 19 RCTs included on medical cannabis use for chronic pain

Country	Study design Study period	Study population	Definition chronic pain	Intervention	Comparator	Sample size of analysed patients	Duration study treatment	Study outcomes	Preliminary risk of bias assessment
- Europe: n=12 - Europe combined with other: n=4 - Other: n=3	- RCTs parallel design: n=11* - RCTs crossover: n=8 - Range study period: 2001-2011 - Not reported: n=11; range publication year: 2003-2018	Adults with the following diagnoses: - Multiple sclerosis: n=5 - Cancer: n=3 - Allodynia: n=2 - Neuropathic pain: n=2 - Abdominal pain or chronic pancreatitis: n=1 - Brachial plexus injury: n=1 - Diabetes mellitus: n=1 - Rheumatoid arthritis: n=1 - Spinal cord injury: n=1	- Persisting for ≥3 months: n=5 - Clinical diagnosis and unalleviated by step 3 opioid therapy: n=2 - Persistent or intermittent, NRS scores ≥3, daily for ≥3 months, severe enough for medical treatment: n=1 - ≥6 months duration: n=2 - Chronic and ≥12 months duration: n=1 - Intensity score ≥3 on 0-10 NRS: n=1 - Severity scale ≥4 on 0-10 NRS, stable pattern over the previous 4 weeks: n=1	- Sativex®: n=10 (1 combined with THC extract) - Nabilone: n=4 - Dronabinol: n=3 - THC alone or tablets (Namisol®): n=1 - Whole-plant cannabis extracts spray: n=1	- Placebo: n=17 - Dihydrocodeine: n=2	- RCTs parallel design (range): 26-299 - RCTs crossover (range): 5-96	- RCTs parallel design (range): 3 weeks-16 weeks - RCTs crossover (range): 3 weeks-9 weeks	See Appendix 6; Tables I, II, III	RCTs parallel design: - Low risk of bias: n=2 - Moderate risk of bias: n=6 - High risk of bias: n=3 RCTs crossover: - Moderate risk of bias: n=1

Country	Study design Study period	Study population	Definition chronic pain	Intervention	Comparator	Sample size of analysed patients	Duration study treatment	Study outcomes	Preliminary risk of bias assessment
		- Upper motor neuron syndrome: n=1 - Skeletal and locomotor system diseases: n=1	- Not obviously musculoskeletal: n=1 - Caused by rheumatoid arthritis: n=1 - Increased spastic muscle tone while passively moving: n=1 - Troublesome symptom which was stable and unresponsive to standard treatment: n=1 - Chronic therapy-resistant which remains VAS >5: n=1 - Mean score >40 mm on a 0-100 mm VAS: n=1						- High risk of bias: n=7

Keys: n = number of studies, NRS = numerical rating scale, RCT = randomised controlled trial, THC = tetrahydrocannabinol, VAS = visual analogue scale; * 1 article included two RCTs [Fallon, 2017]

Table 8. Summary of the study characteristics of the 14 RCTs included on medical cannabis use for spasticity

Country	Study design Study period	Study population	Definition spasticity*	Intervention	Comparator	Sample size of analysed patients	Duration study treatment	Study outcomes	Preliminary risk of bias assessment
- Europe: n=11 - Other: n=2 - Not reported: n=1	- RCTs parallel design: n=9 - RCTs crossover: n=5 - Range study period: 2000-2014 - Not reported: n=7; range publication year: 2003-2019	Adults with the following diagnoses: - Multiple sclerosis: n=11 - Spinal cord injury: n=1 - Motor neuron syndrome: n=1 - Mixed population with neurological diagnosis (MS, SCI, brachial plexus damage, limb amputation due to neurofibromatosis): n=1	**Spasticity:** - Ashworth score of ≥2 at ≥2 muscle groups: n=3 - ≥1 joint scoring ≥2 on the Ashworth scale: n=1 - Modified Ashworth score of ≥3 at the elbow, hip, or knee: n=1 - Modified Ashworth score of ≥1 at ≥2 muscle groups: n=1 - As primary symptom, not further defined: n=1 - Troublesome symptom which was stable and unresponsive to standard treatment: n=1	- Sativex®: n=7 - Synthetic delta-9-THC (Marinol®)/cannabis-extract (Cannador®): n=2 - Cannabis-extract capsules: n=1 - Delta-9-THC tablets: n=1 - Whole-plant cannabis extracts spray: n=1 - Smoked cannabis: n=1 - Nabilone: n=1	Placebo: n=14	- RCTs parallel design (range): 24-611 - RCTs crossover (range): 8-50	- RCTs parallel design (range): 4 weeks-14 weeks - RCTs crossover (range): 3 days-8 weeks	See Appendix 6; Tables IV, VI and VI	RCTs parallel design: - Low risk of bias: n=2 - Moderate risk of bias: n=4 - High risk of bias: n=3

Country	Study design Study period	Study population	Definition spasticity*	Intervention	Compar-ator	Sample size of analysed pa-tients	Duration study treat-ment	Study out-comes	Preliminary risk of bias assessment
			Moderate spasticity: - Severity on 0-10 NRS sums to ≥24 (i.e. minimum mean daily score of 4 out of 10): n=1 - Ashworth score of ≥2: n=1 - Ashworth score of ≥3: n=1 **Moderate to severe spasticity:** - Modified Ashworth score of ≥1 in 1 limb: n=1 - Score of ≥4 on the MS spasticity 0-10 NRS: n=1						RCTs cross-over: - High risk of bias: n=5

Country	Study design Study period	Study population	Definition spasticity*	Intervention	Compar-ator	Sample size of analysed pa-tients	Duration study treat-ment	Study out-comes	Preliminary risk of bias assessment
			Moderately severe spasticity: - Score of ≥4 using a single spastic-ity 0-10 severity NRS: n=1						

Keys: MS: multiple sclerosis; n = number of studies, NRS = numerical rating scale, RCT = randomised controlled trial, SCI = spinal cord injury, THC = tetrahydrocannabinol, VAS = visual analogue scale; * As defined and categorised in spasticity severity in the RCTs.

Table 9. Summary of the study characteristics of the 5 RCTs included on medical cannabis use for unintentional weight loss

Country	Study design Study period	Study population	Definition weight loss	Intervention	Comparator	Sample size of analysed patients	Duration study treatment	Study outcomes	Preliminary risk of bias assessment
- Europe: n=1 - Other: n=4	- RCTs parallel design: n=4 - RCTs crossover: n=1 - Range study period: 1990-2015 - Not reported: n=1; publication year: 1995	Adults with the following diagnoses: - Cancer: n=3 - HIV/AIDS: n=2	**Weight loss:** - A loss of ≥2.3 kg from normal body weight: n=2 - Of ≥2.3 kg (self-reported) in the past 2 months and/or estimated caloric intake of <20 calories/kg of body weight per day: n=1 - Diagnosed with anorexia according to the Anorexia/Cachexia Scale: n=1 - In the past 6 months, involuntary weight loss of 5% not explained by other diseases or recent surgery: n=1	- Dronabinol: n=3 - THC/THC and CBD: n=1 - Nabilone: n=1	- Placebo: n=4 - Megestrol acetate and placebo: n=1	- RCTs parallel design (range): 22-469 - RCTs crossover (range): 5	- RCTs parallel design (range): 4 weeks-11.4 weeks (not reported n=1) - RCTs crossover: 5 weeks	See Appendix 6; Tables VII, VIII, IX	RCTs parallel design: - Moderate risk of bias: n=1 - High risk of bias: n=3 RCT crossover:

Country	Study design Study period	Study population	Definition weight loss	Intervention	Comparator	Sample size of analysed patients	Duration study treatment	Study outcomes	Preliminary risk of bias assessment
									- High risk of bias: n=1

Keys: AIDS = acquired immune deficiency syndrome, CBD = cannabidiol, HIV = human immune-deficiency virus, , n = number of studies, RCT = randomised controlled trial, THC = tetrahydrocannabinol

Table 10. Summary of the study characteristics of the 22 RCTs included on medical cannabis use for nausea and vomiting related to cancer treatment

Country	Study design Study period	Study population	Definition nausea and vomiting	Intervention	Comparator	Sample size of analysed patients	Duration study treatment	Study outcomes	Preliminary risk of bias assessment
Paediatrics									
- Europe: n=1 - Other: n=3	RCTs crossover: n=4 - Range study period: 1982-1983 - Not reported: n=3; range publication year: 1980-1986	Children with various neoplastic disease: n=4	- Total number of episodes of retching or vomiting noted by a nurse or parent on 3-category scale: n=1 - Patient (parent) questionnaires on frequency of actual vomiting, degree of nausea on 4-category scale: n=1 - Patient reports, nausea was rated on a 4-category scale, episodes of emesis were counted: n=1 - 3-category scale questionnaires on vomiting and nausea: n=1	- Nabilone: n=3 - THC: n=1	- Prochlorperazine: n=3 - Domperidone: n=1	RCTs crossover (range): 18-80	RCTs crossover (range): 1 day-1 cycle of chemotherapy (max. 8 days or not reported)	See Appendix 6; Tables X, XII, XIII	RCTs crossover: - High risk of bias: n=4

Country	Study design Study period	Study population	Definition nausea and vomiting	Intervention	Comparator	Sample size of analysed patients	Duration study treatment	Study outcomes	Preliminary risk of bias assessment
Adults									
- Europe: n=7 - Other: n=11	- RCTs parallel design: n=4 - RCTs crossover: n=14 - Range study period: 1978-1991 - Not reported: n=11; range publication year: 1981-2007	- Various neoplastic disease: n=13 - Lung cancer: n=2 - Soft-tissue sarcomas: n=1 - Advanced gynaecological cancer: n=1 - Nonseminomatous testicular cancer: n=1	**Nausea episodes:** - Severity, degree, or intensity: n=12 (4 category scale: n=6; self-report, 4 category scale: n=2; reported by nursing staff: n=1; reported by nursing staff, 4 category scale: n=1; on a 10 cm VAS: n=1; <5 mm on a 100-mm VAS: n=1) - On a 4 category scale: n=4 - Duration: n=4 (reported by nursing staff: n=1; 4 category scale: n=1; no details: n=2) - Number of episodes: n=1 - Rhodes Index of Nausea and Vomiting Form 2, 5 category scale: n=1 - Presence or absence: n=1 - Time of nausea, 4 category scale: n=1	- Nabilone: n=8 - Levonantradol: n=3 - THC capsules and cigarettes: n=1 - Nabilone + placebo for chlorpromazine: n=1 - Metoclopramide and dronabinol or prochlorperazine and dronabinol: n=1	- Prochlorperazine: n=7 - Placebo: n=2 - Prochlorperazine or placebo: n=1 - Prochlorperazine and placebo: n=1 - Placebo capsule and cigarettes: n=1 - Chlorpromazine: n=1	- RCTs parallel design (range): 49-108 - RCTs crossover (range): 8-92	- RCTs parallel design (range): 5 days-1 cycle of chemotherapy - RCTs crossover: 3 days-1 cycle of chemotherapy	See Appendix 6, Tables XI, XII and XIII	RCTs parallel design: - High risk of bias: n=12 - Moderate risk of bias: n=2 RCTs crossover: - High risk of bias: n=3 - Moderate risk of bias: n=1

Country	Study design Study period	Study population	Definition nausea and vomiting	Intervention	Comparator	Sample size of analysed patients	Duration study treatment	Study outcomes	Preliminary risk of bias assessment
			Vomiting episodes: - Number: n=4 (self-report n=1; reported by nursing staff n=1; no details: n=2) - Frequency: n=4 (self-report: n=1; 4 category scale: n=1; per cycle: n=1; no details: n=1) - Duration: n=3 (self-report: n=1; no details: n=2) - Severity or degree: n=2 (self-report: n=1; 4 category scale: n=1) - Rhodes Index of Nausea and Vomiting Form 2, 5 category scale: n=1 - The number of dry vomiting episodes (vomiting action without ejection): n=1 - Self-report and reported by the investigator, not further defined: n=1 **Emesis episodes:**	- THC and prochlorperazine: n=1 - Dronabinol or dronabinol and prochlorperazine: n=1 - Dronabinol or dronabino and odansetron: n=1 - THC: n=1	- Chlorpromazine and placebo: n=1 - Metoclopramide and placebo or prochlorperazine and placebo: n=1 - Metoclopramide: n=1 - Odansetron or placebo: n=1 - Alizapride: n=1				

Country	Study design Study period	Study population	Definition nausea and vomiting	Intervention	Comparator	Sample size of analysed patients	Duration study treatment	Study outcomes	Preliminary risk of bias assessment
			- Volume, reported by nursing staff: n=1 - Emetic Process Rating Scale, 50 mm visual scale: n=1 - Number, during sequences of 6h after antiemetic treatment: n=1 - Frequency, and the time of occurrence n=1 **Other:** - Anorexia via self-report, 4 category scale: n=1 - Retching episodes, not further defined: n=2 (self-report, 4 category scale: n=1; no details: n=1) - Number of retching episodes, reported by nursing staff: n=1 - Duration of retching episodes: n=1 - Volume of oral intake reported by nursing staff: n=1						

Country	Study design Study period	Study population	Definition nausea and vomiting	Intervention	Comparator	Sample size of analysed patients	Duration study treatment	Study outcomes	Preliminary risk of bias assessment
			- Extent of appetite impairment, 4 category scale: n=1 - Appetite via self-report and reported by the investigator: n=1						

Keys: h = hours, n = number of studies, RCT = randomised controlled trial, THC = tetrahydrocannabinol

8.1.3 Findings regarding efficacy, effectiveness, and safety

Chronic pain

For the pre-specified symptom chronic pain 19 RCTs were included covering the objectives of this scoping report. A summary of the study characteristics is included in Table 7. The RCTs studied the efficacy of medical cannabis use for chronic pain in patient populations with 11 divergent causes and different underlying pathophysiology: visceral pain (abdominal pain), neuropathic pain (allodynia, brachial plexus injury, diabetes mellitus, MS, SCI, upper motor neuron syndrome), cancer pain, and musculoskeletal pain (rheumatoid arthritis, skeletal and locomotor system diseases). Appendix 6 provides a list of the different preliminary pre-specified outcomes reported in the RCTs, stratified for the patient population. Besides the differences in causes of chronic pain, there is large heterogeneity in the definitions and outcome measures of the reported outcomes. Change in pain severity is presented in many different ways and outcomes are often tailored to the disease population under study (see Appendix 6 for more details). RCTs tended to report average pain scores or average changes in pain scores. However, this outcome has been described as problematic, because (amongst others) small average pain differences between the intervention and placebo group hide the fact that a substantial minority of the patients achieve extremely good levels of pain relief[81]. Currently, the preferred outcome in chronic pain RCTs is pain intensity reduction of at least 30% or at least 50%, no worse than mild pain, tolerable adverse events, or being able to continue with medication without withdrawal for (ideally) 12 weeks. [81,25] Only four RCTs reported the percentage of patients with at least 50% analgesia. The proportion of patients with at least 30% analgesia is also used as outcome; four RCTs reported on this outcome. Most RCTs reported data on the number and severity of adverse events. The number of patients who discontinued treatment due to adverse events was reported in 10 RCTs. A large variety of other not pre-specified heterogeneous outcomes is reported in the RCTs (see Appendix 6).

One RCT with parallel design on abdominal pain was included.[125] Dutch patients with painful chronic pancreatitis and patients with chronic abdominal postsurgical pain were randomly assigned to an intervention with THC tablets (Namisol®; n=21) or matching placebo (n=29) for 50 to 52 days. The RCT reported outcomes on pain scores, adverse events, and functional disease outcomes. This RCT was assessed as high risk of bias during the preliminary risk of bias assessment.

In this scoping report two European parallel-design RCTs are included on allodynia, a condition where pain is caused by a stimulus that would not normally provoke pain.[75, 126] In both RCTs Sativex® was compared with an identical placebo. Nurmikko et al. studied 50 patients in the Sativex® group and 55 patients in the placebo group during a four-week treatment.[75] During 14 weeks, Serpell et al. compared

79 patients using Sativex® with 94 patients receiving a placebo spray.[126] Both RCTs had a moderate risk of bias and reported outcomes on pain scores, adverse events, and functional disease outcomes.

One RCT with crossover design was included on patients with brachial plexus injury.[127] Forty-eight patients from the UK had three two-week treatment periods during each of which they received one of three oromucosal spray preparations: Sativex®, THC extract, and placebo. The RCT had a high risk of bias and reported outcomes on pain scores, adverse events, and functional disease outcomes.

Three RCTs were included on adult patients with chronic pain caused by cancer.[128-130] Fallon et al. described two multicentre parallel design RCTs.[128] In Study I, patients were randomised to Sativex® (n=136) or placebo (n=158), and then self-titrated study medications over a 2-week period, followed by a 3-week treatment period. In Study II, all patients self-titrated Sativex® over a 2-week period and patients with at least 15% improvement from baseline in pain score were then randomised to Sativex® (n=78) or placebo (n=88), followed by 5-week treatment period. The RCTs reported outcomes on pain scores and adverse events, and the preliminary risk of bias was moderate. In the RCT with parallel design of Lichtman et al. patients with advanced cancer and chronic pain were studied during three weeks of treatment with Sativex® (n=149) or placebo (n=150).[129] The RCT reported outcomes on pain scores, adverse events, and clinical disease outcomes. The preliminary risk of bias was moderate. Lynch et al. studied 16 patients with chemotherapy-induced neuropathic pain receiving four weeks of Sativex® and placebo in a crossover design.[130] The RCT reported outcomes on pain scores, quality of live, adverse events, and functional disease outcomes. The preliminary risk of bias was high.

In Canada a small parallel design RCT was conducted to study the effects of medical cannabis on peripheral neuropathic pain in adult patients with diabetes mellitus.[131] During a treatment period of 4 weeks 13 patients randomised to Nabilone were compared with 13 patients receiving placebo. The RCT had a high risk of bias and reported outcomes on pain scores, quality of life, adverse events, and functional disease outcomes.

Most RCTs on chronic pain were included for the diagnosis MS in adults: 4 RCTs with parallel design[132-135] and 1 RCT with crossover design[136]. The RCT of Langford et al. was conducted in multiple countries (i.e. UK, Czech Republic, Canada, Spain, and France) and the other RCTs in a single European country (i.e. Denmark, Germany, and 2 RCTs in the UK). Langford et al. studied 141 patients in the Sativex® group and 156 patients in the placebo group during a 14-week treatment period.[132] The RCT had a low risk of bias and reported outcomes on pain scores, quality of life, adverse events, and functional disease outcomes. In the RCT of Rog et al. 32 patients were treated with Sativex® during 4 weeks and 32 patients received a placebo.[133] The RCT had a moderate risk of bias and reported outcomes on pain

scores, adverse events, and functional disease outcomes. During 16 weeks of treatment, Schimrigk et al. studied the effect of dronabinol (n=105) versus placebo (n=104) on central neuropathic pain in MS patients.[134] The RCT reported outcomes on pain scores and adverse events; the preliminary risk of bias was low. In the RCT of Wade et al. 18 patients were treated with Sativex® during 6 weeks and 19 patients received a placebo.[135] The RCT reported outcomes on chronic pain scores (i.e. other outcomes were not reported specifically for the patients with chronic pain) and this RCT was assessed as high risk of bias during the preliminary risk of bias assessment. For two treatment periods of three weeks 24 MS patients received dronabinol and placebo capsules in the crossover RCT of Svendsen et al.[136] The RCT reported outcomes on pain scores, quality of life, adverse events, functional disease outcomes, preference, and sensory testing outcomes. The preliminary risk of bias was high.

Two RCTs with crossover design were included, studying the effect of medical cannabis on patients with neuropathic pain and varying underlying causes.[137, 138] Both RCTs were conducted in the UK. During two treatment periods of six weeks Frank et al. compared the effect of nabilone with dihydrocodeine in 96 patients.[137] The RCT had a moderate risk of bias and reported outcomes on pain scores, quality of life, adverse events, and functional disease outcomes. In 12 patients Wade et al. studied the use of whole-plant extracts of THC, cannabidiol, 1:1 CBD:THC, or matched placebo in four two-week treatment periods.[138] The RCT reported outcomes on chronic pain scores (i.e. other outcomes were not reported specifically for the patients with chronic pain) and this RCT was assessed as high risk of bias during the preliminary risk of bias assessment.

One RCT with parallel design in the UK was included on chronic pain in rheumatoid arthritis.[139] Treatment with Sativex® (n=31) was compared with placebo (n=27) over 5 weeks of treatment, including a titration phase of 2 weeks. The RCT reported outcomes on pain scores, adverse events, and functional disease outcomes. The preliminary risk of bias was moderate.

In a small RCT with crossover design in the USA the efficacy and safety of dronabinol compared with an active control, diphenhydramine, in relieving neuropathic pain in five persons with SCI was studied.[140] The maintenance phase of study treatment was 28 days and outcomes were reported on pain scores and adverse events. The preliminary risk of bias was high.

A crossover RCT in Austria studied the efficacy of medical cannabis on chronic pain in a population of 11 adult patients with upper motor neuron syndrome.[141] For two treatment periods of three weeks these patients received Nabilone and placebo capsules. The RCT reported outcomes on pain scores, adverse events, and functional disease outcomes. The preliminary risk of bias was high.

Finally, one RCT with a crossover design was included on the efficacy of medical cannabis use for the symptom chronic pain in patients with skeletal and locomotor system diseases.[142] In total, 21 patients were treated in Austria for 4 weeks with nabilone and after washout with placebo, or vice versa. The RCT reported outcomes on pain scores, quality of life, and adverse events. This RCT had a high risk of bias.

Spasticity

In total, 14 RCTs were included in this scoping report on the efficacy of medical cannabis use for the symptom spasticity in patients with various diseases. The effect of medical cannabis on spasticity caused by MS is most often studied. A summary of the study characteristics is included in Table 8. Table provides a list of the different preliminary pre-specified outcomes reported in the RCTs. The most frequently used outcomes for spasticity are the Ashworth scale score, modified Ashworth scale score, and the spasticity 0-10 numerical rating scale. The use of the outcome Ashworth scale score is complicated by the different versions that are used. As the reliability and sensitivity of the scale to measure significant functional change in spasticity has also been questioned, spasticity numerical rating scale (NRS) scores or visual analogue scales have been used in spasticity studies.[80, 84, 143-145] Currently no ideal objective measure of the highly complex symptom of spasticity is available, however.[145] In the RCTs different thresholds (i.e. ≥20%, ≥30%, or ≥50%) are used for the percentage treatment responders, which complicates comparability of the data. Most RCTs reported data on the number of patients with adverse events and only few RCTs reported data on quality of life. Other not pre-specified outcomes studied in the RCTs are reported in Appendix 6.

Eleven studies were included on adult patients with spasticity caused by MS: 7 RCTs with a parallel design[80, 82-84, 135, 143, 146], 3 RCTs with a crossover design[144, 147, 148], and 1 randomised follow-up of an RCT.[149] One RCT was conducted in the USA and the other RCTs were conducted in one or more European countries. The total sample size of the crossover RCTs ranged from 30 to 50 patients and in the RCTs with parallel design from 24 to 611 patients. Sativex® was the most frequently studied form of medical cannabis (in 6 RCTs). Furthermore, smoked cannabis (1 RCT), delta-9-THC tablets (1 RCT), cannabis-extract capsules (1 RCT), and two intervention groups of synthetic delta-9-THC (Marinol®) capsules or cannabis-extract (Cannador®) capsules (1 RCT and randomised follow-up of the RCT) were investigated. In all RCTs medical cannabis was compared with a placebo. The treatment duration ranged from 3 days in a crossover study to 14 weeks in an RCT with a parallel design. The RCTs reported outcomes on spasticity, quality of life, functional MS outcomes, neurophysiology outcomes, and adverse events. The preliminary risk of bias was assessed for the studies: six RCTs had a high risk

of bias, three a moderate risk of bias, and one RCT and the randomised follow-up of the RCT had a low risk of bias. Further details of the study characteristics are included in Appendix 6.

The other included RCTs in this scoping report studied the symptom spasticity in three different adult patient populations with motor neuron disease, SCI, and a mixed population of different neurological diagnoses.[81, 138, 145] One RCT with a parallel design was included on the efficacy of medical cannabis use for the symptom spasticity in patients with motor neuron disease.[145] This multicentre Italian RCT included 59 adults for 4 weeks of study treatment, of whom 29 were randomly assigned to the nabiximol group and 30 in the placebo group. The RCT reported outcomes on spasticity, functional motor neuron disease outcomes, and adverse events. The preliminary risk of bias was moderate. A crossover RCT in Canada studied the effect of 4 weeks of treatment with nabilone versus placebo treatment in 11 patients with SCI and moderate spasticity.[81] The RCT reported outcomes on spasticity, functional SCI outcomes, and adverse events. This RCT had a high risk of bias. Another RCT with a crossover design described the effect of a whole-plant cannabis extracts spray versus placebo in a mixed population from the UK with different neurological diagnoses (i.e. MS, SCI, brachial plexus damage, or limb amputation due to neurofibromatosis) and troublesome symptoms (i.e. neuropathic pain, spasticity, muscle spasms, impaired bladder control, or tremor).[138] In 8 patients the target symptom was spasticity and these patients were consecutively treated for 2 weeks with whole-plant extracts of THC, CBD, 1:1 CBD:THC, and matched placebo. The RCT reported outcomes on spasticity; other outcomes were not reported specifically for the patients with spasticity. This RCT was assessed as high risk of bias during the preliminary risk of bias assessment.

Unintentional weight loss

Five RCTs were found on the efficacy of medical cannabis use for the symptom unintentional weight loss. A summary of the study characteristics is presented in Table 9. A large number of different outcomes were presented in the RCTs: Appendix 6 shows the different preliminary pre-specified outcomes reported. Appendix 6 shows the other not pre-specified outcomes studied in the RCTs. Although weight loss seems a straightforward outcome, varying outcome measures for weight loss were used across studies (e.g. mean weight gain in kg, median weight gain in kg, and percentage of patients with a specific amount or percentage weigh gain), which complicates comparison between studies and pooling of the data.

Two studies described the effect of medical cannabis on unintentional weight loss in patients with HIV/AIDS.[150, 151] In an RCT with parallel design, Beal et al. 1995 studied the effects of dronabinol 2.5mg twice daily on appetite, weight, mood, and nausea in patients with AIDS who had lost at least 2.3 kg of

their normal body weight.[150] In total, 72 adult patients received dronabinol and 67 patients received an identical placebo. The study reported outcomes on weight, appetite, treatment duration, and adverse events. Struwe et al. 1993 examined the effect of dronabinol on appetite and nutritional status in patients with symptomatic HIV infection and weight loss.[151] The study was designed as crossover study; five adult patients received dronabinol treatment and placebo treatment. The study reported outcomes on weight, body composition, energy intake, and appetite. Both studies were assessed as high risk of bias during the preliminary risk of bias assessment.

Three studies with a parallel RCT design were included on adult patients with cancer and unintentional weight loss.[152-154] Jatoi et al. 2002 studied whether dronabinol administered alone or with megestrol acetate was more, less, or equal in efficacy to single-agent megestrol acetate for palliating cancer-associated anorexia.[152] In total, 152 patients received dronabinol plus placebo, 158 patients received dronabinol plus megestrol, and 159 patients received megestrol plus placebo. The study reported outcomes on weight, appetite, quality of life, treatment duration, and adverse events. Turcott et al. 2018 evaluated the effect of nabilone versus placebo in adult lung cancer patients diagnosed with anorexia.[153] In a parallel study design 9 patients received treatment with nabilone and 13 patients received a placebo. The study reported outcomes on weight, malnourishment, appetite, energy intake, and quality of life. In the third study of Strasser et al. 2006, the effects of a combination therapy (THC+CBD) or a single therapy with THC were investigated on appetite and quality of life in adult patients with advanced incurable cancer.[154] The combination therapy was given to 95 patients, 100 patients received only THC, and 48 patients received an identical placebo treatment. The study reported outcomes on appetite, quality of life, and adverse events. The preliminary risk of bias was assessed for the studies: the study of Strasser et al. had a moderate risk of bias, and Jatoi et al. and Turcott et al. had a high risk of bias.

Nausea and vomiting related to cancer treatment

Twenty-two RCTs were included on the efficacy of medical cannabis for the symptoms nausea and vomiting related to cancer treatment. A summary of the study characteristics is included in Table 10. All patients received medical cannabis as anti-emetic treatment during chemotherapy treatment. Study treatment with medical cannabis was given shortly before or during chemotherapy treatment. The effect on the symptoms nausea and vomiting was measured during chemotherapy treatment. The RCTs are relatively old; 19 of the 22 RCTs were published before 1990. The most recent RCT was published in 2007. The methodological and reporting quality of older RCTs is more often inadequate than in modern RCTs. The description of the study characteristics and the statistical analyses are often limited in older publications. A list of the preliminary pre-specified outcomes reported in the RCTs is presented in Appendix 6. The other not pre-specified outcomes are reported in Appendix 6. A large variety of outcomes

is used to measure the frequency or severity of nausea or vomiting. The heterogeneity of the outcomes has implications for synthesis of the reported data. Direct comparison might only be possible for a limited number of RCTs. Adverse events were described in 21 RCTs. Outcomes related to quality of life were not reported.

In two RCTs only paediatric patients were included.[155, 156] In both studies patients were treated with emetogenic chemotherapy for various malignant diseases. The RCTs were performed in Canada and the UK. Both studies were RCTs with a crossover design. In the RCT of Chan et al. nabilone was compared with prochlorperazine in a group of 30 patients with an age range of 3.5 to 17.8 years (mean age of 11.8 years).[155] In the RCT of Dalzell et al. nabilone was compared with domperidone in a group of 18 patients with an age range of 10 months to 17 years.[156] The RCTs reported outcomes on nausea, vomiting, retching, use of additional antiemetic drugs, drug preference, and adverse events. Both RCTs were assessed as high risk of bias during the preliminary risk of bias assessment.

In two RCTs with crossover design performed in the USA children and adults were included in the study.[157, 158] Patients received chemotherapy for various types of neoplastic disease. In the RCT of Einhorn et al. nabilone was compared with prochlorperazine in a group of 80 patients with an age range of 15 to 74 years (median age of 28 years).[157] In the RCT of Sallan et al. THC was compared with prochlorperazine in 38 patients with an age range of 9 to 70 years (mean age of 32.5 years).[158] The RCTs reported outcomes on nausea, vomiting, drug preference, drop out due to toxicity, and adverse events. Both RCTs were assessed as high risk of bias during the preliminary risk of bias assessment.

In 12 RCTs patients were treated with chemotherapy for a variety of neoplastic disease.[159-170] Nine RCTs were designed as crossover study and three as parallel study. Sample size in the crossover RCTs ranged from 14 to 92. Sample size in the parallel RCTs was 49 to 108. Age in the studies ranged from 17 to 81 years. The intervention treatments in the studies were THC (2 RCTs), levonanstradol (3 RCTs), nabilone (5 RCTs), and dronabinol (2 RCTs). The comparative treatments in the studies were placebo (5 RCTs), prochlorperazine (7 RCTs), metoclopramide (1 RCT), chlorpromazine (1 RCT), and ondansetron (1 RCT). The RCTs reported outcomes on nausea, vomiting, appetite, food intake, drug preference, needing rescue medication, drop outs due to toxicity or lack of efficacy, and adverse events. In the preliminary risk of bias assessment, three RCTs were assessed as having a moderate risk of bias and nine RCTs were assessed as having a high risk of bias.

In six RCTs specific patient groups were studied: patients with lung cancer[171 172], patients with soft-tissue sarcomas[173], female patients with advanced gynaecological cancer[174], male patients with nonseminomatous testicular cancer[175], and patients with breast carcinoma or melanoma receiving bone

marrow support[176]. Five RCTs had a crossover design and one study had a parallel design. Sample size of the crossover RTCs ranged from 8 to 26. The parallel study included 106 patients. Age of the patients in the six studies ranged from 17 to 78 years. In four studies nabilone was used an intervention treatment. Nabilone was compared with alizapride (1 RCT), prochlorperazine (2 RCT), and chlorpromazine (1 RCT). In one RCT THC capsules and cigarettes were compared with placebo capsules and cigarettes. In another RCT dronabinol was studied as add-on treatment. The effect of metoclopramide with dronabinol and prochlorperazine with dronabinol was compared with metoclopramide with placebo and prochlorperazine with placebo. The RCTs reported outcomes on nausea, vomiting, emetic episodes, retching, appetite, anorexia, drug preferences, drop outs due to toxicity, requiring additional anti-emetic drugs, and adverse events. The six RCTs were assessed as high risk of bias during the preliminary risk of bias assessment.

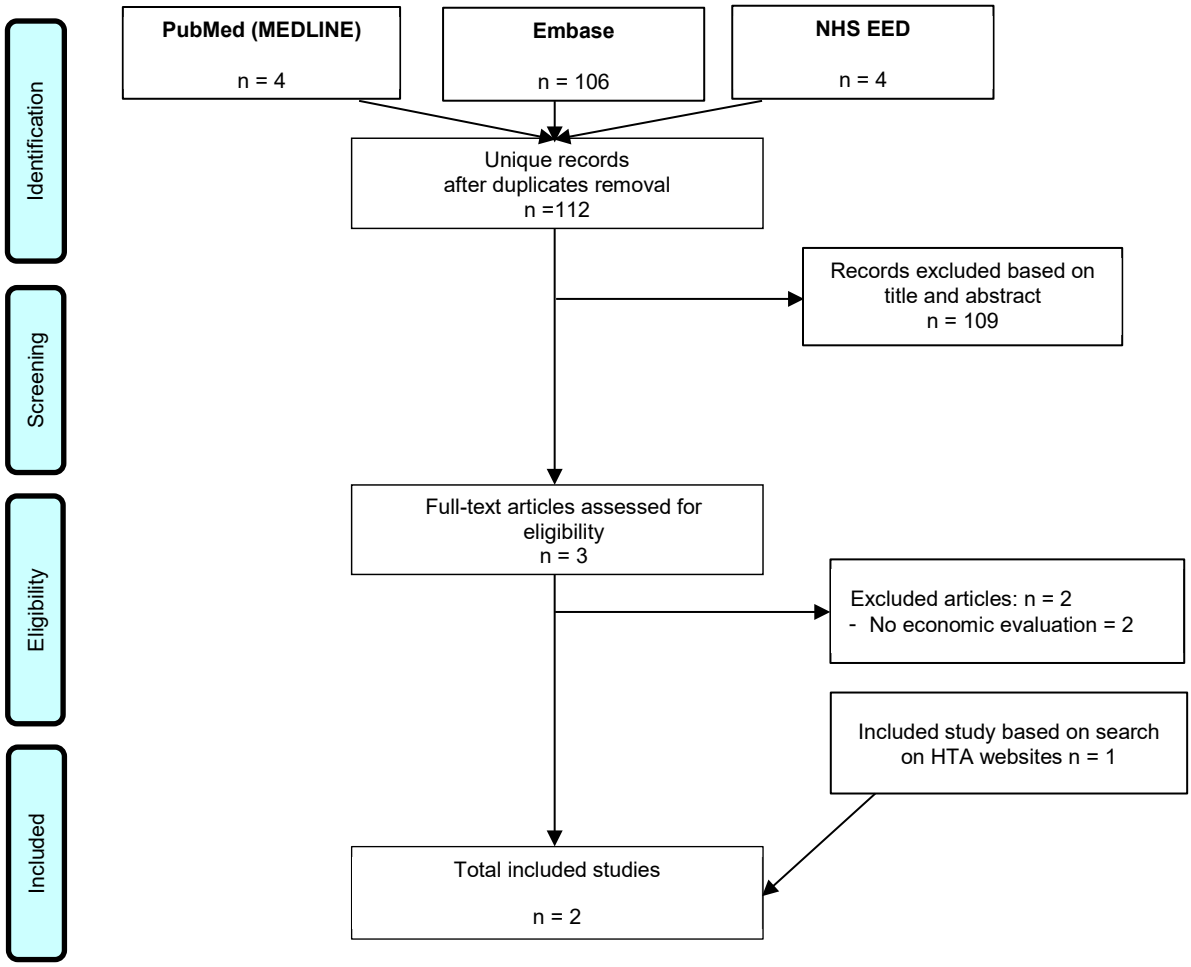
8.2 Evidence base pertaining to costs-effectiveness

8.2.1 PRISMA flow charts

Chronic pain

In total, 112 unique records were identified in PubMed (MEDLINE) and Embase on the use of medical cannabis for the symptom chronic pain. Of those, 109 records were excluded based on their title and abstract, resulting in 3 studies to be screened in full-text. After applying the inclusion and exclusion criteria, 1 study was included. The other studies were excluded for the reason of not being an economic evaluation (n=2). Finally, one additional study was included after identification through a search on the website of HTA agencies, resulting in the inclusion of a total of 2 studies. A complete overview of the selected literature is enclosed in the PRISMA flow chart (Figure 5).

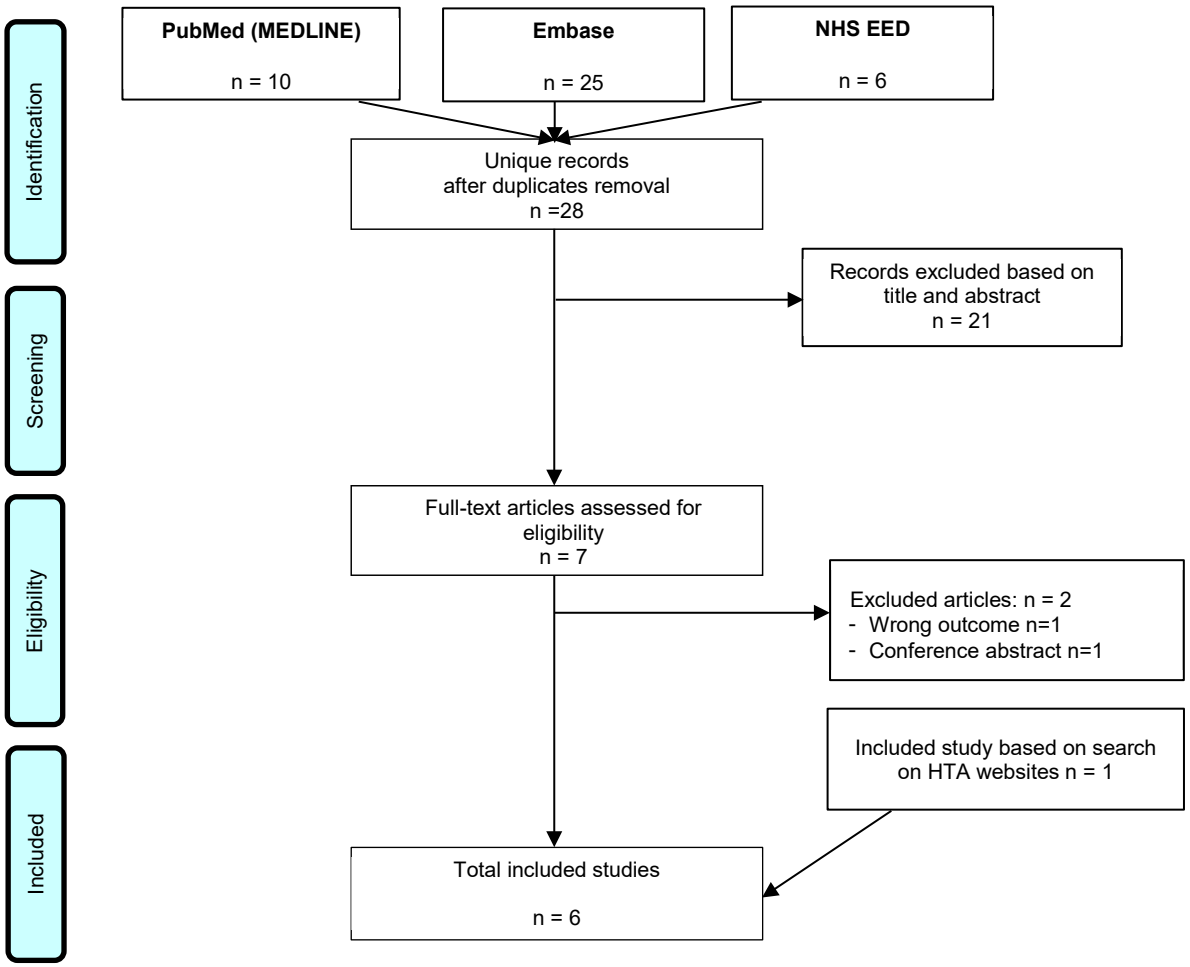
Figure 5. PRISMA flowchart of the cost-effectiveness systematic literature search on the use of medical cannabis for the symptom chronic pain



Spasticity

In total, 28 unique records were identified in PubMed (MEDLINE) and Embase on the use of medical cannabis for the symptom spasticity. Of those, 21 records were excluded based on their title and abstract, resulting in 7 studies to be screened in full-text. After applying the inclusion and exclusion criteria, 5 economic evaluations were included. Two studies were excluded, because of the following reasons: wrong outcome (n=1) and conference abstract (n=1). Finally, one additional study was included after identification through a search on the website of HTA agencies, resulting in the inclusion of a total of 6 studies. A complete overview of the selected literature is enclosed in the PRISMA flow chart (Figure 6).

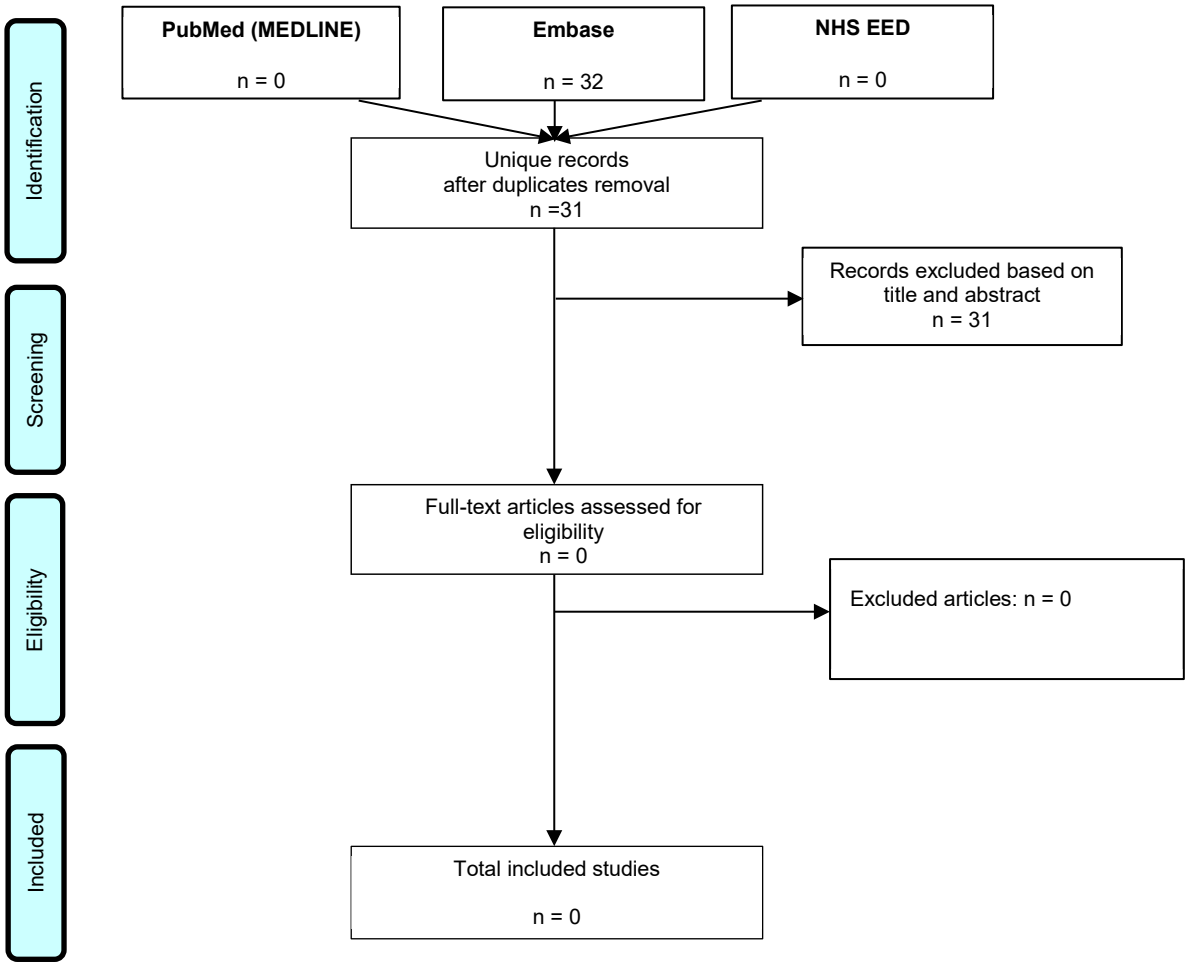
Figure 6. PRISMA flowchart of the cost-effectiveness systematic literature search on the use of medical cannabis for the symptom spasticity



Unintentional weight loss

In total, 31 unique records were identified in PubMed (MEDLINE) and Embase on the use of medical cannabis for the symptom unintentional weight loss. Of those, all records were excluded based on their title and abstract (n=31), resulting in 0 studies to be screened in full-text. Hence, no studies were included (Figure 7).

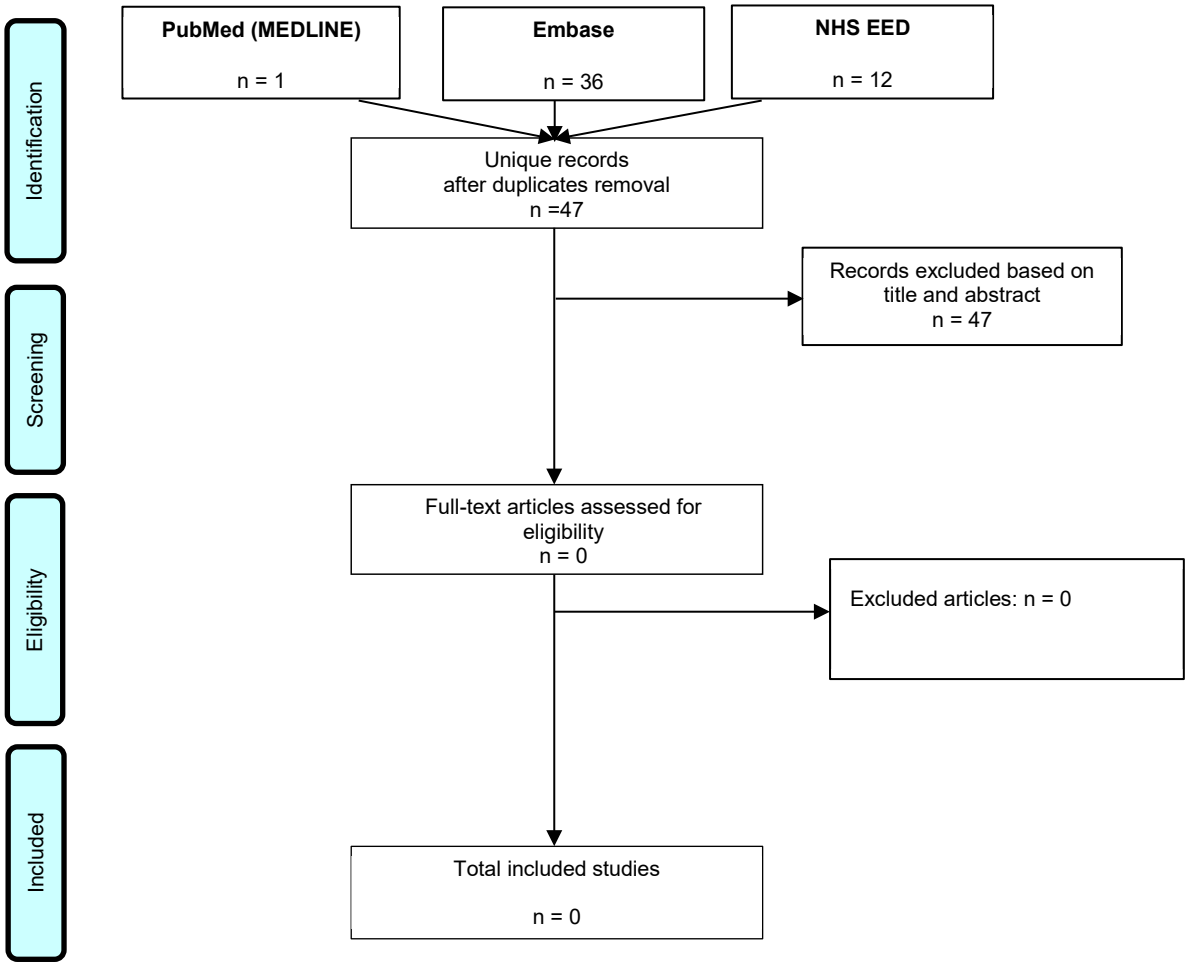
Figure 7. **PRISMA flowchart of the cost-effectiveness systematic literature search on the use of medical cannabis for the symptom unintentional weight loss**



Nausea and vomiting related to cancer treatment

In total, 47 unique records were identified in PubMed (MEDLINE) and Embase on the use of medical cannabis for the symptom nausea and vomiting related to cancer treatment. Of those, all records were excluded based on their title and abstract (n=47), resulting in 0 studies to be screened in full-text. Hence, no studies were included (Figure 8).

Figure 8. PRISMA flowchart of the cost-effectiveness systematic literature search on the use of medical cannabis for the symptom nausea and vomiting related to cancer treatment



8.2.2 Evidence tables

In this section the preliminary extracted data from the studies included on the cost-effectiveness of medical cannabis use in populations with the four pre-specified symptoms chronic pain and spasticity is presented in evidence tables (Table 11 and Table 12). Separate evidence tables are compiled for the study characteristics and costs and effects reported in the studies (Appendix 7). Also, a table is provided with the findings from the preliminary critical appraisal (Appendix 7). All findings are described in more detail in Section 8.2.3.

As no studies were included for the symptoms unintentional weight loss and nausea and vomiting related to cancer treatment, these symptoms will not be discussed in Section 8.2.2 and 8.2.3.

Chronic pain

Table 11. Study characteristics of the studies included on the cost-effectiveness of medical cannabis use for the symptom chronic pain

Reference Country	Study design, type of model (if applicable)	Study population	Intervention	Comparator	Outcome measure used to model disease progress	Perspective	Time horizon	Discount rates (costs / effects)	ICER (incremental costs, incremental effects)
Patients with neuropathic pain									
Tyree 2019, USA	CUA, decision tree	Treatment naïve patients with chronic neuropathic pain due to mixed aetiologies	Smoked cannabis (second-line)	SoC	Pain score reduction on an 11-point Likert scale	US healthcare sector perspective	1-year	3,0% / 3,0%	$48,594 / QALY ($610, 0,013 QALY)
Patients with chronic pain due to mixed aetiologies									

Reference Country	Study design, type of model (if applicable)	Study population	Intervention	Comparator	Outcome measure used to model disease progress	Perspective	Time horizon	Discount rates (costs / effects)	ICER (incremental costs, incremental effects)
NICE 2019, UK	CUA, Markov model	People with chronic pain whose pain was not adequately controlled by conventional management	Four separate medical cannabis products in addition to SoC: 1) THC:CBD spray (Sativex®), 2) Oral nabilone, 3) Oral dronabinol, 4) THC - oromucosal spray	SoC	Pain score reduction on the NRS (in terms of responders / non responders)	NHS and PSS perspective	Lifetime	3.5% / 3.5%	£151,431 / QALY (£24,474, 0,162 QALY)

Keys: SoC = standard of care, NHS = national health service, PSS = personal social services, NRS = numerical rating scale, ICER = incremental cost-effectiveness ratio, QALY = quality-adjusted life year

Spasticity

Table 12. Study characteristics of the studies included on the cost-effectiveness of medical cannabis use for the symptom spasticity

Reference Country	Study design, type of model (if applicable)	Study population	Intervention	Comparator	Outcome measure used to model disease progress	Perspective	Time horizon	Discount rates (costs / effects)	ICER (incremental costs, incremental effects)
Patients with multiple sclerosis									
Gras 2016, UK (Wales)	CUA, Markov model	Patients with moderate to severe spasticity due to MS experiencing insufficient benefit from oral anti-spasticity medicines and who demonstrated a clinically significant improvement in spasticity-related symptoms during an initial trial of	THC:CBD spray (Sativex®) + SoC	SoC alone	Severity of MS-related spasticity, measured with the MS Spasticity 0-1 NRS	Welsh NHS and PSS perspective	30 years	3,5% / 3,5%	£10,891 / QALY (£3,836, 0.35 QALY)

Reference Country	Study design, type of model (if applicable)	Study population	Intervention	Comparator	Outcome measure used to model disease progress	Perspective	Time horizon	Discount rates (costs / effects)	ICER (incremental costs, incremental effects)
		therapy lasting 4 weeks							
Slof 2015, Italy	CUA, Markov model	Patients with moderate to severe spasticity due to MS experiencing insufficient benefit from oral anti-spasticity medicines and who demonstrated a clinically significant improvement in spasticity-related symptoms during an initial trial of therapy lasting 4 weeks	THC:CBD spray (Sativex®) + SoC	SoC alone	Severity of MS-related spasticity, measured with the MS Spasticity 0-1 NRS	Health-payer perspective	5 years	3,0% / 3,0%	€4,968 / QALY (€2,152, 0.443 QALY)

Reference Country	Study design, type of model (if applicable)	Study population	Intervention	Comparator	Outcome measure used to model disease progress	Perspective	Time horizon	Discount rates (costs / effects)	ICER (incremental costs, incremental effects)
Slof 2012, Germany and Spain	CUA, Markov model	Patients with moderate-to-severe MS spasticity (measured using the spasticity 0–10 NRS) who had not responded adequately to other antispasticity medication and who demonstrated a clinically significant improvement in spasticity-related symptoms during an initial trial of therapy lasting 4 weeks	THC:CBD spray (Sativex®) + SoC	SoC alone	Severity of MS-related spasticity, measured with the MS Spasticity 0-1 NRS	Health-payer perspective	5 years	3,5% / 3,5%	Germany: €11,214 / QALY (€3,597, 0.321 QALY) Spain: €3,496 / QALY Spain (€3,679, 0.325 QALY)

Reference Country	Study design, type of model (if applicable)	Study population	Intervention	Comparator	Outcome measure used to model disease progress	Perspective	Time horizon	Discount rates (costs / effects)	ICER (incremental costs, incremental effects)
Lu 2012, UK	CUA, Markov model	Patients with moderate to severe spasticity due to MS experiencing insufficient benefit from oral anti-spasticity medicines and who demonstrated a clinically significant improvement in spasticity-related symptoms during an initial trial of therapy lasting 4 weeks	THC:CBD spray (Sativex®) + SoC	Oral anti-spasticity medicines alone	Severity of MS-related spasticity, measured with the MS Spasticity 0-1 NRS	NHS perspective	5 years	3,5% / 3,5%	£49,300 / QALY (£7,600, 0.15 QALY)
NICE 2019, UK	CUA, Markov model	Patients with moderate to severe spasticity due to	THC:CBD spray (Sativex®) + SoC	SoC alone	Severity of MS-related spasticity, measured with the	NHS and PSS perspective	5 years	3,5% / 3,5%	£19,512 / QALY (£1,580, 0.081 QALY)

Reference Country	Study design, type of model (if applicable)	Study population	Intervention	Comparator	Outcome measure used to model disease progress	Perspective	Time horizon	Discount rates (costs / effects)	ICER (incremental costs, incremental effects)
		MS experiencing insufficient benefit from oral anti-spasticity medicines and who demonstrated a clinically significant improvement in spasticity-related symptoms during an initial trial of therapy lasting 4 weeks			MS Spasticity 0-1 NRS (in terms of responders / non responders)				
Flachenecker 2013, Germany	CUA, Markov model	Patients with moderate to severe spasticity due to MS experiencing insufficient benefit from oral anti-spasticity	THC:CBD spray (Sativex®) + SoC	SoC alone	Severity of MS-related spasticity, measured with the MS Spasticity 0-1 NRS	German healthcare system perspective	5 years	Not substantiated	€11,060 / QALY (€3,597, 0.325 QALY)

Reference Country	Study design, type of model (if applicable)	Study population	Intervention	Comparator	Outcome measure used to model disease progress	Perspective	Time horizon	Discount rates (costs / effects)	ICER (incremental costs, incremental effects)
		medicines and who demonstrated a clinically significant improvement in spasticity-related symptoms during an initial trial of therapy lasting 4 weeks							

Keys: SoC = standard of care, NRS = numerical rating scale, NHS = national health service, PSS = personal social services, ICER = incremental cost-effectiveness ratio, QALY = quality-adjusted life year

8.2.3 Findings regarding cost-effectiveness

Study and model characteristics

Chronic pain

Two economic evaluations were included in the cost-effectiveness systematic literature search.[47, 58] The study and model characteristics are presented in Table 11. One study looked at adjunctive (smoked) cannabis versus standard of care (first-line, second-line if first-line failed, or third-line if first and second-line failed) in treatment naïve patients with chronic neuropathic pain with mixed aetiology.[47] The other study considered several medical cannabis products in addition to standard of care versus standard of care in people with chronic pain (all aetiologies) whose pain was not adequately controlled by conventional management.[58]

One economic evaluation was conducted for the USA[47] setting, and one was conducted for the UK.[58] Both economic evaluations were cost-utility analyses (CUAs), expressing outcomes in QALYs. One economic evaluation used a decision tree[47] and the other constructed a Markov model[58]. The decision tree employed a 1-year time horizon, and the Markov model considered a lifetime time horizon. The health states in the decision tree were moderate to severe pain, mild pain, and death. The Markov model used the following health states: on treatment and responder, on treatment non-responder, discontinued and responder, discontinued non-responder, and death. Treatment response was defined as achieving ≥30% pain reduction on the numerical rating scale. One of the studies was conducted by NICE.[58] Both studies were recently published, in 2019. For the two included economic evaluations reporting on chronic pain, no conflicts of interest were noted.

Spasticity

Six economic evaluations were included in the cost-effectiveness systematic literature search.[41-44, 58, 177] The study and model characteristics are presented in Table 12.

The model structure of the included models was similar. All studies compared Sativex® in addition to standard of care to standard of care alone. The patient population in the models consisted of patients who had moderate to severe spasticity in MS and demonstrated a clinically significant improvement in spasticity-related symptoms during an initial trial of therapy lasting 4 weeks (according to the prescription requirement). Health states were based on the severity of the spasticity symptoms, but studies varied

in the definition of the health states. In all but one study, patients could transition between health states that represent the level of severity, ranging from mild to severe in either 3 or 5 levels. The model by NICE defined health states as either responders (>30% reduction in spasticity score) or non-responders.

The study design of all included studies was a CUA, expressing outcomes in QALYs. All included studies were model-based economic evaluations, using Markov models. Two of the studies were performed for the UK setting, one study for Wales, two studies for Germany, one for Italy, and one study was conducted for Spain. Five studies applied a five-year time horizon, one study used a time horizon of 30 years. One of the studies was conducted by NICE[58]. The most recent model-based study was from 2019.[58]

Input parameters

Chronic pain

An overview of the outcomes reported in the included economic evaluations is displayed in Appendix 7. The economic evaluations used different primary sources for the effectiveness data. In the study by NICE, they conducted an SR on the treatment effect of medical cannabis in chronic pain. Using data from the two biggest trials included in their SR, NICE was able to estimate the treatment effects distribution based on a normal distribution. Other detailed input data (e.g. adverse event parameters and costs, and costs of background pain management per health state) was also obtained from their SR. The study by Tyree et al. based the costs of standard therapy agents, health state utilities, and utility decrements due to adverse events on a study by Bellows et al.[178]. More detailed input parameters were presented, which were based on several other single trials and/or cost-effectiveness analyses. Both economic evaluations included costs and diminished utilities related to adverse events. Neither of the studies included the potential effect of medical cannabis products on mortality, or potential beneficial side effects.

Spasticity

An overview of the outcomes reported in the included trial-based studies is displayed in Appendix 7. Five studies were based on the same RCT, namely the trial by Novotna et al..[83] The study by NICE was based on the findings of their own meta-analysis. All studies reported the intervention (in this case, Sativex®) and the comparator costs (in this case, standard of care). The studies differed in the resource use that was taken into account as part of the background costs of MS for both arms (e.g. anti-spasticity drugs, hospital visits, general practitioner visits, laboratory tests, home care, physiotherapy). The study

by NICE 2019 was the only one to include the costs and disutilities related to adverse events. None of the studies included the potential effect of Sativex® on mortality.

Preliminary quality appraisal

Chronic pain

The economic evaluations that were included in the systematic literature search were assessed with the CHEC. The studies were judged on whether the criteria were fulfilled (“1”), not fulfilled (“0”), or inconclusive (“0.5”). An overview of the preliminary critical quality appraisal is enclosed in Appendix 7.

Both economic evaluations failed to adequately describe the study population, as for example data on the gender distribution of the modelled patients were missing. Overall, the study comparison was adequately described and the study design was appropriate for the stated objectives. Only the NICE 2019 assessment included a lifetime time horizon, which is generally the preferred option for economic evaluations. Both studies scored a 0.5 on item 5 (Is the chosen time horizon appropriate in order to include relevant costs and consequences?), as they did not apply the generally preferred societal perspective.

The economic evaluations both included all relevant costs considering the perspective taken, although adverse event costs were included as an aggregate as opposed to single specific adverse event costs. The costs in the NICE assessment were based on the national tariff list. Tyree et al. 2019 based their costs on the cost inputs of several other studies. Both economic evaluations included costs and diminished utilities related to adverse events.

The economic evaluations included an incremental analysis of costs and outcomes, and costs and outcomes were discounted to account for inflation. Sensitivity analyses were conducted to account for the uncertainty of model inputs. The study by Tyree et al. included analyses using alternate time horizons, alternate adverse event modifiers, and cannabis wastage. The NICE assessment included analyses using different treatment effects, discontinuation thresholds, QoL coefficients, dosing regimen, response values, and baseline pain scores amongst many more. The studies did not report on the ethical and distributional issues associated with the reimbursement of medical cannabis.

Spasticity

The economic evaluations that were included in the systematic literature search for economic evaluations were assessed with the CHEC. The studies were judged on whether the criteria were fulfilled (“1”),

not fulfilled (“0”), or inconclusive (“0.5”). An overview of the preliminary critical quality appraisal is enclosed in Appendix 7.

Among the study design items, all studies scored 0.5 on item 5 (Is the chosen time horizon appropriate in order to include relevant costs and consequences?) and 6 (Is the actual perspective chosen appropriate?) as the generally preferred perspective (societal) and time horizon (lifetime) were not applied. In addition, two studies failed did not provide a clear description of the study population (e.g. mean age or age range, gender distribution).

Only in the NICE model were the effectiveness and cost related model inputs based on systematic literature search. In other studies, the effectiveness inputs were derived from one or two trials. Four studies based their resource use input on their own Delphi Panel or clinical opinion, one study used a literature source to obtain resource use input. All but one study used publicly available sources for obtaining unit costs. The other study derived unit costs from their own Delphi Panel. The study by NICE was the only one to include the costs and diminished utilities related to adverse events.

The included studies performed well regarding reporting and interpreting the results; all studies performed incremental analyses and their conclusions followed from the reported data. Further, almost all studies discounted both costs and effects and most studies subjected all important uncertain variables to sensitivity analyses. However, almost half of the studies did not discuss generalisability of the results and only one study discussed ethical and distributional issues. Furthermore, in four studies at least some of the authors were sponsored by pharmaceutical companies. Also, the studies did not report on the ethical and distributional issues associated with the reimbursement of medical cannabis.

8.3 Evidence base pertaining to legal, social and ethical issues

Legal, social and ethical issues

The cultivation, consumption, distribution, and reimbursement of medical cannabis is subject to different laws in Switzerland, i.e. the agronomical law[179], the narcotics law[105, 106], the legislation on therapeutic products[180], and the health insurance law[181]. The various laws are interconnected. Potential reimbursement of medical cannabis may therefore provoke legal issues. In addition, it should be noted that a change in the reimbursement policy of medical cannabis may have social, and ethical consequences that need to be evaluated with care in the HTA phase. Ethical and social issues related to medical cannabis prescription and reimbursement may include e.g. stigma, risk of substance addiction, and misuse. However, the included economic evaluations revealed insufficient information on potential social

and ethical issues related to medical cannabis. In the HTA phase, a selection of grey literature will be explored to gain additional information on these aspects.

8.4 Evidence base pertaining to organisational issues

The included economic evaluations revealed no information on potential organisational issues related to medical cannabis. In the HTA phase, a selection of grey literature will be explored to gain information on these aspects.

9 Feasibility HTA

The aim of this scoping report is to determine the feasibility of conducting an HTA evaluation comparing the efficacy, effectiveness, safety, and cost-effectiveness of medical cannabis in patients with the symptoms of chronic pain, spasticity, unintentional weight loss and nausea and vomiting related to cancer treatment. This Chapter summarises the outcomes of the scoping phase.

The efficacy, effectiveness, and safety systematic literature search included 19 RCTs for the symptom chronic pain, 14 RCTs for spasticity, 5 RCTs for unintentional weight loss, and 22 RCTs for the symptoms nausea and vomiting related to cancer treatment. Based on the preliminary data extraction in this scoping report, the conclusion was drawn that the evidence base for the symptoms chronic pain and spasticity is sufficient and can be implemented in an HTA. These RCTs study the efficacy of medical cannabis use for chronic pain or spasticity and are in line with our review objectives, PICO criteria, and study quality criteria. The pre-specified outcomes of interest (clinically relevant patient-reported pain relief or improvement in a specific spasticity aspect, withdrawal due to lack of efficacy of medical cannabis, health-related quality of life, occurrence of cannabis-associated adverse events, and withdrawal of treatment due to adverse effects of medical cannabis) are reported in the included RCTs on chronic pain and spasticity. When conducting the HTA, further decisions will be made to create more homogeneity among the data (see Chapter 10 for more details).

The RCTs describing the efficacy of medical cannabis use for unintentional weight loss are in line with our review objectives, however the number of included RCTs is limited and the methodological quality is low. A quantitative comparison between the RCTs is complicated due to a large variety of outcome measures and the limited number of studies. Overall, it was concluded that the evidence base of medical cannabis use for the symptom unintentional weight loss is insufficient to continue with complete data extraction as input for the development of cost-effectiveness models in an HTA. The evidence will be described in a narrative manner in the HTA report (see Chapter 10 for more details).

The RCTs reporting on the efficacy of medical cannabis use for the symptoms nausea and vomiting related to cancer treatment, are in line with our review objectives. The preliminary data extraction showed a large variety of outcomes to measure the frequency or severity of nausea or vomiting. For a small number of studies results are comparable and a quantitative comparison of outcomes would be feasible. However, the RCTs found for the symptoms nausea and vomiting are dated (i.e. 19 of the 22 RCTs were published before 1990) and no recently published RCTs were found (i.e. the most recently published RCT was published 13 years ago). In 2015, the evidence on cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy is published in a Cochrane review.[31] It is plausible that cancer treatments have evolved over time and other effective anti-emetic therapies are available now for patients with cancer. As a consequence, the comparator treatment in these studies may be inadequate and the applicability of the evidence might be limited. Overall, it was concluded that the evidence base of medical cannabis use for nausea and vomiting related to cancer treatment is insufficient to continue with complete data extraction as input for the development of cost-effectiveness models in an HTA. The evidence will be described in a narrative manner in the HTA report (see Chapter 10 for more details).

The evidence base for the cost-effectiveness systematic literature search included two economic evaluations on medical cannabis use for the symptom chronic pain, six for the symptom spasticity, and none for the symptoms unintentional weight loss and nausea and vomiting related to cancer treatment. The identified economic evaluations for the chronic pain and spasticity symptoms do not provide evidence on the cost-effectiveness of medical cannabis versus no medical cannabis specific to the Swiss context, as none of the evaluations used Swiss data.

NICE developed *de novo* cost-effectiveness models to assess the cost-effectiveness of medical cannabis for both chronic pain and spasticity symptoms. Using the CHEC for critical appraisal, the NICE economic evaluations on chronic pain and spasticity relief with medical cannabis were judged to be of (very) high quality. As is common in most NICE assessments, the cost-effectiveness models (including clinical and cost inputs) are described in a clear and transparent way, which allows for the use of these models as ‘base models’ for the HTA. Thus, it will be possible to rebuild the NICE models and discuss the appropriateness of the model (including all relevant model inputs and assumptions) with a clinical expert. The other identified economic evaluations and their respective models may be used to validate and/or adapt the NICE models. An additional search for Swiss costs and quality of life data can be performed to better fit the Swiss context.

Therefore, based on the findings in this scoping report, conducting an HTA for medical cannabis in Switzerland is deemed feasible. For the symptoms chronic pain and spasticity, the HTA phase can

include comprehensive data extraction of the individual study outcomes and the development of a cost-effectiveness model. For the symptoms nausea and vomiting and unintentional weight loss, analysis of the individual study outcomes was not deemed feasible. The methodological limitations of the studies limit the ability to draw conclusions and further research reflecting current chemotherapy regimens and newer anti-emetic drugs is likely to modify these conclusions. Correspondingly, cost-effectiveness models cannot be developed for these two symptoms. Instead, the HTA phase for these two symptoms will consist of an in-depth description on why the evidence is insufficient to answer the HTA questions of the FOPH. The next Chapter provides a detailed description of the proposed HTA, with a focus on the symptoms chronic pain and spasticity.

10 Outlook

To answer the HTA key questions of the FOPH, an HTA specific for the Swiss context is necessary. In this Chapter, the methodological steps to be taken for the HTA will be described.

10.1 Proposed approach

Unintentional weight loss and nausea and vomiting related to cancer treatment and unintentional weight loss

Due to methodological limitations of the studies found in the systematic literature search, it was concluded during the scoping phase that it is not feasible to continue with complete data extraction or the development of cost-effectiveness models for medical cannabis use for the symptoms unintentional weight loss and nausea and vomiting related to cancer treatment. Hence, the HTA phase for these two symptoms will consist of an in-depth discussion on why the evidence is insufficient to draw a conclusion on the efficacy, effectiveness, safety as well as the cost-effectiveness of medical cannabis for these symptoms.

Chronic pain and spasticity

A rigorous systematic review methodology, adhering to the international methodological standards of Cochrane and the PRISMA reporting guidelines, will be applied to further critically appraise, analyse, and synthesise the relevant clinical evidence on the pre-specified outcomes of interest. The SR methodology will elaborate on the methodology as reported in this scoping report and will be further outlined in a separate HTA protocol. Shortly, the risk of bias in the RCTs included on medical cannabis for the symptoms chronic pain and spasticity will be assessed based on the key risk of bias criteria used in the GRADE approach.[120] During the scoping phase RCTs were included based on the objectives and PICO

criteria. RCTs were not yet excluded for methodological criteria, such as a small sample size. Based on the input required for the cost-effectiveness model parameters, the necessity to further specify the inclusion criteria for the RCTs will be determined, for example by setting a minimum sample size, specific medical cannabis product, or treatment duration. Data from the final selection of RCTs will be fully extracted, including the study characteristics and pre-specified outcomes of interest (i.e. clinically relevant patient-reported pain relief or improvement in a specific spasticity aspect; withdrawal due to lack of pain relief efficacy or anti-spasticity efficacy of medical cannabis; health-related quality of life; occurrence of cannabis-associated adverse events; and withdrawal of treatment due to adverse effects of medical cannabis). Since different levels of heterogeneity are observed for the RCTs on chronic pain and spasticity, the possibility for conducting a meta-analysis for the outcomes to be included in the cost-effectiveness models will be explored, taking into account the applied model assumptions to create more homogeneity among the data. The meta-analysis includes a full GRADE assessment of the outcomes.[182] Outcomes for which meta-analysis is not possible will be presented narratively in summary tables / figures and accompanying text, to provide insight into the direction of the treatment effects found in the clinical literature.

Two cost-effectiveness models will be built to determine the cost-effectiveness of medical cannabis compared to no medical cannabis in adults with the symptoms chronic pain and spasticity. As mentioned before, there is too little evidence to proceed with analysis of the individual study outcomes and cost-effectiveness modelling for the symptoms of unintentional weight loss and nausea and vomiting related to cancer treatment. Building the cost-effectiveness models for chronic pain and spasticity includes the following steps: 1) rebuilding and adapting the NICE models; 2) collecting data for the input parameters of the model specific to the Swiss context; 3) programming the cost-effectiveness model; and 4) analysing the results of the model.

Although the published studies do not provide sufficient information to draw firm conclusions on the cost-effectiveness of medical cannabis for chronic pain and spasticity in Switzerland, the model structures and findings of the identified economic evaluations can be used as a basis for the development of the model for the HTA. In particular, the models from the NICE evidence reviews can be used as the basis for the HTA for both the symptom chronic pain and spasticity. Note that these models may be adapted during the HTA phase after review of the clinical guidelines and consultation with clinical experts, to gain further understanding of the clinical pathway of chronic pain and spasticity with medical cannabis treatment specifically for the situation in Switzerland. The NICE models for medical cannabis for the use of medical cannabis in patients with the symptoms chronic pain and spasticity are detailed below.

10.2 Cost-effectiveness modelling

10.2.1 Model structure of the NICE models

Chronic pain

The base case model developed by NICE includes all aetiologies of chronic pain. In addition, they modelled three scenarios including different subgroups of aetiologies, including 1) neuropathic pain, 2) cancer pain, and 3) musculoskeletal pain. In total four different medical cannabis products were modelled, these include: THC:CBD spray, oral nabilone, oral dronabinol, and THC - oromucosal spray. These medical cannabis products plus standard of care were compared with standard of care alone.

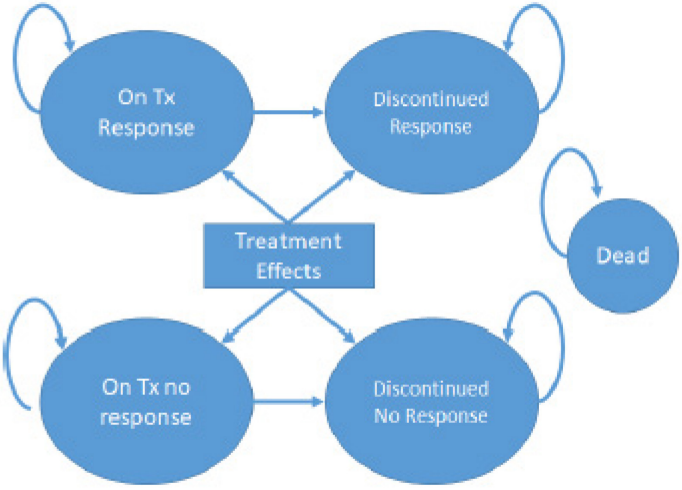
The treatment effects were modelled using continuous (mean changes in pain scores) rather than dichotomous (e.g. proportion of people achieving a 30% analgesic response) data. NICE made this decision since more clinical trials reported continuous rather than dichotomous data and because it provided a more detailed breakdown of efficacious treatment effects. Furthermore, NICE assumed treatment effects would be normally distributed. The baseline pain in both model arms was calculated using a beta distribution to assign patients into 200 'bins' representing each 0.05 pain increment from 0.025 to 9.975 on the NRS scale. Utilities were modelled for each pain level based on a published study.

There was no data available on treatment discontinuation available for the entire modelled population. The base case used data on treatment discontinuation from response data from one large, publicly available individual patient dataset on patients with advanced MS treated with THC:CBD spray. NICE acknowledges this as a limitation, as this data reflects only a subgroup of all modelled patient and only one of four modelled medical cannabis products.

The effect of medical cannabis on mortality is not well researched. Regardless, NICE assumed that medical cannabis does not fundamentally modify disease progression as it is mainly used for relief of symptoms. Hence, the same standard mortality rate for patients with chronic pain was applied to both treatment arms.

A 4-week cycle length was adopted based on the reported time period associated with the treatment effects in the clinical trials. In addition, NICE adopted a discount rate of 3.5% for both costs and benefits and a lifetime time horizon. The structure of the model developed by NICE is shown in Figure 9.

Figure 9. Model structure NICE model – Chronic pain



Source: NICE [NG144]. Note: Tx = Treatment

Spasticity

In the base case analysis patients experiencing spasticity with all underlying aetiologies were included in the assessment. The model compared medical cannabis in addition to standard of care with standard of care alone. Due to the lack of data the model focused on THC:CBD spray (Sativex®). The model utilised a relatively simple structure including three health states: response, no response, and dead. This model structure was similar to the model developed by Lu et al. (2012), which was funded by the National Institute for Health Research (NIHR).[44] The analysis was conducted using a NHS (National Health Service) perspective, as is in line with the NICE guidelines for economic evaluations.

A clinically significant treatment effect was defined as a reduction of more than 30% on the spasticity NRS. NICE conducted a SR which identified four RCTs of THC:CBD spray in patients with spasticity as a symptom of MS. The NICE SR did not provide evidence for other types of medicinal cannabis or for spasticity due to other aetiologies. However, the model allows for other medical cannabis products to be included if data becomes available.

The treatment effects of THC:CBD spray were derived from the meta-analysis that was conducted by NICE as part of their SR. The model applied Odds ratios (ORs) from all four identified RCTs in the base case (considering a defined daily dose of less than 12 sprays per day). For the response data, NICE used the Messina registry.

The model assumed that the majority of patients who did not respond to THC:CBD spray would discontinue the treatment and switch to standard of care only. Additionally, following initial response, patients

could still discontinue medical cannabis treatment due to loss of efficacy or adverse events. Patients in the comparator arm of the model also experienced loss of treatment response over time.

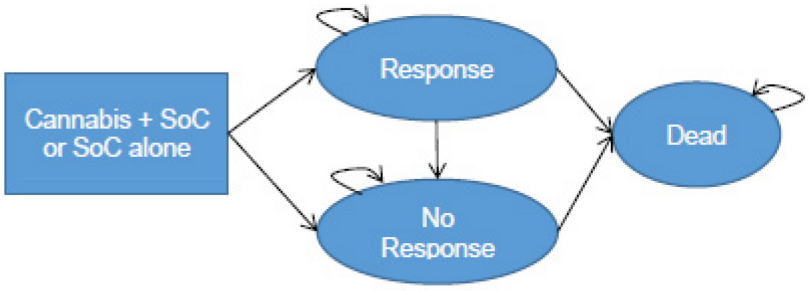
NICE employed a higher mortality risk compared to the standard mortality ratios of the general population for the modelled patients due to their MS diagnosis. Published standardised mortality ratios were applied to the UK life table to estimate the mortality risk of patients with MS-related spasticity. NICE found no evidence for an impact of medical cannabis on survival, therefore the same mortality risk for both the medical cannabis in addition to standard of care and standard of care alone arms was applied.

The rate of adverse events of medical cannabis was based on a single published study. Costs for medical cannabis and standard of care were sourced from NHS Drug Tariff or other publicly available sources. The resource uses associated with various levels of spasticity were taken from a published UK study, which reported costs per NRS category. Assumptions were made for resource use associated with adverse events.

Due to lack of UK utility data, health state utilities were based on a published utility regression model of EuroQol 5 dimensions (EQ-5D) instrument, spasticity numeric rating scale (NRS), and Expanded Disability Status Scale (EDSS) of 98 Swedish patients. A disutility for adverse events was estimated as a decrement.

The model adopted a cycle length of 4-weeks. The base case time horizon was 5 years. Sensitivity analyses employed time horizons of 10, 20, and 30 years. The structure of the model developed by NICE is shown in Figure 10.

Figure 10. Model structure NICE model – Spasticity



Source: NICE [NG144]. Note: SoC = standard of care

10.2.2 General approach to modelling

For the HTA, the NICE cost-effectiveness models for chronic pain and spasticity and the underlying decisions/assumptions (as described above) will be discussed with the FOPH and clinical experts.

There are multiple possibilities when it comes to incorporating subgroups of aetiologies associated with the symptoms of pain and spasticity. In the HTA phase, the subgroups that were incorporated in the NICE models will be discussed with the FOPH.

For the symptoms chronic pain and spasticity, a complete data extraction of clinical outcomes will be done in the HTA. It is important to note that preferably the clinical outcomes in our models will be the same as the outcomes used in the NICE models. Other outcomes will be presented narratively in summary tables / figures and accompanying text, to provide insight into the direction of the treatment effects found in the clinical literature. The effect of medical cannabis on the selected outcome will be modelled by lowering the risk of chronic pain or spasticity events in the intervention arm based on results from the efficacy, effectiveness, and safety systematic literature search (e.g. using relative risks). It is expected that the efficacy, effectiveness, and safety systematic literature search, together with other targeted searches and clinical expert inputs, will provide evidence to populate the clinical input parameters of the cost-effectiveness model using Swiss data.

In the HTA phase an additional search may be performed for costing studies in combination with key words regarding Switzerland to find studies that provide relevant costing data for Switzerland. In addition, searches in medical databases and the Swiss medical databases (e.g. Swiss Diagnosis-related group (DRG) or Tariff Pool) may be performed in collaboration with the FOPH to determine medication use, healthcare resource use, and unit costs associated with medical cannabis and no medical cannabis treatment.

Furthermore, scenarios will be adopted with 0%, 3%, and 6% discount rates for both costs and effects in line with previous HTAs conducted for the FOPH. Preferably a lifetime time horizon is adopted and varying shorter time horizons can be applied in sensitivity analyses similar to NICE's approach. A healthcare perspective will be used.

The model and collected input parameters will then be translated into a cost-effectiveness model (in Excel or R) that can estimate the cost-effectiveness of medical cannabis for the relief of chronic pain and spasticity symptoms in Switzerland. The results of the HTA can be used to inform the decision on reimbursement of medical cannabis for these specific symptoms.

In addition to the cost-effectiveness model, the HTA phase will also include the development of a budget impact model to calculate the projected population-level five-year overall costs of medical cannabis for both chronic pain and spasticity. The budget impact model will be built as an extension to the cost-effectiveness model, described above. Hence, the core model characteristics for the budget impact

model will be largely the same as those used for the cost-effectiveness model. The time horizon of the budget impact model will be restricted to 5 years. For the budget impact model, data is required about the number of eligible patients in Switzerland. If this data is not available, assumptions will be made based on data from other comparable countries and/or expert opinion.

10.3 Proposed approach – other HTA domains

The economic evaluations did not yield sufficient evidence for legal, social, ethical, and organisational issues concerning medical cannabis for the time being, however it is expected that an exploration of the identified HTA documents and guidelines will generate additional evidence for the research questions in the HTA.

11 References

1. Hall W. Medical use of cannabis and cannabinoids: questions and answers for policymaking: Publication Office of the European Union; 2018.

2. The National Academies of Sciences Engineering and Medicine. The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research. 2017.

3. Wang T, Collet J-P, Shapiro S, Ware MA. Adverse effects of medical cannabinoids: a systematic review. Cmaj. 2008;178(13):1669-78.

4. Allan GM, Finley CR, Ton J, Perry D, Ramji J, Crawford K, et al. Systematic review of systematic reviews for medical cannabinoids: Pain, nausea and vomiting, spasticity, and harms. Canadian Family Physician. 2018;64(2):e78-e94.

5. Andreae MH, Carter GM, Shaparin N, Suslov K, Ellis RJ, Ware MA, et al. Inhaled cannabis for chronic neuropathic pain: a meta-analysis of individual patient data. The Journal of Pain. 2015;16(12):1221-32.

6. Aviram J, Samuelly-Leichtag G. Efficacy of Cannabis-Based Medicines for Pain Management: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. 2017.

7. Batalla A, Janssen H, Gangadin SS, Bossong MG. The Potential of Cannabidiol as a Treatment for Psychosis and Addiction: Who Benefits Most? A Systematic Review. Journal of clinical medicine. 2019;8(7):1058.

8. Black N, Stockings E, Campbell G, Tran LT, Zagic D, Hall WD, et al. Cannabinoids for the treatment of mental disorders and symptoms of mental disorders: a systematic review and meta-analysis. The Lancet Psychiatry. 2019;6(12):995-1010.

9. Bonaccorso S, Ricciardi A, Zangani C, Chiappini S, Schifano F. Cannabidiol (CBD) use in psychiatric disorders: A systematic. Neurotoxicology. 2019.

10. Brown D, Watson M, Schloss J. Pharmacological evidence of medicinal cannabis in oncology: a systematic review. Supportive Care in Cancer. 2019:1-13.

11. Cooper ZD, Abrams D. Considering abuse liability and neurocognitive effects of cannabis and cannabis-derived products when assessing analgesic efficacy: a comprehensive review of randomized-controlled studies. The American journal of drug and alcohol abuse. 2019:1-16.

12. Darkovska-Serafimovska M, Serafimovska T, Arsova-Sarafinovska Z, Stefanoski S, Keskovski Z, Balkanov T. Pharmacotherapeutic considerations for use of cannabinoids to relieve pain in patients with malignant diseases. Journal of pain research. 2018;11:837.

13. Deshpande A, Mailis-Gagnon A, Zoheiry N, Lakha SF. Efficacy and adverse effects of medical marijuana for chronic noncancer pain: Systematic review of randomized controlled trials. Canadian Family Physician. 2015;61(8):e372-e81.

14. Fitzcharles MA, Ste-Marie PA, Häuser W, Clauw DJ, Jamal S, Karsh J, et al. Efficacy, tolerability, and safety of cannabinoid treatments in the rheumatic diseases: a systematic review of randomized controlled trials. Arthritis care & research. 2016;68(5):681-8.

15. Goldenberg M, Reid MW, IsHak WW, Danovitch I. The impact of cannabis and cannabinoids for medical conditions on health-related quality of life: A systematic review and meta-analysis. Drug and Alcohol Dependence. 2017;174:80-90.

16. Häuser W, Petzke F, Fitzcharles M. Efficacy, tolerability and safety of cannabis-based medicines for chronic pain management–An overview of systematic reviews. European Journal of Pain. 2018;22(3):455-70.

17. Hoch E, Niemann D, von Keller R, Schneider M, Friemel CM, Preuss UW, et al. How effective and safe is medical cannabis as a treatment of mental disorders? A systematic review. European archives of psychiatry and clinical neuroscience. 2019;269(1):87-105.

18. Houze B, El-Khatib H, Arbour C. Efficacy, tolerability, and safety of non-pharmacological therapies for chronic pain: an umbrella review on various CAM approaches. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2017;79:192-205.

19. Kafil TS, Nguyen TM, MacDonald JK, Chande N. Cannabis for the Treatment of Crohn's Disease and Ulcerative Colitis: Evidence From Cochrane Reviews. Inflammatory Bowel Diseases. 2019.

20. Khoury JM, Neves MdCLd, Roque MAV, Queiroz DAdB, Corrêa de Freitas AA, de Fátima Â, et al. Is there a role for cannabidiol in psychiatry? The World Journal of Biological Psychiatry. 2019;20(2):101-16.

21. Kilcher G, Zwahlen M, Ritter C, Fenner L, Egger M. Medical use of cannabis in Switzerland: analysis of approved exceptional licences. Swiss medical weekly. 2017;147:w14463.

22. Lattanzi S, Brigo F, Trinka E, Zaccara G, Cagnetti C, Del Giovane C, et al. Efficacy and safety of cannabidiol in epilepsy: a systematic review and meta-analysis. Drugs. 2018;78(17):1791-804.

23. Lim K, See YM, Lee J. A systematic review of the effectiveness of medical cannabis for psychiatric, movement and neurodegenerative disorders. Clinical Psychopharmacology and Neuroscience. 2017;15(4):301.

24. Millar SA, Stone N, Bellman Z, Yates A, England T, O'Sullivan S. A systematic review of cannabidiol dosing in clinical populations. British journal of clinical pharmacology. 2019;85(9):1888-900.

25. Mücke M, Phillips T, Radbruch L, Petzke F, Häuser W. Cannabis-based medicines for chronic neuropathic pain in adults. Cochrane Database of Systematic Reviews. 2018(3).

26. Nielsen S, Germanos R, Weier M, Pollard J, Degenhardt L, Hall W, et al. The use of cannabis and cannabinoids in treating symptoms of multiple sclerosis: a systematic review of reviews. Current neurology and neuroscience reports. 2018;18(2):8.

27. Nugent SM, Morasco BJ, O'Neil ME, Freeman M, Low A, Kondo K, et al. The effects of cannabis among adults with chronic pain and an overview of general harms: a systematic review. Annals of internal medicine. 2017;167(5):319-31.

28. Parmar JR, Forrest BD, Freeman RA. Medical marijuana patient counseling points for health care professionals based on trends in the medical uses, efficacy, and adverse effects of cannabis-based pharmaceutical drugs. Research in Social and Administrative Pharmacy. 2016;12(4):638-54.

29. Rabgay K, Waranuch N, Chaiyakunapruk N, Sawangjit R, Ingkaninan K, Dilokthornsakul P. The effects of cannabis, cannabinoids, and their administration routes on pain control efficacy and safety: A systematic review and network meta-analysis. Journal of the American Pharmacists Association. 2019.

30. Shin S, Mitchell C, Mannion K, Smolyn J, Meghani SH. An Integrated Review of Cannabis and Cannabinoids in Adult Oncologic Pain Management. Pain Management Nursing. 2018.

31. Smith LA, Azariah F, Lavender VT, Stoner NS, Bettiol S. Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy. Cochrane Database of Systematic Reviews. 2015(11).

32. Stockings E, Campbell G, Hall WD, Nielsen S, Zagic D, Rahman R, et al. Cannabis and cannabinoids for the treatment of people with chronic noncancer pain conditions: a systematic review and meta-analysis of controlled and observational studies. Pain. 2018;159(10):1932-54.

33. Tafelski S, Häuser W, Schäfer M. Efficacy, tolerability, and safety of cannabinoids for chemotherapy-induced nausea and vomiting—a systematic review of systematic reviews. Der Schmerz. 2016;30(1):14-24.

34. Walitt B, Klose P, Fitzcharles MA, Phillips T, Häuser W. Cannabinoids for fibromyalgia. Cochrane Database of Systematic Reviews. 2016(7).

35. Werneck MA, Kortas GT, de Andrade AG, Castaldelli-Maia JM. A Systematic Review of the Efficacy of Cannabinoid Agonist Replacement Therapy for Cannabis Withdrawal Symptoms. CNS drugs. 2018;32(12):1113-29.

36. Whiting PF, Wolff RF, Deshpande S, Di Nisio M, Duffy S, Hernandez AV, et al. Cannabinoids for medical use: a systematic review and meta-analysis. Jama. 2015;313(24):2456-73.

37. Wong SS, Wilens TE. Medical cannabinoids in children and adolescents: a systematic review. Pediatrics. 2017;140(5):e20171818.

38. Zaheer S, Kumar D, Khan MT, Giyanwani PR, Kiran F. Epilepsy and Cannabis: A Literature Review. Cureus. 2018;10(9).

39. Herzog S, Shanahan M, Grimison P, Tran A, Wong N, Lintzeris N, et al. Systematic review of the costs and benefits of prescribed cannabis-based medicines for the management of chronic illness: lessons from multiple sclerosis. Pharmacoeconomics. 2018;36(1):67-78.

40. Elliott J, van Katwyk S, McCoy B, Clifford T, Potter BK, Skidmore B, et al. Decision Models for Assessing the Cost Effectiveness of Treatments for Pediatric Drug-Resistant Epilepsy: A Systematic Review of Economic Evaluations. PharmacoEconomics. 2019:1-16.

41. Gras A, Broughton J. A cost-effectiveness model for the use of a cannabis-derived oromucosal spray for the treatment of spasticity in multiple sclerosis. Expert review of pharmacoeconomics & outcomes research. 2016;16(6):771-9.

42. Slof J, Gras A. Sativex® in multiple sclerosis spasticity: a cost–effectiveness model. Expert review of pharmacoeconomics & outcomes research. 2012;12(4):439-41.

43. Slof J, Ruiz L, Vila C. Cost-effectiveness of Sativex in multiple sclerosis spasticity: new data and application to Italy. Expert review of pharmacoeconomics & outcomes research. 2015;15(3):379-91.

44. Lu L, Pearce H, Roome C, Shearer J, Lang IA, Stein K. Cost effectiveness of oromucosal cannabis-based medicine (Sativex®) for spasticity in multiple sclerosis. Pharmacoeconomics. 2012;30(12):1157-71.

45. Ball S, Vickery J, Hobart J, Wright D, Green C, Shearer J, et al. The Cannabinoid Use in Progressive Inflammatory Brain Disease (CUPID) trial: a randomised double-blind placebo-controlled parallel-group multicentre trial and economic evaluation of cannabinoids to slow progression in multiple sclerosis. Health technology assessment (Winchester, England). 2015;19(12):vii.

46. Iskedjian M, Desjardins O, Piwko C, Bereza B, Jaszewski B, Einarson TR. Willingness to pay for a treatment for pain in multiple sclerosis. Pharmacoeconomics. 2009;27(2):149-58.

47. Tyree GA, Sarkar R, Bellows BK, Ellis RJ, Atkinson JH, Marcotte TD, et al. A Cost-Effectiveness Model for Adjunctive Smoked Cannabis in the Treatment of Chronic Neuropathic Pain. Cannabis and cannabinoid research. 2019;4(1):62-72.

48. Seal K, Severn M. Medical Cannabis in Residential Transition or Addiction Programs: A Review of Clinical and Cost-Effectiveness and Guidelines. 2017.

49. Häuser W, Fitzcharles M-A, Radbruch L, Petzke F. Cannabinoide in der Schmerz-und Palliativmedizin. 2017.

50. Häuser W, Welsch P, Klose P, Radbruch L, Fitzcharles M-A. Efficacy, tolerability and safety of cannabis-based medicines for cancer pain: A systematic review with meta-analysis of randomised controlled trials. Schmerz (Berlin, Germany). 2019.

51. Barnes. Michael P, Barnes. Jennifer C. Cannabis: The Evidence for Medical Use. 2016. Available from: https://www.drugsandalcohol.ie/26086/1/Cannabis_medical_use_evidence.pdf

52. CADTH. Medical Cannabis for the Treatment of Chronic Pain: A Review of Clinical Effectiveness and Guidelines. 2019. Available from: https://www.cadth.ca/sites/default/files/pdf/htis/2019/RC1153%20Cannabis%20Chronic%20Pain%20Final.pdf

53. Amato L, Davoli M, Minozzi S, Mitrova Z, Parmelli E, Saulle R, et al. Systematic reviews on therapeutic efficacy and safety of Cannabis (including extracts and tinctures) for patients with multiple sclerosis, chronic neuropathic pain, dementia and Tourette syndrome, HIV/AIDS, and cancer receiving chemotherapy. World Health Organization. 2016.

54. EMCDDA. Medical use of cannabis and cannabinoids: Questions and answers for policymaking. . 2018. Available from: http://www.emcdda.europa.eu/system/files/publications/10171/20185584_TD0618186ENN_PDF.pdf

55. HPRA. Cannabis for Medical Use - A Scientific Review. 2017. Available from: https://www.hpra.ie/docs/default-source/publications-forms/newsletters/cannabis-for-medical-use---a-scientific-review.pdf?sfvrsn=7

56. MCCS, APPG. Guidance on the use of cannabis-based products for medicinal use. 2019. Available from: https://www.ukmccs.org/wp-content/uploads/2019/10/MCCS_BROCHURE_ONLINE_AW.pdf

57. National Academies of Sciences E, Medicine. The health effects of cannabis and cannabinoids: The current state of evidence and recommendations for research: National Academies Press; 2017. Available from: https://www.nap.edu/resource/24625/Cannabis_committee_conclusions.pdf

58. NICE. NICE guideline [NG144]. Available from: https://www.nice.org.uk/guidance/ng144/chapter/Recommendations

59. NICE. NICE guideline [NG144]. Evidence review B: chronic pain. 2019. Available from: https://www.nice.org.uk/guidance/ng144/evidence/b-chronic-pain-pdf-6963831759

60. TGA. Guidance for the use of medicinal cannabis in the treatment of chronic non-cancer pain in Australia. 2017. Available from: https://www.tga.gov.au/sites/default/files/guidance-use-medicinal-cannabis-treatment-chronic-non-cancer-pain-australia.pdf

61. Zorginstituut Nederland. Verkenning naar mogelijke herbeoordeling medicinale cannabis. 2017. Available from: https://www.zorginstituutnederland.nl/binaries/zinl/documenten/adviezen/2017/11/06/herbeoordeling-medicinale-cannabis-geen-verzekerde-zorg/Verkenning+naar+mogelijke+herbeoordeling+medicinale+cannabis.pdf

62. An Roinn Slánte. Clinical Guidance on Cannabis for Medical Use. 2019. Available from: https://www.gov.ie/ga/foilsiuchan/f5daf1-medical-cannabis-clinical-guidelines/

63. CADTH. Delta-9-tetrahydrocannabinol/Cannabidiol for Spasticity in Multiple Sclerosis: Clinical Effectiveness and Guidelines. 2016. Available from: https://www.cadth.ca/sites/default/files/pdf/htis/may-2016/RB0983%20Sativex%20for%20MS%20Final.pdf

64. Department of epidemiology Lazio region. Systematic reviews on therapeutic efficacy and safety of cannabis (including extracts and tinctures) for patients with multiple sclerosis, chronic neuropathic pain, dementia and tourette syndrome, hiv. 2016.

65. G-BA. zum Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII – Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Extrakt aus Cannabis sativa L., folium cum flore (Wirkstoffkombination aus Delta-9-Tetrahydrocannabinol und Cannabidiol)(Neubewertung nach Fristablauf). 2018. Available from: https://www.g-ba.de/downloads/40-268-5386/2018-11-01_AM-RL-XII_Extrakt-Cannabis-sativa_D-358_TrG.pdf

66. IQWiG. [A18-27] Extrakt aus Cannabis sativa (Spastik aufgrund von multipler Sklerose) - Nutzenbewertung gemäß § 35a SGB V (Ablauf Befristung). 2018.

67. NICE. NICE guideline [NG144]. Evidence review C: spasticity. 2019. Available from: https://www.nice.org.uk/guidance/ng144/evidence/c-spasticity-pdf-6963831760

68. TGA. Guidance for the use of medicinal cannabis in the treatment of multiple sclerosis in Australia. 2017. Available from: https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&cad=rja&uact=8&ved=2ahUKEwjq4baK46_mAhUD1xoKHS9DBp8QFjAAegQIARAC&url=https%3A%2F%2Fwww.tga.gov.au%2Fsites%2Fdefault%2Ffiles%2Fguidance-use-medicinal-cannabis-treatment-multiple-sclerosis-australia.pdf&usg=AOvVaw0Z6oeTvuc-0RqiZVJdoedd

69. Zorginstituut Nederland. Delta-9-tetrahydrocannabinol/cannabidiol (Sativex) bij matige tot ernstige spasticiteit bij multiple sclerose (MS) - GVS-advies. 2014. Available from: https://www.zorginstituutnederland.nl/binaries/zinl/documenten/adviezen/2014/03/05/delta-9-tetrahydrocannabinol-cannabino-sativex-bij-matige-tot-ernstige-spasticiteit-bij-multiple-sclerose/Delta-9-tetrahydrocannabinol-cannabino+%28Sativex%29+bij+matige+tot+ernstige+spasticiteit+bij+multiple+sclerose.pdf

70. CADTH. Nabilone for the Treatment of Nausea and Vomiting, or Anorexia: Clinical Effectiveness and Guidelines – An Update. 2019. Available from: https://www.cadth.ca/sites/default/files/pdf/htis/2018/RA0973%20Nabilone%20for%20Nausea%2C%20Vomiting%2C%20and%20Anorexia%20Final.pdf

71. NICE. Evidence review A: intractable nausea and vomiting. 2019. Available from: https://www.nice.org.uk/guidance/ng144/evidence/a-intractable-nausea-and-vomiting-pdf-6963831758

72. TGA. Guidance for the use of medicinal cannabis for the prevention or management of nausea and vomiting in Australia. 2017. Available from: https://www.tga.gov.au/sites/default/files/guidance-use-medicinal-cannabis-prevention-or-management-nausea-and-vomiting-australia.pdf

73. Treede R-D, Rief W, Barke A, Aziz Q, Bennett MI, Benoliel R, et al. Chronic pain as a symptom or a disease: the IASP Classification of Chronic Pain for the: International Classification of Diseases:(: ICD-11:). Pain. 2019;160(1):19-27.

74. Mücke M, Phillips T, Radbruch L, Petzke F, Haeuser W. Cannabis-based medicines for chronic neuropathic pain in adults. Cochrane Database of Systematic Reviews. 2018(3).

75. Nurmikko TJ, Serpell MG, Hoggart B, Toomey PJ, Morlion BJ, Haines D. Sativex successfully treats neuropathic pain characterised by allodynia: a randomised, double-blind, placebo-controlled clinical trial. Pain®. 2007;133(1-3):210-20.

76. Nielsen S, Sabioni P, Trigo JM, Ware MA, Betz-Stablein BD, Murnion B, et al. Opioid-sparing effect of cannabinoids: a systematic review and meta-analysis. Neuropsychopharmacology. 2017;42(9):1752.

77. Malhotra S, Pandyan A, Day C, Jones P, Hermens H. Spasticity, an impairment that is poorly defined and poorly measured. Clinical rehabilitation. 2009;23(7):651-8.

78. Etoom M, Khraiwesh Y, Lena F, Hawamdeh M, Hawamdeh Z, Centonze D, et al. Effectiveness of Physiotherapy Interventions on Spasticity in People With Multiple Sclerosis: A Systematic Review and Meta-Analysis. American journal of physical medicine & rehabilitation. 2018;97(11):793-807.

79. Lakhan SE, Rowland M. Whole plant cannabis extracts in the treatment of spasticity in multiple sclerosis: a systematic review. BMC neurology. 2009;9(1):59.

80. Zajicek J, Fox P, Sanders H, Wright D, Vickery J, Nunn A, et al. Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomised placebo-controlled trial. The lancet. 2003;362(9395):1517-26.

81. Pooyania S, Ethans K, Szturm T, Casey A, Perry D. A randomized, double-blinded, crossover pilot study assessing the effect of nabilone on spasticity in persons with spinal cord injury. Archives of physical medicine and rehabilitation. 2010;91(5):703-7.

82. Collin C, Ehler E, Waberzinek G, Alsindi Z, Davies P, Powell K, et al. A double-blind, randomized, placebo-controlled, parallel-group study of Sativex, in subjects with symptoms of spasticity due to multiple sclerosis. Neurological research. 2010;32(5):451-9.

83. Novotna A, Mares J, Ratcliffe S, Novakova I, Vachova M, Zapletalova O, et al. A randomized, double-blind, placebo-controlled, parallel-group, enriched-design study of nabiximols*(Sativex®), as add-on therapy, in subjects with refractory spasticity caused by multiple sclerosis. European Journal of Neurology. 2011;18(9):1122-31.

84. van Amerongen G, Kanhai K, Baakman AC, Heuberger J, Klaassen E, Beumer TL, et al. Effects on spasticity and neuropathic pain of an oral formulation of Δ9-tetrahydrocannabinol in patients with progressive multiple sclerosis. Clinical therapeutics. 2018;40(9):1467-82.

85. Stratton RJ, Green CJ, Elia M. Disease-related malnutrition: an evidence-based approach to treatment: Cabi; 2003.

86. De Stefani FdC, Pietraroia PS, Fernandes-Silva MM, Faria-Neto J, Baena CP. Observational Evidence for Unintentional Weight Loss in All-Cause Mortality and Major Cardiovascular Events: A Systematic Review and Meta-Analysis. Scientific reports. 2018;8(1):15447.

87. Rondel A, Langius J, de van der Schueren M, Kruizenga H. The new ESPEN diagnostic criteria for malnutrition predict overall survival in hospitalised patients. Clinical Nutrition. 2018;37(1):163-8.

88. de van der Schueren MA, de Smoker M, Leistra E, Kruizenga H. The association of weight loss with one-year mortality in hospital patients, stratified by BMI and FFMI subgroups. Clinical Nutrition. 2018;37(5):1518-25.

89. Segura A, Pardo J, Jara C, Zugazabeitia L, Carulla J, de las Peñas R, et al. An epidemiological evaluation of the prevalence of malnutrition in Spanish patients with locally advanced or metastatic cancer. Clinical Nutrition. 2005;24(5):801-14.

90. Ross P, Ashley S, Norton A, Priest K, Waters J, Eisen T, et al. Do patients with weight loss have a worse outcome when undergoing chemotherapy for lung cancers? British journal of cancer. 2004;90(10):1905-11.

91. Coodley GO, Loveless MO, Merrill TM. The HIV wasting syndrome: a review. Journal of acquired immune deficiency syndromes. 1994;7(7):681-94.

92. Gelato M, McNurlan M, Freedland E. Role of recombinant human growth hormone in HIV-associated wasting and cachexia: pathophysiology and rationale for treatment. Clinical Therapeutics. 2007;29(11):2269-88.

93. Henriquez JE, Rizzo MD, Schultz MA, Crawford RB, Gulick P, Kaminski NE. Δ9-Tetrahydrocannabinold (THC) suppresses secretion of IFNα by plasmacytoid dendritic cells (pDC) from healthy and HIV-infected individuals. Journal of acquired immune deficiency syndromes (1999). 2017;75(5):588.

94. Wanke C, Silva M, Knox T, Forrester J, Speigelman D, Gorbach S. Weight loss and wasting remain common complications in individuals infected with human immunodeficiency virus in the era of highly active antiretroviral therapy. Clinical Infectious Diseases. 2000;31(3):803-5.

95. Schwartzberg LS. Chemotherapy-induced nausea and vomiting: clinician and patient perspectives. The journal of supportive oncology. 2007;5(2 Suppl 1):5-12.

96. Hanuš LO, Meyer SM, Muñoz E, Taglialatela-Scafati O, Appendino G. Phytocannabinoids: a unified critical inventory. Natural product reports. 2016;33(12):1357-92.

97. Lu H-C, Mackie K. An introduction to the endogenous cannabinoid system. Biological psychiatry. 2016;79(7):516-25.

98. Howlett AC, Abood ME. CB1 and CB2 receptor pharmacology. Advances in Pharmacology. 80: Elsevier; 2017. p. 169-206.

99. Grotenhermen F, Müller-Vahl K. The therapeutic potential of cannabis and cannabinoids. . Deutsches Arzteblatt international. 2012;109:495–501.

100. Freeman TP, Hindocha C, Green SF, Bloomfield MA. Medicinal use of cannabis based products and cannabinoids. Bmj. 2019;365:l1141.

101. Mavrot C, Hadorn S, Sprecher F, Sager F. Evaluation spezifischer Vollzugsaufgaben des BAG im Rahmen des Betäubungsmittelgesetzes (BetmG). 2019.

102. Osakwe O. Pharmaceutical Regulation: The Role of Government in the Business of Drug Discovery. Social Aspects of Drug Discovery, Development and Commercialization. 2016:1.

103. Rägo L, Santoso B. Drug regulation: history, present and future. Drug benefits and risks: International textbook of clinical pharmacology. 2008;2:65-77.

104. Moser-Kamm P. Präparate, Galenik, Hersteller, Dosierung und Kosten. 2019.

105. Bundesgesetz über die Betäubungsmittel und die psychotropen Stoffe (Betäu-bungsmittelgesetz, BetmG)1 vom 3. Oktober 1951.

106. Verordnung des EDI über die Verzeichnisse der Betäubungsmittel, psychotro-pen Stoffe, Vorläuferstoffe und Hilfschemikalien (Betäubungsmittelverzeichnisverordnung, BetmVV-EDI) vom 30. Mai 2011.

107. Bundesamt für Gesundheit. Cannabis für Schwerkranke: Bericht des Bundesrates in Erfüllung der Motion 14.4164. 2018.

108. Gesundheit Bf. Medizinische Anwendung von Cannabis. In: Krankheiten APn, editor.: BAG; 2019.

109. Jorio L. Cannabis für medizinische Zwecke 2019.

110. Bundesinstitut fur Arzneimittel und Medizinprodukte. Hinweise für Apotheker.

111. Krankenversicherung - Versorgung mit Cannabis - kein Anspruch, wenn Alternativtherapie zur Verfügung, (2019).

112. Deutscher Bundestag. Drucksache 19/13890. 2019.

113. Danish Medicines Agency. Medicinal cannabis pilot programme 2019 [Available from: https://laegemiddelstyrelsen.dk/en/special/medicinal-cannabis/citizens/medicinal-cannabis-pilot-programme/#.

114. l'Agence nationale de sécurité du médicament et des produits de santé. DECISION DG n° 2019 - 381. 2019. Available from: https://ansm.sante.fr/Decisions/Comites-permanents-Autres-comites-Creation-et-nomination-des-autres-comites/Decision-DG-n-2019-381-du-15-10-2019-Nomination-CST-Mise-en-oeuvre-de-l-experimentation-du-cannabis-medical-en-France

115. CHAMBRE DES REPRÉSENTANTS DE BELGIQUE. PROPOSITION DE RÉSOLUTION en faveur de l'usage thérapeutique de cannabinoïdes sous des conditions strictes en vue d'atténuer la douleur en cas de symptômes spasmodiques spécifi ques. 2019. Available from: https://www.dekamer.be/flwb/pdf/55/0309/55K0309001.pdf

116. Office of Medical Cannabis. The Office of Medical Cannabis: CIBG; 2020 [Available from: https://english.cannabisbureau.nl/.

117. Office of Medical Cannabis. Grounds for use: CIBG; 2020 [Available from: https://english.cannabisbureau.nl/medicinal-cannabis/grounds-for-use.

118. EUnetHTA. HTA Core Model. [Available from: https://eunethta.eu/hta-core-model/.

119. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Systematic reviews. 2015;4(1):1.

120. Higgins JP, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1. 0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org. 2011.

121. Moore R, Derry S, Wiffen P. Challenges in design and interpretation of chronic pain trials. British journal of anaesthesia. 2013;111(1):38-45.

122. Schünemann H, Brożek J, Guyatt G, Oxman A. GRADE handbook for grading quality of evidence and strength of recommendations. Updated October 2013. The GRADE Working Group, 2013. 2017.

123. Watts RD, Li IW. Use of Checklists in Reviews of Health Economic Evaluations, 2010 to 2018. Value in Health. 2019;22(3):377-82.

124. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al. Consolidated health economic evaluation reporting standards (CHEERS) statement. International journal of technology assessment in health care. 2013;29(2):117-22.

125. de Vries M, van Rijckevorsel DC, Vissers KC, Wilder-Smith OH, van Goor H, Pain, et al. Tetrahydrocannabinol does not reduce pain in patients with chronic abdominal pain in a phase 2 placebo-controlled study. Clinical gastroenterology and hepatology. 2017;15(7):1079-86. e4.

126. Serpell M, Ratcliffe S, Hovorka J, Schofield M, Taylor L, Lauder H, et al. A double-blind, randomized, placebo-controlled, parallel group study of THC/CBD spray in peripheral neuropathic pain treatment. European journal of pain. 2014;18(7):999-1012.

127. Berman JS, Symonds C, Birch R. Efficacy of two cannabis based medicinal extracts for relief of central neuropathic pain from brachial plexus avulsion: results of a randomised controlled trial. Pain. 2004;112(3):299-306.

128. Fallon MT, Albert Lux E, McQuade R, Rossetti S, Sanchez R, Sun W, et al. Sativex oromucosal spray as adjunctive therapy in advanced cancer patients with chronic pain unalleviated by optimized opioid therapy: two double-blind, randomized, placebo-controlled phase 3 studies. British journal of pain. 2017;11(3):119-33.

129. Lichtman AH, Lux EA, McQuade R, Rossetti S, Sanchez R, Sun W, et al. Results of a double-blind, randomized, placebo-controlled study of nabiximols oromucosal spray as an adjunctive therapy in advanced cancer patients with chronic uncontrolled pain. Journal of pain and symptom management. 2018;55(2):179-88. e1.

130. Lynch ME, Cesar-Rittenberg P, Hohmann AG. A double-blind, placebo-controlled, crossover pilot trial with extension using an oral mucosal cannabinoid extract for treatment of chemotherapy-induced neuropathic pain. Journal of pain and symptom management. 2014;47(1):166-73.

131. Toth C, Mawani S, Brady S, Chan C, Liu C, Mehina E, et al. An enriched-enrolment, randomized withdrawal, flexible-dose, double-blind, placebo-controlled, parallel assignment efficacy study of nabilone as adjuvant in the treatment of diabetic peripheral neuropathic pain. PAIN®. 2012;153(10):2073-82.

132. Langford R, Mares J, Novotna A, Vachova M, Novakova I, Notcutt W, et al. A double-blind, randomized, placebo-controlled, parallel-group study of THC/CBD oromucosal spray in combination with the existing treatment regimen, in the relief of central neuropathic pain in patients with multiple sclerosis. Journal of neurology. 2013;260(4):984-97.

133. Rog DJ, Nurmikko TJ, Friede T, Young CA. Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. Neurology. 2005;65(6):812-9.

134. Schimrigk S, Marziniak M, Neubauer C, Kugler EM, Werner G, Abramov-Sommariva D. Dronabinol is a safe long-term treatment option for neuropathic pain patients. European neurology. 2017;78(5-6):320-9.

135. Wade DT, Makela P, Robson P, House H, Bateman C. Do cannabis-based medicinal extracts have general or specific effects on symptoms in multiple sclerosis? A double-blind, randomized, placebo-controlled study on 160 patients. Multiple Sclerosis Journal. 2004;10(4):434-41.

136. Svendsen KB, Jensen TS, Bach FW. Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? Randomised double blind placebo controlled crossover trial. Bmj. 2004;329(7460):253.

137. Frank B, Serpell M, Hughes J, Matthews J, Kapur D. Comparison of analgesic effects and patient tolerability of nabilone and dihydrocodeine for chronic neuropathic pain: randomised, crossover, double blind study. Bmj. 2008;336(7637):199-201.

138. Wade DT, Robson P, House H, Makela P, Aram J. A preliminary controlled study to determine whether whole-plant cannabis extracts can improve intractable neurogenic symptoms. Clinical rehabilitation. 2003;17(1):21-9.

139. Blake DR, Robson P, Ho M, Jubb RW, McCabe CS. Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis. Rheumatology. 2006;45(1):50-2.

140. Rintala DH, Fiess RN, Tan G, Holmes SA, Bruel BM. Effect of dronabinol on central neuropathic pain after spinal cord injury: a pilot study. American journal of physical medicine & rehabilitation. 2010;89(10):840-8.

141. Wissel J, Haydn T, Müller J, Brenneis C, Berger T, Poewe W, et al. Low dose treatment with the synthetic cannabinoid Nabilone significantly reduces spasticity-related pain. Journal of neurology. 2006;253(10):1337-41.

142. Pinsger M, Schimetta W, Volc D, Hiermann E, Riederer F, Pölz W. Benefits of an add-on treatment with the synthetic cannabinomimetic nabilone on patients with chronic pain--a randomized controlled trial. Wiener Klinische Wochenschrift. 2006;118(11-12):327-35.

143. Collin C, Davies P, Mutiboko I, Ratcliffe S, Group SSiMS. Randomized controlled trial of cannabis-based medicine in spasticity caused by multiple sclerosis. European journal of neurology. 2007;14(3):290-6.

144. Vaney C, Heinzel-Gutenbrunner M, Jobin P, Tschopp F, Gattlen B, Hagen U, et al. Efficacy, safety and tolerability of an orally administered cannabis extract in the treatment of spasticity in patients with multiple sclerosis: a randomized, double-blind, placebo-controlled, crossover study. Multiple Sclerosis Journal. 2004;10(4):417-24.

145. Riva N, Mora G, Sorarù G, Lunetta C, Ferraro OE, Falzone Y, et al. Safety and efficacy of nabiximols on spasticity symptoms in patients with motor neuron disease (CANALS): a multicentre, double-blind, randomised, placebo-controlled, phase 2 trial. The Lancet Neurology. 2019;18(2):155-64.

146. Markovà J, Essner U, Akmaz B, Marinelli M, Trompke C, Lentschat A, et al. Sativex® as add-on therapy vs. further optimized first-line ANTispastics (SAVANT) in resistant multiple sclerosis spasticity: a double-blind, placebo-controlled randomised clinical trial. International Journal of Neuroscience. 2019;129(2):119-28.

147. Corey-Bloom J, Wolfson T, Gamst A, Jin S, Marcotte TD, Bentley H, et al. Smoked cannabis for spasticity in multiple sclerosis: a randomized, placebo-controlled trial. Cmaj. 2012;184(10):1143-50.

148. Leocani L, Nuara A, Houdayer E, Schiavetti I, Del Carro U, Amadio S, et al. Sativex® and clinical–neurophysiological measures of spasticity in progressive multiple sclerosis. Journal of neurology. 2015;262(11):2520-7.

149. Zajicek JP, Sanders H, Wright D, Vickery P, Ingram W, Reilly S, et al. Cannabinoids in multiple sclerosis (CAMS) study: safety and efficacy data for 12 months follow up. Journal of Neurology, Neurosurgery & Psychiatry. 2005;76(12):1664-9.

150. Beal JE, Olson R, Laubenstein L, Morales JO, Bellman P, Yangco B, et al. Dronabinol as a treatment for anorexia associated with weight loss in patients with AIDS. Journal of pain and symptom management. 1995;10(2):89-97.

151. Struwe M, Kaempfer SH, Geiger CJ, Pavia AT, Plasse TF, Shepard KV, et al. Effect of dronabinol on nutritional status in HIV infection. SAGE Publications Sage CA: Los Angeles, CA; 1993.

152. Jatoi A, Windschitl HE, Loprinzi CL, Sloan JA, Dakhil SR, Mailliard JA, et al. Dronabinol versus megestrol acetate versus combination therapy for cancer-associated anorexia: a North Central Cancer Treatment Group study. Journal of clinical oncology. 2002;20(2):567-73.

153. Turcott JG, Núñez MdRG, Flores-Estrada D, Oñate-Ocaña LF, Zatarain-Barrón ZL, Barrón F, et al. The effect of nabilone on appetite, nutritional status, and quality of life in lung cancer patients: a randomized, double-blind clinical trial. Supportive Care in Cancer. 2018;26(9):3029-38.

154. Strasser F, Luftner D, Possinger K, Ernst G, Ruhstaller T, Meissner W, et al. Comparison of orally administered cannabis extract and delta-9-tetrahydrocannabinol in treating patients with cancer-related anorexia-cachexia syndrome: a multicenter, phase III, randomized, double-blind, placebo-controlled clinical trial from the Cannabis-In-Cachexia-Study-Group. Journal of Clinical Oncology. 2006;24(21):3394-400.

155. Chan HS, Correia JA, MacLeod SM. Nabilone versus prochlorperazine for control of cancer chemotherapy-induced emesis in children: a double-blind, crossover trial. Pediatrics. 1987;79(6):946-52.

156. Dalzell A, Bartlett H, Lilleyman J. Nabilone: an alternative antiemetic for cancer chemotherapy. Archives of disease in childhood. 1986;61(5):502-5.

157. Einhorn L, Nagy C, Furnas B, Williams S. Nabilone: an effective antiemetic in patients receiving cancer chemotherapy. The Journal of Clinical Pharmacology. 1981;21(S1):64S-9S.

158. Sallan SE, Cronin C, Zelen M, Zinberg NE. Antiemetics in patients receiving chemotherapy for cancer: a randomized comparison of delta-9-tetrahydrocannabinol and prochlorperazine. New England Journal of Medicine. 1980;302(3):135-8.

159. Heim ME, Queißer W, Altenburg H-P. Randomized crossover study of the antiemetic activity of levonantradol and metoclopramide in cancer patients receiving chemotherapy. Cancer chemotherapy and pharmacology. 1984;13(2):123-5.

160. Hutcheon AW, Palmer JB, Soukop M, Cunningham D, McArdle C, Welsh J, et al. 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 and Clinical Oncology. 1983;19(8):1087-90.

161. Johansson R, Kilkku P, Groenroos M. A double-blind, controlled trial of nabilone vs. prochlorperazine for refractory emesis induced by cancer chemotherapy. Cancer Treatment Reviews. 1982;9:25-33.

162. Jones SE, Durant JR, Greco FA, Robertone A. A multi-institutional Phase III study of nabilone vs. placebo in chemotherapy-induced nausea and vomiting. Cancer Treatment Reviews. 1982;9:45-8.

163. Kleinman S, Weitzman S, Cassem N, Andrews E. Double blind trial of delta-9-tetrahydrocannabinol (THC) versus placebo as an adjunct to prochlorperazine for chemotherapy-induced vomiting. Current Therapeutic Research-Clinical and Experimental. 1983;33(6 I):1014-7.

164. Lane M, Vogel CL, Ferguson J, Krasnow S, Saiers JL, Hamm J, et al. Dronabinol and prochlorperazine in combination for treatment of cancer chemotherapy-induced nausea and vomiting. Journal of pain and symptom management. 1991;6(6):352-9.

165. Levitt M. Nabilone vs. placebo in the treatment of chemotherapy-induced nausea and vomiting in cancer patients. Cancer Treatment Reviews. 1982;9:49-53.

166. Meiri E, Jhangiani H, Vredenburgh JJ, Barbato LM, Carter FJ, Yang H-M, et al. Efficacy of dronabinol alone and in combination with ondansetron versus ondansetron alone for delayed chemotherapy-induced nausea and vomiting. Current medical research and opinion. 2007;23(3):533-43.

167. Orr L, McKernan J. Antiemetic effect of Δ9-tetrahydrocannabinol in chemotherapy-associated nausea and emesis as compared to placebo and compazine. The Journal of Clinical Pharmacology. 1981;21(S1):76S-80S.

168. Steele N, Gralla RJ, Braun JD, Young C. Double-blind comparison of the antiemetic effects of nabilone and prochlorperazine on chemotherapy-induced emesis. Cancer treatment reports. 1980;64(2-3):219-24.

169. Wada JK, Bogdon DL, Gunnell JC, Hum GJ, Gota CH, Rieth TE. Double-blind, randomized, crossover trial of nabilone vs. placebo in cancer chemotherapy. Cancer Treatment Reviews. 1982;9:39-44.

170. SHEIDLER VR, Ettinger DS, Diasio RB, ENTERLINE JP, BROWN MD. Double-blind multiple-dose crossover study of the antiemetic effect of intramuscular levonantradol compared to prochlorperazine. The Journal of Clinical Pharmacology. 1984;24(4):155-9.

171. Ahmedzai S, Carlyle D, Calder I, Moran F. Anti-emetic efficacy and toxicity of nabilone, a synthetic cannabinoid, in lung cancer chemotherapy. British Journal of Cancer. 1983;48(5):657-63.

172. Niiranen A, Mattson K. A cross-over comparison of nabilone and prochlorperazine for emesis induced by cancer chemotherapy. American journal of clinical oncology. 1985;8(4):336-40.

173. Shiling DJ, Stillman RC, Chang AE, Goldberg NH, Seipp CA, Barofsky I, et al. A prospective evaluation of delta-9-tetrahydrocannabinol as an antiemetic in patients receiving adriamycin and cytoxan chemotherapy. Cancer. 1981;47(7):1746-51.

174. George M, Pejovic MH, M. T. Randomized trial of nabilone as antimetic in cancer patients treated with cisplatin. . Biomedicine and Pharmacotherapy 1983;37(1):24-7.

175. Niederle N, Schütte J, Schmidt C. Crossover comparison of the antiemetic efficacy of nabilone and alizapride in patients with nonseminomatous testicular cancer receiving cisplatin therapy. Klinische Wochenschrift. 1986;64(8):362-5.

176. Gilbert CJ, Ohly KV, Rosner G, Peters WP. Randomized, double-blind comparison of a prochlorperazine-based versus a metoclopramide-based antiemetic regimen in patients undergoing autologous bone marrow transplantation. Cancer. 1995;76(11):2330-7.

177. Flachenecker P. A new multiple sclerosis spasticity treatment option: effect in everyday clinical practice and cost–effectiveness in Germany. Expert review of neurotherapeutics. 2013;13(sup1):15-9.

178. Bellows BK, Nelson RE, Oderda GM, LaFleur J. Long-term cost-effectiveness of initiating treatment for painful diabetic neuropathy with pregabalin, duloxetine, gabapentin, or desipramine. Pain. 2016;157(1):203-13.

179. Bundesgesetz über die Landwirtschaft (Landwirtschaftsgesetz, LwG) vom 29. April 1998.

180. Bundesgesetz über Arzneimittel und Medizinprodukte (Heilmittelgesetz, HMG) vom 15. De-zember 2000.

181. Der Schweizerische Bundesrat. Verordnung über die Krankenversicherung (KVV). 832102. Switzerland1995.

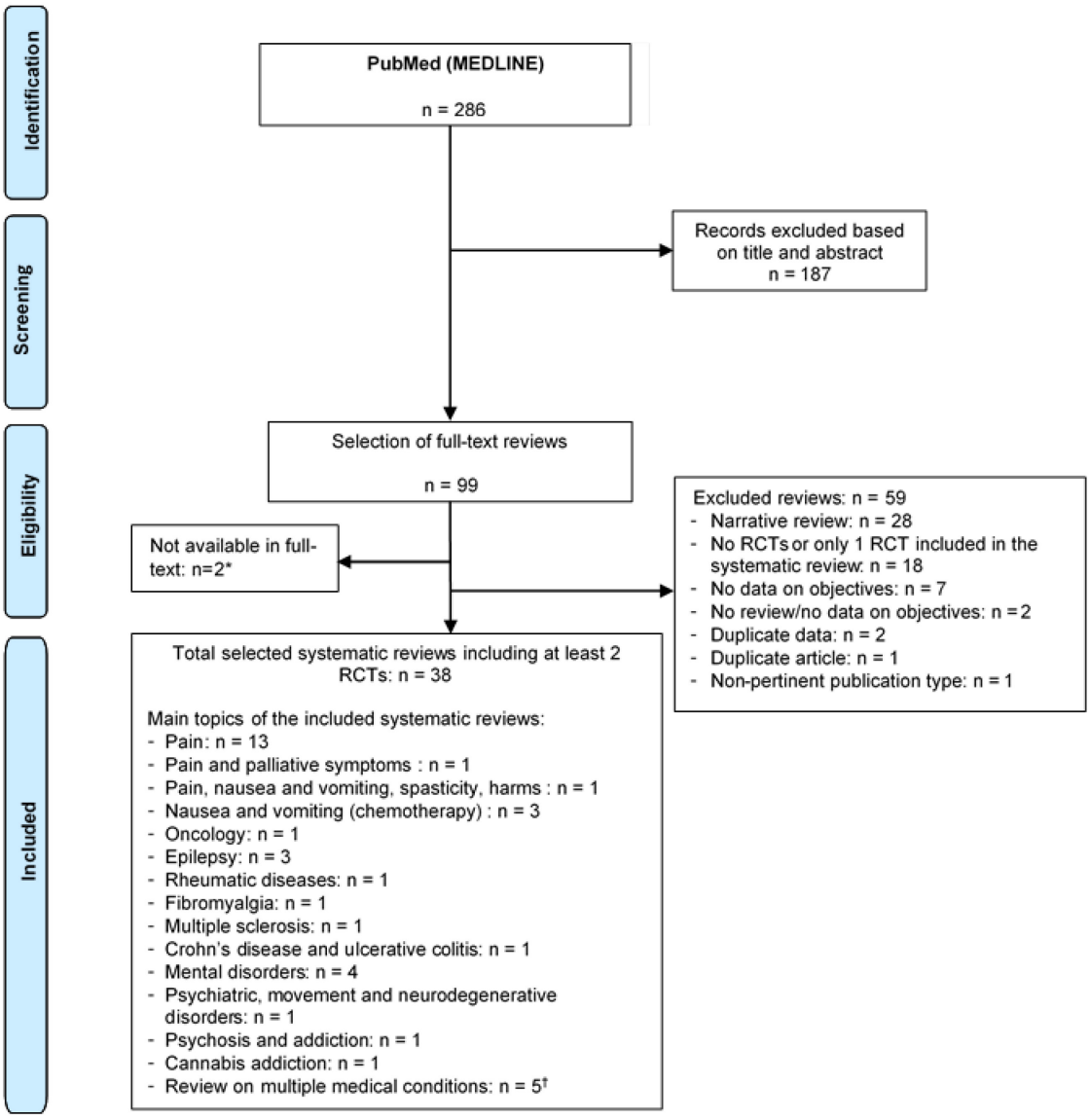
182. Schünemann H, Brożek J, Guyatt G, Oxman A. GRADE handbook for grading quality of evidence and strength of recommendations. Updated October 2013. The GRADE Working Group; 2013.

Appendix 1. Methods preliminary literature search

Table I. Search strategy PubMed (MEDLINE) preliminary clinical effectiveness literature search

Intervention: cannabis	("Medical Marijuana"[Mesh] OR medical marijuana[tiab] OR medicinal marijuana[tiab] OR marijuana treatment*[tiab] OR marijuana therapy[tiab] OR therapeutic marijuana[tiab] OR marijuana dispensar*[tiab] OR medical marihuana[tiab] OR medicinal marihuana[tiab] OR marihuana treatment*[tiab] OR marihuana therap*[tiab] OR therapeutic marihuana[tiab] OR marihuana dispensar*[tiab] OR medical cannabis[tiab] OR medicinal cannabis[tiab] OR cannabis treatment*[tiab] OR cannabis therap*[tiab] OR therapeutic cannabis[tiab] OR cannabis dispensar*[tiab] OR cannabis-based medicine*[tiab] OR cannabis-based medication[tiab] OR cannabis-based drug*[tiab])
Limits	*Study design SRs:* ((((systematic*[tiab] OR comprehensive*[tiab]) AND (bibliographic*[tiab] OR literature[tiab] OR review*[tiab])) OR literature review*[tiab] OR meta-analysis[pt] OR meta-analys*[tiab] OR meta-analys*[tiab] OR meta-analyt*[tiab] OR metaanalys*[tiab] OR metaanalys*[tiab] OR metaanalyt*[tiab]))
	Publication period: 2014 – 13 November 2019
	Language: English

Figure I. PRISMA flowchart of preliminary literature search of published SRs on clinical effectiveness



* Derakhshan N, Kazemi M. Cannabis for Refractory Psoriasis-High Hopes for a Novel Treatment and a Literature Review. Curr Clin Pharmacol, 2016:11(2);146-7. Rodriguez A, Zavala C. Cannabinoids for the treatment of cannabis abuse disorder. Medwave, 2018:18(6);e7287. † One included study on multiple medical conditions is an evaluation study and not an SR.

Table II. List of excluded reviews during the preliminary clinical effectiveness literature search

Reference	Reason for exclusion
Abrams, D. I. (2018). The therapeutic effects of Cannabis and cannabinoids: An update from the National Academies of Sciences, Engineering and Medicine report. Eur J Intern Med, 49, 7-11.	Narrative review
Agarwal, R., Burke, S. L., & Maddux, M. (2019). Current state of evidence of cannabis utilisation for treatment of autism spectrum disorders. BMC Psychiatry, 19(1), 328.	Narrative review
Artukoglu, B. B., & Bloch, M. H. (2019). The Potential of Cannabinoid-Based Treatments in Tourette Syndrome. CNS Drugs, 33(5), 417-430.	Narrative review
Babayeva, M., Assefa, H., Basu, P., Chumki, S., & Loewy, Z. (2016). Marijuana Compounds: A Nonconventional Approach to Parkinson's Disease Therapy. Parkinsons Dis, 2016, 1279042.	Narrative review
Bao, Y., Kong, X., Yang, L., Liu, R., Shi, Z., Li, W., . . . Hou, W. (2014). Complementary and alternative medicine for cancer pain: an overview of systematic reviews. Evid Based Complement Alternat Med, 2014, 170396.	Narrative review
Baron, E. P. (2015). Comprehensive Review of Medicinal Marijuana, Cannabinoids, and Therapeutic Implications in Medicine and Headache: What a Long Strange Trip It's Been. Headache, 55(6), 885-916.	Narrative review
Baron, E. P. (2018). Medicinal Properties of Cannabinoids, Terpenes, and Flavonoids in Cannabis, and Benefits in Migraine, Headache, and Pain: An Update on Current Evidence and Cannabis Science. Headache, 58(7), 1139-1186.	Narrative review
Beauchet, O. (2018). Medical cannabis use in older patients: Update on medical knowledge. Maturitas, 118, 56-59.	Narrative review
Been, F., Schneider, C., Zobel, F., Delemont, O., & Esseiva, P. (2016). Integrating environmental and self-report data to refine cannabis prevalence estimates in a major urban area of Switzerland. Int J Drug Policy, 36, 33-42.	No review/no data on objectives

Reference	Reason for exclusion
Bonini, S. A., Premoli, M., Tambaro, S., Kumar, A., Maccarinelli, G., Memo, M., & Mastinu, A. (2018). Cannabis sativa: A comprehensive ethnopharmacological review of a medicinal plant with a long history. J Ethnopharmacol, 227, 300-315.	Narrative review
Botsford, S. L., Yang, S., & George, T. P. (2019). Cannabis and Cannabinoids in Mood and Anxiety Disorders: Impact on Illness Onset and Course, and Assessment of Therapeutic Potential. Am J Addict.	No data on objectives
Boychuk, D. G., Goddard, G., Mauro, G., & Orellana, M. F. (2015). The effectiveness of cannabinoids in the management of chronic nonmalignant neuropathic pain: a systematic review. J Oral Facial Pain Headache, 29(1), 7-14.	Narrative review
Campbell, G., Hall, W., & Nielsen, S. (2018). What does the ecological and epidemiological evidence indicate about the potential for cannabinoids to reduce opioid use and harms? A comprehensive review. Int Rev Psychiatry, 30(5), 91-106.	No data on objectives
Castaneto, M. S., Gorelick, D. A., Desrosiers, N. A., Hartman, R. L., Pirard, S., & Huestis, M. A. (2014). Synthetic cannabinoids: epidemiology, pharmacodynamics, and clinical implications. Drug Alcohol Depend, 144, 12-41.	No data on objectives
Dale, T., Downs, J., Olson, H., Bergin, A. M., Smith, S., & Leonard, H. (2019). Cannabis for refractory epilepsy in children: A review focusing on CDKL5 Deficiency Disorder. Epilepsy Res, 151, 31-39.	Narrative review
Fife, T. D., Moawad, H., Moschonas, C., Shepard, K., & Hammond, N. (2015). Clinical perspectives on medical marijuana (cannabis) for neurologic disorders. Neurol Clin Pract, 5(4), 344-351.	Narrative review
Fitzcharles, M. A., Baerwald, C., Ablin, J., & Hauser, W. (2016). Efficacy, tolerability and safety of cannabinoids in chronic pain associated with rheumatic diseases (fibromyalgia syndrome, back pain, osteoarthritis, rheumatoid arthritis): A systematic review of randomized controlled trials. Schmerz, 30(1), 47-61.	Duplicate data

Reference	Reason for exclusion
Gandhi, S., Vasisth, G., & Kapoor, A. (2017). Systematic review of the potential role of cannabinoids as antiproliferative agents for urological cancers. Can Urol Assoc J, 11(3-4), E138-e142.	Narrative review
Hauser, W., Finnerup, N. B., & Moore, R. A. (2018). Systematic reviews with meta-analysis on cannabis-based medicines for chronic pain: a methodological and political minefield. Pain, 159(10), 1906-1907.	No data on objectives
Herzog, S., Shanahan, M., Grimison, P., Tran, A., Wong, N., Lintzeris, N., . . . Morton, R. L. (2018). Systematic Review of the Costs and Benefits of Prescribed Cannabis-Based Medicines for the Management of Chronic Illness: Lessons from Multiple Sclerosis. Pharmacoeconomics, 36(1), 67-78.	No data on objectives
Hill, K. P., Palastro, M. D., Johnson, B., & Ditre, J. W. (2017). Cannabis and Pain: A Clinical Review. Cannabis Cannabinoid Res, 2(1), 96-104.	Narrative review
Hindocha, C., Cousijn, J., Rall, M., & Bloomfield, M. A. P. (2019). The Effectiveness of Cannabinoids in the Treatment of Posttraumatic Stress Disorder (PTSD): A Systematic Review. J Dual Diagn, 1-20.	No RCTs or only 1 RCT included in the systematic review
Houze, B., El-Khatib, H., & Arbour, C. (2017). Efficacy, tolerability, and safety of non-pharmacological therapies for chronic pain: An umbrella review on various CAM approaches. Prog Neuropsychopharmacol Biol Psychiatry, 79(Pt B), 192-205.	Duplicate article
Koppel, B. S. (2015). Cannabis in the Treatment of Dystonia, Dyskinesias, and Tics. Neurotherapeutics, 12(4), 788-792.	Narrative review
Koppel, B. S., Brust, J. C., Fife, T., Bronstein, J., Youssof, S., Gronseth, G., & Gloss, D. (2014). Systematic review: efficacy and safety of medical marijuana in selected neurologic disorders: report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology, 82(17), 1556-1563.	Narrative review
Kosiba, J. D., Maisto, S. A., & Ditre, J. W. (2019). Patient-reported use of medical cannabis for pain, anxiety, and depression symptoms: Systematic review and meta-analysis. Soc Sci Med, 233, 181-192.	No RCTs or only 1 RCT included in the systematic review

Reference	Reason for exclusion
Langhorst, J., Wulfert, H., Lauche, R., Klose, P., Cramer, H., Dobos, G. J., & Korzenik, J. (2015). Systematic review of complementary and alternative medicine treatments in inflammatory bowel diseases. J Crohns Colitis, 9(1), 86-106.	No RCTs or only 1 RCT included in the systematic review
Lowin, T., Schneider, M., & Pongratz, G. (2019). Joints for joints: cannabinoids in the treatment of rheumatoid arthritis. Curr Opin Rheumatol, 31(3), 271-278.	Narrative review
Madden, K., George, A., van der Hoek, N. J., Borim, F. M., Mammen, G., & Bhandari, M. (2019). Cannabis for pain in orthopedics: a systematic review focusing on study methodology. Can J Surg, 62(6), 001018.	No data on objectives
McLoughlin, B. C., Pushpa-Rajah, J. A., Gillies, D., Rathbone, J., Variend, H., Kalakouti, E., & Kyprianou, K. (2014). Cannabis and schizophrenia. Cochrane Database Syst Rev(10), Cd004837.	No RCTs or only 1 RCT included in the systematic review
Merlin, J. S., Bulls, H. W., Vucovich, L. A., Edelman, E. J., & Starrels, J. L. (2016). Pharmacologic and non-pharmacologic treatments for chronic pain in individuals with HIV: a systematic review. AIDS Care, 28(12), 1506-1515.	No RCTs or only 1 RCT included in the systematic review
Neale, M. (2017). Efficacy and safety of cannabis for treating children with refractory epilepsy. Nurs Child Young People, 29(7), 32-37.	No RCTs or only 1 RCT included in the systematic review
O'Neil, M. E., Nugent, S. M., Morasco, B. J., Freeman, M., Low, A., Kondo, K., . . . Kansagara, D. (2017). Benefits and Harms of Plant-Based Cannabis for Posttraumatic Stress Disorder: A Systematic Review. Ann Intern Med, 167(5), 332-340.	No RCTs or only 1 RCT included in the systematic review
Orsolini, L., Chiappini, S., Volpe, U., Berardis, D., Latini, R., Papanti, G. D., & Corkery, A. J. M. (2019). Use of Medicinal Cannabis and Synthetic Cannabinoids in Post-Traumatic Stress Disorder (PTSD): A Systematic Review. Medicina (Kaunas), 55(9).	No RCTs or only 1 RCT included in the systematic review
Pamplona, F. A., da Silva, L. R., & Coan, A. C. (2018). Potential Clinical Benefits of CBD-Rich Cannabis Extracts Over Purified CBD in Treatment-Resistant Epilepsy: Observational Data Meta-analysis. Front Neurol, 9, 759.	No RCTs or only 1 RCT included in the systematic review

Reference	Reason for exclusion
Park, J. Y., & Wu, L. T. (2017). Prevalence, reasons, perceived effects, and correlates of medical marijuana use: A review. Drug Alcohol Depend, 177, 1-13.	No RCTs or only 1 RCT included in the systematic review
Pdq Integrative, A., & Complementary Therapies Editorial, B. (2002). Cannabis and Cannabinoids (PDQ(R)): Health Professional Version. PDQ Cancer Information Summaries.	Non-pertinent publication type
Prud'homme, M., Cata, R., & Jutras-Aswad, D. (2015). Cannabidiol as an Intervention for Addictive Behaviors: A Systematic Review of the Evidence. Subst Abuse, 9, 33-38.	No RCTs or only 1 RCT included in the systematic review
Rice, J., & Cameron, M. (2018). Cannabinoids for Treatment of MS Symptoms: State of the Evidence. Curr Neurol Neurosci Rep, 18(8), 50.	Narrative review
Sarzi-Puttini, P., Ablin, J., Trabelsi, A., Fitzcharles, M. A., Marotto, D., & Hauser, W. (2019). Cannabinoids in the treatment of rheumatic diseases: Pros and cons. Autoimmun Rev, 102409.	Narrative review
Schubart, C. D., Sommer, I. E., Fusar-Poli, P., de Witte, L., Kahn, R. S., & Boks, M. P. (2014). Cannabidiol as a potential treatment for psychosis. Eur Neuropsychopharmacol, 24(1), 51-64.	Narrative review
Sekar, K., & Pack, A. (2019). Epidiolex® as adjunct therapy for treatment of refractory epilepsy: a comprehensive review with a focus on adverse effects. F1000Res, 8.	Narrative review
Sharafi, G., He, H., & Nikfarjam, M. (2019). Potential Use of Cannabinoids for the Treatment of Pancreatic Cancer. J Pancreat Cancer, 5(1), 1-7.	No RCTs or only 1 RCT included in the systematic review
Shishko, I., Oliveira, R., Moore, T. A., & Almeida, K. (2018). A review of medical marijuana for the treatment of posttraumatic stress disorder: Real symptom re-leaf or just high hopes? Ment Health Clin, 8(2), 86-94.	No RCTs or only 1 RCT included in the systematic review

Reference	Reason for exclusion
Steele, G., Arneson, T., & Zylla, D. (2019). A Comprehensive Review of Cannabis in Patients with Cancer: Availability in the USA, General Efficacy, and Safety. Curr Oncol Rep, 21(1), 10.	Narrative review
Steenkamp, M. M., Blessing, E. M., Galatzer-Levy, I. R., Hollahan, L. C., & Anderson, W. T. (2017). Marijuana and other cannabinoids as a treatment for posttraumatic stress disorder: A literature review. Depress Anxiety, 34(3), 207-216.	Narrative review
Subbaraman, M. S. (2014). Can cannabis be considered a substitute medication for alcohol? Alcohol Alcohol, 49(3), 292-298.	Narrative review
Sule-Suso, J., Watson, N. A., van Pittius, D. G., & Jegannathen, A. (2019). Striking lung cancer response to self-administration of cannabidiol: A case report and literature review. SAGE Open Med Case Rep, 7, 2050313x19832160.	Narrative review
Sznitman, S. R., & Zolotov, Y. (2015). Cannabis for therapeutic purposes and public health and safety: a systematic and critical review. Int J Drug Policy, 26(1), 20-29.	No data on objectives
Tait, R. J., Caldicott, D., Mountain, D., Hill, S. L., & Lenton, S. (2016). A systematic review of adverse events arising from the use of synthetic cannabinoids and their associated treatment. Clin Toxicol (Phila), 54(1), 1-13.	No RCTs or only 1 RCT included in the systematic review
Turna, J., Patterson, B., & Van Ameringen, M. (2017). Is cannabis treatment for anxiety, mood, and related disorders ready for prime time? Depress Anxiety, 34(11), 1006-1017.	Narrative review
Turna, J., Syan, S. K., Frey, B. N., Rush, B., Costello, M. J., Weiss, M., & MacKillop, J. (2019). Cannabidiol as a Novel Candidate Alcohol Use Disorder Pharmacotherapy: A Systematic Review. Alcohol Clin Exp Res, 43(4), 550-563.	No RCTs or only 1 RCT included in the systematic review
van den Elsen, G. A., Ahmed, A. I., Lammers, M., Kramers, C., Verkes, R. J., van der Marck, M. A., & Rikkert, M. G. (2014). Efficacy and safety of medical cannabinoids in older subjects: a systematic review. Ageing Res Rev, 14, 56-64.	No RCTs or only 1 RCT included in the systematic review

Reference	Reason for exclusion
Walsh, Z., Gonzalez, R., Crosby, K., M, S. T., Carroll, C., & Bonn-Miller, M. O. (2017). Medical cannabis and mental health: A guided systematic review. Clin Psychol Rev, 51, 15-29.	Duplicate data
Wilkinson, S. T., Radhakrishnan, R., & D'Souza, D. C. (2016). A Systematic Review of the Evidence for Medical Marijuana in Psychiatric Indications. J Clin Psychiatry, 77(8), 1050-1064.	No RCTs or only 1 RCT included in the systematic review
Yap, M., Easterbrook, L., Connors, J., & Koopmans, L. (2015). Use of cannabis in severe childhood epilepsy and child protection considerations. J Paediatr Child Health, 51(5), 491-496.	No RCTs or only 1 RCT included in the systematic review
Yarnell, S. (2015). The Use of Medicinal Marijuana for Posttraumatic Stress Disorder: A Review of the Current Literature. Prim Care Companion CNS Disord, 17(3).	Narrative review
Zaka, M., Sehgal, S. A., Shafique, S., & Abbasi, B. H. (2017). Comparative in silico analyses of Cannabis sativa, Prunella vulgaris and Withania somnifera compounds elucidating the medicinal properties against rheumatoid arthritis. J Mol Graph Model, 74, 296-304.	No review/no data on objectives
Zlebnik, N. E., & Cheer, J. F. (2016). Beyond the CB1 Receptor: Is Cannabidiol the Answer for Disorders of Motivation? Annu Rev Neurosci, 39, 1-17.	Narrative review

Table III. Search strategy PubMed (MEDLINE) preliminary cost-effectiveness literature search

Intervention: cannabis	("Medical Marijuana"[Mesh] OR medical marijuana[tiab] OR medicinal marijuana[tiab] OR marijuana treatment*[tiab] OR marijuana therapy[tiab] OR therapeutic marijuana[tiab] OR marijuana dispensar*[tiab] OR medical marihuana[tiab] OR medicinal marihuana[tiab] OR marihuana treatment*[tiab] OR marihuana therap*[tiab] OR therapeutic marihuana[tiab] OR marihuana dispensar*[tiab] OR medical cannabis[tiab] OR medicinal cannabis[tiab] OR cannabis treatment*[tiab] OR cannabis therap*[tiab] OR therapeutic cannabis[tiab] OR cannabis dispensar*[tiab] OR cannabis-based medicine*[tiab] OR cannabis-based medication[tiab] OR cannabis-based drug*[tiab])
Outcome: cost-effectiveness	((“Technology Assessment, Biomedical”[Mesh] OR “Cost-Benefit Analysis”[Mesh] OR “Quality-Adjusted Life Years”[Mesh] OR “technology assessment” [tiab] OR “economic evaluation” [tiab] OR “economic value” [tiab] OR “cost-benefit” [tiab] OR “cost-effective” [tiab] OR “cost-effectiveness” [tiab] OR “cost-utility” [tiab] OR “cost-consequence” [tiab] OR “quality-adjusted life year” [tiab] OR “QALY” [tiab] OR "budget impact" [tiab]))
Limits	*Study design SRs:* ((((systematic*[tiab] OR comprehensive*[tiab]) AND (bibliographic*[tiab] OR literature[tiab] OR review*[tiab])) OR literature review*[tiab] OR meta-analysis[pt] OR meta-analys*[tiab] OR meta-analys*[tiab] OR meta-analyt*[tiab] OR metaanalys*[tiab] OR metaanalys*[tiab] OR metaanalyt*[tiab]))
	Publication period: Database initiation – 6 January 2020
	Language: English

Figure II. PRISMA flowchart of preliminary literature search of published SRs on cost-effectiveness

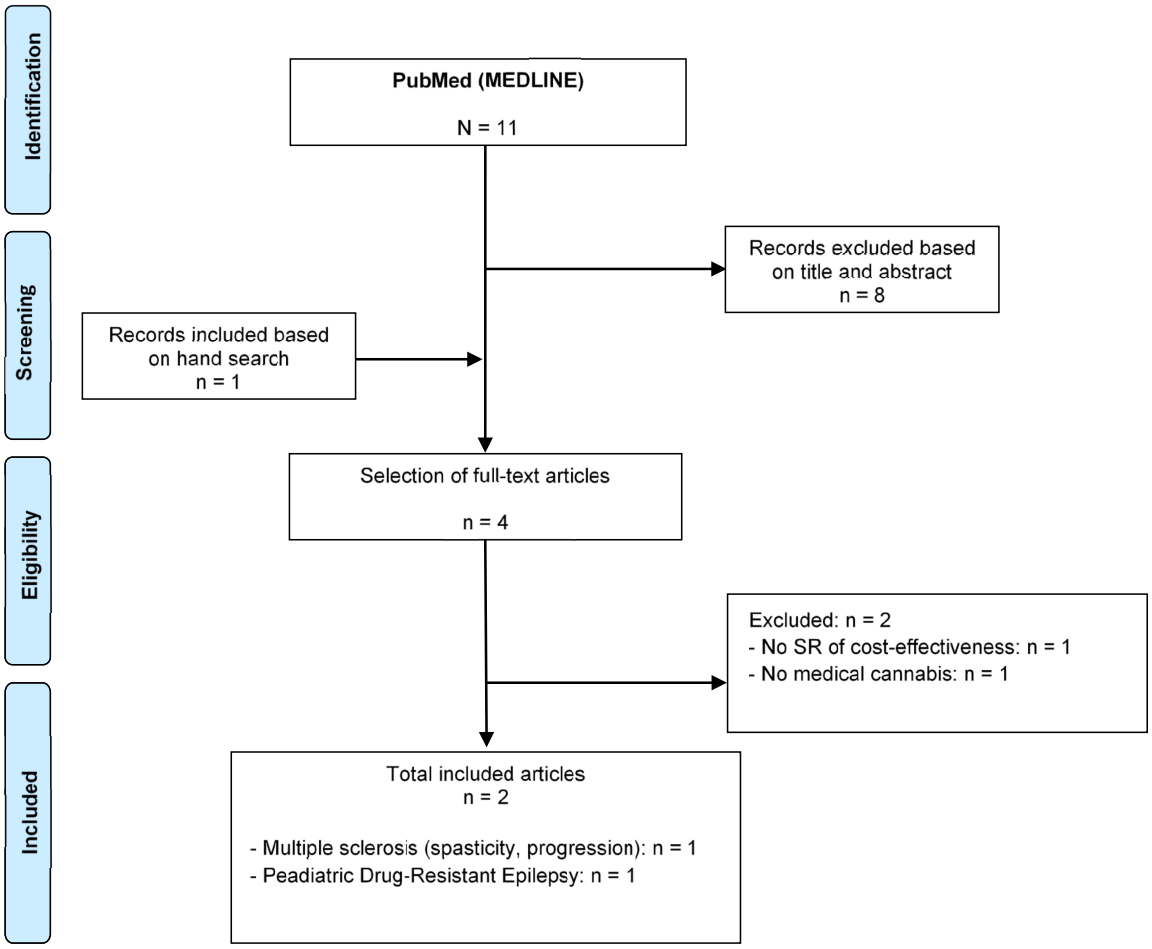


Figure III. PRISMA flowchart articles/studies on cost-effectiveness of medical cannabis

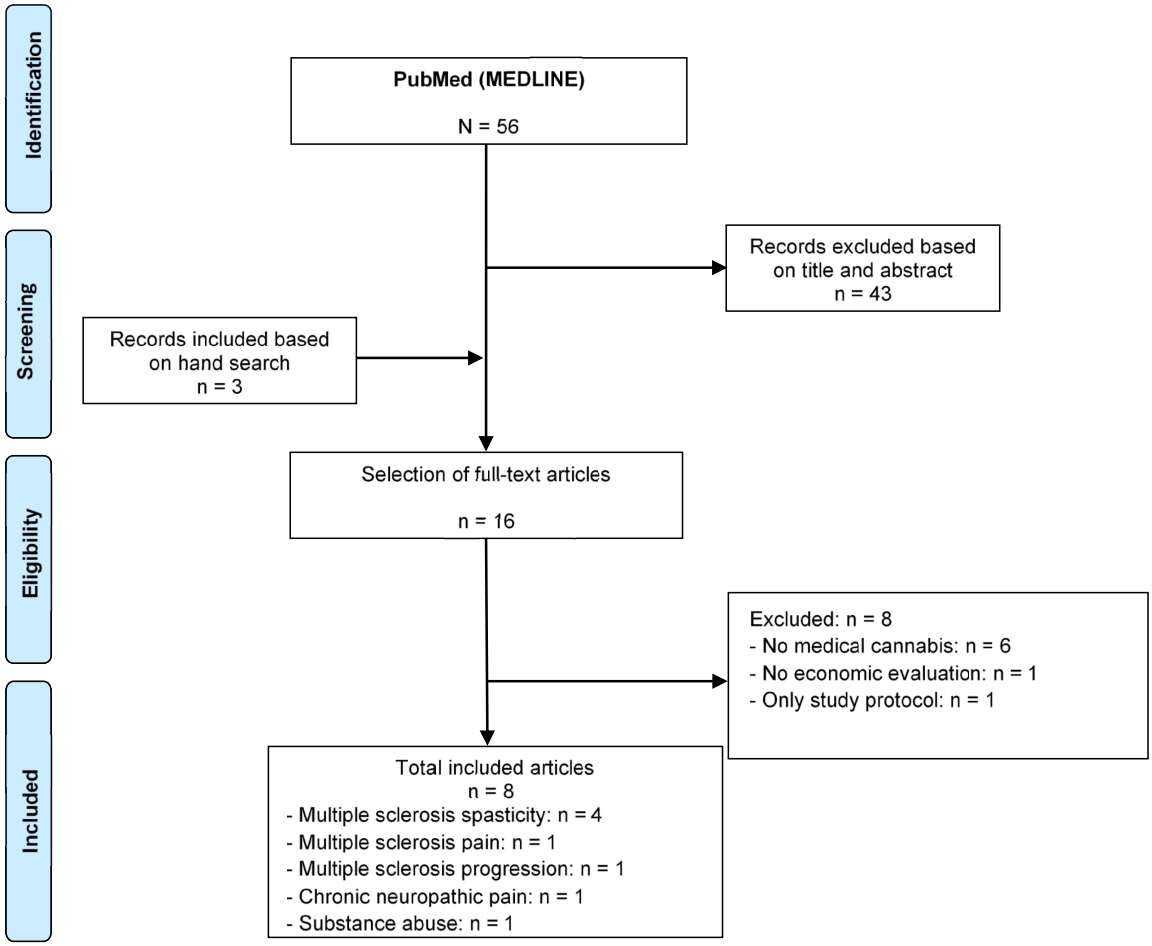


Table IV. List of excluded articles during the preliminary cost-effectiveness literature search

Reference	Reason for exclusion
Branas P, Jordan R, Fry-Smith A, Burls A, Hyde C. Treatments for fatigue in multiple sclerosis: a rapid and systematic review. National Coordinating Centre for HTA. Great Britain; 2000 Jan 1.	No medical cannabis
Cooper K, Chatters R, Kaltenthaler E, Wong R. Psychological and psychosocial interventions for cannabis cessation in adults: a systematic review short report. Health Technology Assessment. 2015;19(56).	No medical cannabis
Elliott J, McCoy B, Clifford T, Potter BK, Skidmore B, Wells GA, Coyle D. Cost-effectiveness of cannabinoids for pediatric drug-resistant epilepsy: protocol for a systematic review of economic evaluations. Systematic reviews. 2019 Dec;8(1):75.	Only study protocol
El-Guebaly N, Armstrong SJ, Hodgins DC. Substance abuse and the emergency room: programmatic implications. Journal of addictive diseases. 1998 Mar 25;17(2):21-40.	No medical cannabis
Hedman E, Ljótsson B, Lindefors N. Cognitive behavior therapy via the Internet: a systematic review of applications, clinical efficacy and cost–effectiveness. Expert review of pharmacoeconomics & outcomes research. 2012 Dec 1;12(6):745-64.	No medical cannabis
Kaltenthaler E, Cooper K, Pandor A, James MM, Chatters R, Wong R. The use of rapid review methods in health technology assessments: 3 case studies. BMC medical research methodology. 2016 Dec;16(1):108.	No medical cannabis/ wrong study design
Rooke S, Thorsteinsson E, Karpin A, Copeland J, Allsop D. Computer-delivered interventions for alcohol and tobacco use: a meta-analysis. Addiction. 2010 Aug;105(8):1381-90.	No medical cannabis
Wong S, Ordean A, Kahan M, Gagnon R, Hudon L, Basso M, Bos H, Crane J, Davies G, Delisle MF, Farine D. Substance use in pregnancy. Journal of Obstetrics and Gynaecology Canada. 2011 Apr 1;33(4):367-84.	No medical cannabis

Appendix 2. Search strategy efficacy, effectiveness, and safety

Table I. Search strategy for the efficacy, effectiveness, and safety systematic literature searches: PubMed (MEDLINE)

	Use of medical cannabis for 4 different symptoms			
	I. Chronic pain	**II. Spasticity**	**III. Unintentional weight-loss**	**IV. Nausea and vomiting related to cancer treatment**
Population	"Chronic Pain"[Mesh] OR "Analgesia"[Mesh] OR pain*[tiab] OR analgesia[tiab]	"Muscle Spasticity"[Mesh] OR spastic*[tiab]	"Anorexia"[Mesh] OR "Weight Loss"[Mesh] OR "Thinness"[Mesh] OR anorexia[tiab] OR weight loss*[tiab] OR weightloss*[tiab] OR weight reduction*[tiab] OR thinness[tiab] OR leanness[tiab] OR underweight[tiab] OR appetite loss[tiab] OR "loss of appetite"[tiab]	("Neoplasms"[Mesh] OR neoplasm[tiab] OR neoplasms[tiab] OR neoplasia[tiab] OR neoplasias[tiab] OR cancer[tiab] OR cancers[tiab] OR tumor*[tiab] OR tumour*[tiab] OR malignancy[tiab] OR malignancies[tiab]) AND ("Nausea"[Mesh] OR "Vomiting"[Mesh] OR "Antiemetics"[Mesh] OR nausea[tiab] OR vomit*[tiab] OR emesis[tiab] OR emetic*[tiab] OR antiemetic*[tiab] OR antiemetic*[tiab] OR emetogenic*[tiab])
Intervention: cannabis	"Medical Marijuana"[Mesh] OR "Cannabinoids"[Mesh] OR "Nabilone"[Supplementary Concept] OR "HU 211"[Supplementary Concept] OR cannab*[tiab] OR marijuana[tiab] OR marihuana[tiab] OR hash*[tiab] OR hemp[tiab] OR dronabinol[tiab] OR Marinol®[tiab] OR tetrahydrocannabinol[tiab] OR THC[tiab] OR THCV[tiab] OR delta-9-tetrahydrocannabinol[tiab] OR			

	delta-9-THC[tiab] OR 9-ene-tetrahydrocannabinol[tiab] OR delta(1)-thc[tiab] OR delta(1)-tetra-hydrocannabinol[tiab] OR 9-delta-tetra-hydrocannabinol[tiab] OR 9-delta-THC[tiab] OR 9-ene-tetrahydrocannabinol[tiab] OR nabilone[tiab] OR Cesamet®[tiab] OR Sativex®[tiab] OR HU 211[tiab] OR HU211[tiab] OR dexanabinol[tiab] OR CBD[tiab] OR CBDV[tiab] OR Epidio-lex®[tiab] OR nabiximols[tiab] OR abalone[tiab] OR tilray[tiab] OR bedrocan[tiab] OR bed-robinol[tiab] OR bediol[tiab] OR bedrolite[tiab] OR syndros[tiab] OR tetrahydrocannabiva-rin[tiab] OR THC:CBD spray[tiab]
Comparison	No search string
Outcomes	No search string
Limits	*Study design RCTs:* ("randomized controlled trial"[pt] OR "controlled clinical trial"[pt] OR RCT[tiab] OR RCTs[tiab] OR random*[tiab] OR controlled[tiab] OR control-treated[tiab] OR placebo[tiab] OR cross-over studies[Mesh] OR "single-blind method"[Mesh] OR single-blind*[tiab] OR singleblind*[tiab] OR single-masked[tiab] OR double-blind method[Mesh] OR double-blind*[tiab] OR double-blind*[tiab] OR double-masked[tiab] OR triple-blind*[tiab] OR tripleblind*[tiab] OR triple-masked[tiab])
	Publication period: 1980 – 22 January 2020
	Language: English, French, German, Dutch
	No animal studies: NOT (Animals[Mesh] NOT (Humans[Mesh] AND Animals[Mesh]))
	No reviews and meta-analyses: NOT ("systematic review"[pt] OR review[ti] OR "meta-analysis"[pt] OR meta-analysis[ti])

Table II. Search strategy for the efficacy, effectiveness, and safety systematic literature searches: Embase

	Use of medical cannabis for 4 different symptoms			
	I. Chronic pain	**II. Spasticity**	**III. Unintentional weight-loss**	**IV. Nausea and vomiting related to cancer treatment**
Population	'chronic pain'/exp OR 'analgesia'/exp OR pain*:ti,ab OR analgesia:ti,ab	'spasticity'/exp OR spastic*:ti,ab	'anorexia'/exp OR 'body weight loss'/exp OR 'underweight'/exp OR anorexia:ti,ab OR "weight loss*":ti,ab OR weightloss*:ti,ab OR "weight reduction*":ti,ab OR thinness:ti,ab OR leanness:ti,ab OR underweight:ti,ab OR "appetite loss":ti,ab OR "loss of appetite":ti,ab	('Neoplasms'/exp OR neoplasm:ti,ab OR neoplasms:ti,ab OR neoplasia:ti,ab OR neoplasias:ti,ab OR cancer:ti,ab OR cancers:ti,ab OR tumor*:ti,ab OR tumour*:ti,ab OR malignancy:ti,ab OR malignancies:ti,ab) AND ('Nausea'/exp OR 'Vomiting'/exp OR 'Antiemetics'/exp OR nausea:ti,ab OR vomit*:ti,ab OR emesis:ti,ab OR emetic*:ti,ab OR antiemetic*:ti,ab OR anti-emetic*:ti,ab OR emetogenic*:ti,ab) AND ('nausea and vomiting'/exp OR 'antiemetic agent'/exp OR nausea:ti,ab OR vomit*:ti,ab OR emesis:ti,ab OR emetic*:ti,ab OR antiemetic*:ti,ab OR anti-emetic*:ti,ab OR emetogenic*:ti,ab)

Intervention: cannabis	'medical cannabis'/exp OR 'cannabinoid'/exp OR 'nabilone'/exp OR 'dexanabinol'/exp OR cannab*:ti,ab OR marijuana:ti,ab OR marihuana:ti,ab OR hash*:ti,ab OR hemp:ti,ab OR dronabinol:ti,ab OR Marinol®:ti,ab OR tetrahydrocannabinol:ti,ab OR THC:ti,ab OR THCV:ti,ab OR 'delta-9-tetrahydrocannabinol':ti,ab OR 'delta-9-THC':ti,ab OR '9-ene-tetrahydrocannabinol':ti,ab OR 'delta(1)-thc':ti,ab OR 'delta(1)-tetrahydrocannabinol':ti,ab OR '9-delta-tetra-hydrocannabinol':ti,ab OR '9-delta-THC':ti,ab OR '9-ene-tetrahydrocannabinol':ti,ab OR nabilone:ti,ab OR Cesamet®:ti,ab OR Sativex®:ti,ab OR 'HU 211':ti,ab OR 'HU211':ti,ab OR dexanabinol:ti,ab OR CBD:ti,ab OR CBDV:ti,ab OR Epidiolex®:ti,ab OR nabiximols:ti,ab OR abalone:ti,ab OR tilray:ti,ab OR bedrocan:ti,ab OR bedrobinol:ti,ab OR bediol:ti,ab OR bedrolite:ti,ab OR syndros:ti,ab OR tetrahydrocannabivarin:ti,ab OR 'THC:CBD spray':ti,ab
Comparison	No search string
Outcomes	No search string
Limits	*Study design RCTs:* ('randomized controlled trial'/exp OR 'controlled clinical trial'/exp OR RCT:ti,ab OR RCTs:ti,ab OR random*:ti,ab OR controlled:ti,ab OR control-treated:ti,ab OR placebo:ti,ab OR 'crossover procedure'/exp OR 'single blind procedure'/exp OR single-blind*:ti,ab OR singleblind*:ti,ab OR single-masked:ti,ab OR 'double blind procedure'/exp OR double-blind*:ti,ab OR double-blind*:ti,ab OR double-masked:ti,ab OR 'triple blind procedure'/exp OR triple-blind*:ti,ab OR tripleblind*:ti,ab OR triple-masked:ti,ab)
	Publication period: 1980 – 22 January 2020
	Language: English, French, German, Dutch
	No animal studies: NOT ([animal cell]/lim OR [animal experiment]/lim OR [animal model]/lim OR [animal tissue]/lim)
	No reviews and meta-analyses: NOT ('systematic review'/exp OR review:ti OR 'meta analysis'/exp OR meta-analysis:ti)

Appendix 3. Excluded RCTs during full-text selection efficacy, effectiveness, and safety search

Table I. Excluded RCTs found with the systematic literature search on the use of medical cannabis for the symptom chronic pain

Reference	Reason for exclusion
No author. Marijuana eases HIV-related nerve pain. The AIDS reader. 2004;14(4):164-5.	Non-pertinent publication type
Abrams DI, Jay CA, Shade SB, Vizoso H, Reda H, Press S, et al. Cannabis in painful HIV-associated sensory neuropathy: A randomized placebo-controlled trial. Neurology. 2007;68(7):515-21.	Short treatment duration (<2 weeks)
Bar-Sela G, Zalman D, Semenysty V, Ballan E. The Effects of Dosage-Controlled Cannabis Capsules on Cancer-Related Cachexia and Anorexia Syndrome in Advanced Cancer Patients: Pilot Study. Integr Cancer Ther. 2019;18:1534735419881498.	No RCT
Conte A, Bettolo CM, Onesti E, Frasca V, Iacovelli E, Gilio F, et al. Cannabinoid-induced effects on the nociceptive system: A neurophysiological study in patients with secondary progressive multiple sclerosis. European Journal of Pain. 2009;13(5):472-7.	No data on review objectives
Corey-Bloom J, Wolfson T, Gamst A, Jin S, Marcotte TD, Bentley H, et al. Smoked cannabis for spasticity in multiple sclerosis: A randomized, placebo-controlled trial. CMAJ. 2012;184(10):1143-50.	Short treatment duration (<2 weeks)
Côté M, Trudel M, Wang C, Fortin A. Improving Quality of Life With Nabilone During Radiotherapy Treatments for Head and Neck Cancers: A Randomized Double-Blind Placebo-Controlled Trial. Ann Otol Rhinol Laryngol. 2016;125(4):317-24.	Data presented in a Figure, not possible to extract all exact data from the text
De Vries M, Van Rijckevorsel DCM, Vissers KCP, Wilder-Smith OHG, Van Goor H. Single dose delta-9-tetrahydrocannabinol in chronic pancreatitis patients: Analgesic efficacy, pharmacokinetics and tolerability. Br J Clin Pharmacol. 2016;81(3):525-37.	No data on review objectives
Ellis RJ, Toperoff W, Vaida F, Van Den Brande G, Gonzales J, Gouaux B, et al. Smoked medicinal cannabis for neuropathic pain in	Short treatment duration (<2 weeks)

HIV: A randomized, crossover clinical trial. Neuropsychopharmacology. 2009;34(3):672-80.	
Good P, Haywood A, Gogna G, Martin J, Yates P, Greer R, et al. Oral medicinal cannabinoids to relieve symptom burden in the palliative care of patients with advanced cancer: a double-blind, placebo controlled, randomised clinical trial of efficacy and safety of cannabidiol (CBD). BMC Palliat Care. 2019;18(1):110.	Study protocol
Guy G, Gover J, Rogerson M, Atwell B, Dineen J. Positive data in Sativex® phase IIb trial: Support advancing into phase III development in cancer pain. Revista de la Sociedad Espanola del Dolor. 2010;17(4):219-21.	Non-pertinent publication type
Holdcroft A, Smith M, Jacklin A, Hodgson H, Smith B, Newton M, et al. Pain relief with oral cannabinoids in familial Mediterranean fever. Anaesthesia. 1997;52(5):483-6.	Case report
Issa MA, Narang S, Jamison RN, Michna E, Edwards RR, Penetar DM, et al. The subjective psychoactive effects of oral dronabinol studied in a randomized, controlled crossover clinical trial for pain. Clin J Pain. 2014;30(6):472-8.	No data on review objectives
Johnson JR, Burnell-Nugent M, Lossignol D, Ganae-Motan ED, Potts R, Fallon MT. Multicenter, double-blind, randomized, placebo-controlled, parallel-group study of the efficacy, safety, and tolerability of THC:CBD extract and THC extract in patients with intractable cancer-related pain. J Pain Symptom Manage. 2010;39(2):167-79.	Short treatment duration (<2 weeks)
Johnson JR, Lossignol D, Burnell-Nugent M, Fallon MT. 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. J Pain Symptom Manage. 2013;46(2):207-18.	Open-label extension study of an RCT
Karst M, Salim K, Burstein S, Conrad I, Hoy L, Schneider U. Analgesic Effect of the Synthetic Cannabinoid CT-3 on Chronic Neuropathic Pain: A Randomized Controlled Trial. Journal of the American Medical Association. 2003;290(13):1757-62.	Short treatment duration (<2 weeks)
Malik Z, Bayman L, Valestin J, Rizvi-Toner A, Hashmi S, Schey R. Dronabinol increases pain threshold in patients with functional chest pain: A pilot double-blind placebo-controlled trial. Diseases of the	No useful results for efficacy

Esophagus. 2017;30(2).	
Narang S, Gibson D, Wasan AD, Ross EL, Michna E, Nedeljkovic SS, et al. Efficacy of Dronabinol as an Adjuvant Treatment for Chronic Pain Patients on Opioid Therapy. Journal of Pain. 2008;9(3):254-64.	No data on review objectives
Nitecka-Buchta A, Nowak-Wachol A, Wachol K, Walczyńska-Dragon K, Olczyk P, Batoryna O, et al. Myorelaxant Effect of Transdermal Cannabidiol Application in Patients with TMD: A Randomized, Double-Blind Trial. J Clin Med. 2019;8(11):1886.	No population of interest
Pini LA, Guerzoni S, Cainazzo MM, Ferrari A, Sarchielli P, Tiraferri I, et al. Nabilone for the treatment of medication overuse headache: results of a preliminary double-blind, active-controlled, randomized trial. J Headache Pain. 2012;13(8):677-84.	No population of interest
Pittler MH. No effect of cannabis on induced inflammatory pain. Focus on Alternative and Complementary Therapies. 2009;14(1):19-20.	Non-pertinent publication type
Portenoy RK, Ganae-Motan ED, Allende S, Yanagihara R, Shaiova L, Weinstein S, et al. Nabiximols for opioid-treated cancer patients with poorly-controlled chronic pain: a randomized, placebo-controlled, graded-dose trial. J Pain. 2012;13(5):438-49.	Data presented in a Figure, not possible to extract all exact data from the text
Rog DJ, Nurmikko TJ, Young CA. Oromucosal delta9-tetrahydrocannabinol/cannabidiol for neuropathic pain associated with multiple sclerosis: an uncontrolled, open-label, 2-year extension trial. Clin Ther. 2007;29(9):2068-79.	Open-label extension study of an RCT
Salim K, Schneider U, Burstein S, Hoy L, Karst M. Pain measurements and side effect profile of the novel cannabinoid ajulemic acid. Neuropharmacology. 2005;48(8 SPEC. ISS.):1164-71.	Secondary analyses of RCT excluded in the systematic review
Schulz V. Cannabis inhalation against neuropathic pains: Randomized double blind study on the benefit-risk assessment. Zeitschrift fur Phytotherapie. 2009;30(2):75-6.	Non-pertinent publication type
Selvarajah D, Gandhi R, Emery CJ, Tesfaye S. Randomized placebo-controlled double-blind clinical trial of cannabis-based medicinal product (Sativex®) in painful diabetic neuropathy: depression is a major confounding factor. Diabetes Care. 2010;33(1):128-30.	Number of patients and number of dropouts in treatment groups not reported
Skrabek RQ, Galimova L, Ethans K, Perry D. Nabilone for the treatment of pain in fibromyalgia. J Pain. 2008;9(2):164-73.	Data presented in a Figure, not possible to extract all exact data from the text
Turcotte D, Doupe M, Torabi M, Gomori A, Ethans K, Esfahani F, et	No data on review objectives

al. Nabilone as an adjunctive to gabapentin for multiple sclerosis-induced neuropathic pain: a randomized controlled trial. Pain Med. 2015;16(1):149-59.	
Van Amerongen G, Kanhai K, Baakman AC, Heuberger J, Klaassen E, Beumer TL, et al. Effects on Spasticity and Neuropathic Pain of an Oral Formulation of Δ9-tetrahydrocannabinol in Patients With Progressive Multiple Sclerosis. Clin Ther. 2018;40(9):1467-82.	No population of interest
Van de Donk T, Niesters M, Kowal MA, Olofsen E, Dahan A, van Velzen M. An experimental randomized study on the analgesic effects of pharmaceutical-grade cannabis in chronic pain patients with fibromyalgia. Pain. 2019;160(4):860-9.	No data on review objectives
Wallace MS, Marcotte TD, Umlauf A, Gouaux B, Atkinson JH. Efficacy of Inhaled Cannabis on Painful Diabetic Neuropathy. Journal of Pain. 2015;16(7):616-27.	No data on review objectives
Ware MA, Wang T, Shapiro S, Robinson A, Ducruet T, Huynh T, et al. Smoked cannabis for chronic neuropathic pain: A randomized controlled trial. CMAJ. 2010;182(14):E694-E701.	Short treatment duration (<2 weeks)
Weizman L, Dayan L, Brill S, Nahman-Averbuch H, Hendler T, Jacob G, et al. Cannabis analgesia in chronic neuropathic pain is associated with altered brain connectivity. Neurology. 2018;91(14):E1285-E94.	No data on review objectives
Wilsey B, Marcotte T, Deutsch R, Gouaux B, Sakai S, Donaghe H. Low-dose vaporized cannabis significantly improves neuropathic pain. Journal of Pain. 2013;14(2):136-48.	No data on review objectives
Wilsey B, Marcotte T, Tsodikov A, Millman J, Bentley H, Gouaux B, et al. A Randomized, Placebo-Controlled, Crossover Trial of Cannabis Cigarettes in Neuropathic Pain. Journal of Pain. 2008;9(6):506-21.	No data on review objectives
Wilsey B, Marcotte TD, Deutsch R, Zhao H, Prasad H, Phan A. An Exploratory Human Laboratory Experiment Evaluating Vaporized Cannabis in the Treatment of Neuropathic Pain From Spinal Cord Injury and Disease. Journal of Pain. 2016;17(9):982-1000.	No data on review objectives
Wilsey BL, Deutsch R, Samara E, Marcotte TD, Barnes AJ, Huestis MA, et al. A preliminary evaluation of the relationship of cannabinoid blood concentrations with the analgesic response to vaporized cannabis. J Pain Res. 2016;9:587-98.	No data on review objectives

Zadikoff C, Wadia PM, Miyasaki J, Chen R, Lang AE, So J, et al. Cannabinoid, CB1 agonists in cervical dystonia: Failure in a phase IIa randomized controlled trial. Basal Ganglia. 2011;1(2):91-5.	No population of interest
Zajicek J, Fox P, Sanders H, Wright D, Vickery J, Nunn A, et al. Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): Multicentre randomised placebo-controlled trial. Lancet. 2003;362(9395):1517-26.	No population of interest
Zajicek JP, Hobart JC, Slade A, Barnes D, Mattison PG. MUltiple sclerosis and extract of cannabis: Results of the MUSEC trial. Journal of Neurology, Neurosurgery and Psychiatry. 2012;83(11):1125-32.	No population of interest

Table II. Excluded RCTs found with the systematic literature search on the use of medical cannabis for the symptom spasticity

Reference	**Reason for exclusion**
No author. Latest trial suggests cannabis does not relieve spasticity of multiple sclerosis. Pharmaceutical Journal. 2002;268(7198):675.	Non-pertinent publication type
Ball S, Vickery J, Hobart J, Wright D, Green C, Shearer J, et al. The Cannabinoid Use in Progressive Inflammatory brain Disease (CUPID) trial: A randomised double-blind placebo-controlled parallel-group multicentre trial and economic evaluation of cannabinoids to slow progression in multiple sclerosis. Health Technology Assessment. 2015;19(12):1-187.	Non-pertinent publication type
Farrar JT, Troxel AB, Stott C, Duncombe P, Jensen MP. Validity, reliability, and clinical importance of change in a 0-10 numerical rating scale measure of spasticity: a post hoc analysis of a randomized, double-blind, placebo-controlled trial. Clinical Therapeutics. 2008;30(5):974-85.	No data on review objectives
Grotenhermen F. Cannabinoids do not reduce objective measurements in muscle spasticity, but people with multiple sclerosis perceive some benefit. Evidence-Based Healthcare. 2004;8(3):159-61.	Non-pertinent publication type
Hagenbach U, Luz S, Ghafoor N, Berger JM, Grotenhermen F, Brenneisen R, et al. The treatment of spasticity with Δ9-tetrahydrocannabinol in persons with spinal cord injury. Spinal Cord.	No data on review objectives

2007;45(8):551-62.	
Haupts M, Vila C, Jonas A, Witte K, Álvarez-Ossorio L. Influence of Previous Failed Antispasticity Therapy on the Efficacy and Tolerability of THC:CBD Oromucosal Spray for Multiple Sclerosis Spasticity. Eur Neurol. 2016;75(5-6):236-43.	(Irrelevant) post-hoc analysis of an RCT included in the systematic literature search
Killestein J, Hoogervorst ELJ, Reif M, Kalkers NF, Van Loenen AC, Staats PGM, et al. Safety, tolerability, and efficacy of orally administered cannabinoids in MS. Neurology. 2002;58(9):1404-7.	Data presented in a Figure, not possible to extract all exact data from the text
Notcutt W, Langford R, Davies P, Ratcliffe S, Potts R. A placebo-controlled, parallel-group, randomized withdrawal study of subjects with symptoms of spasticity due to multiple sclerosis who are receiving long-term Sativex® (nabiximols). Mult Scler. 2012;18(2):219-28.	No useful results for efficacy
Petro DJ, Ellenberger Jr C. Treatment of human spasticity with delta 9-tetrahydrocannabinol. Journal of clinical pharmacology. 1981;21(8-9 Suppl):413S-6S.	Data presented in a Figure, not possible to extract all exact data from the text
Pryce G, Baker D. Cannabinoids fail to show evidence of slowing down the progression of multiple sclerosis. Evidence-Based Medicine. 2015;20(4):124.	Non-pertinent publication type
Serpell MG, Notcutt W, Collin C. Sativex® long-term use: an open-label trial in patients with spasticity due to multiple sclerosis. J Neurol. 2013;260(1):285-95.	Open-label extension study of an RCT
Wade DT, Makela PM, House H, Bateman C, Robson P. Long-term use of a cannabis-based medicine in the treatment of spasticity and other symptoms in multiple sclerosis. Mult Scler. 2006;12(5):639-45.	Open-label extension study of an RCT
Zajicek J, Ball S, Wright D, Vickery J, Nunn A, Miller D, et al. Effect of dronabinol on progression in progressive multiple sclerosis (CUPID): A randomised, placebo-controlled trial. The Lancet Neurology. 2013;12(9):857-65.	No data on review objectives
Zajicek JP, Hobart JC, Slade A, Barnes D, Mattison PG. MUltiple sclerosis and extract of cannabis: Results of the MUSEC trial. Journal of Neurology, Neurosurgery and Psychiatry. 2012;83(11):1125-32.	No population of interest (i.e. not aimed at spasticity)

Table III. Excluded RCTs found with the systematic literature search on the use of medical cannabis for the symptom unintentional weight loss

Reference	Reason for exclusion
Beal JE, Olson R, Lefkowitz L, Laubenstein L, Bellman P, Yangco B, et al. Long-term efficacy and safety of dronabinol for acquired immunodeficiency syndrome-associated anorexia. Journal of Pain and Symptom Management. 1997;14(1):7-14.	Non-randomised follow-up study of an RCT
Côté M, Trudel M, Wang C, Fortin A. Improving Quality of Life With Nabilone During Radiotherapy Treatments for Head and Neck Cancers: A Randomized Double-Blind Placebo-Controlled Trial. Ann Otol Rhinol Laryngol. 2016;125(4):317-24.	No data on review objectives
Jatoi A, Yamashita JI, Sloan JA, Novotny PJ, Windschitl HE, Loprinzi CL. Does megestrol acetate down-regulate interleukin-6 in patients with cancer-associated anorexia and weight loss? A North Central Cancer Treatment Group investigation. Supportive Care in Cancer. 2002;10(1):71-5.	Subgroup analysis of RCT included in the systematic review
Volicer L, Stelly M, Morris J, McLaughlin J, Volicer BJ. Effects of dronabinol on anorexia and disturbed behavior in patients with Alzheimer's disease. International Journal of Geriatric Psychiatry. 1997;12(9):913-9.	No data on review objectives

Table IV. Excluded RCTs found with the systematic literature search on the use of medical cannabis for the symptom nausea and vomiting related to cancer treatment

Reference	Reason for exclusion
No author. Nabilone and high-dose metoclopramide: anti-emetics for cancer chemotherapy. Drug Ther Bull. 1984;22(3):9-11.	Non-pertinent publication type
Broder LE, Lean NL, Hilsenbeck SG. A randomized blinded clinical trial comparing delta-9-tetrahydrocannabinol (THC) and hydroxizine (HZ) as antiemetics (AE) for cancer chemotherapy (CT). Proceedings of the American Association for Cancer Research. 1982;Vol. 23:514.	Abstract

Citron, ML, Herman TS, Vreeland F. Antiemetic efficacy of levonantradol compared to delta-9-tetrahydrocannabinol for chemotherapy-induced nausea and vomiting. Cancer treatment reports 1985;69(1): 109-112.	No comparison with non-cannabis standard treatment
Colls BM. Cannabis and cancer chemotherapy. Lancet. 1980;1(8179):1187-8.	Non-pertinent publication type
Colls BM, Ferry DG, Gray AJ. The antiemetic activity of tetrahydrocannabinol versus metoclopramide and thiethylperazine in patients undergoing cancer chemotherapy. New Zealand Medical Journal. 1980;91(662):449-51.	Lacking methodology
Côté M, Trudel M, Wang C, Fortin A. Improving Quality of Life With Nabilone During Radiotherapy Treatments for Head and Neck Cancers: A Randomized Double-Blind Placebo-Controlled Trial. Ann Otol Rhinol Laryngol. 2016;125(4):317-24.	Data presented in a Figure, not possible to extract all exact data from the text
Cunningham D, Bradley CJ, Forrest GJ, Hutcheon AW, Adams L, Sneddon M, et al. A randomized trial of oral nabilone and prochlorperazine compared to intravenous metoclopramide and dexamethasone in the treatment of nausea and vomiting induced by chemotherapy regimens containing cisplatin or cisplatin analogues. Eur J Cancer Clin Oncol. 1988;24(4):685-9.	No data on review objectives
Kluin-Nelemans JC, Meuwissen Th OJA, Nelemans FA, Maes RAA. Tetrahydrocannabinol as antiemetic in patients treated with cytostatics: double blind crossover trial against placebo. Nederlands Tijdschrift voor Geneeskunde. 1981;125(22):900-1.	Abstract
Kluin-Nelemans JC, Meuwissen Th OJA, Nelemans FA, Maes RAA. Δ9-Tetrahydrocannabinol (THC) as an anti-emetic in patients treated with cancer chemotherapy. A double-blind cross-over trial against placebo. Netherlands Journal of Medicine. 1981;24(2):90.	Abstract
Lane M, Smith FE, Sullivan RA, Plasse TF. Dronabinol and prochlorperazine alone and in combination as antiemetic agents for cancer chemotherapy. American Journal of Clinical Oncology: Cancer Clinical Trials. 1990;13(6):480-4.	Duplicate data
Levitt M, Wilson A, Bowman D, Kemel S, Krepart G, Marks V, et al. Physiologic observations in a controlled clinical trial of the antiemetic effectiveness of 5, 10, and 15 mg of delta 9-tetrahydrocannabinol in	Article does not describe antiemetic effect of study treatment

cancer chemotherapy. Ophthalmologic implications. J Clin Pharmacol. 1981;21(8-9 Suppl):103S-9S.	
Lucraft HH, Palmer MK. Randomised clinical trial of levonantradol and chlorpromazine in the prevention of radiotherapy-induced vomiting. Clinical Radiology. 1982;33(6):621-2.	Lacking methodology
McCabe M, Smith FP, Macdonald JS, Woolley PV, Goldberg D, Schein PS. Efficacy of tetrahydrocannabinol in patients refractory to standard antiemetic therapy. Investigational New Drugs. 1988;6(3):243-6.	No useful results for efficacy
Niiranen A, Mattson K. Antiemetic efficacy of nabilone and dexamethasone: a randomized study of patients with lung cancer receiving chemotherapy. Am J Clin Oncol. 1987;10(4):325-9.	No data on review objectives
Orr LE, McKernan JF, Bloome B. Antiemetic effect of tetrahydrocannabinol. Compared with placebo and prochlorperazine in chemotherapy-associated nausea and emesis. Archives of Internal Medicine. 1980;140(11):1431-3.	Duplicate article
Perez EA, Lembersky B, Kaywin P, Kalman L, Yocom K, Friedman C. Comparable safety and antiemetic efficacy of a brief (30-second bolus) intravenous granisetron infusion and a standard (15-minute) intravenous ondansetron infusion in breast cancer patients receiving moderately emetogenic chemotherapy. Cancer Journal from Scientific American. 1998;4(1):52-8.	No data on review objectives
Schmoll HJ, Aapro MS, Poli-Bigelli S, Kim HK, Park K, Jordan K, et al. Comparison of an aprepitant regimen with a multiple-day ondansetron regimen, both with dexamethasone, for antiemetic efficacy in high-dose cisplatin treatment. Annals of Oncology. 2006;17(6):1000-6.	No data on review objectives
Schuette J, Niederle N, Krischke W. Randomized crossover trial comparing the antiemetic efficacy of nabilone versus alizapride in patients (pts) with nonseminomatous testicular cancer (NSTC) receiving low-dose cisplatin therapy. Proceedings of the American Association for Cancer Research. 1985;VOL. 26:No. 665.	Abstract
Stambaugh JE, McAdams J, Vreeland F. A phase II randomized trial of the antiemetic activity of levonantradol (CP-50,556) in cancer patients receiving chemotherapy. Proceedings of the American Society	Abstract

of Clinical Oncology. 1982;Vol. 1:C-240.	
Stambaugh Jr JE, McAdams J, Vreeland F. Dose ranging evaluation of the antiemetic efficacy and toxicity of intramuscular levonantradol in cancer subjects with chemotherapy-induced emesis. J Clin Pharmacol. 1984;24(11-12):480-5.	Very limited information on study population
Ungerleider JT, Andrysiak T, Fairbanks L. Cannabis and cancer chemotherapy. A comparison of oral delta-9-THC and prochlorperazine. Cancer. 1982;50(4):636-45.	No useful results for efficacy
Ungerleider JT, Fairbanks LA, Andrysiak T. THC or compazine® for the cancer chemotherapy patient - The UCLA study. Part II: Patient drug preference. American Journal of Clinical Oncology: Cancer Clinical Trials. 1985;8(2):142-7.	No useful results for efficacy
Williams CJ, Bolton A, de Pemberton R, Whitehouse JM. Antiemetics for patients treated with antitumor chemotherapy. Cancer Clin Trials. 1980;3(4):363-7.	No data on review objectives

Appendix 4. Search strategy cost-effectiveness

Table I. Search strategy for the cost-effectiveness search: PubMed (MEDLINE)

	Use of medical cannabis for 4 different symptoms			
	I. Chronic pain	**II. Spasticity**	**III. Unintentional weight-loss**	**IV. Nausea and vomiting related to cancer treatment**
Population	"Chronic Pain"[Mesh] OR "Analgesia"[Mesh] OR pain*[tiab] OR analgesia[tiab]	"Muscle Spasticity"[Mesh] OR spastic*[tiab]	"Anorexia"[Mesh] OR "Weight Loss"[Mesh] OR "Thinness"[Mesh] OR anorexia[tiab] OR weight loss*[tiab] OR weightloss*[tiab] OR weight reduction*[tiab] OR thinness[tiab] OR leanness[tiab] OR underweight[tiab] OR appetite loss[tiab] OR "loss of appetite"[tiab]	("Neoplasms"[Mesh] OR neoplasm[tiab] OR neoplasms[tiab] OR neoplasia[tiab] OR neoplasias[tiab] OR cancer[tiab] OR cancers[tiab] OR tumor*[tiab] OR tumour*[tiab] OR malignancy[tiab] OR malignancies[tiab]) AND ("Nausea"[Mesh] OR "Vomiting"[Mesh] OR "Antiemetics"[Mesh] OR nausea[tiab] OR vomit*[tiab] OR emesis[tiab] OR emetic*[tiab] OR antiemetic*[tiab] OR antiemetic*[tiab] OR emetogenic*[tiab])
Intervention: cannabis	"Medical Marijuana"[Mesh] OR "Cannabinoids"[Mesh] OR "Nabilone"[Supplementary Concept] OR "HU 211"[Supplementary Concept] OR cannab*[tiab] OR marijuana[tiab] OR marihuana[tiab]			

	OR hash*[tiab] OR hemp[tiab] OR dronabinol[tiab] OR Marinol®[tiab] OR tetrahydrocannabinol[tiab] OR THC[tiab] OR THCV[tiab] OR delta-9-tetrahydrocannabinol[tiab] OR delta-9-THC[tiab] OR 9-ene-tetrahydrocannabinol[tiab] OR delta(1)-thc[tiab] OR delta(1)-tetrahydrocannabinol[tiab] OR 9-delta-tetra-hydrocannabinol[tiab] OR 9-delta-THC[tiab] OR 9-ene-tetrahydrocannabinol[tiab] OR nabilone[tiab] OR Cesamet®[tiab] OR Sativex®[tiab] OR HU 211[tiab] OR HU211[tiab] OR dexanabinol[tiab] OR CBD[tiab] OR CBDV[tiab] OR Epidiolex®[tiab] OR nabiximols[tiab] OR abalone[tiab] OR tilray[tiab] OR bedrocan[tiab] OR bedrobinol[tiab] OR bediol[tiab] OR bedrolite[tiab] OR syndros[tiab] OR tetrahydrocannabivarin[tiab] OR THC:CBD spray[tiab]
Comparison	No search string
Outcomes	No search string
Limits	*Study design:* "Technology Assessment, Biomedical"[Mesh] OR "Cost-Benefit Analysis"[Mesh] OR "Quality-Adjusted Life Years"[Mesh] OR "technology assessment" [tiab] OR "economic evaluation" [tiab] OR "economic value" [tiab] OR "cost-benefit" [tiab] OR "cost-effective" [tiab] OR "cost-effectiveness" [tiab] OR "cost-utility" [tiab] OR "cost-consequence" [tiab] OR "quality-adjusted life year" [tiab] OR "QALY" [tiab] OR "budget impact" [tiab] OR "health-related quality of life" [tiab]
	Publication period: 1980 – 22 January 2020
	Language: English, French, German, Dutch
	No animal studies: NOT (Animals[Mesh] NOT (Humans[Mesh] AND Animals[Mesh]))
	No reviews and meta-analyses: NOT ("systematic review"[pt] OR review[ti] OR "meta-analysis"[pt] OR meta-analysis[ti])

Table II. Search strategy for the cost-effectiveness search: Embase

	Use of medical cannabis for 4 different symptoms			
	I. Chronic pain	**II. Spasticity**	**III. Unintentional**	**IV. Nausea and vomiting related to**

			weight-loss	**cancer treatment**
Population	'chronic pain'/exp OR 'analgesia'/exp OR pain*:ti,ab OR analgesia:ti,ab	'spasticity'/exp OR spastic*:ti,ab	'anorexia'/exp OR 'body weight loss'/exp OR 'underweight'/exp OR anorexia:ti,ab OR "weight loss*":ti,ab OR weightloss*:ti,ab OR "weight reduction*":ti,ab OR thinness:ti,ab OR leanness:ti,ab OR underweight:ti,ab OR "appetite loss":ti,ab OR "loss of appetite":ti,ab	('Neoplasms'/exp OR neoplasm:ti,ab OR neoplasms:ti,ab OR neoplasia:ti,ab OR neoplasias:ti,ab OR cancer:ti,ab OR cancers:ti,ab OR tumor*:ti,ab OR tumour*:ti,ab OR malignancy:ti,ab OR malignancies:ti,ab) AND ('Nausea'/exp OR 'Vomiting'/exp OR 'Antiemetics'/exp OR nausea:ti,ab OR vomit*:ti,ab OR emesis:ti,ab OR emetic*:ti,ab OR antiemetic*:ti,ab OR antiemetic*:ti,ab OR emetogenic*:ti,ab) AND ('nausea and vomiting'/exp OR 'antiemetic agent'/exp OR nausea:ti,ab OR vomit*:ti,ab OR emesis:ti,ab OR emetic*:ti,ab OR antiemetic*:ti,ab OR antiemetic*:ti,ab OR emetogenic*:ti,ab)

Intervention: cannabis	'medical cannabis'/exp OR 'cannabinoid'/exp OR 'nabilone'/exp OR 'dexanabinol'/exp OR cannab*:ti,ab OR marijuana:ti,ab OR marihuana:ti,ab OR hash*:ti,ab OR hemp:ti,ab OR dronabinol:ti,ab OR Marinol®:ti,ab OR tetrahydrocannabinol:ti,ab OR THC:ti,ab OR THCV:ti,ab OR 'delta-9-tetrahydrocannabinol':ti,ab OR 'delta-9-THC':ti,ab OR '9-ene-tetrahydrocannabinol':ti,ab OR 'delta(1)-thc':ti,ab OR 'delta(1)-tetrahydrocannabinol':ti,ab OR '9-delta-tetra-hydrocannabinol':ti,ab OR '9-delta-THC':ti,ab OR '9-ene-tetrahydrocannabinol':ti,ab OR nabilone:ti,ab OR Cesamet®:ti,ab OR Sativex®:ti,ab OR 'HU 211':ti,ab OR 'HU211':ti,ab OR dexanabinol:ti,ab OR CBD:ti,ab OR CBDV:ti,ab OR Epidiolex®:ti,ab OR nabiximols:ti,ab OR abalone:ti,ab OR tilray:ti,ab OR bedrocan:ti,ab OR bedrobinol:ti,ab OR bediol:ti,ab OR bedrolite:ti,ab OR syndros:ti,ab OR tetrahydrocannabivarin:ti,ab OR 'THC:CBD spray':ti,ab
Comparison	No search string
Outcomes	No search string
Limits	*Study design:* ('biomedical technology assessment'/exp OR 'economic evaluation'/exp OR 'quality adjusted life year'/exp OR 'program cost effectiveness'/de OR ((technology NEAR/3 assessment*) OR (economic* NEAR/3 (evaluat* OR value)) OR ((cost OR costs) NEAR/3 (benefit* OR effectiv* OR efficien* OR efficac* OR minim* OR utilit* OR consequen*)) OR (budget* NEAR/3 impact*):ab,ti OR (qualit* NEAR/3 adjust* NEAR/3 (life-year* OR lifeyear*)) OR qaly*):ab,ti OR (health NEAR/3 relat* NEAR/3 qualit* NEAR/3 life*):ab,ti)
	Publication period: 1980 – 22 January 2020
	Language: English, French, German, Dutch
	No animal studies: NOT ([animal cell]/lim OR [animal experiment]/lim OR [animal model]/lim OR [animal tissue]/lim)
	No reviews and meta-analyses: NOT ('systematic review'/exp OR review:ti OR 'meta analysis'/exp OR meta-analysis:ti)

Table 3. Search strategy for the cost-effectiveness search: NHSEED / DARE / HTA

Search terms:
1. (“chronic pain” AND “cannabis”) in “Any field” 2. (“spasticity” AND “cannabis”) in “Any field” 3. (“weight loss” AND “cannabis”) in “Any field” 4. (“chemotherapy” AND “cannabis”) in “Any field” OR (“cancer” AND “cannabis”) in “Any field” OR (“nausea” AND “cannabis”) OR (“vomit” AND “cannabis”)

Appendix 5. Excluded economic evaluations during full-text selection cost-effectiveness

Table I. Excluded economic evaluations during full-text selection cost-effectiveness – chronic pain

Reference	Reason for exclusion
Oral, Reduced Pain Sensitivity Following. AAPM 2018 Annual Meeting Abstracts. Pain Medicine, 2018, 19: 818-905.	No economic evaluation
Bellnier, Terrance, Geoffrey W. Brown, and Tulio R. Ortega. "Preliminary evaluation of the efficacy, safety, and costs associated with the treatment of chronic pain with medical cannabis." Mental Health Clinician 8.3, 2018: 110-115.	No economic evaluation

Table II. Excluded economic evaluations during full-text selection cost-effectiveness – spasticity

Reference	Reason for exclusion
Ball, Susan, et al. "The Cannabinoid Use in Progressive Inflammatory Brain Disease (CUPID) trial: a randomised double-blind placebo-controlled parallel-group multicentre trial and economic evaluation of cannabinoids to slow progression in multiple sclerosis." Health technology assessment (Winchester, England) 19.12, 2015: vii.	No economic evaluation
Oppe, Mark, et al. PND86 cost-utility analysis of delta-9-tetrahidrocannabinol and cannabidiol oromucosal spray. Value in Health, 2019, 22: S753.	Conference abstract

Appendix 6. Evidence tables efficacy, effectiveness, and safety

Chronic pain

Table I. Study characteristics of the RCTs included on medical cannabis use for the symptom chronic pain

Reference **Country**	**Study design** **Study period**	**Study population**	**Definition chronic pain**	**Intervention**	**Comparator**	**Sample size of analysed patients**	**Duration**	**Study outcomes**	**Preliminary risk of bias assessment**
Patients with abdominal pain									
De Vries, 2017 The Nether-lands	RCT - parallel NR	Adult patients with chronic abdominal pain: postsurgical pain (PSP) or chronic pancreatitis (CP) *Age (mean ± SD in y)* CP: medical cannabis*:* *53.9 ± 7.5; P: 53.9 ± 10.3* *PSP: medical cannabis:* *52.2 ± 11.3; P: 51.9 ± 8.2*	Persistent or inter-mittent abdominal pain, NRS scores ≥3, on a daily basis for ≥3 months, severe enough for medical treatment	**THC** 5 mg or 8 mg tablets (Namisol®); 3 times a day (TID) Step-up phase: - days 1-5: 3mg 3 TID - days 6-10: 5 mg TID Stable dose phase: - days 11–52: 8 mg TID	**Placebo** Matching placebo	Total: n = 50 THC: n = 21 Placebo: n = 29	*Duration titration phase*: 10 days *Duration study treatment*: 42 days *Duration follow-up:* at end of treatment period	- Outcomes on pain - Adverse events - Functional disease outcomes	High risk of bias

Reference Country	Study design Study period	Study population	Definition chronic pain	Intervention	Comparator	Sample size of analysed patients	Duration	Study outcomes	Preliminary risk of bias assessment
		Sex (% female) CP: 21.8%; PSP: 74.1%		It was permitted to taper the dosage to 5 mg TID when 8 mg was not tolerated					
Patients with allodynia									
Nurmikko, 2007 UK, Belgium	RCT - parallel NR	Adult patients with a current history of unilateral peripheral neuropathic pain and allodynia *Age (mean ± SD in y)* medical cannabis: 52.4 ± 15.8; P: 54.3 ± 15.2 *Sex (% female)* medical cannabis: 55.6%; P:62.9%	A history of ≥6 months duration of pain due to a clinically identifiable nerve lesion	**Sativex®** Spray for sublingual and oro-pharyngeal administration; 100 µl spray delivers 2.7 mg of THC and 2.5 mg of CBD; max. of 48 sprays/24 h	**Placebo** Identical in composition, appearance, odour and taste with the study medication but without cannabis extract	Total: n = 105 Sativex®: n = 50 Placebo: n = 55	*Duration titration phase*: 1 week *Duration study treatment*: 4 weeks *Duration follow-up:* at end of treatment period	- Outcomes on pain - Adverse events - Functional disease outcomes	Moderate risk of bias

Reference **Country**	**Study design** **Study period**	**Study population**	**Definition chronic pain**	**Intervention**	**Comparator**	**Sample size of analysed patients**	**Duration**	**Study outcomes**	**Preliminary risk of bias assessment**
Serpell, 2014 UK, Czech Republic, Romania, Belgium, Canada	RCT - parallel Sept 2005-Oct 2006	Adult patients with allodynia *Age (mean ± SD in y)* 57.3 ± 14.2 *Sex (% female)* 61%	At least a 6-month history of peripheral neuropathic pain	**Sativex®** Spray with 2.7 mg of THC and 2.5 mg of CBD; max. of 24 sprays/24 h	**Placebo** Spray of placebo delivered the same excipients plus colorants	Total: n = 173 THC/CBD: n = 79 Placebo: n = 94	*Duration titration phase*: 1 week *Duration study treatment*: 14 weeks *Duration follow-up:* at end of treatment period	- Outcomes on pain - Adverse events - Functional disease outcomes	Moderate risk of bias
Patients with brachial plexus injury									
Berman, 2004 UK	RCT - crossover Dec 2001-July 2002	Adult patients with at least 1 avulsed brachial plexus root and with the injury occurring ≥18 months previously *Age (mean (range) in y)* 39 (23-63)	Patients who scored ≥4 on a 0-10 point ordinal pain severity scale at visits 1 and 2 and had a pattern of pain that in the investigator's opin-	**Sativex®** Spray; approximate 1:1 ratio of THC:CBD; 27 mg/ml THC and 25 mg/ml CBD; max. of 48 sprays/24 h **THC extract**	**Placebo** Inactive placebo	Total: n = 48 Sativex®: n = 46 THC extract: n = 47 Placebo: n = 48	*Duration titration phase*: 2 weeks *Duration study treatment*: 3X2 weeks *Duration wash-out*: no washout period	- Outcomes on pain - Adverse events - Functional disease outcomes	High risk of bias

Reference Country	Study design Study period	Study population	Definition chronic pain	Intervention	Comparator	Sample size of analysed patients	Duration	Study outcomes	Preliminary risk of bias assessment
		Sex (% female) 4%	ion had been stable over the previous 4 weeks	THC extract, 27 mg/ml THC; max. dose of 48 sprays/24 h			*Duration follow-up:* at end of treatment period		
Patients with cancer									
Fallon, 2017 Australia, Belgium, Bulgaria, Czech Republic, Estonia, Germany, Hungary, India, Israel, Italy, Latvia, Lithuania,	2 RCTs - parallel NR	Adult patients with advanced cancer suffering from cancer-related pain, various types of cancer *Age (mean ± SD in y)* Study I: medical cannabis: 60.0 ± 11.0; P: 59.6 ± 11.0 Study II: medical cannabis: 61.4 ± 10.9; P: 61.6 ± 11.8	A clinical diagnosis of cancer-related pain that was unalleviated by an optimized maintenance dose of Step 3 opioid therapy	**Sativex®** Oral mucosal spray (THC (27 mg/ml): CBD (25 mg/ml)); max. of 10 sprays/day	**Placebo** Matching placebo	Study I, total: n = 294 Sativex®: n = 136 Placebo: n = 158 Study II, total: n = 166 Sativex®: n = 78 Placebo: n = 88	*Duration titration phase*: study I 2 weeks; study II 2 weeks *Duration study treatment*: study I 3 weeks; study II 5 weeks *Duration follow-up:* at end of treatment period	- Outcomes on pain - Adverse events	Moderate risk of bias

Reference Country	Study design Study period	Study population	Definition chronic pain	Intervention	Comparator	Sample size of analysed patients	Duration	Study outcomes	Preliminary risk of bias assessment
Poland, Romania, Spain, Taiwan, UK		*Sex (% female)* Study I: medical cannabis: 47.0%; P: 51.3% Study II: medical cannabis: 38.8%; P: 46.6%							
Lichtman, 2018 Belgium, Bulgaria, Czech Republic, Estonia, Germany, Hungary, Latvia, Lithuania, Poland, Romania, UK, USA	RCT - parallel NR	Adult patients with advanced cancer, various types of cancer *Age (mean ± SD in y)* medical cannabis: 59.2 ± 12.0; P: 60.7 ± 11.1 *Sex (% female)* medical cannabis: 44.2%; P: 48.0%	A clinical diagnosis of cancer-related pain that was unalleviated by an optimized maintenance dose of Step 3 opioid therapy	**Sativex®** Oral mucosal spray, (THC (27 mg/ml): CBD (25 mg/ml)); max. of 10 sprays/day	**Placebo** Matching placebo	Total: n = 299 Sativex®: n = 149 Placebo: n = 150	*Duration titration phase*: 2 weeks *Duration study treatment*: 3 weeks *Duration follow-up:* at end of treatment period	- Outcomes on pain - Adverse events - Functional disease outcomes	Moderate risk of bias

Reference **Country**	**Study design** **Study period**	**Study population**	**Definition chronic pain**	**Intervention**	**Comparator**	**Sample size of analysed patients**	**Duration**	**Study outcomes**	**Preliminary risk of bias assessment**
Lynch, 2014 Canada	RCT - crosso-ver NR	Adult patients with chem-otherapy-induced neuro-pathic pain, various types of cancer *Age (mean ± SD in y)* 56 ± 10.8 *Sex (% female)* 83%	Neuropathic pain persisting for 3 months after completing chemo-therapy	**Sativex®** Oral mucosal spray; concentration NR; max. of 12 sprays/day	**Placebo** Matching placebo	Total: n = 16 Sativex®: n = 16 Placebo: n = 16	*Duration titration phase*: 2 weeks *Duration study treatment*: 4 weeks *Duration wash-out*: 2 weeks *Duration follow-up:* at end of treatment period	- Outcomes on pain - Outcomes on QoL - Adverse events - Functional disease outcomes	High risk of bias
Patients with diabetes mellitus									
Toth, 2012 Canada	RCT - parallel Dec 2006- March 2011	Adult patients with pe-ripheral neuropathic pain *Age (mean ± SD in y)* 62.2 ± 9.3	Pain must have persisted for at least 3 months	**Nabilone** Flexible-dose nabilone 1-4 mg/day	**Placebo** Capsules of identical size, colour, taste, and smell	Total: n = 26 Nabilone: n = 13 Placebo: n = 13	*Duration titration phase*: 1 week (first week of treat-ment) *Duration study treatment*: 4 weeks	- Outcomes on pain - Outcomes on QoL - Adverse events - Functional disease outcomes	High risk of bias

Reference Country	Study design Study period	Study population	Definition chronic pain	Intervention	Comparator	Sample size of analysed patients	Duration	Study outcomes	Preliminary risk of bias assessment
		Sex (% female) 55%					*Duration follow-up:* at end of treatment period		
Patients with multiple sclerosis									
Langford, 2013 UK, Czech Republic, Canada, Spain, France	RCT - parallel NR	Adult patients with MS *Age (mean ± SD in y)* 48.97 ± 10.47 *Sex (% female)* 68%	Central neuro-pathic pain due to MS of at least 3 months duration	**Sativex®** Oromucosal spray 2.7 mg of THC and 2.5 mg of CBD; max. of 12 sprays/24 h	**Placebo** Placebo delivered the excipient plus colorants	Total: n = 297 THC-CBD: n = 141 Placebo: n = 156	*Duration titration phase*: 1 week *Duration study treatment*: 14 weeks *Duration follow-up:* at end of treatment period	- Outcomes on pain - Outcomes on QoL - Adverse events - Functional disease outcomes	Low risk of bias
Rog, 2005 UK	RCT - parallel March 2002-July 2002	Adult patients with MS *Age (mean ± SD in y)* 49.2 ± 8.3	Central pain for which a nociceptive	**Sativex®** Oromucusal spray with 2.7 mg of THC and 2.5 mg of CBD; max. of 48 sprays/24 h	**Placebo** Matched the appear-ance, smell, and taste of the active	Total: n = 64 CBM: n = 32 Placebo: n = 32	*Duration titration phase*: 1 week *Duration study treatment*: 4 weeks	- Outcomes on pain - Adverse events - Functional disease outcomes	Moderate risk of bias

Reference Country	Study design Study period	Study population	Definition chronic pain	Intervention	Comparator	Sample size of analysed patients	Duration	Study outcomes	Preliminary risk of bias assessment
		Sex (% female) 78.8%	cause appeared unlikely was required to be of at least 3 months' duration		formulation, but contained no active components		*Duration follow-up:* at end of treatment period		
Schimrigk, 2017 Germany	RCT - parallel June 2007-March 2010	Adult patients with MS *Age (mean ± SD in y)* 47.7 ± 9.7 *Sex (% female)* 72.9%	Moderate to severe CNP at maximal pain area for at least 3 months	**Dronabinol** Daily dose between 7.5 and 15.0 mg	**Placebo** NR	Total: n = 209 Dronabinol: n = 105 Placebo: n = 104	*Duration titration phase*: 4 weeks (first 4 weeks of treatment) *Duration study treatment*: 16 weeks *Duration follow-up:* at end of treatment period	- Outcomes on pain - Adverse events	Low risk of bias
Svendsen, 2004 Denmark	RCT - crossover	Adult patients with MS *Age (median (range) in y)*	Central pain at the maximal pain site with a pain intensity score ≥3 on a	**Dronabinol** Orally administered dronabinol; initial dose 2.5 mg daily, increased	**Placebo** Identical looking capsules	Total: n = 24 Dronabinol: n = 24 Placebo: n = 24	*Duration titration phase*: NR (within study treatment) *Duration study treatment*:	- Outcomes on pain - Outcomes on QoL - Adverse events	High risk of bias

Reference Country	Study design Study period	Study population	Definition chronic pain	Intervention	Comparator	Sample size of analysed patients	Duration	Study outcomes	Preliminary risk of bias assessment
	Feb 2002 - July 2002	50 (23-55) *Sex (% female)* 58.3%	0-10 NRS, no time period for chronic pain reported	by 2.5 mg every other day to a maximum dose of 5 mg (two capsules) twice daily			3 weeks *Duration wash-out*: 3 weeks *Duration follow-up:* at end of treatment period	- Functional disease outcomes - Preference - Sensory testing outcomes	
Wade, 2004 UK	RCT - parallel NR	Adult patients with MS experiencing significant problems from at least 1 of the following symptoms: spasticity, spasms, bladder problems, tremor, or pain *Age (mean ± SD in y)* medical cannabis: 51.0 ± 9.4; P: 50.4 ± 9.3	Pain that was not obviously musculoskeletal, no time period for chronic pain reported	**Sativex®** 2.7 mg THC and 2.5 mg CBD; self-titration to the optimal dose; max. of 120 mg THC and 120 mg CBD per day. No fixed dose per patient (dose reported in Figure only)	**Placebo** Placebo spray contained excipients only; all preparations incorporated a peppermint flavour and colouring to disguise the taste and appearance of cannabis	Total: n = 37 Sativex®: n = 18 Placebo: n = 19	*Duration titration phase*: NR *Duration study treatment*: 6 weeks *Duration follow-up:* at end of treatment period	- Outcomes on pain - Other outcomes not reported specifically for the patients with pain	High risk of bias

Reference Country	Study design Study period	Study population	Definition chronic pain	Intervention	Comparator	Sample size of analysed patients	Duration	Study outcomes	Preliminary risk of bias assessment
		Sex (% female) medical cannabis: 58.8%; P: 65%							
Patients with neuropathic pain									
Frank, 2008 UK	RCT - crosso-ver July 2001- Nov 2002	Adult patients with neuro-pathic pain (e.g. burning, stabbing, paraesthesia within the distribution of a periph-eral nerve) and a clear clini-cal history of its cause *Age (mean ± SD in y)* 48 patients 1st dihydro-codeine then nabilone: 50.6 ± 15.2	Mean pain score >40 mm on a 0-100 mm VAS	**Nabilone** Max. daily dose of 2 mg nabilone; if the patient developed side effects, the dosage was reduced to the previous value for the remainder of the RCT Escalating schedule: - week 1: 250 µg - week 2: 500 µg - week 3-4: 1 mg	**Dihydrocodeine** Max. daily dose of 240 mg dihydro-co-deine; if the patient developed side ef-fects, the dosage was reduced to the previous value for the remainder of the RCT Escalating schedule: - week 1: 30 mg	Total: n = 96 - Nabilone: n = 96 - Dihydrocodeine: n = 96	*Duration titration phase*: 1st 4 weeks of study treat-ment period *Duration study treatment*: 6 weeks *Duration wash-out*: 2 weeks *Duration follow-up:* at end of treatment period	- Outcomes on pain - Outcomes on QoL - Adverse events - Functional disease outcomes	Moderate risk of bias

Reference Country	Study design Study period	Study population	Definition chronic pain	Intervention	Comparator	Sample size of analysed patients	Duration	Study outcomes	Preliminary risk of bias assessment
		48 patients 1st nabilone then dihydrocodeine: 49.7 ± 12.0 *Sex (% female)* 48 patients 1st dihydro-codeine then nabilone: 52.1% 48 patients 1st nabilone then dihydrocodeine: 43.8%		- week 5-6: 2 mg	- week 2: 60 mg - week 3-4: 120 mg - week 5-6: 240 mg				
Wade, 2003 UK	RCT - crosso-ver Period NR	Adult patients with a neu-rological diagnosis (MS, SCI, brachial plexus damage, limb amputation due to neurofibromato-sis) and troublesome	Troublesome symptom which was stable and un-responsive to standard treatment; neuropathic pain not further defined	**Whole-plant cannabis extracts** Sublingual spray that delivered 2.5 mg THC and/or CBD at each ac-tuation; max. of 120 mg/day	**Placebo** Sublingual spray containing inert plant material and solvent only	Total: n = 12 - THC:CBD: n = 12 - CBD: n = 12 - THC: n = 12 - Placebo: n= 12	*Duration titration phase*: 1 week *Duration study treatment*: 4X2 weeks (1 week of titra-tion & 1 week of mainte-nance treatment)	- Outcomes on pain - Other outcomes not reported specifically for the patients with chronic pain	High risk of bias

Reference Country	Study design Study period	Study population	Definition chronic pain	Intervention	Comparator	Sample size of analysed patients	Duration	Study outcomes	Preliminary risk of bias assessment
		symptoms (i.e. **neuro-pathic pain**, spasticity, muscle spasms, impaired bladder control, and tremor) → **target symp-tom neuropathic pain = 13** *Age (mean ± SD in y) for all 20 patients* 48 ± NR *Sex (% female) for all 20 patients* 50%		- THC:CBD: 2.5 mg THC & 2.5 mg CBD - CBD alone: 2.5 mg CBD - THC alone: 2.5 mg THC			*Duration wash-out*: NR *Duration follow-up:* at end of treatment period		

Reference Country	Study design Study period	Study population	Definition chronic pain	Intervention	Comparator	Sample size of analysed patients	Duration	Study outcomes	Preliminary risk of bias assessment
Patients with rheumatoid arthritis									
Blake, 2006 UK	RCT - parallel NR	Adult patients with pain due to rheumatoid arthritis *Age (mean ± SD in y)* 62.8 ± 9.8 *Sex (% female)* 79%	Pain caused by rheumatoid arthritis	**Sativex®** Oromucusal spray, 2.7 mg THC and 2.5 mg CBD; max. of 6 spray/day	**Placebo** NR	Total: n = 58 Sativex®: n = 31 Placebo: n = 27	*Duration titration phase*: 2 weeks *Duration study treatment*: 3 weeks *Duration follow-up:* at end of treatment period	- Outcomes on pain - Adverse events - Functional disease outcomes	Moderate risk of bias
Patients with spinal cord injury									
Rintala, 2010 USA	RCT - crossover NR	Adult patients with central neuropathic pain after SCI *Age (mean ± SD in y)* 50.1 ± 8.3	Patients who had sustained a SCI at least 12 months before study entry and who reported chronic (>6	**Dronabinol** Started on 5 mg, titrated the dose every third day, by adding 5 mg per day each time up to a max. of 20	**Diphenhydramine** Started on 25 mg, titrating up by 25 mg every fifth day to a max. of 75 mg/day	Total: n = 5 Dronabinol: n = 5 Diphenhydramine: n = 5	*Duration titration phase*: 12 days + 7 days stabilisation *Duration study treatment*: 28 days	- Outcomes on pain - Adverse events	High risk of bias

Reference Country	Study design Study period	Study population	Definition chronic pain	Intervention	Comparator	Sample size of analysed patients	Duration	Study outcomes	Preliminary risk of bias assessment
		Sex (% female) 28.6%	months) neuro-pathic pain	mg/day, which was taken in 5 mg doses 4 times per day			*Duration wash-out*: 9 days downward titration + 7 days washout *Duration follow-up:* at end of treatment period		
Patients with upper motor neuron syndrome									
Wissel, 2006 Austria	RCT - crosso-ver NR	Adult patients with chronic upper motor neu-ron syndrome (UMNS) suffer from disabling spasticity-related pain *Age (mean in y)* 44.8 *Sex (% female)*	Spasticity-associ-ated pain was defined as pain sensation corresponding to increased spastic muscle tone while passively moving the painful body segment or limb	**Nabilone** Capsules; first week 0.5 mg Nabilone per day; 3 weeks 1 mg Na-bilone per day	**Placebo** Capsules of identical colour and taste	Total: n = 11 Nabilone: n = 11 Placebo: n = 11	*Duration titration phase*: 1 week *Duration study treatment*: 3 weeks *Duration wash-out*: 1 week *Duration follow-up:*	- Outcomes on pain - Adverse events - Functional disease outcomes	High risk of bias

Reference Country	Study design Study period	Study population	Definition chronic pain	Intervention	Comparator	Sample size of analysed patients	Duration	Study outcomes	Preliminary risk of bias assessment
		69.2%					at end of treatment period		
Patients with skeletal and locomotor system diseases									
Pinsger, 2006 Austria	RCT - crosso-ver 2003-2004	Adult patients with chronic therapy-resistant pain in causal relation-ship with a pathologic status of the skeletal and locomotor system *Age (median (quartiles) in y)* 55 (49-64) *Sex (% female)*	Chronic therapy-re-sistant pain which remains VAS >5	**Nabilone** 0.25-1 mg/day	**Placebo** Matching placebo capsules	Total: n = 21 Nabilone: n = 21 Placebo: n = 21	*Duration titration phase*: NR *Duration study treatment*: 4 weeks *Duration wash-out*: 5 weeks *Duration follow-up:* at end of treatment period	- Outcomes on pain - Outcomes on QoL - Adverse events	High risk of bias

Reference Country	Study design Study period	Study population	Definition chronic pain	Intervention	Comparator	Sample size of analysed patients	Duration	Study outcomes	Preliminary risk of bias assessment
		71%							

Keys: CBD = cannabidiol, NA = not applicable, NR = not reported, NRS = numerical rating scale, P = placebo, SD = standard deviation, VAS = visual analogue scale, y = years

Table II. Outcomes on medical cannabis use for the symptom chronic pain - Preliminary pre-specified outcomes reported in RCTs with patients with abdominal pain (AP), allodynia (A), brachial plexus injury (BPI), cancer (C), diabetes mellitus (DM), multiple sclerosis (MS), neuropathic pain (NP), rheumatoid arthritis (RA), spinal cord injury (SCI), upper motor neuron syndrome (UMNS), or skeletal and locomotor system diseases (SLSD)

Outcomes in protocol	Preliminary pre-specified outcomes reported in the RCTs	Number of RCTS reporting data on the specific outcome										
		AP	A	BPI	C	DM	MS	NP	RA	SCI	UMNS	SLSD
Efficacy of medical cannabis												
Clinically relevant patient-reported pain relief	Mean at endpoint Neuropathic Pain Scale (NPS)						1					
	Difference in NPS (Neuropathic Pain Scale) composite score		1									
	Mean change in NRS score (0-10 NRS)		1		2	1	1					
	Median percent improvement in NRS pain score				1							
	Mean VAS pain score	1					1	2				
	Minimal VAS pain score	1										

Outcomes in protocol	Preliminary pre-specified outcomes reported in the RCTs	Number of RCTS reporting data on the specific outcome										
		AP	A	BPI	C	DM	MS	NP	RA	SCI	UMNS	SLSD
	Maximal VAS pain score	1										
	Mean change in worst pain NRS score				1							
	Mean VAS pain scores differences	1										
	Mean Continuous 100-mm visual analogue scale (VAS) (pain severity)					1						
	% of patients with 30% reduction of pain score		2			1	1					
	% of patients with 50% reduction of pain score		1			1	2					
	Median percent improvement from baseline in average pain NRS score				1							
	Subject Global Impression of Change (SGIC)				1	1						
	Physician Global Impression of Change (PGIC)				1							

Outcomes in protocol	Preliminary pre-specified outcomes reported in the RCTs	Number of RCTS reporting data on the specific outcome										
		AP	A	BPI	C	DM	MS	NP	RA	SCI	UMNS	SLSD
	Number of patients rating themselves as much or very much improved (PGIC)						1					
	Difference in Pain Disability Index		1									
	Pain Disability Index (mean at endpoint)						1					
	Patient Global Impression of Change (all neuropathic pain)		1									
	Patient Global Impression of Change (pain at allodynic site)		1									
	Punctate pain pressure thresholds at end of study (in g)		1									
	SF-MPQ Pain Rating Index SF-MPQ VAS (mm)			1								

Outcomes in protocol	Preliminary pre-specified outcomes reported in the RCTs	Number of RCTS reporting data on the specific outcome										
		AP	A	BPI	C	DM	MS	NP	RA	SCI	UMNS	SLSD
	Pain Disability Index (total Score) Pain Review BS-11 Score											
	Median 11-Point-Box-Test (pain rating)										1	
	Mean Pain Treatment Satisfaction Scale (PTSS) (including 14 categories) Mean Modified Brief Pain Inventory (MBPI) (including 12 categories) Mean Neuropathic Pain Symptom Inventory (NPSI) (including 12 categories					1						
	BPI-SF (mean at endpoint) Breakthrough analgesia						1					
	Mean pain intensity (average pain intensity item from the Brief Pain Inventory, with NRS 0-10)									1		
	Mean NRS-11 pain score final treatment week Mean NRS-11 pain score mean treatment difference						1					

Outcomes in protocol	Preliminary pre-specified outcomes reported in the RCTs	Number of RCTS reporting data on the specific outcome										
		AP	A	BPI	C	DM	MS	NP	RA	SCI	UMNS	SLSD
	Mean NPS total score final treatment week Mean NPS total score mean treatment difference											
	Median spontaneous pain intensity (0-10 NRS) Median radiating pain intensity (0-10 NRS) Pain relief (0-10 NRS)						1					
	Mean pain on movement (0-10 NRS) Median pain on movement (0-10 NRS) Mean pain at rest (0-10 NRS) Median pain at rest (0-10 NRS) Short-Form McGill Pain Questionnaire (SF-MPQ); total intensity of pain Short-Form McGill Pain Questionnaire (SF-MPQ); intensity of pain at present Short-Form McGill Pain Questionnaire (SF-MPQ); pain at present								1			
	Mean spine pain intensity in the last 4 weeks (0-10 VAS) Mean current spine pain intensity (0-10 VAS) Mean headache intensity in the last 4 weeks (0-10 VAS)											1

Outcomes in protocol	Preliminary pre-specified outcomes reported in the RCTs	Number of RCTS reporting data on the specific outcome										
		AP	A	BPI	C	DM	MS	NP	RA	SCI	UMNS	SLSD
	Number of days without headache in the last 4 weeks											
	Expanded disability status scale score						1					
Withdrawal due to lack of pain relief efficacy of medical cannabis	Number of dropouts due to lack of efficacy in study arms					1	1					
Health-related quality of life	Difference in GHQ-12		1	1								
	Mean SF-36 physical				1							
	Mean SF-36 mental				1		2	1				

Outcomes in protocol	Preliminary pre-specified outcomes reported in the RCTs	Number of RCTS reporting data on the specific outcome										
		AP	A	BPI	C	DM	MS	NP	RA	SCI	UMNS	SLSD
	Physical functioning (SF-36) Role physical (SF-36) Bodily pain (SF-36) General health (SF-36) Vitality (SF-36) Social functioning (SF-36) Role emotion (SF-36)						2	1				
	Mean EQ-5D utility score at end of treatment Mean EQ-5D index score at end of treatment					1						
	EQ-5D Health state index EQ-5D Health status VAS						1					
	Increase in the QoL score (Mezzich & Cohen)											1
Safety of medical cannabis												

Outcomes in protocol	Preliminary pre-specified outcomes reported in the RCTs	Number of RCTS reporting data on the specific outcome										
		AP	A	BPI	C	DM	MS	NP	RA	SCI	UMNS	SLSD
Occurrence of cannabis-associated adverse events	Number of patients with adverse events	1	2	1	3	1	4	1	1	1	1	1
Withdrawal of treatment due to adverse effects of medical cannabis	Number of patients who discontinued treatment due to adverse events	1	1	1	2	1	2	1		1		
	Dose reduction due to adverse events						1					

Keys: NRS = numerical rating scale, VAS = visual analogue scale

Table III. Outcomes on medical cannabis use for the symptom chronic pain - Other not pre-specified outcomes reported in RCTs with patients with abdominal pain (AP), allodynia (A), brachial plexus injury (BPI), cancer (C), diabetes mellitus (DM), multiple sclerosis (MS), neuropathic pain (NP), rheumatoid arthritis (RA), spinal cord injury (SCI), upper motor neuron syndrome (UMNS), or skeletal and locomotor system diseases (SLSD)

	Other not pre-specified outcomes reported in the RCTs	Number of RCTS reporting data on the specific outcome										
		AP	A	BPI	C	DM	MS	NCP	RA	SCI	UMNS	SLSD
Efficacy of medical cannabis												
Sleep	Difference in Sleep disturbance NRS		1									
	Mean change in sleep disruption NRS				1							
	Mean sleep quality (0-10 NRS) Median sleep quality (0-10 NRS)								1			
	Sleep quality NRS (mean)						1					
	Sleep quality ratings by study visit- Adjusted mean change from baseline		1									
	Sleep Quality BS-11			1								

	Other not pre-specified outcomes reported in the RCTs	Number of RCTS reporting data on the specific outcome										
		AP	A	BPI	C	DM	MS	NCP	RA	SCI	UMNS	SLSD
	Sleep disturbance (4-point score)											
	Mean MOSSS sleep problems index score at end of treatment					1						
	Mean NRS-11 sleep disturbance score final treatment week Mean NRS-11 sleep disturbance score mean treatment difference						1					
	Treatment effect on sleep: difference between treatments							1				
Depression	Mean HADS-D (Depression) score at end of treatment					1		1				
Anxiety	Mean HADS-A (Anxiety) score at end of treatment					1		1				
Allodynia	Difference in Dynamic allodynia NRS Difference in Punctate allodynia NRS Mean reduction of dynamic allodynia in %		1									

	Other not pre-specified outcomes reported in the RCTs	Number of RCTS reporting data on the specific outcome										
		AP	A	BPI	C	DM	MS	NCP	RA	SCI	UMNS	SLSD
	Mean Allodynia score (QST)				1							
	Mean Hyperalgesia score (QST)				1							
	Allodynia pain scores		1									
Cognitive decline	Adjusted mean change Selective reminding Adjusted mean change 10/36 Spatial recall Adjusted mean change Symbol digit modalities Adjusted mean change Paced serial addition Adjusted mean change Word list generation		1									
	Mean improvement of Selective Reminding Test (SRT)						1					
Patient Satisfaction	PSQ score(value at last visit)				1							

	Other not pre-specified outcomes reported in the RCTs	Number of RCTS reporting data on the specific outcome										
		AP	A	BPI	C	DM	MS	NCP	RA	SCI	UMNS	SLSD
Multiple sclerosis	Spasticity NRS Bladder NRS Spasm severity NRS Tremor NRS Fatigue NRS						1					
Stiffness	Mean morning stiffness (0-10 NRS) Median morning stiffness (0-10 NRS)								1			
Spasticity	Mean Ashworth-Score (spasticity rating)										1	
Disease activity	28-joint disease activity score (DAS28)								1			
Sensory testing	Quantitative sensory testing: Cold detection threshold Quantitative sensory testing: Warm detection threshold Quantitative sensory testing: Cold pain threshold						1					

	Other not pre-specified outcomes reported in the RCTs	Number of RCTS reporting data on the specific outcome										
		AP	A	BPI	C	DM	MS	NCP	RA	SCI	UMNS	SLSD
	Quantitative sensory testing: Heat pain threshold Quantitative sensory testing: Cold sensibility index Quantitative sensory testing: Warm sensibility index Quantitative sensory testing: Tactile detection threshold Quantitative sensory testing: Tactile pain threshold Quantitative sensory testing: Pressure pain threshold Quantitative sensory testing: Vibration threshold Quantitative sensory testing: Temporal summation Quantitative sensory testing: Mechanical allodynia Quantitative sensory testing: Cold allodynia											
Weight loss	Mean weight loss in kg	1										
Safety of medical cannabis												
Dosing	Mean (SD) number of sprays taken during the first week of dose titration		1									
	Mean (SD) number of sprays taken daily during the study				1							

	Other not pre-specified outcomes reported in the RCTs	Number of RCTS reporting data on the specific outcome										
		AP	A	BPI	C	DM	MS	NCP	RA	SCI	UMNS	SLSD
	Mean dose of medication used				1							
	% of patients that took more than 6 sprays per day				1							
Other outcomes	Use of escape medication; number of paracetamol pills taken daily						1					
	Treatment preference						1					
	Intoxication VAS (100 mm) scores at the end of each dosing period			1								

Spasticity

Table IV. Study characteristics of the RCTs included on medical cannabis use for the symptom spasticity

Reference Country	Study design Study period	Study population	Definition spasticity	Intervention	Comparator	Sample size of analysed patients	Duration	Study outcomes	Preliminary risk of bias assessment
Patients with multiple sclerosis									
Collin, 2007 Romania, UK	RCT - parallel April 2002-March 2004	Adult patients with MS, stable disease for at least 3 months before study entry, and significant spasticity in at least 2 muscle groups *Age (mean ± SD in y)* medical cannabis: 49.7 ± 10.2 / P: 47.8 ± 9.5 *Sex (% female)* medical cannabis: 64.5% / P: 52.3%	Significant spasticity in at least two muscle groups with an Ashworth score of 2 or more	**Sativex®** 100 µl actuation: 2.7 mg THC and 2.5 mg CBD; self-titration to the optimal dose; max. of 48 sprays/day *Dose (mean ± SD):* 9.4 ± 6.4 sprays/day	**Placebo** Identically flavoured spray *Dose (mean ± SD):* 14.7 ± 8.4 sprays/day	Total: n = 184 Sativex®: n = 120 Placebo: n = 64	*Duration titration phase*: 2 weeks *Duration study treatment*: 6 weeks *Duration follow-up:* at end of treatment period	- Outcomes on spasticity - Functional MS outcomes - Adverse events	Moderate risk of bias

Reference Country	Study design Study period	Study population	Definition spasticity	Intervention	Comparator	Sample size of analysed patients	Duration	Study outcomes	Preliminary risk of bias assessment
Collin, 2010 Czech Republic, UK	RCT - parallel Period NR	Adult patients with any disease subtype of MS of at least 6-months duration, and at least a 3-month history of spasticity *Age (mean ± SD in y)* medical cannabis: 48.0 ± 10.06/ P: 47.1 ± 9.15 *Sex (% female)* medical cannabis: 63% / P: 59%	Moderate spasticity: spasticity severity of on a 0-10 NRS had to sum to at least 24 (i.e. minimum mean daily score of 4 out of 10)	**Sativex®** 100 µl actuation: 2.7 mg THC and 2.5 mg CBD; self-titration to the optimal dose; max. of 24 sprays/day *Dose (mean (range)):* 8.5 (1-22) sprays/day	**Placebo** Each actuation of placebo delivered 100 µl of vehicle containing excipients plus colourants *Dose (mean (range)):* 15.4 (2-23) sprays/day	Total: n = 337 Sativex®: n = 167 Placebo: n = 170	*Duration titration phase*: 1 week *Duration study treatment*: 14 weeks *Duration follow-up:* at end of treatment period	- Outcomes on spasticity - Outcomes on QoL - Functional MS outcomes - Adverse events	Moderate risk of bias
Corey-Bloom, 2012	RCT - crossover Period NR	Adult patients with MS and spasticity *Age (mean ± SD in y)*	Spasticity and at least moderate increase in tone: score ≥3 points on	**Smoked cannabis** About 4% delta-9-THC by weight; pre-rolled cannabis cigarettes of	**Placebo** Pre-rolled placebo cigarettes, with	Total: n = 30 Smoked cannabis: n = 30 Placebo: n = 30	*Duration study treatment*: 3 days *Duration wash-out*:	- Outcomes on spasticity - Functional MS outcomes - Adverse events	High risk of bias

Reference Country	Study design Study period	Study population	Definition spasticity	Intervention	Comparator	Sample size of analysed patients	Duration	Study outcomes	Preliminary risk of bias assessment
USA		51 ± 8 *Sex (% female)* 63%	the modified Ashworth scale at the elbow, hip or knee	~800 mg; once daily for 3 days	identical appearance and weight, once daily for 3 days		11 days *Duration follow-up:* 45 minutes after each treatment		
Leocani, 2005 NR (authors from Italy and Spain)	RCT - crossover April 2012-June 2013	Adult patients with progressive primary or secondary MS and lower limb spasticity of at least 12 months' duration *Age (mean ± SD in y)* 48 ± 7 *Sex (% female)* 44%	Moderate to severe spasticity: modified Ashworth scale score of at least 1+ in one limb	**Sativex®** THC/CBD concentration NR; self-titration to the optimal dose; max. of 12 sprays/day *Dose (mean ± SD):* 7 ± 3 sprays/day	**Placebo** NR *Dose (mean ± SD):* 10 ± 3 sprays/day	Total: n = 34 Sativex®: n = 34 Placebo: n = 34	*Duration titration phase*: 2 weeks *Duration study treatment*: 4 weeks *Duration wash-out*: 2 weeks *Duration follow-up:* at end of treatment period	- Outcomes on spasticity - Functional MS outcomes - Neurophysiology outcomes - Adverse events	High risk of bias

Reference Country	**Study design Study period**	**Study population**	**Definition spasticity**	**Intervention**	**Comparator**	**Sample size of analysed patients**	**Duration**	**Study outcomes**	**Preliminary risk of bias assessment**
Markovà, 2019 Austria, Czech Republic	RCT - parallel Period NR	Adult patients with MS and existing moderate to severe MS spasticity symptoms for at least 12 months *Age (mean ± SD in y) for 191 patients in phase A* 51.3 ± 10.2 *Sex (% female) for 191 patients in phase A* 70.2%	Moderate to severe MS spasticity: score of ≥4 on the MS spasticity 0-10 NRS	**Sativex®** THC/CBD concentration NR; self-titration to the optimal dose; max. of 12 sprays/day *Dose (mean ± SD):* 7.3 ± 2.7 sprays/day	**Placebo** NR *Dose (mean ± SD):* 8.5 ± 3.0 sprays/day	Total: n = 96 Sativex®: n = 50 Placebo: n = 46	*Duration titration phase A*: 4 weeks *Duration wash-out*: 1-4 weeks *Duration study treatment phase B*: 12 weeks *Duration follow-up:* at end of treatment period	- Outcomes on spasticity - Outcomes on QoL - Functional MS outcomes - Adverse events	High risk of bias
Novotna 2011	RCT - parallel Period NR	Adult patients with MS of any subtype for ≥6	Moderately severe spasticity: score of ≥4 using a single	**Sativex®** 100 µl actuation: 2.7 mg THC and 2.5 mg CBD;	**Placebo** NR *Dose (mean ± SD):*	Total: n = 224 Sativex®: n = 109 Placebo: n = 115	*Duration titration phase*: 4 weeks in phase A & 10 days in phase B	- Outcomes on spasticity - Outcomes on QoL - Functional MS outcomes	Moderate risk of bias

Reference Country	Study design Study period	Study population	Definition spasticity	Intervention	Comparator	Sample size of analysed patients	Duration	Study outcomes	Preliminary risk of bias assessment
Czech Republic, Italy, Poland, Spain, UK		months, with moderately severe spasticity for ≥3 months *Age (mean ± SD in y) for 241 patients randomised to phase B*: 48.6 ± 9.3 *Sex (% female) for 241 patients randomised to phase B*: 60%	spasticity 0-10 severity NRS	self-titration to the optimal dose; max. of 12 sprays/day *Dose (mean ± SD):* 8.3 ± 2.4 sprays/day	8.9 ± 2.3 sprays/day		*Duration study treatment phase B*: 12 weeks *Duration follow-up:* plus 2 weeks end of treatment	- Adverse events	
Van Amerongen, 2018 The Netherlands	RCT - parallel Aug 2011-Jan 2013	Adult patients with progressive (primary or secondary) MS with a duration of >1 year, moderate spasticity and pain	Moderate spasticity: Ashworth score of ≥2 (range 0-4)	**Delta-9-THC tablets** Tablets with 1.5 or 5 mg of delta-9-THC and contained no other active ingredients; fixed dosing regimen thrice daily of	**Placebo** Matching placebo tablets *Dose (mean ± SD):* NR	Total: n = 24 Delta-9-THC tablets: n = 12 Placebo: n = 12	*Duration titration phase*: 2 weeks *Duration study treatment*: 4 weeks	- Outcomes on spasticity - Functional MS outcomes - Adverse events	High risk of bias

Reference Country	Study design Study period	Study population	Definition spasticity	Intervention	Comparator	Sample size of analysed patients	Duration	Study outcomes	Preliminary risk of bias assessment
		Age (mean ± SD in y) medical cannabis: 57.3 ± 9.0 / P: 51.4 ± 8.0 *Sex (% female)* medical cannabis: 66.7% / P: 66.7%		the starting dose as determined during the challenge phase; max. of 28.5 mg/day *Dose (mean ± SD):* NR; in Figure and narratively in text			*Duration follow-up:* at end of treatment period		
Vaney, 2004 Switzerland	RCT - crossover April 2000-April 2001	Adult patients with MS and clinically stable spasticity *Age (mean ± SD in y)* n=57 randomised: 54.9 ± 10.0 *Sex (% female)* n=57 randomised: 29%	Spasticity: at least 1 joint scoring ≥2 on the Ashworth scale	**Cannabis-extract capsules** Standardised to 2.5 mg THC and 0.9 mg CBD; orally taken as an add-on therapy; max. of 12 capsules daily (i.e. 30 mg THC/day)	**Placebo** Capsules identical in shape, taste and colour; max. of 12 capsules daily	Total: n = 50 Cannabis capsules: n = 50 Placebo: n = 50	*Duration titration phase*: 5 days *Duration study treatment*: 9 days maintenance dose; 7 days placebo *Duration wash-out*: 3 days	- Outcomes on spasticity - Functional MS outcomes - Adverse events	High risk of bias

Reference Country	Study design Study period	Study population	Definition spasticity	Intervention	Comparator	Sample size of analysed patients	Duration	Study outcomes	Preliminary risk of bias assessment
							Duration follow-up: at end of treatment periods		
Wade, 2004 UK	RCT - parallel Period NR	Adult patients with MS experiencing significant problems from at least one of the following symptoms: spasticity, spasms, bladder problems, tremor, or pain *Age (mean ± SD in y) for all 160 patients:* medical cannabis: 51.0 ± 9.4 / P: 50.4 ± 9.3 *Sex (% female) for all 160 patients:* medical	Spasticity as primary symptom, not further defined	**Sativex®** 2.7 mg THC and 2.5 mg CBD; self-titration to the optimal dose; max. of 120 mg THC and 120 mg CBD per day *Dose (mean ± SD):* In Figure only	**Placebo** Placebo spray contained excipients only; all preparations incorporated a peppermint flavour and colouring to disguise the taste and appearance of cannabis *Dose (mean ± SD):* In Figure only	Total: n = 39 Sativex®: n = 20 Placebo: n = 19	*Duration titration phase*: NR *Duration study treatment*: 6 weeks *Duration follow-up:* at end of treatment period	- Outcomes on spasticity - Other outcomes not reported specifically for the patients with spasticity	High risk of bias

Reference Country	Study design Study period	Study population	Definition spasticity	Intervention	Comparator	Sample size of analysed patients	Duration	Study outcomes	Preliminary risk of bias assessment
		cannabis: 47% / P: 52%							
Zajicek, 2003 & Zajicek, 2005 UK	RCT - parallel & follow-up RCT Dec 2000-Oct 2003	Adult patients with stable MS in the previous 6 months and problematic spasticity *Age (mean ± SD in y)* Delta-9-THC: 50.2 ± 8.2 / Cannabis extract: 50.5 ± 7.6 / P: 50.9 ± 7.6 *Sex (% female)* Delta-9-THC: 69.4% / Cannabis extract: 64.0% / P: 63.4%	Problematic spasticity: Ashworth score of ≥2 in 2 or more lower limb muscle groups	**Synthetic delta-9-THC (Marinol®) or cannabis-extract (Cannador®)** - Marinol®: synthetic delta-9-THC capsules - Cannador®: cannabis extract, containing delta-9-THC and cannabidiol as the main cannabinoids - Capsules contained 2.5 mg of delta-9-THC equivalent, 1.25 mg of cannabidiol, and <5% other cannabinoids; dose based on bodyweight, max. of 25 mg daily	**Placebo** Capsules matched to either Marinol® or Cannador®	**Original RCT** Total: n = 611 Delta-9-THC: n = 197 Cannabis extract: n = 207 Placebo: n = 207 **Follow-up of RCT** Total: n = 502 Delta-9-THC: n = 154 Cannabis extract: n = 172 Placebo: n = 176	*Duration titration phase*: 5 weeks *Duration study treatment*: 8 weeks *Duration study treatment reduction to 0*: 2 weeks *Duration follow-up:* - at end of treatment period - at 12 months in a follow-up study of the RCT	- Outcomes on spasticity - Functional MS outcomes - Adverse events	Low risk of bias (however, no table with all raw data for primary outcomes)

Reference Country	Study design Study period	Study population	Definition spasticity	Intervention	Comparator	Sample size of analysed patients	Duration	Study outcomes	Preliminary risk of bias assessment
Patients with motor neuron disease									
Riva, 2018 Italy	RCT - parallel Jan 2013-Dec 2014	Adult patients with MND (i.e. amyotrophic lateral sclerosis or primary lateral sclerosis) and spasticity for at least 3 months *Age (mean ± SD in y)* medical cannabis: 58.4 ± 10.6 / P: 57.2 ± 13.8 *Sex (% female)* medical cannabis: 38% / P: 47%	Spasticity score of ≥1 on the 5-point Modified Ashworth Scale in ≥2 muscle groups	**Nabiximols (Sativex® not specifically reported)** 100 µl actuation: 2.7 mg THC and 2.5 mg CBD in a 50:50 solution of ethanol and propylene glycol; self-titration to the optimal dose; max. of 12 sprays/day *Dose (mean ± SD):* 8.03 ± 2.9 sprays/day	**Placebo** Placebo solutions were transparent and indistinguishable from intervention *Dose (mean ± SD):* 11.2 ± 1.4 sprays/day	Total: n = 59 Nabiximols: n = 29 Placebo: n = 30	*Duration titration phase*: 2 weeks *Duration study treatment*: 4 weeks *Duration follow-up:* at end of treatment period	- Outcomes on spasticity - Functional MND outcomes - Adverse events	Moderate risk of bias
Patients with spinal cord injury									

Reference Country	Study design Study period	Study population	Definition spasticity	Intervention	Comparator	Sample size of analysed patients	Duration	Study outcomes	Preliminary risk of bias assessment
Pooyania, 2010 Canada	RCT - crossover Period NR	Adult patients with SCI (level of injury at C5 or below), injury occurred ≥1 year previously, stable neurologic level, and with moderate spasticity *Age (mean ± SD in y)* 42.4 ± 7.79 *Sex (% female)* 0%	Moderate spasticity: Ashworth ≥3	**Nabilone** 0.5 mg once a day first 2 weeks with option to increase to 0.5 mg twice a day in the last 2 weeks of treatment *Dose increase:* n=7; n=2 dropped back; n=5 till end of study	**Placebo** Orally administered; once a day first 2 weeks with option to increase to twice a day in the last 2 weeks of treatment *Dose increase:* n=11	Total: n = 11 Nabilone: n = 11 Placebo: n = 11	*Duration titration phase*: NA *Duration study treatment*: 4 weeks *Duration wash-out*: 2 weeks *Duration follow-up:* at end of treatment period	- Outcomes on spasticity - Functional SCI outcomes - Adverse events	High risk of bias
Mixed population of different diagnoses									
Wade, 2003 UK	RCT - crossover Period NR	Adult patients with a neurological diagnosis (MS, SCI, brachial plexus damage, limb	Troublesome symptom which was stable and unresponsive to standard treatment;	**Whole-plant cannabis extracts** Sublingual spray that delivered 2.5 mg THC	**Placebo** Sublingual spray containing inert plant material and solvent only	Total: n = 8 - THC:CBD: n = 8 - CBD: n = 8 - THC: n = 8	*Duration titration phase*: 1 week *Duration study treatment*:	- Outcomes on spasticity - Other outcomes not reported specifically for the patients with spasticity	High risk of bias

Reference Country	Study design Study period	Study population	Definition spasticity	Intervention	Comparator	Sample size of analysed patients	Duration	Study outcomes	Preliminary risk of bias assessment
		amputation due to neurofibromatosis) and troublesome symptoms (i.e. neuropathic pain, **spasticity**, muscle spasms, impaired bladder control, and tremor) **→ target symptom spasticity = 9** *Age (mean ± SD in y) for all 20 patients* 48 ± NR *Sex (% female) for all 20 patients* 50%	spasticity not further defined	and/or CBD at each actuation; max. of 120 mg/day - THC:CBD: 2.5 mg THC & 2.5 mg CBD - CBD alone: 2.5 mg CBD - THC alone: 2.5 mg THC		- Placebo: n = 8	4X2 weeks (1 week of titration & 1 week of maintenance treatment) *Duration wash-out*: NR *Duration follow-up:* at end of treatment period		

Keys: MND = motor neuron disease, NA = not applicable, NR = not reported, NRS = numerical rating scale, P = placebo, SD = standard deviation, y = years

Table V. Outcomes on medical cannabis use for the symptom spasticity - Preliminary pre-specified outcomes reported in RCTs with patients with multiple sclerosis (MS), motor neuron disease (MND), spinal cord injury (SCI), or a mixed population (MIX)

Outcomes in protocol	Preliminary pre-specified outcomes reported in the RCTs	Number of RCTS reporting data on the specific outcome			
		MS	MND	SCI	MIX
Efficacy of medical cannabis					
Clinically relevant improvement in a specific spasticity aspect	Mean Ashworth scale score	3	0	0	1
	Mean Ashworth scale score in most involved muscle group	0	0	1	0
	Mean Ashworth scale score in 8 muscle groups	0	0	1	0
	Mean modified Ashworth scale score	6	1	0	0
	Mean modified Ashworth scale score per muscular group, 0-4 scale	1	0	0	0
	Spasticity 0-10 NRS	6	1	0	0
	Spasticity severity NRS	0	0	0	1
	Mean VAS for spasticity	2	0	1	1
	Mean Motricity Index (legs)	2	0	0	0
	Mean Motricity Index (arms)	2	0	0	0
	% treatment responders (patients with ≥20% improvement in MAS score or spasticity NRS)	1	0	0	0

Outcomes in protocol	Preliminary pre-specified outcomes reported in the RCTs	Number of RCTS reporting data on the specific outcome			
		MS	MND	SCI	MIX
	% treatment responders (patients with ≥30% improvement in spasticity NRS)	3	0	0	0
	% treatment responders (patients with ≥50% improvement in spasticity NRS)	3	0	0	0
	Wartenberg Pendulum Test, rotational damping ratio (n=1 SCI)	0	0	1	0
	Wartenberg Pendulum Test, rotational natural frequency (n=1 SCI)	0	0	1	0
Withdrawal due to lack of anti-spasticity efficacy of medical cannabis	Number of dropouts due to lack of efficacy in study arms	2	0	0	0
Health-related quality of life	Mean EQ-5D (health state index)	2	0	0	0
	Mean EQ-5D (health status VAS score)	2	0	0	0
	Mean MSQoL-54 (physical health composite)	1	0	0	0
	Mean MSQoL-54 (mental health composite)	1	0	0	0
	SF-36	2	0	0	0
Safety of medical cannabis					

Outcomes in protocol	Preliminary pre-specified outcomes reported in the RCTs	Number of RCTS reporting data on the specific outcome			
		MS	MND	SCI	MIX
Occurrence of cannabis-associated adverse events	Number of patients with adverse events	10	1	1	0
Withdrawal of treatment due to adverse effects of medical cannabis	Number of patients who discontinued treatment due to adverse events	6	0	0	0
	Number of patients who discontinued treatment due to non-serious adverse events	1	0	0	0

Keys: MAS = modified Ashworth scale score, MIX = mixed population, MND = motor neuron disease, MS = multiple sclerosis, NRS = numerical rating scale, SCI = spinal cord injury, VAS = visual analogue scale

Table VI. Outcomes on medical cannabis use for the symptom spasticity - Other not pre-specified outcomes reported in RCTs with patients with multiple sclerosis (MS), motor neuron disease (MND), spinal cord injury (SCI), or a mixed population (MIX)

	Other not pre-specified outcomes reported in the RCTs	Number of RCTS reporting data on the specific outcome			
		MS	MND	SCI	MIX
Efficacy of medical cannabis					
	H/M ratio	2	0	0	0

	Other not pre-specified outcomes reported in the RCTs	Number of RCTS reporting data on the specific outcome			
		MS	MND	SCI	MIX
Neurophysiological measures of spasticity	RMT	1	0	0	0
	MEP 120	1	0	0	0
	SICI	1	0	0	0
	ICF	1	0	0	0
	MEP/MAP ratio	1	0	0	0
Neurological disability	United Kingdom neurological disability score (UKNDS)	1	0	0	0
Spasms	Mean daily spasm scores on 5-point spasm frequency score	1	0	0	0
	Mean daily spasm scores on 3-point spasm frequency score	1	0	0	0
	Mean spasm frequency scale	0	1	1	0
	Mean number of spasm frequency	2	0	0	0
	Mean spasm severity NRS	1	0	0	0
	Mean spasm severity 0-3 scale	1	0	0	0
	Mean tremor 0-10 NRS	1	0	0	0

	Other not pre-specified outcomes reported in the RCTs	Number of RCTS reporting data on the specific outcome			
		MS	MND	SCI	MIX
Tremor	Tremor in diary	1	0	0	0
Walk function	Timed 10-meter walk	7	1	0	0
	Timed 25-Foot Walk	1	0	0	0
Mobility	Rivermead Mobility Index	2	0	0	0
Finger dexterity	9-Hole Peg Test	2	0	0	0
Muscle strength	Medical Research Council sum score	0	1	0	0
Pain	Mean pain 0-10 NRS	4	1	0	0
	Mean pain on VAS	2	0	0	0
Sleep	Sleep quality 0-10 NRS	2	0	0	0
	Sleep disruption NRS score, 0-10 scale	2	1	0	0
	Pittsburgh Sleep Quality Index	1	0	0	0
	Falling asleep fast, in diary	1	0	0	0

	Other not pre-specified outcomes reported in the RCTs	Number of RCTS reporting data on the specific outcome			
		MS	MND	SCI	MIX
	Waking up again, in diary	1	0	0	0
Fatigue	Fatigue Severity Scale	2	0	0	0
	Mean fatigue 0-10 NRS	1	0	0	0
	Mean fatigue, mFIS score	1	0	0	0
Bladder symptoms	Mean bladder symptom 0-10 NRS	1	0	0	0
	Micturition in diary	1	0	0	0
Global disease impression	Global impression of change (PGIC) in their disease	3	0	0	0
	Mean carers global impression of change	2	1	0	0
	Mean clinician global impression of change	0	1	1	0
	Mean patient or subject global impression of change (SGIC)	1	1	1	0
	Mean perceived deficits, PDQ score	1	0	0	0
	Mean symptoms, BSI score	1	0	0	0
	MS EDSS score	2	0	0	0
	Amyotrophic Lateral Sclerosis Functional Rating Score-Revised	0	1	0	0

	Other not pre-specified outcomes reported in the RCTs	Number of RCTS reporting data on the specific outcome			
		MS	MND	SCI	MIX
	Upper motor neuron score	0	1	0	0
General health	General health questionnaire (GHQ-30)	1	0	0	0
Body-mass index	BMI, kg/m^2 (n=1 MND)	0	1	0	0
Lung function	Forced vital capacity, max % predicted (n=1 MND)	0	1	0	0
Activities of daily living	Mean Barthel ADL index	4	1	0	0
	Nottingham Extended ADL Index (n=1 MS)	1	0	0	0
Cognitive function	Mean cognitive function, PASAT score	3	0	0	0
	Digit span of the WAIS R intelligence scale	2	0	0	0
Safety of medical cannabis					
	Mean perceived “highness”, SRHS–R score	1	0	0	0
	Intensity of adverse events (moderate, mild, severe)	1	0	0	0

Keys: H/M ratio = calculated as the maximal peak-to-peak amplitudes of the H-reflex and M-response to supramaximal nerve stimulation, ICF = intracortical facilitation, MAP = motor action potentials, MEP = motor evoked potentials, MIX = mixed population, MND = motor neuron disease, NRS = numerical rating scale, RMT = resting motor threshold, SICI = average of conditioned MEP amplitude evoked at ISI 1-3 ms, VAS = visual analogue scale

Unintentional weight loss

Table VII. Study characteristics of the RCTs included on medical cannabis use for the symptom unintentional weight loss

Reference Country	Study design Study period	Study population	Definition weight loss	Intervention	Comparator	Sample size of analysed patients	Duration	Study outcomes	Preliminary risk of bias assessment
Patients with HIV or AIDS									
Beal, 1995 USA	RCT - parallel NR	Adult patients with at least one AIDS-defining event *Age (mean ± SD in y)* medical cannabis: 38.3 ± 8.54 / P: 39.3 ± 7.79 *Sex (% female)* medical cannabis: 6.9% / P: 7.5%	A loss of at least 2.3 kg from normal body weight; period of weight loss NR)	**Dronabinol** Oral dronabinol 2.5 mg twice daily	**Placebo** Identical capsules containing no dronabinol to be taken according to the same schedule	Total: n = 139 Dronabinol: n = 72 Placebo: n = 67	*Duration study treatment*: not clear *Duration follow-up:* at least 4 weeks *Duration concurrent weight loss treatment:* NA – not allowed during trial	- Outcomes on weight - Outcomes on appetite - Outcomes on treatment duration - Adverse events	High risk of bias
Struwe, 1993	RCT - crossover	Adult patients with HIV	A loss at least 2.25 kg of usual body	**Dronabinol**	**Placebo** NR	Total: n = 5 Dronabinol: n = 5	*Duration study treatment*: 5 weeks	- Outcomes on weight	High risk of bias

Reference Country	Study design Study period	Study population	Definition weight loss	Intervention	Comparator	Sample size of analysed patients	Duration	Study outcomes	Preliminary risk of bias assessment
USA	Dec 1990 - Oct 1991	*Age (mean ± SD in y)* 38.0 ± 7.3 *Sex (% female)* 0% - all males	weight (from clinic records documented by sequential weights on the same scale; period of weight loss NR)	Oral dronabinol 5.0 mg bid one-half hour before lunch and dinner		Placebo: n = 5	*Duration follow-up:* 35 days *Duration concurrent weight loss treatment:* NA – not allowed during trial	- Outcomes on body composition - Outcomes on energy intake - Outcomes on appetite	
Patients with cancer									
Jatoi, 2002 USA	RCT - parallel Dec 1996 - Dec 1999	Adult patients with histologic evidence of an incurable malignancy other than brain, breast, ovarian, or endometrial cancer *Age (mean ± SD in y)*	Self-reported weight loss of at least 2.3 kg during the preceding 2 months and/or a physician-estimated caloric intake of less than 20 calories/kg of body weight per day	**Dronabinol + placebo** Oral dronabinol 2.5 mg twice daily plus capsule placebo **Dronabinol + megestrol acetate** Combination of both in the same dosages	**Megestrol acetate + placebo** Liquid suspension 800 mg daily plus capsule placebos	Total: n = 469 Dronabinol + placebo: n = 152 Dronabinol + megestrol acetate: n = 158 Megestrol acetate + placebo: n = 159	*Duration study treatment*: median time on study: - Dronabinol + placebo: 57 days - Dronabinol + megestrol acetate: 74 days - Megestrol acetate + placebo: 80 days *Duration follow-up:* 1 month	- Outcomes on weight - Outcomes on appetite - Outcomes on QoL - Outcomes on treatment duration - Adverse events	High risk of bias

Reference Country	Study design Study period	Study population	Definition weight loss	Intervention	Comparator	Sample size of analysed patients	Duration	Study outcomes	Preliminary risk of bias assessment
		medical cannabis+P: 67 ± 10 / medical cannabis+AT: 67 ± 10 / AT+P: 65 ± 11 *Sex (% female)* medical cannabis+P: 34% / medical cannabis+AT: 34% / AT+P: 35%					*Duration concurrent cancer treatment*: NA		
Turcott, 2018 Mexico	RCT - parallel Dec 2013 - Dec 2015	Adult patients with stage III and IV non-small cell lung cancer *Age (mean ± SD in y)* medical cannabis: 61.1 ± 10.6 / P: 52.6 ± 11.8	Diagnosed with anorexia according to the Anorexia/ Cachexia Scale	**Nabilone** 0.5 mg daily, the dose was subsequently increased to 1 mg daily	**Placebo** NR	Total: n = 22 Nabilone: n = 9 Placebo: n = 13	*Duration study treatment*: 8 weeks *Duration follow-up:* 4 weeks, 8 weeks	- Outcomes on weight - Outcomes on malnourishment - Outcomes on appetite - Outcomes on energy intake - Outcomes on QoL	High risk of bias

Reference Country	Study design Study period	Study population	Definition weight loss	Intervention	Comparator	Sample size of analysed patients	Duration	Study outcomes	Preliminary risk of bias assessment
		Sex (% female) medical cannabis: 78.6% / P: 78.9%					*Duration concurrent cancer treatment*: 8 weeks (chemotherapy)		
Strasser, 2006 Germany	RCT - parallel Oct 1999 - Sept 2002	Adult patients with advanced incurable cancer who were candidates for appetite stimulation *Age (mean ± SD in y)* THC: 60 ± 12 / THC+CBD: 61 ± 12 / P: 62 ± 10 *Sex (% female)* THC: 48% / THC+CBD: 53% / P: 48%	Having had, within the past 6 months, involuntary weight loss of 5% not explained by other diseases or recent surgery	**THC** Oral THC 2.5 mg twice daily **THC + CBD** Oral THC 2.5 mg + 1 mg CBD daily	**Placebo** Identical capsules containing standardisation medium	Total: n = 243 THC: n= 100 THC + CBD: n = 95 Placebo: n = 48	*Duration study treatment*: 6 weeks *Duration follow-up*: 6 weeks *Duration concurrent cancer treatment*: NA	- Outcomes on appetite - Outcomes on QoL - Adverse events	Moderate risk of bias

Keys: AT = alternative treatment, NA = not applicable, NR = not reported, P = placebo, SD = standard deviation, y = year

Table VIII. Outcomes on medical cannabis use for the symptom unintentional weight loss - Preliminary pre-specified outcomes reported in RCTs with patients with HIV/AIDS (HA) or cancer (C)

Outcomes in protocol	Preliminary pre-specified outcomes reported in the RCTs	Number of RCTS reporting data on the specific outcome	
		HA (n)	C (n)
Efficacy of medical cannabis			
Weight gain	Mean weight gain in kg	1	1
	Median weight change in kg	1	0
	% of patients with 2 kg weight gain	1	0
	% of patients with 0%, 1-4%, 5-9% maximal weight gain	0	1
	% of patients with ≥10% weight gain (self-reported and physician-reported)	0	1
Daily caloric intake	Mean energy intake kcal/day	0	1
	Median caloric intake (kcal/kg/24h)	1	0
Withdrawal due to lack of appetite stimulating efficacy of medical cannabis	% dropout rate in study arms	1	0
Health-related quality of life	Maximum QoL Minus Baseline Scores – Uniscale and FAACT-AN	0	1
	Mean QoL status at baseline, 4 and 8 weeks (EORTC-QLQ-C30 and QLQ-LC13)	0	1

Outcomes in protocol	Preliminary pre-specified outcomes reported in the RCTs	Number of RCTS reporting data on the specific outcome	
		HA (n)	C (n)
	Mean QoL measures (functioning, fatigue, nausea & vomiting, pain, appetite loss, insomnia) (EORTC-QLQ-C30 and QLQ-LC13)	0	1
	Mean (SD) overall QoL after 6 weeks (Quality of life: mean of the two categorical scales of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30, questions 29 (Global Health Status) and 30 (Quality of Life), transformed to a 0% to 100% scale)	0	1
Safety of medical cannabis			
Occurrence of cannabis-associated adverse events	Number of patients with mild, moderate, or severe adverse events	1	0
	Number of patients with events	0	1
	Proportion of patients with maximum patient-reported toxicities	0	1
Withdrawal of treatment due to adverse effects of medical cannabis	Not reported	-	-

Keys: C = cancer, HA = HIV/AIDS, QoL = quality of life

Table IX. Outcomes on medical cannabis use for the symptom unintentional weight loss - Other not pre-specified outcomes reported in RCTs with patients with HIV/AIDS (HA) or cancer (C)

Other not pre-specified outcomes reported in the RCTs		Number of RCTS reporting data on the specific outcome	
		HA (n)	C (n)
Efficacy of medical cannabis			
Body composition	Mean BMI	0	1
	Median body fat change %	1	0
Anorexia	Presence of anorexia according to AC/S	0	1
	Improvement in the overall score (arithmetic mean) on the Anorexia-Cachexia EORTC QLQ-C30 module	0	1
Daily intake	Mean protein, carbohydrates, fats, iron intake (mg or g/day) (n=1 C)	0	1
Appetite	% mean increase in appetite (VAS 100 mm scale) [VAS score presented in Figure]	1	0
	Median appetite change (VAS 100 mm scale)	1	0
	% of patients with increase in appetite (8 questionnaire questions – no VAS)	0	1
	Appetite loss (VAS – scale not described)	0	1
	Improvement in appetite (VAS 100 mm scale)	0	1
	Increased appetite (best biweekly value over baseline)	0	1

Other not pre-specified outcomes reported in the RCTs		Number of RCTS reporting data on the specific outcome	
		HA (n)	C (n)
	% of patients with improvement in appetite VAS score (100 mm scale)	0	1
Mood	% of patients with improved mood (VAS 100 mm scale)	1	0
	Mood improvements? (VAS? – score not clear)	0	1
Nausea	% of patients with decreased nausea (VAS 100 mm scale)	1	0
Performance status	Mean difference performance status according to Karnofsky scale (100 points scale)	1	0
Blood tests	Multiple blood measures (blood cells, albumin, neutrophils/lymphocytes ratio, platelets/lymphocytes Ratio)	0	1
	Median serum prealbumin change	1	0
Safety of medical cannabis			
Duration of treatment	Duration of therapy (median days + mean ± SD)	1	0
	Median time in the study in days	0	1

Keys: BMI = body mass index, C = cancer, HA = HIV/AIDS, QoL = quality of life, VAS = visual analogue scale

Table X. Study characteristics of the RCTs included on medical cannabis use for the symptom nausea & vomiting related to cancer treatment - paediatrics

Reference Country	Study design Study period	Study population	Definition nausea & vomiting	Intervention	Comparator	Sample size of analysed patients	Duration	Study outcomes	Preliminary risk of bias assessment
Studies including only children									
Chan, 1987 Canada	RCT - crossover Feb 1982-April 1983	Paediatric patients treated with chemotherapy for various malignancies *Age (mean (range) in y)* 11.8 (3.5-17.8) *Sex (% female)* NR	During each cycle of chemotherapy, the total number of episodes of retching or vomiting noted were immediately recorded onto a card by a nurse or a parent, 3 category scale	**Nabilone** - 1 mg capsules, patients received a single dose 8 to 12 hours preceding chemotherapy, and the same dose was repeated 2 or 3 times daily, according to a dosage schedule based on the patient's weight	**Prochlorperazine** 5 mg capsules, similar schedules as nabilone	Total: n = 30 Nabilone: n = 30 Prochlorperazine: n = 30 - 17 patients were treated with reduced doses	*Duration study treatment*: 1 cycle of chemotherapy *Duration follow-up:* Within 24 hours of completion of each cycle *Duration concurrent cancer treatment:* various chemotherapy regimen were used, duration of cycles NR	- Outcomes on vomiting and retching - Preference - Adverse events	High risk of bias

Reference Country	Study design Study period	Study population	Definition nausea & vomiting	Intervention	Comparator	Sample size of analysed patients	Duration	Study outcomes	Preliminary risk of bias assessment
				- During the tenth month of the trial, the doses of nabilone and prochlorperazine were reduced because of major adverse effects					
Dalzell, 1986 UK	RCT - crossover NR (during a 16 months period)	Paediatric patients receiving emetogenic antineoplastic chemotherapy for malignant disease *Age (mean (range)* <17 years (10 mo-17 y)	Patient (parent) questionnaires on frequency of actual vomiting, degree of nausea, 4 category scale	**Nabilone** <18 kg: 0.5 mg twice a day 18-36 kg: 1 mg twice a day >36 kg: 1 mg three times a day - If vomiting was severe enough to prevent effectively oral	**Domperidone** <18 kg: 5 mg 3 times a day 18-36 kg: 10 mg 3 times a day >36 kg: 15 mg 3 times a day	Total: n = 18 Nabilone: n = 18 Domperidone: n = 18	*Duration study treatment*: 1 cycle of chemotherapy *Duration follow-up:* During 1 cycle *Duration concurrent cancer treatment:*	- Outcomes on nausea - Outcomes on vomiting - Requiring extra antiemetic drugs - Preference - Adverse events	High risk of bias

Reference Country	Study design Study period	Study population	Definition nausea & vomiting	Intervention	Comparator	Sample size of analysed patients	Duration	Study outcomes	Preliminary risk of bias assessment
		Sex (% female) 17.4%		antiemetic therapy then parenteral (intravenous) domperidone was allowed			Various chemotherapies were used, duration of cycles NR		
Studies including children and adults									
Einhorn, 1981 USA	RTC - crossover NR	Patients receiving combination chemotherapy for neoplastic disease *Age (median (range) in y)* 28 (15-74) *Sex (% female)*	Patients completed a case report every 24 hours. Nausea was rated on 4 category scale; episodes of emesis were counted	**Nabilone** - 2 mg orally every 6 hours as required - Subsequently, the study design was altered for the last 44 patients to allow for 3 dosages starting 12 hours before chemotherapy	**Prochlorperazine** 10 mg orally every 6 hours as required	Total: n = 80 Nabilone: n = 80 Prochlorperazine: n = 80	*Duration study treatment*: 1 cycle of chemotherapy *Duration follow-up:* During 1 cycle *Duration concurrent cancer treatment:* Various chemotherapies were used, chemotherapy cycles ranged from 1-8 days	- Outcomes on nausea - Outcomes on vomiting - Preference - Drop out due to toxicity - Adverse events	High risk of bias

Reference Country	Study design Study period	Study population	Definition nausea & vomiting	Intervention	Comparator	Sample size of analysed patients	Duration	Study outcomes	Preliminary risk of bias assessment
		NR, 87.5% of the patients had testicular cancer							
Sallan, 1980 USA	RCT - crossover NR	Patients known to have neoplasms *Age (mean (range) in y)* 32.5 (9-70) *Sex (% female)* 39.3%	Nausea and vomiting were assessed with a questionnaire, 3 category scale was used for response	**THC** Gelatine capsules, THC dosage was 10 mg per square meter of body surface area, with 15 mg the amount most commonly administered	**Prochlorperazine** Tablets were crushed, and 10 mg of the drug was placed into capsules to look identical to the THC capsules	Total: n = 38 THC: n = 56 courses Prochlorperazine: n = 58 courses Each patient receives 3 1-day courses of a study drug (2 courses with 1 drug and 1 course with the other)	*Duration study treatment*: One day, starting 1 h before chemotherapy *Duration follow-up:* Assessment were made the day after treatment *Duration concurrent cancer treatment:* Various chemotherapies were used, duration of cycles NR	- Outcomes on nausea - Outcomes on vomiting - Drop out due to toxicity - Adverse events	High risk of bias

Keys: h = hours, NR = not reported, y = years

Table XI. Study characteristics of the RCTs included on medical cannabis use for the symptom nausea & vomiting related to cancer treatment - adults

Reference **Country**	**Study design** **Study period**	**Study population**	**Definition nausea & vomiting**	**Intervention**	**Comparator**	**Sample size of analysed patients**	**Duration**	**Study outcomes**	**Preliminary risk of bias assessment**
Ahmedzai, 1983 UK	RCT - crossover NR	Patients with small cell bronchial carcinoma *Age (median (range) in y)* 58 (27-72) *Sex (% female)* 44%	Self-rating symptom questionnaire, covering anorexia, nausea, retching and vomiting, 4 category scale	**Nabilone** Dosage 2 x 1 mg capsules at 10.00 am and 10.00 pm	**Prochlorperazine** Dosage 2 x 5mg tablets at 6.00 am, 2.00 pm and 10.00 pm	Total: n = 26 Nabilone: n = 26 Prochlorperazine: n = 26	*Duration study treatment*: Restricted to day 1-3 pulses of chemotherapy *Duration follow-up:* Measurement in the week before chemotherapy and on each of the 3 treatment days *Duration concurrent cancer treatment:* 21-day cycles of combination chemotherapy	- Outcomes on nausea - Outcomes on vomiting and retching - Outcomes on anorexia - Requiring extra antiemetic drugs - Preference - Adverse events	High risk of bias

Reference Country	Study design Study period	Study population	Definition nausea & vomiting	Intervention	Comparator	Sample size of analysed patients	Duration	Study outcomes	Preliminary risk of bias assessment
Chang, 1981 USA	RCT - crossover Jan 1978-Jan 1979	Patients with soft-tissue sarcomas *Age (median (range) in y)* 41 (17-58) *Sex (% female)* 25%	Objective questionnaire by nursing staff rating number of vomiting or retching episodes, volume of emesis, degree of nausea (4 category scale), duration of nausea and volume of oral intake	**THC capsules + cigarettes** THC was suspended in sesame oil and placed in gelatine capsules. Marijuana cigarettes each weighed 900 mg and contained 1.93% THC (approximately 17.4 mg). THC was administered at a dose of 10 mg/M^2 given orally every 3 h for a total of 5 doses	**Placebo capsule + cigarette** - Identical-appearing placebo capsules contained only sesame oil - Identical-appearing placebo cigarettes were produced by multiple extractions of natural marijuana with ethanol	Total: n = 8 THC: n=8 placebo: n=8	*Duration study treatment*: 1 cycle of chemotherapy *Duration follow-up:* Data collection for each trial started at 2 h prior to the chemotherapy infusion and lasted until 12 midnight the day of chemotherapy *Duration concurrent cancer treatment:* 1 day	- Outcomes on nausea - Outcomes on vomiting - Adverse events	High risk of bias

Reference **Country**	**Study design** **Study period**	**Study population**	**Definition nausea & vomiting**	**Intervention**	**Comparator**	**Sample size of analysed patients**	**Duration**	**Study outcomes**	**Preliminary risk of bias assessment**
George, 1983 France	RCT -crossover Oct 1981-March 1982	Patients with advanced gynaecological cancer who received chemotherapy including cis-platinum *Age (mean ± SD in y)* 54.1 ± 11.7 *Sex (% female)* 100%	Patients self-reported the number of vomiting	**Nabilone + placebo for chlorpromazine** 3 mg orally (1 mg 3 times a day), starting 24 h before cis-platinum and ending the day after	**Chlorpromazine + placebo for nabilone** 12.5 mg intramuscular, 15 minutes before the start of cis-platinum; this injection could be repeated once at the request of the patient	Total: n = 20 Nabilone: n = 20 Chlorpromazine: n = 20	*Duration study treatment*: 1 cycle of chemotherapy, starting 24 h before chemotherapy treatment *Duration follow-up:* During 1 cycle *Duration concurrent cancer treatment:* NR	- Outcomes on vomiting - Preference - Adverse events	High risk of bias
Gilbert, 1995 USA	RCT - parallel Sept 1989-July 1991	Patients admitted to the adult bone marrow transplant unit for chemotherapy and	The Emetic Process Rating Scale (EPRS) and the Rhodes	**Metoclopramide + dronabinol** Metoclopramide 80 mg/m^2 LD followed	**Metoclopramide + placebo** Metoclopramide 80 mg/m^2 LD followed by 20	Total: n = 106 Metoclopramide + placebo: n = 24 Metoclopramide + dronabinol: n = 27	*Duration study treatment*: 1 cycle of chemotherapy *Duration follow-up:*	- Outcomes on emetic episodes - Outcomes on nausea - Outcomes on vomiting	High risk of bias

Reference Country	Study design Study period	Study population	Definition nausea & vomiting	Intervention	Comparator	Sample size of analysed patients	Duration	Study outcomes	Preliminary risk of bias assessment
		autologous bone marrow rescue *Age (median (range) in y)* AT1+medical cannabis: 42 (25-52); AT2+medical cannabis: 42 (26-57); AT1+P: 39 (24-53); AT2+P: 42 (32-57) *Sex (% female)* 2.4%	Index of Nausea and Vomiting Form 2 (INV Form 2) were used; 50 mm visual scale and 5 category scale	by 20 mg/m^2/h plus dronabinol5 mg/m^2 orally every 6 h X 2 on day -3 of therapy **Prochlorperazine + dronabinol** Prochlorperazine 6 mg/m^2 LD followed by 1.5 mg/m^2/h plus dronabinol 5 mg/m^2 orally every 6 h X 2 on day -3 of therapy	mg/m^2/h plus placebo capsules orally every 6 h X 2 on day -3 of therapy **Prochlorperazine + placebo** Prochlorperazine 6 mg/ m^2 LD followed by 1.5 mg/m^2/h plus placebo capsules orally every 6 h X 2 on day -3 of therapy	Prochlorperazine + placebo: n = 28 Prochlorperazine + dronabinol: n = 27	During chemotherapy administration and 12 hours after completion of chemotherapy *Duration concurrent cancer treatment:* Cisplatin was given 4 days (day -6 till -3 before bone marrow transplantation, cyclophosphamide was given on day -6 till -4, carmustine was given on day -3; dronabinol was given on day -3	- Outcomes on retching	

Reference Country	Study design Study period	Study population	Definition nausea & vomiting	Intervention	Comparator	Sample size of analysed patients	Duration	Study outcomes	Preliminary risk of bias assessment
Heim, 1984 Germany	RCT - crossover NR	Patients with various advanced malignancies *Age (median (range) in y)* 49 (18-73) *Sex (% female)* 22.8%	Nausea was assessed with a 4-category scale, vomiting was quantified as the number of incidences	**Levonantradol** 0.5 mg intramuscular 1 h before and 2 and 6 h after chemotherapy as the first antiemetic treatment	**Metoclopramide** 10 mg intra-muscular 1 h before and 2 and 6 h after chemotherapy as the first antiemetic treatment	Total: n = 45 Levonantradol: n = 45 Metoclopramide: n = 45	*Duration study treatment*: 1 cycle of chemotherapy *Duration follow-up:* 24 h after chemotherapy *Duration concurrent cancer treatment:* NR	- Outcomes on nausea - Outcomes on vomiting - Outcomes on appetite - Preference - Adverse events	Moderate risk of bias
Hutcheon, 1983 UK	RCT - parallel NR	Patients with a variety of malignant disease receiving high emetic chemotherapy *Age (mean (range) in y)*	The extent of appetite impairment and nausea was assessed on ordered 4 category scales prior to each dose	**Levonantradol** Intramuscularly 2 h prior to starting chemotherapy, 2 h after the commencement of chemotherapy and a further 2	**Chlorpromazine** 25 mg, intra-muscularly 2 h prior to starting chemotherapy, 2 h after the commencement of	Total: n = 108 levonantradol 0.5 mg: n = 27 levonantradol 0.75 mg: n = 28 levonantradol 1 mg: n = 26	*Duration study treatment*: 1 cycle of chemotherapy *Duration follow-up:* During 1 cycle	- Outcomes on nausea - Outcomes on vomiting - Outcomes on appetite - Preference - Adverse events	Moderate risk of bias

Reference Country	Study design Study period	Study population	Definition nausea & vomiting	Intervention	Comparator	Sample size of analysed patients	Duration	Study outcomes	Preliminary risk of bias assessment
		0.5 mg medical cannabis: 50.4 (21-72); 0.75 mg medical cannabis: 49.0 (17-70); 1.0 mg medical cannabis: 53.0 (25-80); AT: 48.7 (21-80) *Sex (% female)* 54.6%	of anti-emetic therapy. The incidence of vomiting was also recorded	doses were given at 4-h intervals - In doses of 0.5 mg, 0.75 mg, or 1 mg	chemotherapy and a further 2 doses were given at 4-h intervals	Chlorpromazine: n = 27	*Duration concurrent cancer treatment:* Various chemotherapies were used, duration of cycles NR		
Johansson, 1982 Finland	RCT - crossover Sept 1981-April 1982	Patients receiving the same cycles of cancer chemotherapy as previously, who had uncontrolled nausea and vomiting despite	Patients rated the severity of nausea, 4 category scale, emesis was estimated according to the number of vom-	**Nabilone** 2 mg b.i.d. orally	**Prochlorperazine** 10 mg b.i.d. orally	Total: n = 18 nabilone: n = 18 prochlorperazine: n = 18	*Duration study treatment*: Patients should receive 2 consecutive cycle while on the 2 different drug treatments *Duration follow-up:* During 1 cycle	- Outcomes on nausea - Outcomes on vomiting - Preference - Adverse events	High risk of bias

Reference Country	Study design Study period	Study population	Definition nausea & vomiting	Intervention	Comparator	Sample size of analysed patients	Duration	Study outcomes	Preliminary risk of bias assessment
		the use of standard antiemetic drugs *Age (range)* 18-70 *Sex (% female)* NR, mixed	iting ejection episodes during sequences of 6 h each after antiemetic treatment, the number of dry vomiting episodes (vomiting action without ejection)				*Duration concurrent cancer treatment:* Various chemotherapies were used, duration of all chemotherapies was 1 day		
Jones, 1982 USA	RCT -crossover 1980	Patients with a variety of cancer receiving various cancer chemotherapies *Age* Patients in the following 3 age groups:	The degree of nausea (4 category scale), the number of vomiting episodes per unit time were assessed	**Nabilone** - A dose of 2 mg for nabilone was administered the evening before, the morning of chemotherapy and every 12 h thereafter for at least 24 h	**Placebo** NR	Total: n = 24 nabilone: n = 24 placebo: n = 24	*Duration study treatment*: 1 cycle of chemotherapy *Duration follow-up:* During 1 cycle *Duration concurrent cancer treatment:*	- Outcomes on nausea - Outcomes on vomiting - Preference - Drop out due to toxicity - Adverse events	High risk of bias

Reference Country	Study design Study period	Study population	Definition nausea & vomiting	Intervention	Comparator	Sample size of analysed patients	Duration	Study outcomes	Preliminary risk of bias assessment
		20-37 (9 patients), 38-57 (23 patients) and >58 (22 patients) *Sex (% female)* 35.2%					Various chemotherapies were used, duration of cycles NR		
Kleinman, 1983 USA	RCT -crossover NR	Patients being treated for cancer with chemotherapy, patients had variety of cancers *Age (median (range) in y)* *38 (18-53)* *Sex (% female)*	Self-administered questionnaire to measure severity of nausea and vomiting	**THC + Prochlorperazine** 15 mg THC + 10 mg prochlorperazine - 1 h prior to chemotherapy, same drugs were taken again 4 h later, and a third, final doses in another 4 h	**Prochlorperazine + placebo** 10 mg capsule prochlorperazine + placebo	Total: n = 14 THC + Prochlorperazine: n = 14 Prochlorperazine + placebo: n = 14	*Duration study treatment*: 1 cycle of chemotherapy *Duration follow-up:* During 1 cycle *Duration concurrent cancer treatment:* Limited information on cancer treatment	- Outcomes on vomiting - Adverse events	High risk of bias

Reference Country	Study design Study period	Study population	Definition nausea & vomiting	Intervention	Comparator	Sample size of analysed patients	Duration	Study outcomes	Preliminary risk of bias assessment
		43.8%							
Lane, 1991 USA	RCT - parallel NR	Patients being treated for cancer with other than investigational agents or high-dose (> 60mg/m^2) cisplatin *Age (median (range) in y)* 52 (20-68) *Sex (% female)* 53.2%	Assessed were number and duration of episodes of nausea and vomiting, and severity of nausea as indicated on a 10 cm VAS	**Dronabinol** 10 mg by mouth every 6 r plus placebo **Dronabinol + prochlorperazine** Dronabinol plus prochlorperazine, each 10 mg by mouth every 6 h	**Prochlorperazine** 10 mg by mouth every 6 h plus placebo	Total: n = 62 Dronabinol: n = 21 Prochlorperazine: n = 21 Combination: n = 20	*Duration study treatment*: Antiemetics were continued for 24 hr after the last dose of chemotherapy, up to a total of 6 days (1 day prior and up to 5 days on chemotherapy) *Duration follow-up:* Daily through 1 day after the last dose of chemotherapy *Duration concurrent cancer treatment:*	- Outcomes on nausea - Outcomes on vomiting - Drop out due to toxicity - Adverse events	High risk of bias

Reference Country	**Study design Study period**	**Study population**	**Definition nausea & vomiting**	**Intervention**	**Comparator**	**Sample size of analysed patients**	**Duration**	**Study outcomes**	**Preliminary risk of bias assessment**
							Various chemotherapies were used, duration up to 5 days		
Levitt, 1982 Canada	RCT - crossover NR	Patients being treated for cancer with chemotherapy, patients had variety of cancers *Age (range in y)* 17-78 *Sex (% female)* 56.9%	Frequency of vomiting; severity of nausea, 4 category scale	**Nabilone** Ist dose = 2 mg (evening before chemotherapy) 2nd dose = 2 mg (1-3 h before first dose of chemotherapy) Subsequent doses : 2 mg b.i.d.	**Prochlorperazine** NR	Total: n = 36 Nabilone: n = 36 Prochlorperazine: n = 36	*Duration study treatment*: 1 cycle of chemotherapy *Duration follow-up:* During 1 cycle *Duration concurrent cancer treatment:* Various chemotherapies were used, duration of cycles NR	- Outcomes on nausea - Outcomes on vomiting - Outcomes on food intake - Preference - Drop out due to toxicity - Adverse events	High risk of bias
Meiri, 2007 USA	RCT - parallel NR	Patients receiving moderately to highly emetogenic chemo-	Presence or absence of nausea, episodes of vomiting and/or retching,	**Dronabinol** 2.5 mg and 5 mg by mouth QID used in	**Ondansetron**	Total: n = 49 Dronabinol: n = 13 Ondansetron: n = 12 Combination: n = 13	*Duration study treatment*: 5 days *Duration follow-up:*	- Outcomes on nausea - Outcomes on vomiting	High risk of bias

Reference Country	Study design Study period	Study population	Definition nausea & vomiting	Intervention	Comparator	Sample size of analysed patients	Duration	Study outcomes	Preliminary risk of bias assessment
		therapy, having malignancy that did not involve the bone marrow *Age (mean ± SD (range) in y)* 57.9 ± 12.0 (24-81) *Sex (% female)* 61%	duration of nausea and vomiting and/or retching, intensity of nausea < 5 mm on a 100-mm VAS	the fixed (day 2) and flexible (days 3–5) **Dronabinol + Ondansetron** Combination of the 2 doses	4 mg (fixed dose) and 8 mg (flexible dose) by mouth BID **Placebo** By mouth four times a day	Placebo: n = 11	During 1 cycle + 4 days after chemotherapy *Duration concurrent cancer treatment:* Various chemotherapies were used, duration 1 day	- Needing rescue medication -Adverse events	
Niederle, 1986 Germany	RCT - crossover 1982-1984	Nonseminomatous testicular cancer patients *Age (median (range) in y)*	Time, duration, and severity of nausea (4 category scale), frequency of emetic episodes and the time of occurrence	**Nabilone** 2 mg of naboline were given orally at 8 am and 6 pm	**Alizapride** Dosage of 150 mg was administered orally at 8 am as well as 2	Total: n = 20 Nabilone: n = 20 Alizapride: n = 20	*Duration study treatment*: Night before chemotherapy and on day 1-5 *Duration follow-up:* During 1 cycle	- Outcomes on nausea - Outcomes on vomiting - Preference - Adverse events	High risk of bias

Reference Country	Study design Study period	Study population	Definition nausea & vomiting	Intervention	Comparator	Sample size of analysed patients	Duration	Study outcomes	Preliminary risk of bias assessment
		25 (19-45) *Sex (% female)* 0%			(12 am) and 8 (6 pm)		*Duration concurrent cancer treatment:* 6 days		
Niiranen, 1985 Finland	RCT - crossover NR	Patients with lung cancer *Age (mean (range) in y)* 61 (48-78) *Sex (% female)* 16.7%	Nausea (4 category scale), vomiting and appetite were assessed both by the patients and by the investigator	**Nabilone** capsule with 1 mg nabilone; given orally the night before chemo, 1 h before chemo, and thereafter at 12-h intervals as required up to 24 h after chemotherapy	**Prochlorperazine** Capsules with 7.5 mg, given orally the night before chemo, 1 h before chemo, and thereafter at 12-h intervals as required up to 24 h after chemotherapy	Total: n = 24 Nabilone: n = 24 Prochlorperazine: n = 24	*Duration study treatment*: 1h before chemotherapy, up to 24 h after chemotherapy *Duration follow-up:* Vomiting was recorded the first 24 h of chemotherapy; appetite during the 24 h after chemotherapy *Duration concurrent cancer treatment:*	- Outcomes on nausea - Outcomes on vomiting - Outcomes on appetite - Drop out due to toxicity - Adverse events	High risk of bias

Reference Country	Study design Study period	Study population	Definition nausea & vomiting	Intervention	Comparator	Sample size of analysed patients	Duration	Study outcomes	Preliminary risk of bias assessment
							Various chemotherapies were used, chemotherapy cycles ranged from 1 to 5 days		
Orr, 1981 USA	RCT - crossover NR	Patients harbouring a variety of neoplasms requiring drug therapy *Age (mean (range) in y)* 45 (22-71) *Sex (% female)* 64.6%	Assessed with questionnaires: degree of nausea (4 category scale) and number of vomiting episodes	**THC** Capsules; THC 7 mg/m^2 orally every 4 h for 4 doses, initially ingested 1 h before chemotherapy	**Prochlorperazine** 7 mg/m^2 prochlorperazine orally every 4 h for 4 doses **Placebo** Capsules containing lactose	Total: n = 55 THC: n = 55 Prochlorperazine: n = 55 Placebo: n = 55	*Duration study treatment*: 1 h before chemotherapy *Duration follow-up:* Within 24 hours of drug ingestion *Duration concurrent cancer treatment:* Various chemotherapies were used, duration of cycles NR	- Outcomes on nausea - Outcomes on vomiting - Adverse events	High risk of bias
Sheidler, 1984	RCT - crossover	New and previously treated cancer patients who were to be	Patients' responses to each antiemetic were determined	**Levonantradol** 1 mg levonantradol, the drugs were given	**Prochlorperazine**	Total: n = 16 Levonantradol: n = 16	*Duration study treatment*: 2 h before chemotherapy till 10 h after chemotherapy	- Outcomes on nausea - Outcomes on vomiting	High risk of bias

Reference Country	Study design Study period	Study population	Definition nausea & vomiting	Intervention	Comparator	Sample size of analysed patients	Duration	Study outcomes	Preliminary risk of bias assessment
USA	NR	admitted to receive chemotherapy, various cancers and chemotherapies *Age (range in y)* 18-70 *Sex (% female)* 55%	by categorizing the different grades of nausea and vomiting, 4 category scale	intramuscularly 2 h before chemotherapy and 2, 6, and 10 h after chemotherapy for a total of 4 doses for each course of treatment	10 mg prochlorperazine	Prochlorperazine: n = 16	*Duration follow-up:* During 1 cycle *Duration concurrent cancer treatment:* Various chemotherapies were used, duration of cycles NR	- Drop out due to toxicity - Adverse events	
Steele, 1980 USA	RCT - crossover April 1978- Jan 1979	Patients with a variety of cancer receiving various cancer chemotherapies *Age (median (range) in y)*	Daily questionnaires. Patients rated the severity of nausea (4 category scale), esti-	**Nabilone** Oral nabilone 2 mg every 12 h for 3-5 doses, with the first dose given the night before chemotherapy	**Prochlorperazine** Oral slow-release 10 mg prochlorperazine	Total: n = 37 Nabilone: n = 37 Prochlorperazine: n = 37	*Duration study treatment*: 1 cycle, starting with the first dose the night before chemotherapy *Duration follow-up:* During 1 cycle	- Outcomes on nausea - Outcomes on vomiting - Drop out due to toxicity and lack of efficacy - Adverse events	High risk of bias

Reference Country	Study design Study period	Study population	Definition nausea & vomiting	Intervention	Comparator	Sample size of analysed patients	Duration	Study outcomes	Preliminary risk of bias assessment
		50 (19-65) *Sex (% female)* NR	mating the frequency and duration of vomiting				*Duration concurrent cancer treatment:* Various chemotherapies were used, duration 1 day		
Wada, 1982 USA	RCT - crossover NR	Patients with a variety of cancer receiving various cancer chemotherapies *Age (mean (range) in y)* 57 (18-81) *Sex (% female)* 58.8%	Observations were made on each cycle for frequency of vomiting. Patients were asked to rate their nausea on 4 category scale, on a daily basis	**Nabilone** 2 mg; 1 capsule was taken at 8.00 pm the preceding evening and 1 at 8.00 am on the morning of the administration of chemotherapy. Chemotherapy was given within 1-3 h of the 8.00 am dose of nabilone. The study	**Placebo** Identical capsules as nabilone	Total: n = 92 Nabilone: n = 92 Placebo: n = 92	*Duration study treatment*: 1 cycle, starting the first dose the night before chemotherapy *Duration follow-up:* During 1 cycle *Duration concurrent cancer treatment:* Various chemotherapies were used, duration of cycles NR	- Outcomes on nausea - Outcomes on vomiting - Preference - Drop out due to toxicity and lack of efficacy - Adverse events	Moderate risk of bias

Reference Country	Study design Study period	Study population	Definition nausea & vomiting	Intervention	Comparator	Sample size of analysed patients	Duration	Study outcomes	Preliminary risk of bias assessment
				drug was continued on an every 12-h schedule for 1 dose after the final administration of chemotherapy					

Keys: AT = alternative treatment, BID = twice a day, h = hours, NR = not reported, P = placebo, QID = 4 times a day, SD = standard deviation, VAS = visual analogue scale, y = years

Table XII. Outcomes on medical cannabis use for the symptom nausea & vomiting related to cancer treatment - Preliminary pre-specified outcomes reported in RCTs with paediatric or adult patients receiving treatment for cancer

Outcomes in protocol	Preliminary pre-specified outcomes reported in the RCTs	Number of RCTS reporting data on the specific outcome	
		Paediatrics	Adults
Efficacy of medical cannabis			
Absence of nausea, vomiting, or nausea and vomiting after cancer treatment	Rate of reduction of retching and vomiting	1	0
	Absence of vomiting	1	4
	Absence of nausea	0	6
	Absence of nausea and vomiting	1	1
	Patients with complete control	0	4
	Number of patients vomiting	0	2
Frequency of nausea, vomiting, or nausea and vomiting after cancer treatment	Mean number of vomits	3	0
	Total number of vomiting and retching episode	0	4
	Mean number of vomiting	0	6
	Median number of vomiting	0	3
	Number of 1-4, 5-10, >10 vomiting episodes vomiting	0	1
	Number of 1-5, 6-10, 11-20 or >20 vomiting episodes vomiting	0	1

Outcomes in protocol	Preliminary pre-specified outcomes reported in the RCTs	Number of RCTS reporting data on the specific outcome	
		Paediatrics	Adults
Severity of nausea after cancer treatment	Mean score for nausea	2	0
	Overall rate of improvement of retching and Vomiting	1	0
	Mean score for nausea	0	7
	Mean score for retching	0	1
	Mean score for vomiting	0	2
	Response to treatment	0	1
	Number of patients with severe nausea	0	1
	Number of patients with severe vomiting	0	1
	Median INV scores for vomiting	0	1
	Number of patients with less nausea	0	3
	Number of patients with less vomiting	0	3
	Number of patients with mild, moderate or severe nausea	0	3
	Number of patients with mild, severe emesis	0	1
	Partial response	0	1

Outcomes in protocol	Preliminary pre-specified outcomes reported in the RCTs	Number of RCTS reporting data on the specific outcome	
		Paediatrics	Adults
Withdrawal due to lack of anti-emetic efficacy of medical cannabis	Withdrawal due to lack of anti-emetic efficacy of medical cannabis	0	3
Health-related quality of life	Not reported	0	0
Safety of medical cannabis			
Occurrence of cannabis-associated adverse events	Number of patients with adverse events	3	18
Withdrawal of treatment due to adverse effects of medical cannabis	Number drop outs due to presumed toxicity	3	9

Keys: INV = inventory of nausea and vomiting

Table XIII. Outcomes on medical cannabis use for the symptom nausea & vomiting related to cancer treatment - Other not pre-specified outcomes reported in RCTs with paediatric or adult patients receiving treatment for cancer

Other not pre-specified outcomes reported in the RCTs		Number of RCTS reporting data on the specific outcome	
		Paediatrics	Adults
Efficacy of medical cannabis			
Other outcomes for nausea and vomiting	Total volume of emesis per person per treatment	0	1
	Total duration of nausea	0	2
	Median duration of nausea	0	1
	Range duration of nausea	0	1
	Median duration of vomiting	0	1
	Range duration of vomiting	0	1
	Number of time intervals with nausea and vomiting present	0	1
	Mean therapeutic effect	0	1
	% of patients with anticipatory nausea	0	1
	Investigators' global assessment on efficacy of the drugs studied – number of patients scoring very good, good, fair, poor, very poor	0	1
Other outcomes	Mean anorexia score, % patients with maximum score	0	1
Appetite and food intake	Number of patients with more appetite	0	1
	Number of patients with good, normal, fair, poor appetite	0	1
	Number of patients with appetite not, moderately or markedly diminished	0	1
	Mean change in food intake (4 category scale)	0	1
Preference of drug treatment	Preference of crossover drugs	4	11
	Which agent was associated with less vomiting	0	1
	Which agent was associated with less nausea	0	1

Other not pre-specified outcomes reported in the RCTs		Number of RCTS reporting data on the specific outcome	
		Paediatrics	Adults
Lack of anti-emetic efficacy of medical cannabis	Requiring extra parenteral anti-emetics	0	2

Appendix 7. Evidence tables cost-effectiveness

Chronic pain

Table I. Outcomes on the cost-effectiveness of medical cannabis use for the symptom chronic pain - costs

COSTS	Tyree 2019	NICE 2019
Treatment-related costs		
Medical cannabis costs	1	1
Comparator costs	1	1
Adverse event-related treatment costs	1	1
Future unrelated healthcare costs		
Future unrelated healthcare costs	0	0
Non-health care costs		
Travel	0	0
Time	0	0
Informal care	0	0
Productivity	0	0

Keys: 1 = yes, 0 = no

Table II. Outcomes on the cost-effectiveness of medical cannabis use for the symptom chronic pain – effectiveness and utilities

Effectiveness and utilities	Tyree 2019	NICE 2019
Effectiveness		
Pain severity	1	1
Mortality	0	0
Adverse events	1	1
Beneficial side effects	0	0
Utilities		
Pain severity	1	1
Adverse events	1	1
Disutility of medical cannabis administration	0	0
Beneficial side effects	0	0

Keys: 1 = yes, 0 = no

Table III. Preliminary critical appraisal using the CHEC checklist for the symptom chronic pain

Item	CHEC checklist	Tyree 2019	NICE 2019
Study design			
1	Is the study population clearly described?	0	0
2	Are competing alternatives clearly described?	1	1
3	Is a well-defined research question posed in answerable form?	0	0
4	Is the economic study design appropriate to the stated objective?	1	1
5	Is the chosen time horizon appropriate in order to include relevant costs and consequences?[m]	0.5	0.5
6	Is the actual perspective chosen appropriate?[n]	0.5	1
Costs			
7	Are all important and relevant costs for each alternative identified?	See table 27	
8	Are all costs measured appropriately in physical units?		
9	Are costs valued appropriately?		
Outcomes			
10	Are all important and relevant outcomes for each alternative identified?	See table 28	
11	Are all outcomes measured appropriately?		
12	Are outcomes valued appropriately?		
Results			
13	Is an incremental analysis of costs and outcomes of alternatives performed?	1	1
14	Are all future costs and outcomes discounted appropriately?	0	1
15	Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis?	1	1
16	Do the conclusions follow from the data reported?	1	1

[m] 0.5 if not lifetime
[n] 0.5 if not societal

17	Does the study discuss the generalizability of the results to other settings and patient/client groups?	1	1
18	Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?°	0	1
19	Are ethical and distributional issues discussed appropriately?	0	0

Keys: 1 = yes, 0 = no, 0.5 = inconclusive

Spasticity

Table IV. Outcomes on the cost-effectiveness of medical cannabis use for the symptom spasticity - costs

COSTS	**Gras 2016**	**Slof 2015**	**Slof 2012**	**Lu 2012**	**NICE 2019**	**Flachenecker 2013**
Treatment-related costs						
Medical Cannabis costs	1	1	1	1	1	1
Comparator costs (SoC)	1	1	1	1	1	1
Adverse event-related treatment costs	0	0	0	0	1	0
Future unrelated healthcare costs						
Future unrelated healthcare costs	0	0	0	0	0	0

° 0.5 if a conflict of interest is stated

Non-health care costs						
Travel	0	0	0	0	0	0
Time	0	0	0	0	0	0
Informal care	0	0	0	0	0	0
Productivity	0	0	0	0	0	0

Keys: 1 = yes, 0 = no

Table V. Outcomes on the cost-effectiveness of medical cannabis use for the symptom spasticity – effectiveness and utilities

Effectiveness and utilities	**Gras 2016**	**Slof 2015**	**Slof 2012**	**Lu 2012**	**NICE 2019**	**Flachenecker 2013**
Effectiveness						
Spasticity severity	1	1	1	1	1	1
Mortality	0	0	0	0	0	0
Adverse events	0	0	0	0	1	0
Beneficial side effects	0	0	0	0	0	0
Utilities						
Spasticity severity	1	1	1	1	1	1
Adverse events	0	0	0	0	1	0
Disutility of medical cannabis administration	0	0	0	0	0	0
Beneficial side effects	0	0	0	0	0	0

Keys: 1 = yes, 0 = no

Unintentional weight loss

No studies were included for this symptom.

Nausea and vomiting related to cancer treatment

No studies were included for this symptom.

Table VI. Preliminary critical appraisal using the CHEC checklist for the symptom spasticity

CHEC checklist		Gras 2016	Slof 2015	Slof & Gras 2012	Lu 2012	NICE 2019	Flachenecker 2013
Study design							
1	Is the study population clearly described?	**0**	1	0	1	1	1
2	Are competing alternatives clearly described?	**1**	1	1	1	1	1
3	Is a well-defined research question posed in answerable form?	**1**	1	1	1	1	1
4	Is the economic study design appropriate to the stated objective?	**1**	1	1	1	1	1
5	Is the chosen time horizon appropriate in order to include relevant costs and consequences?[p]	**0.5**	0.5	0.5	0.5	0.5	0.5
6	Is the actual perspective chosen appropriate?[q]	**0.5**	0.5	0.5	0.5	0.5	0.5
Costs							
7	Are all important and relevant costs for each alternative identified?	See Table 31					
8	Are all costs measured appropriately in physical units?						
9	Are costs valued appropriately?						
Outcomes							
10	Are all important and relevant outcomes for each alternative identified?						

[p] 0.5 if not lifetime
[q] 0.5 if not societal

11	Are all outcomes measured appropriately?	See Table 32					
12	Are outcomes valued appropriately?						
Results							
13	Is an incremental analysis of costs and outcomes of alternatives performed?	1	1	1	1	1	1
14	Are all future costs and outcomes discounted appropriately?	1	1	1	1	1	0
15	Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis?	1	1	1	1	1	1
16	Do the conclusions follow from the data reported?	1	1	1	1	1	1
17	Does the study discuss the generalizability of the results to other settings and patient/client groups?	0	1	0	1	1	0
18	Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?[r]	0.5	0.5	0.5	1	1	0.5
19	Are ethical and distributional issues discussed appropriately?	0	0	0	0	0	0

Keys: 1 = yes, 0 = no, 0.5 = inconclusive

[r] 0.5 if a conflict of interest is stated