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Health Technology Assessment (HTA)

HTA Report

Title	Medical cannabis for treating various symptoms in Switzerland
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Executive Summary

Background. Medical cannabis encompasses all cannabis-based products which are used for medical treatment. The so far most studied cannabinoids, and thought to be the most important in terms of clinical effects, are tetrahydrocannabinol (THC) and cannabidiol (CBD). 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 are unsuccessful. Preceding this Health Technology Assessment (HTA) report, a scoping review was conducted of which the results were published in the scoping report. The scoping report describes the evidence base for the use of medical cannabis for treating the following symptoms: chronic pain, spasticity, unintentional weight loss, and nausea and vomiting related to cancer treatment. For the latter two symptoms, the evidence from the randomised controlled trials (RCTs) was insufficient to make pertinent recommendations and it was therefore decided not to continue with complete data extraction and cost-effectiveness modelling for these two symptoms in the HTA phase. The overall aim of this HTA report was to investigate the efficacy, effectiveness, safety, cost-effectiveness, and budget impact of medical cannabis use in chronic pain and spasticity in Switzerland.

Methods. Systematic reviews were conducted adhering to international methodological standards. Systematic literature searches were performed in PubMed (MEDLINE), Embase.com, and other complementary databases to identify relevant efficacy, effectiveness, safety, and cost-effectiveness evidence. Only RCTs and economic evaluations were included in the corresponding searches. Data were extracted from the included studies in evidence tables, and the outcomes of the quality assessment were reported. The data on medical cannabis use for chronic pain was stratified in three subpopulations: cancer pain, neuropathic pain, and musculoskeletal pain. Data on medical cannabis use for spasticity was stratified in two subpopulations: multiple sclerosis (MS) and motor neuron disease.

During the scoping phase, the systematic literature search on the cost-effectiveness of medical cannabis use in chronic pain and spasticity did not provide evidence for Switzerland. Therefore, cost-effectiveness models were developed, characterising the natural history of the disease in a patient's lifetime in the Swiss clinical practice. The models were used to determine the cost-effectiveness of medical cannabis in addition to standard of care (SOC) to SOC alone for all subpopulations for which usable efficacy evidence was available. Non-systematic searches were performed to identify cost

and health-related quality of life (expressed in utilities on a scale from 0 to 1) input for cost-effectiveness modelling. The uncertainty around input parameters was explored in sensitivity and scenario analyses. In addition, the projected budget impact was calculated, using input for the budget impact calculations were derived via a survey among clinical experts. Websites of HTA agencies were searched for information on social, legal, ethical, and organisational aspects related to prescribing medical cannabis. For these HTA domains, the evidence was described narratively.

Results. Heterogeneity between studies in outcomes and outcome measures, data skewness, and incompleteness of study results precluded the calculation of pooled estimates for efficacy data for the stratified pain and spasticity populations. Overall, the efficacy data on medical cannabis use for chronic pain and spasticity was inconsistent (i.e. studies with comparable patient populations and similar type of medical cannabis did not show consistent results pointing in the same direction) and inconclusive (i.e. none of the studies was able to draw a definitive conclusion on the efficacy of medical cannabis). Furthermore, multiple factors increase the risk of bias in studies on medical cannabis, however the extent as well as the direction of the potential bias are difficult to comprehend. Although it was possible to calculate pooled estimates for part of the safety outcomes and some patient populations, the issues highlighted for efficacy also apply to safety, resulting in an incomplete safety profile of medical cannabis.

For cost-effectiveness modelling, the absolute change in numeric rating scale (NRS) score was the preferred efficacy outcome measure in the chronic pain models, and the proportion of responders at ≥30% reduction in NRS score was the preferred efficacy outcome in the spasticity models. Resulting from this, usable efficacy evidence for cost-effectiveness modelling was available for two chronic pain populations (neuropathic pain and musculoskeletal pain) and two spasticity populations (MS and motor neuron disease). These studies reported the efficacy of THC:CBD spray (Sativex®). Using a healthcare perspective, lifetime horizon, and 3% discounting of costs and effects, THC:CBD spray in addition to SOC resulted in a minimal loss in quality-adjusted life years (QALYs) for neuropathic pain compared to SOC alone, and only small QALY gains for the other populations. In all models, the costs of THC:CBD spray in addition to SOC were higher than SOC alone. Sensitivity analyses showed that treatment effect, utility values, and baseline pain or spasticity scores were the most influential parameters. The budget impact estimates were surrounded by substantial uncertainty. Websites and documents from HTA agencies pointed out several relevant legal, social, ethical, and organisational issues related to the use and reimbursement of medical cannabis.

Conclusions. While the research question encompassed all chronic pain and all spasticity populations, there was only sufficient evidence to assess the efficacy and safety of the use of medical

cannabis for people with neuropathic pain, musculoskeletal pain, cancer pain, spasticity in MS and spasticity in motor neuron disease. However, due to incomplete, inconclusive, and inconsistent study findings, no conclusions could be drawn on the efficacy and safety of medical cannabis in these patient populations. In studies on medical cannabis, an unpredictable bias and uncertainty in the evidence base arises caused by the risk of unblinding of patients to their treatment allocation in combination with the patient-reported outcomes for the symptoms chronic pain and spasticity. Given these considerations it is neither possible to conclude that medical cannabis is an efficacious and safe treatment option for chronic pain and spasticity, nor to conclude that medical cannabis is not efficacious and safe for the treatment of chronic pain and spasticity. Future studies on medical cannabis to treat these symptoms will likely be exposed to similar challenges and limitations, of which only part can be solved with improved study designs and complete reporting of results.

Modelling was performed to provide indicative cost-effectiveness estimates, and showed that THC:CBD spray in addition to SOC was associated with minimal changes in QALYs against additional costs compared to SOC alone. The generalisability of the cost-effectiveness and budget impact estimates to other populations, other medical cannabis products or other routes of administration is unknown.

When considering reimbursement of medical cannabis for certain populations, relevant legal, social, ethical, and organisational issues should also be considered. For example, reimbursement of medical cannabis will be subject to different and interconnected Swiss laws with regard to cultivation, consumption, distribution, and prescription. In addition, reimbursement of medical cannabis may have social and ethical consequences, for example as a result of a gap between patient expectations and scientific evidence. Other concerns include accessibility restrictions, vulnerable populations at risk of unintended consequences, and illicit use. Furthermore, organisational challenges may arise in the supply and quality control of medical cannabis products.

Zusammenfassung

Hintergrund. Der Begriff medizinischer Cannabis umfasst alle Produkte auf Cannabisbasis, die zur medizinischen Behandlung eingesetzt werden. Die bisher am meisten untersuchten Cannabinoide, von denen die grösste Bedeutung in Hinsicht auf die klinische Wirkung angenommen wird, sind Tetrahydrocannabinol (THC) und Cannabidiol (CBD). In der Schweiz werden die Kosten für medizinisches Cannabis nicht generell durch die obligatorische Krankenversicherung übernommen. Medizinischer Cannabis kann zur Behandlung verschiedener Symptome eingesetzt werden und wird überwiegend als Zusatztherapie oder nachdem andere sich andere therapeutische Optionen als erfolglos

erwiesen hatten, angewendet. Vor der Verfassung dieses HTA-Berichts (Health Technology Assessment) wurde ein Scoping-Review durchgeführt, dessen Ergebnisse im Scoping-Bericht veröffentlicht wurden. Der Scoping-Bericht beschreibt die Evidenzbasis für die Anwendung von medizinischem Cannabis zur Behandlung folgender Symptome: chronische Schmerzen, Spastik, ungewollter Gewichtsverlust sowie Übelkeit und Erbrechen im Zusammenhang mit einer Krebstherapie. Die randomisierten kontrollierten Studien (RCTs) lieferten für die beiden letztgenannten Symptome keine ausreihende Evidenz, die entsprechende Empfehlungen erlauben würde. Es wurde daher beschlossen, in der HTA-Phase die vollständige Datenextraktion und Modellierung der Kosteneffektivität für diese Symptome nicht fortzusetzen. Das übergeordnete Ziel dieses HTA-Berichts bestand darin, die Wirksamkeit, Effektivität, Sicherheit, Kosteneffektivität sowie den Budgeteinfluss der Anwendung von medizinischem Cannabis bei chronischen Schmerzen und Spastik in der Schweiz zu untersuchen.

Methoden. Systematische Reviews erfolgten unter Einhaltung internationaler methodischer Standards. Systematische Literaturrecherchen wurden in PubMed (MEDLINE), Embase.com und anderen ergänzenden Datenbanken durchgeführt, um relevante Evidenz zur Wirksamkeit, Effektivität, Sicherheit und Kosteneffektivität zu identifizieren. Nur RCTs und ökonomische Evaluationen wurden in die entsprechenden Recherchen einbezogen. Die Daten wurden aus den eingeschlossenen Studien in Evidenztabellen extrahiert, und die Ergebnisse der Qualitätsbewertung wurden erfasst. Die Daten zum medizinischen Cannabiskonsum bei chronischen Schmerzen wurden in drei Subpopulationen stratifiziert: onkologische, neuropathische und muskuloskelettale Schmerzen. Die Daten bezüglich der Anwendung von medizinischem Cannabis zur Behandlung von Spastik wurden in zwei Subpopulationen stratifiziert: Multiple Sklerose (MS) und Motoneuronerkrankung.

Während der Scoping-Phase lieferte die systematische Literaturrecherche zur Kosteneffektivität der Anwendung von medizinischem Cannabis bei chronischen Schmerzen und Spastik keine Evidenz für die Schweiz. Daher wurden Modelle zur Kosteneffektivität entwickelt, die den natürlichen Verlauf der Erkrankung im Leben eines Patienten in der Schweizer klinischen Praxis charakterisieren. Die Modelle wurden verwendet, um die Kosteneffektivität von medizinischem Cannabis zusätzlich zur Standardbehandlung (SOC) im Vergleich zur SOC allein für alle Subpopulationen zu ermitteln, für die verwertbare Wirksamkeitsnachweise vorlagen. Es wurden nicht-systematische Suchen durchgeführt, um Kosten und gesundheitsbezogene Lebensqualität (ausgedrückt in Nutzen auf einer Skala von 0 bis 1) als Input für die Kosten-Effektivitäts-Modellierung zu identifizieren. Die Unsicherheit hinsichtlich der die Inputparameter wurde in Sensitivitäts- und Szenarioanalysen untersucht. Zudem wurde der voraussichtliche Budgeteinfluss berechnet, wobei der Input für die Berechnung des Budgeteinflusses von einer Umfrage unter klinischen Experten abgeleitet wurde. Websites von HTA-Agenturen wurden

nach Informationen über soziale, rechtliche, ethische und organisatorische Aspekte im Zusammenhang mit der Verschreibung von medizinischem Cannabis durchsucht. Für diese HTA-Domänen wurde die Evidenz narrativ beschrieben.

Ergebnisse. Aufgrund der Heterogenität der Studien in Bezug auf Ergebnisse und Endpunkte, Datenverzerrungen sowie die Unvollständigkeit der Studienergebnisse war die Erstellung gepoolter Schätzungen für die Wirksamkeitsdaten zu stratifizierten Populationen mit Schmerzen und Spastik ausgeschlossen. Insgesamt waren die Daten zur Wirksamkeit der Anwendung von medizinischem Cannabis bei chronischen Schmerzen und Spastik inkonsistent (d. h. Studien mit vergleichbaren Patientenpopulationen und ähnlicher Art von medizinischem Cannabis zeigten keine konsistenten Ergebnisse, die in dieselbe Richtung weisen würden) und nicht schlüssig (d. h. keine der Studien erlaubte es, eine endgültige Schlussfolgerung zur Wirksamkeit von medizinischem Cannabis zu ziehen). Darüber hinaus erhöhen mehrere Faktoren das Risiko einer Verzerrung in Studien zu medizinischem Cannabis, wobei sowohl das Ausmaß als auch die Richtung der möglichen Verzerrung schwer zu erfassen sind. Obwohl es möglich war, gepoolte Schätzungen für einen Teil der Sicherheitsergebnisse und einige Patientenpopulationen zu erstelle, gelten die für die Wirksamkeit hervorgehobenen Probleme auch für die Sicherheit, woraus sich die Unvollständigkeit des Sicherheitsprofils von medizinischem Cannabis ergibt.

Hinsichtlich der Modellierung der Kosteneffektivität war die absolute Veränderung des NRS-Scores (Numeric Rating Scale) in den Modellen zu chronischen Schmerzen der bevorzugte Wirksamkeitsendpunkt. Der Anteil der Responder mit einer ≥30%igen Reduktion des NRS-Scores stellte den bevorzugten Wirksamkeitsendpunkt in den Modellen zur Spastik dar. Daraus ergaben sich verwertbare Wirksamkeitsnachweise für die Modellierung der Kosteneffektivität bei zwei Populationen mit chronischen Schmerzen (neuropathische und muskuloskelettale Schmerzen) sowie zwei Populationen mit Spastik (MS und Motoneuronerkrankung). Diese Studien befassten sich mit der Wirksamkeit des THC/CBD-Sprays (Sativex®). Unter Verwendung einer Gesundheitsperspektive, eines Lebenszeithorizonts und einer 3 %igen Diskontierung von Kosten und Effekten führte das das zusätzlich zur SOC angewendete THC/CBD-Spray zu einem minimalen Verlust an qualitätsbereinigten Lebensjahren (QALYs) bei neuropathischen Schmerzen im Vergleich zu SOC allein und nur zu geringen QALY-Gewinnen bei den anderen Populationen. In allen Modellen waren die Kosten für SOC und THC/CBD-Spray höher als für SOC allein. In Sensitivitätsanalysen haben aufgezeigt, dass der Behandlungseffekt, die Nutzenbewertung und die Schmerz- oder Spastik-Scores bei Baseline die wichtigsten Parameter waren. Die Schätzungen des Budgeteinflusses waren mit erheblichen Unsicherheiten behaftet. Websites und Dokumente von HTA-Agenturen verwiesen auf mehrere relevanten rechtlichen, sozia-

len, ethischen und organisatorischen Probleme im Zusammenhang mit der Anwendung und Erstattung von medizinischem Cannabis.

Fazit. Während die Forschungsfrage alle chronischen Populationen mit Schmerzen und Spastik einschloss, erlaubte die vorliegende Evidenz nur die Beurteilung der Wirksamkeit und Sicherheit der Anwendung von medizinischem Cannabis bei Menschen mit neuropathischen Schmerzen, Schmerzen des Bewegungsapparats, onkologischen Schmerzen sowie Spastik bei MS und Motoneuronerkrankungen. Aufgrund der unvollständigen, nicht schlüssigen und inkonsistenten Studienergebnisse konnten jedoch keine Schlussfolgerungen hinsichtlich der Wirksamkeit und Sicherheit von medizinischem Cannabis in diesen Patientenpopulationen gezogen werden. Studien zu medizinischem Cannabis gingen mit einer unvorhersehbaren Verzerrung und Unsicherheit in der Evidenzbasis einher, die durch das Risiko der Entblindung der Patienten hinsichtlich ihrer Behandlungszuweisung in Kombination mit den von den Patienten berichteten Ergebnissen bezüglich der Symptome chronische Schmerzen und Spastik verursacht wurde. Vor diesem Hintergrund ist es weder möglich, zu dem Schluss zu kommen, dass medizinischer Cannabis eine wirksame und sichere Behandlungsoption für chronische Schmerzen und Spastik darstellt, noch dies zu verneinen. Zukünftige Studien zu medizinischem Cannabis zur Behandlung dieser Symptome werden wahrscheinlich ähnlichen Herausforderungen und Einschränkungen ausgesetzt sein, wobei nur ein Teil davon durch verbesserte Studiendesigns und vollständige Ergebnis-Berichterstattung gelöst werden kann.

Die Modellierung der Kosteneffektivität hat aufgezeigt, dass die Anwendung des THC/CBD-Sprays zur Behandlung der Symptome Schmerzen oder Spastik im Vergleich zu SOC allein mit minimalen Veränderungen der QALYs bei zusätzlichen Kosten verbunden war. Es ist nicht bekannt, inwiefern die Schätzungen der Kostenwirksamkeit und des Budgeteinflusses auf andere Bevölkerungsgruppen, andere medizinische Cannabisprodukte oder andere Verabreichungswege übertragen werden kann.

Bei der Erwägung der Erstattung von medizinischem Cannabis für bestimmte Populationen sollten auch relevante rechtliche, soziale, ethische und organisatorische Probleme berücksichtigt werden. So wird beispielsweise die Erstattung von medizinischem Cannabis verschiedenen und miteinander zusammenhängenden in der Schweiz geltenden Gesetzen betreffend Anbau, Konsum, Vertrieb und Verschreibung unterliegen. Zudem kann die Erstattung von medizinischem Cannabis soziale und ethische Folgen haben, zum Beispiel aufgrund einer Kluft zwischen den Erwartungen der Patienten und der wissenschaftlichen Evidenz. Weitere Bedenken betreffen die eingeschränkte Zugänglichkeit, vulnerable Bevölkerungsgruppen, bei denen das Risiko von unbeabsichtigten Folgen besteht, sowie die illegale Verwendung. Darüber hinaus können sich im Hinblick auf die Lieferung und Qualitätskontrolle von medizinischen Cannabisprodukten organisatorische Herausforderungen ergeben.

Résumé

Contexte. Le cannabis médical comprend tous les produits à base de cannabis utilisés à des fins thérapeutiques. Les cannabinoïdes les plus étudiés jusqu'à présent, et considérés comme les plus importants en termes d'effets cliniques, sont le tétrahydrocannabinol (THC) et le cannabidiol (CBD). 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. En amont du présent rapport d'évaluation des technologies de la santé (ETS ou HTA pour health technology assessment), une étude a été menée, dont les résultats ont fait l'objet d'un scoping report décrivant les preuves de l'efficacité 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. Pour ces deux derniers symptômes, les essais contrôlés randomisés (RCT pour randomized controlled trials) n'ont pas fourni suffisamment de preuves permettant de formuler des recommandations pertinentes, raison pour laquelle il a été décidé de ne pas poursuivre l'extraction complète des données et l'élaboration de modèles d'économicité à ce sujet dans la phase d'ETS. Le présent rapport d'ETS vise essentiellement à évaluer les preuves de l'efficacité, de l'innocuité et de l'économicité ainsi que l'impact budgétaire du cannabis médical pour le traitement des douleurs chroniques et de la spasticité en Suisse.

Méthodologie. Les analyses systématiques se sont basées sur les normes internationales. Des recherches systématiques ont été réalisées dans PubMed (MEDLINE), Embase.com et d'autres bases de données complémentaires pour identifier des publications attestant l'efficacité, l'innocuité et l'économicité du cannabis médical. Seuls des RCT et des évaluations économiques ont été inclus dans les recherches. Les données extraites des études réalisées ont été présentées sous forme de tableaux synoptiques, et les résultats de l'évaluation de la qualité ont été présentés. Les données relatives au cannabis médical pour le traitement des douleurs chroniques ont été stratifiées en trois sous-populations : douleurs cancéreuses, douleurs neuropathiques et douleurs musculosquelettiques. Les données relatives au cannabis médical pour le traitement de la spasticité ont été stratifiées en deux sous-populations : sclérose en plaques (SEP) et maladie du motoneurone.

Durant la phase d'étude, les recherches systématiques dans la littérature n'ont pas fourni de preuve sur l'économicité du cannabis médical pour traiter les douleurs chroniques et la spasticité en Suisse. Des modèles d'économicité ont donc été élaborés, compte tenu de l'histoire naturelle de la maladie tout au long de la vie du patient dans la pratique clinique en Suisse. Ces modèles visaient à déterminer l'économicité du cannabis médical associé au traitement Standard Of Care (SOC) par rapport au traitement SOC seul pour toutes les sous-populations pour lesquelles des données probantes sur

l'efficacité étaient disponibles. Des recherches non systématiques ont été effectuées pour identifier les données relatives aux coûts et à la qualité de vie liée à la santé (exprimée en utilités sur une échelle de 0 à 1) pour la modélisation du rapport coût-efficacité. Les incertitudes liées aux paramètres ont été examinées dans des analyses de sensibilité et de scénarios. Par ailleurs, l'impact budgétaire projeté a été calculé sur la base d'une étude menée auprès d'experts cliniques. Les aspects sociaux, légaux, éthiques et organisationnels liés au cannabis médical ont fait l'objet de recherches sur les sites internet des agences d'ETS. Pour ces domaines d'ETS, les preuves étaient décrites de façon narrative.

Résultats. Du fait de l'hétérogénéité des résultats et des méthodes pour mesurer les résultats, de l'asymétrie des données et des résultats incomplets, il n'a pas été possible de procéder à une évaluation globale des données d'efficacité concernant les populations stratifiées d'après les critères de la douleur et de la spasticité. D'une manière générale, les données d'efficacité du cannabis médical pour traiter les douleurs chroniques et la spasticité étaient contradictoires (les études portant sur des populations de patients comparables et le même type de cannabis médical n'ont pas débouché sur des résultats cohérents allant dans le même sens) et non concluantes (aucune étude n'a permis de tirer de conclusion définitive sur l'efficacité du cannabis médical). En outre, de multiples facteurs augmentent le risque de biais dans les études sur le cannabis médical, mais l'ampleur ainsi que la direction du biais potentiel sont difficiles à appréhender. Même si une évaluation globale a pu être effectuée pour une partie des résultats d'innocuité et certains patients, les problèmes rencontrés au niveau de l'efficacité concernent également l'innocuité, d'où un profil d'innocuité incomplet.

S'agissant des modèles d'économicité, les résultats d'efficacité des modèles concernant les douleurs chroniques ont été mesurés en fonction de la modification en chiffres absolus du score de l'échelle numérique (EN), et la proportion de répondants indiquant une réduction de ≥ 30 % pour le score de l'EN a servi de base pour établir l'efficacité des modèles pour la spasticité. Ainsi, des preuves avérées de l'efficacité des modèles d'économicité étaient disponibles pour deux populations de patients souffrant de douleurs chroniques (douleurs neuropathiques et douleurs musculosquelettiques) et deux populations de patients atteints de spasticité (sclérose en plaques et maladie du motoneurone). Ces études ont porté sur l'efficacité du spray Sativex® à base de THC/CBD. Sous l'angle des soins de santé, avec un horizon temporel de la vie entière et avec un taux d'actualisation de 3 % pour les coûts et les effets, le spray à base de THC/CBD associé à un traitement SOC a montré une perte minime en termes d'années de vie pondérées par la qualité (QALY) pour les douleurs neuropathiques par rapport au seul traitement SOC et seulement de faibles gains de QALY pour les autres populations. Dans tous les modèles, les coûts du spray à base de THC/CBD associé au traitement SOC étaient plus élevés qu'avec le traitement SOC uniquement. Les analyses de sensibilité montrent que les

effets du traitement, les valeurs d'utilité, ainsi que les scores de la douleur ou de la spasticité sont les paramètres les plus pertinents. Une grande incertitude entoure les estimations budgétaires. Les sites internet et les documents d'agences d'ETS soulignent un certain nombre de problèmes importants sur les plans légaux, sociaux, éthiques et organisationnels concernant l'usage et le remboursement du cannabis médical.

Conclusions. Tandis que la recherche s'étendait à toutes les populations atteintes de douleurs chroniques et de spasticité, les preuves disponibles n'ont permis d'évaluer l'efficacité et l'innocuité du cannabis médical que pour les personnes souffrant de douleurs neuropathiques, musculosquelettiques ou cancéreuses, de spasticité en cas de sclérose en plaques ou de maladie du motoneurone. Toutefois, étant donné que les résultats des études étaient incomplets, non concluants et contradictoires, il n'a pas été possible de tirer de conclusions sur l'efficacité et l'innocuité du cannabis médical pour ces patients. Il ressort des études sur le cannabis médical un parti pris imprévisible ainsi que des incertitudes au niveau des preuves en raison du risque d'une levée de l'insu pour l'allocation du traitement ainsi que des résultats rapportés par les patients pour les symptômes de douleurs chroniques et de spasticité. Dans ces conditions, s'il est impossible de conclure que le cannabis médical est efficace et sans danger pour traiter les douleurs chroniques et la spasticité, on ne saurait non plus conclure que le cannabis médical n'est pas efficace ni sans danger pour ces traitements. Les futures études à ce sujet devront probablement faire face aux mêmes difficultés et restrictions, qui ne pourront être résolues qu'en partie grâce à l'amélioration des études et à la production de rapports complets.

Les modèles d'économicité ont montré que le spray à base de THC/CBD pour le traitement de la douleur ou de la spasticité n'avait qu'une faible incidence sur la QALY mais qu'il occasionnait des coûts supplémentaires par rapport au seul traitement SOC. On ignore si l'économicité et les estimations budgétaires peuvent être généralisées à d'autres populations, produits à base de cannabis médical ou voies d'administration.

S'agissant de rembourser le cannabis médical pour certaines populations, il convient également de tenir compte des aspects légaux, sociaux, éthiques et organisationnels. À titre d'exemple, le remboursement du cannabis médical sera soumis à différentes lois suisses interdépendantes concernant la culture des plants, la consommation, la distribution et la prescription. De plus, il peut y avoir des conséquences sociales et éthiques, par exemple en raison de la disparité entre les attentes des patients et les preuves scientifiques. Les restrictions en termes d'accessibilité, les patients vulnérables susceptibles de subir des conséquences involontaires et l'usage illicite sont source d'inquiétudes supplémentaires. Enfin, des problèmes d'ordre organisationnel peuvent se poser au niveau de l'approvisionnement et du contrôle de la qualité des produits à base de cannabis médical.

Riepilogo Situazione iniziale. Per canapa medicinale si intendono tutti i prodotti a base di canapa utilizzati nei trattamenti medici. I cannabinoidi finora più studiati, e ritenuti i più importanti in termini di effetti clinici, sono il tetraidrocannabinolo (THC) e il cannabidiolo (CBD). In Svizzera, per la canapa medicinale non è prevista una rimunerazione generale da parte dell'assicurazione obbligatoria delle cure medico-sanitarie (AOMS). La canapa medicinale può essere utilizzata per trattare diversi sintomi ed è impiegata prevalentemente come terapia aggiuntiva o dopo che altre opzioni terapeutiche sono risultate inefficaci. Prima del presente rapporto di Health Technology Assessment (HTA), è stata condotta una scoping review i cui risultati sono stati pubblicati nel rapporto di scoping. Il rapporto descrive la base di evidenze scientifiche per l'utilizzo della canapa medicinale nel trattamento dei seguenti sintomi: dolore cronico, spasticità, perdita involontaria di peso, nausea e vomito associati al trattamento del cancro. Riguardo agli ultimi due sintomi, l'evidenza degli studi randomizzati controllati (RCT) si è rivelata insufficiente per formulare raccomandazioni pertinenti e si è pertanto deciso di non procedere all'estrazione completa dei dati e allo sviluppo di un modello del rapporto costo-efficacia per questi due sintomi nella fase HTA. L'obiettivo generale del rapporto HTA è di analizzare l'efficacia, l'efficienza, la sicurezza, il rapporto costo-efficacia e l'incidenza sul bilancio dell'utilizzo della canapa medicinale per il dolore cronico e la spasticità in Svizzera.

Metodi. Le revisioni sistematiche sono state condotte rispettando gli standard metodologici internazionali. Le ricerche sistematiche nella letteratura scientifica sono state svolte in PubMed (MEDLINE), Embase.com e in altre banche dati complementari per identificare le pertinenti evidenze di efficacia, efficienza, sicurezza e rapporto costo-efficacia. Nelle relative ricerche sono stati inclusi solo gli RCT e le valutazioni economiche. Si è proceduto quindi all'organizzazione dei dati degli studi in tabelle di evidenza e alla pubblicazione dei risultati della valutazione della qualità. I dati relativi all'utilizzo della canapa medicinale per il dolore cronico sono stati classificati in tre sottogruppi: dolore da cancro, dolore neuropatico e dolore muscolo-scheletrico. I dati relativi all'utilizzo della canapa per la spasticità sono stati classificati in due sottogruppi: sclerosi multipla (SM) e malattia del motoneurone.

Durante la fase di scoping, le ricerche sistematiche nella letteratura riguardo al rapporto costo-efficacia dell'utilizzo della canapa medicinale per il dolore cronico e la spasticità non hanno fornito evidenze per la Svizzera. Pertanto, sono stati sviluppati modelli di costo-efficacia basati sul decorso naturale della malattia durante la vita di un paziente nella prassi clinica svizzera. I modelli sono stati impiegati per determinare il rapporto costo-efficacia della canapa medicinale in aggiunta allo standard di cura (SOC) rispetto al solo SOC in tutti i sottogruppi per i quali fossero disponibili evidenze di efficacia utilizzabili. Sono state effettuate ricerche non sistematiche per identificare i costi e la qualità della vita correlata alla salute (espressa in utilità su una scala da 0 a 1) per la modellazione del rapporto costo-efficacia. L'incertezza riguardo ai parametri di calcolo è stata oggetto di analisi di sensibilità e di analisi

di scenario. Inoltre, è stata calcolata l'incidenza prevista sul bilancio utilizzando fattori per i calcoli dell'incidenza sul bilancio derivati da un sondaggio tra esperti clinici. Sono stati consultati i siti web delle agenzie HTA per ottenere informazioni sugli aspetti sociali, legali, etici e organizzativi relativi alla prescrizione di canapa medicinale. Per questi ambiti HTA, le evidenze sono state descritte in modo narrativo.

Risultati. L'eterogeneità tra gli studi sui risultati e sulle misure di risultato, l'asimmetria dei dati e l'incompletezza dei risultati degli studi non hanno permesso di calcolare stime aggregate per i dati sull'efficacia relativi ai gruppi di popolazione affetti da dolore e spasticità. Nel complesso, i dati sull'efficacia dell'utilizzo della canapa medicinale per il dolore cronico e la spasticità sono risultati incoerenti (vale a dire che gli studi con gruppi di pazienti comparabili e con tipologie simili di canapa medicinale non hanno prodotto risultati coerenti che andassero nella stessa direzione) e inconcludenti (vale a dire che nessuno studio è stato in grado di trarre una conclusione definitiva sull'efficacia della canapa medicinale). Inoltre, molteplici fattori aumentano il rischio di distorsioni negli studi sulla cannabis medica, tuttavia l'estensione e la direzione delle potenziali distorsioni sono difficili da comprendere. Sebbene sia stato possibile calcolare stime aggregate per una parte dei risultati relativi alla sicurezza e per alcuni gruppi di pazienti, le questioni emerse in merito all'efficacia si applicano anche alla sicurezza, il che implica un profilo di sicurezza incompleto per la canapa medicinale.

Per elaborare un modello del rapporto costo-efficacia, nei modelli di dolore cronico la misura di efficacia preferita è stato il cambiamento assoluto nel punteggio della scala numerica di valutazione (NRS), mentre nei modelli di spasticità tale misura è stata la proporzione di responder con una riduzione ≥30 per cento del punteggio NRS. Di conseguenza, per l'elaborazione di un modello del rapporto costo-efficacia sono disponibili evidenze di efficacia utilizzabili per due gruppi di popolazione affetti da dolore cronico (dolore neuropatico e dolore muscolo-scheletrico) e due gruppi affetti da spasticità (nella SM e nella malattia del motoneurone). Tali studi hanno valutato l'efficacia dello spray THC:CBD (Sativex). Applicando una prospettiva sanitaria, una stima dei costi e dei benefici in tempo-vita e un tasso di sconto del 3 per cento del rapporto costo-efficacia, lo spray THC:CBD in aggiunta al SOC ha mostrato una perdita minima in termini di anni di vita ponderati per la qualità (QALY) per il dolore neuropatico rispetto al solo SOC, e solo piccoli benefici in termini di QALY per gli altri gruppi. In tutti i modelli, i costi dello spray THC:CBD in aggiunta al SOC erano maggiori rispetto al solo SOC. Le analisi di sensibilità hanno mostrato che i parametri più influenti sono gli effetti del trattamento, i valori di utilità e i punteggi di dolore o spasticità al basale. Le stime relative all'incidenza sul bilancio sono caratterizzate da una sostanziale incertezza. I siti web e la documentazione delle agenzie HTA sollevano numerose questioni legali, sociali, etiche e organizzative legate all'utilizzo e al rimborso della canapa medicinale.

Conclusioni. Mentre la domanda di ricerca comprendeva tutti i gruppi di popolazione affetti da dolore cronico e spasticità, vi erano evidenze appena sufficienti per valutare l'efficacia e la sicurezza dell'utilizzo della canapa medicinale per le persone affette da dolore neuropatico, dolore muscolo-scheletrico, dolore da cancro, spasticità nella SM e spasticità nella malattia del motoneurone. Tuttavia, a causa dei risultati incompleti, inconcludenti e incoerenti emersi dagli studi, non è stato possibile trarre conclusioni in merito all'efficacia e alla sicurezza della canapa medicinale in questi gruppi di pazienti. Negli studi sulla canapa medicinale si verificano distorsioni (bias) e incertezze nella base delle evidenze scientifiche, a causa del rischio di smascheramento del trattamento assegnato ai pazienti in combinazione con i risultati riferiti dai pazienti per i sintomi del dolore cronico e della spasticità. Per questi motivi, non è possibile concludere che la canapa medicinale non sia un'opzione di trattamento efficace e sicura per il dolore cronico e la spasticità, né che non sia affatto efficace e sicura per il trattamento del dolore cronico e della spasticità. Gli studi futuri sulla canapa medicinale per il trattamento di questi sintomi dovranno probabilmente affrontare difficoltà e restrizioni simili, di cui solo una parte potrà essere risolta con migliori tipologie di studio e un'analisi completa dei risultati.

L'elaborazione del modello del rapporto costo-efficacia ha mostrato che l'utilizzo dello spray THC:CBD per il trattamento del dolore o dei sintomi della spasticità comporta variazioni minime nei QALY, a fronte di costi aggiuntivi rispetto al solo SOC. Si ignora se sia possibile estrapolare le stime di costo-efficacia e di incidenza sul budget ad altri gruppi, altri prodotti a base di canapa medicinale o altre vie di somministrazione.

Nel considerare la rimunerazione della canapa medicinale per determinati gruppi, andrebbe tenuto conto anche delle questioni legali, sociali, etiche e organizzative attinenti. Ad esempio, la rimunerazione della canapa medicinale sarà soggetta a diverse leggi svizzere, interconnesse tra loro, in materia di coltivazione, consumo, consegna e prescrizione. Inoltre, la rimunerazione della canapa medicinale potrebbe avere implicazioni sociali ed etiche, per esempio come risultato di un divario tra le aspettative dei pazienti e le evidenze scientifiche. Altre preoccupazioni potrebbero riguardare le restrizioni di accessibilità, i gruppi vulnerabili a rischio di conseguenze indesiderate e l'uso illecito. Inoltre, potrebbero sorgere difficoltà di natura organizzativa nella fornitura e nel controllo della qualità dei prodotti a base di canapa medicinale.

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Abbreviations and acronyms

A&E	Accident & emergency
AIC	Akaike Information Criterion
AIDS	Acquired immune deficiency syndrome
ALS	Amyotrophic lateral sclerosis
APPG	All-Party Parliamentary Group
BIA	Budget Impact Analysis
BIC	Bayesian Information Criterion
CADTH	Canadian Agency for Drugs and Technologies in Health
CB1	Cannabinoid Receptor 1
CB2	Cannabinoid Receptor 2
CBD	Cannabidiol
CHEC	Consensus Health Economic Criteria
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CHF	Swiss franc
CUA	Cost-Utility Analysis
EDSS	Expanded Disability Status Scale
EMCDDA	European Monitoring Centre for Drugs and Drug Addiction
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
HAS	Haute Autorité de santé
HIV	Human Immuno-Deficiency Virus
HPRA	Health Products Regulatory Authority
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
ICER	Incremental Cost-Effectiveness Ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
LMP	Licensed medical product
MS	Multiple Sclerosis
NA	Not applicable
NASEM	National Academies of Sciences
NHS	National Health Service
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NIP	Narcotic individual prescription
NRS	Numeric Rating Scale
OMC	Office of Medical Cannabis
OR	Odds Ratio
PBAC	Pharmaceutical Benefits Advisory Committee
PICO	Population-Intervention-Comparison-Outcome
PLS	Primary lateral sclerosis
QALY	Quality-Adjusted Life Years
QoL	Quality of life

RCT	Randomised Controlled Trial
SAE	Serious Adverse Event
SCI	Spinal cord injury
SOC	Standard of Care
SMR	Standardised mortality ratio
SR	Systematic Review
TGA	Therapeutic Goods Administration
THC	Tetrahydrocannabinol
TLEL	Timely Limited Exceptional License
UK	United Kingdom
USA	United States of America
ZiN	National Health Care Institute

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Objective of the HTA report

The objective of a health technology assessment (HTA) is to generate a focused assessment of various aspects of a health technology. The analytic methods applied to assess the value of using a health technology are described. The analytical process is comparative, systematic, transparent, and involves multiple stakeholders. The domains covered in an HTA report include 1) efficacy, effectiveness, and safety, 2) cost-effectiveness and budget impact, and 3) legal, social, ethical, and organisational issues. The purpose is to inform health policy and decision-making to promote an efficient, sustainable, equitable, and high-quality health system.

The process involved three phases: 1) pre-scoping phase, 2) scoping phase, and 3) HTA phase. This document represents the outcome of the HTA phase.

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-Tetrahydro-cannabinol (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 currently exist.

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

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, in patients of all ages with one of the four pre-specified symptoms chronic pain, spasticity, unintentional weight loss, or nausea and vomiting related to cancer treatment?

[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).

3 Summary of the scoping phase findings

A first appreciation of the available evidence on medical cannabis at the start of the project 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 HTA had to be narrowed down to a pre-specified selection of symptoms. A preliminary literature search for systematic reviews (search period 2014 to November 13, 2019) was conducted to help decide on the selection of symptoms to be included in the HTA report. The methods and results of this preliminary literature search are described in the scoping report[d]. The final selection of symptoms was based on the availability of literature and HTA appraisal documents from various countries on the use of medical cannabis for treating the symptom, as well as information on the main symptoms for which medical cannabis has been previously prescribed in Switzerland. In dialogue with the FOPH it was decided to focus the scoping phase on the symptoms chronic pain, spasticity, unintentional weight loss, and nausea and vomiting related to cancer treatment. Other symptoms which may be treated with medical cannabis may be considered to be the subject of a future HTA. Details on the systematic literature search and preliminary data extraction for these four symptoms are reported in the scoping report[d].

Based on the preliminary data extraction of the selected RCTs in the scoping phase, the conclusion was drawn that the evidence base for the symptoms chronic pain and spasticity was sufficient and could be further extracted and implemented in robust cost-effectiveness models. For the symptoms unintentional weight loss and nausea and vomiting related to cancer treatment the evidence from the RCTs found during the scoping phase was scarce. After extensive discussion with the FOPH, it was concluded that the evidence was insufficient to make pertinent recommendations for the use of medical cannabis in unintentional weight loss and nausea and vomiting related to cancer treatment and it was therefore not feasible to continue with complete data extraction for these two symptoms. The following reasons led to this conclusion:

Unintentional weight loss

[d] https://www.bag.admin.ch/dam/bag/en/dokumente/kuv-leistungen/bezeichnung-der-leistungen/Re-Evaluation-HTA/medizinal-cannabis-zur-behandlung-verschiedener-symptome-in-der-schweiz-scoping-bericht.pdf.download.pdf/Medical%20cannabis%20for%20treating%20various%20symptoms%20in%20Switzerland_Scoping%20report.pdf

- With a broad systematic literature search and broad selection criteria, only five RCTs describing the efficacy of medical cannabis use for unintentional weight loss were found. This number of RCTs is limited and the methodological quality was low (e.g. in two studies the sample size was very small (N<25) and in another study the treatment duration was not reported). When the more strict exclusion criteria for a minimal treatment duration and sample size would be applied to these RCTs (see section 'Selection procedure' in 8.1.1), most RCTs would have been excluded in the HTA phase.
- The preliminary data extraction showed large heterogeneity, for example a variety of outcomes were reported to determine the amount of weight loss, and only few outcomes were comparable and a quantitative comparison of study results would not be feasible. Therefore, it would not be possible to draw a generally representative conclusion on the efficacy and safety of medical cannabis in unintentional weight loss.

Nausea and vomiting related to cancer treatment

- The RCTs found with a broad systematic literature search and broad selection criteria in the scoping phase for nausea and vomiting related to cancer treatment were outdated (i.e. 19 of the 22 RCTs were published before 1990) and the most recent RCT was published 13 years ago. When the more strict exclusion criteria for sample size would be applied to these RCTs (see section 'Selection procedure' in 8.1.1), part of these RCTs would have been excluded in the HTA phase. In general, reporting of older studies is of less quality compared to recent studies. The description of the study characteristics and applied statistical analyses are often limited in older publications. Recent RCTs are required, because of new developments in the field of cancer treatment and anti-emetic therapies. Despite the progress achieved in the last 30 years, nausea and vomiting continue to be two of the most distressing side-effects of cancer chemotherapy.[1] It is therefore remarkable that no recent RCTs were found with our systematic literature search in the scoping phase on medical cannabis use for nausea and vomiting related to cancer treatment.
- Generally, anti-emetic therapy should be customised to the type of chemotherapeutic agents administered to a patient.[1] In current guidelines the first choice for anti-emetic therapy is a 5-HT3 antagonist in combination with dexamethasone; with an addition of NK-1 receptor antagonist and/or olanzapine in highly emetic cancer treatments.[1] Many different types of anti-emetic therapy as comparator treatment to medical cannabis were used in the RCTs found with the systematic literature search in the scoping phase, though no RCTs compared these new anti-emetic regimens with medical cannabis. As a consequence, the comparator treatment in these RCTs may be inadequate and the applicability of the evidence might be limited. In 2015, the

evidence on cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy was summarised in a Cochrane review.[31] The authors concluded that medical cannabis may be useful for treating refractory chemotherapy-induced nausea and vomiting. However, they emphasised the methodological limitations with respect to the study design of the RCTs, lacking reflection of current chemotherapy and anti-emetic treatment regimens, and the low quality of evidence when combined with meta-analyses.

- The preliminary data extraction showed large heterogeneity, for example a variety of outcomes were reported to determine the frequency or severity of nausea or vomiting. Moreover, only few outcomes were comparable and a quantitative comparison of study results would not be feasible. Therefore, it would not be possible to draw a generally representative conclusion on the efficacy and safety of medical cannabis in nausea and vomiting related to cancer treatment.

Overall, more and higher quality RCTs are needed to give insight in the efficacy of medical cannabis use for the symptoms unintentional weight loss and nausea and vomiting related to cancer treatment. Future RTCs should at least be designed according to current high standards for RCTs, have sufficient power to detect differences between study arms, avoid unnecessary heterogeneity in outcomes and outcome measures, and be more complete in the reporting of their data (i.e. baseline data, follow-up data, treatment differences, measures of spread, and p-values) to allow for future meta-analyses. Only when these kind of RCTs will become available complete data extraction and the development of cost-effectiveness models could be re-considered. As it was decided not to continue with data extraction for the symptoms unintentional weight loss and nausea and vomiting related to cancer treatment, the remaining of the HTA report will focus on the symptoms chronic pain and spasticity only.

4 Medical background

4.1 Background on chronic pain

Chronic pain is defined as persistent or recurrent pain lasting longer than 3 months.[2] Chronic pain is a highly prevalent condition, affecting about 20% of the people worldwide and is associated with a significant personal, social, medical, and economic burden.[3] 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, multiple sclerosis (MS), human immuno-deficiency virus (HIV), and postoperative or traumatic peripheral nerve lesions.[2,3] The treatment of chronic pain is multimodal, but mostly contains a pharmacological agent.[2] 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 rate of opioids is associated with an increase in opioid use disorders and opioid-related mortality.[4,5] Since chronic pain is difficult to treat, other treatment options such as medical cannabis or other pharmacotherapies, are explored with different mechanisms of action for treatment or the various conditions underlying the pain.[3,4] This HTA will explore the available evidence on the efficacy of medical cannabis on all types of chronic pain, not limited to a specific underlying disease.

4.2 Background on spasticity

Spasticity is often inconsistently defined in scientific studies and also the applied outcome measures do not always correspond to the reported spasticity definition.[6] 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.[7] This definition changed during the years by adding other features of spasticity such as spasm and clonus.[7] 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.[8] MS is a progressive disease and eventually up to 90% of people with MS will suffer from the symptom muscle spasticity.[9] Also in SCI the epidemiology of spasticity affirms the significance of this medical problem.[10] 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.[11–13] 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.[11]

Medicinal treatment is prescribed to reduce spasticity, but may be insufficiently effective, difficult to obtain, or associated with intolerable side-effects.[8] As a consequence, people with MS or SCI have experimented with alternative therapies, including cannabis, to ease their physical problems.[9,10] Medical cannabis is suggested as an effective and tolerable alternative treatment for patients with residual spasticity not adequately controlled using existing treatments.[8]

5 Technology

5.1 Technology description

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.[14,15] After discovery of the human endocannabinoid 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.[14,15] 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.[14]

5.2 Mechanism of action

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.[16] The so far most studied cannabinoids, and thought to be the most important in terms of clinical effects, are THC and cannabidiol (CBD).[14,15] 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 Cannabinoid receptor type 1 (CB1) and Cannabinoid receptor type 2 (CB2) in the body. The endocannabinoid system is composed of these cannabinoid receptors, their endogenous ligands (endocannabinoids), and endocannabinoid-degrading enzymes as part of the central and peripheral nervous system that perform a large role in maintaining homeostasis in many physiological functions.[17] The effects of cannabinoids are primarily mediated by CB1 and CB2 receptors. CB1 receptors are predominantly located in the central nervous system, mainly in the cortex, basal ganglia, hippocampus, and cerebellum.[17,18] 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.[17,18] CB2 receptors play a role in immune cell activation and inflammation and are mainly expressed in peripheral immune-related organs .[17,18]

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 a variety of 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.[14,15,19] 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.[15] 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, decreased anxiety, and improved mental health outcomes in schizophrenia.[20,21] 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 so-called entourage effect is a topic of ongoing research.

5.3 Mode of administration

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.[22] 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.[14] 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 symptoms to be treated, its effectiveness, experienced side-effects by the patient, and costs.[23]

5.4 Safety

The rising interest in the medical use of cannabis also raises safety concerns. An example of a systematic review (SR) of safety studies of medical cannabis reporting a wide range of non-serious adverse events found that the rate of non-serious adverse events was 1.86 times higher among people using medical cannabis for short-term versus controls.[24] Dizziness was the most commonly reported non-serious adverse event among medical cannabis users. There was no evidence of a higher incidence of serious adverse events (SAEs) following medical cannabis use compared with control. The most common SAEs were relapse of MS, vomiting, and urinary tract infection. The difference in mortality between the medical cannabis and the control groups was not statistically significant. The authors highlight that the risks associated with long-term medical cannabis use were poorly characterised in published RCTs and observational studies.

5.5 Types of medical cannabis products

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.[25,26] Table 1 contains the details of the most commonly referred to licensed medical products (LMPs).[14,15]

Table 1. 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 2.[27]

Table 2. Description of Swiss Extemporaneous Preparations and Sativex®

	Sativa oil 1mg THC	Dronabinol solution	Standard-	Standard-	Sativex® 2.7mg THC	Praescrip-	Praescrip-

		2.5mg THC	ised cannabis tincture	ised cannabis oil		tio magistralis Cannabis 1mg THC	tio magistralis Cannabis 2.7mg 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)	1.46	1.60-1.80	1.10	1.60	0.89	1.60	1.57

Keys: CHF = Swiss Franc, CBD = cannabidiol, THC = tetrahydrocannabinol, mg = milligram

5.6 Alternative technologies

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

5.7 Regulatory status / provider

Regulation in Switzerland

The cultivation, the trade, and the consumption of cannabis with a THC content of more than 1% is forbidden in Switzerland, although the possession of a small amount (10 grams of cannabis) for own consumption is only mildly punished.[28,29] 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.[30]

Between 2012 and 2019 approximately 15’000 patients received access to medical cannabis via TLEL, with around 3’000 authorisations being granted in 2019 alone.[31,32] These figures exclude patients who obtain cannabis from the black market (i.e. illicit users). The number of patients who use medical cannabis in Switzerland is therefore estimated to be higher, ranging from from 66’000 to 110’000.[33,34] 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. For illustration, the regulation in some European countries has been described below.

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.[35] 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.[36] The Deutscher Bundestag revealed the six most-reported diagnoses for which medical cannabis has been prescribed and covered by statutory health insurers from 2018 to September 2019: pain (70.9%), spasticity (10.8%), anorexia (6.9%), epilepsy (1.6%), Attention Deficit Hyperactivity Disorder (ADHD) (1.5%), and Tourette Syndrome (1.0%).[37]

Denmark

Since January 2018, medical doctors can prescribe medical cannabis in Denmark as part of a 4-year trial period. The pilot programme aims to offer patients a legal access to medical cannabis if they have not benefitted from authorised medicines. An assessment after the trial period intends to provide better basis for the use of medical cannabis. People in Denmark are reimbursed at the rate of 50% for cannabis products in the pilot programme, people who have been granted reimbursement for the terminally ill receiving 100% reimbursement.[38] 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.[39]

Belgium

In 2015, Belgium legalised the use of approved medical cannabis products. Currently, only Sativex® can be prescribed and reimbursed to patients with moderate to severe spasticity in MS patients resistant to existing therapies. A draft resolution was submitted in September 2019, which calls for approval of and research into the use of medical cannabis in indications beyond MS, namely in amyotrophic lateral sclerosis and epilepsy.[40]

The Netherlands

In the Netherlands patients are allowed to use cannabis for medical use. Since 2001 the government agency Office of Medical Cannabis (OMC) is responsible for overseeing the production of cannabis for medical and scientific purposes. The OMC has a monopoly position 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.[41] Pharmacies can supply medical cannabis on doctor's prescription only. While it is up to medical doctors to determine which conditions would benefit from treatment with medical cannabis, the OMC states that current data shows that medical cannabis can help relieve pain and muscle spasms associated with MS or SCI; nausea, reduced appetite, weight loss, and debilitation associated with cancer and AIDS; nausea and vomiting caused by medication or radio-therapy for cancer and HIV/AIDS; long-term neuropathic pain, phantom limb pain, facial neuralgia, or chronic pain following an attack of shingles; and tics associated with Tourette Syndrome.[42] Medical cannabis is not generally reimbursed in the Netherlands, but health insurers may decide to cover (part of) the costs for individual cases.

6 PICO

The PICO framework was used to further specify the research question and facilitate the systematic literature search; PICO is an acronym for Population, Intervention, Comparator, and Outcome.[42]

Table 3. PICO (population - intervention - comparator - outcome) box

P:	1. Patients (all ages) with the symptom chronic pain with any underlying cause 2. Patients (all ages) with the symptom treatment-resistant residual spasticity with any underlying cause

I:	Medical cannabis, prescribed as standalone treatment or add-on treatment
C:	• Placebo • No treatment for the symptom of interest • Standard of care according to the treatment guidelines (i.e. conventional drugs for the chronic pain condition, spasticity)
O (clinical):	**1. Efficacy/effectiveness 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 health-related quality of life (HRQoL) **2. Efficacy/effectiveness 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. Safety of medical cannabis:** a. Occurrence of cannabis-associated serious adverse event b. Withdraw of treatment due to adverse effects of medical cannabis
O (health economic):	1. Resource use due to serious 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

7 HTA key questions

For the evaluation of medical cannabis the following key questions covering the central HTA domains, as designated by the European Network for Health Technology Assessment (EUnetHTA) Core Model[40] (efficacy, effectiveness, safety, cost-effectiveness, budget impact, legal, social, ethical, and organisational aspects), are addressed for the symptoms chronic pain and spasticity.

Key questions - efficacy, effectiveness, and safety

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

1. What is the efficacy of medical cannabis (prescribed as standalone treatment or add-on treatment) compared to placebo, no treatment, or standard of care (depending on the symptom), in patients of all ages with chronic pain or spasticity with any underlying cause?

2. What is the effectiveness of medical cannabis (prescribed as standalone treatment or add-on treatment) compared to placebo, no treatment, or standard of care (depending on the symptom), in patients of all ages with chronic pain or spasticity with any underlying cause?
3. What is the safety of medical cannabis (prescribed as standalone treatment or add-on treatment) compared to placebo, no treatment, or standard of care (depending on the symptom), in patients of all ages with chronic pain or spasticity with any underlying cause?

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

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

1. What is the healthcare resource use of patients of all ages with chronic pain or spasticity with any underlying cause 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), serious adverse events, and chronic pain or spasticity?
4. What are the estimated differences in costs and outcomes of medical cannabis use compared to no treatment, or standard of care (depending on the symptom), in patients of all ages with chronic pain or spasticity with any underlying cause?
5. What is the likely budget impact of the reimbursement of medical cannabis in patients of all ages with chronic pain or spasticity with any underlying cause?
6. What are the uncertainties surrounding the costs and outcomes of medical cannabis compared to no medical cannabis in patients of all ages with chronic pain or spasticity with any underlying cause?

Key questions - legal, social, ethical, and organisational issues

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

1. Are there specific legal issues associated with potential reimbursement of medical cannabis for patients of all ages with chronic pain or spasticity with any underlying cause?
2. What are the socially and ethically relevant consequences of potential reimbursement of medical cannabis for patients of all ages with chronic pain or spasticity with any underlying cause?
3. What organisational issues are attached to the use of medical cannabis in patients of all ages with chronic pain or spasticity with any underlying cause?

7.1 Additional question(s)

No additional questions have been formulated.

8 Efficacy, effectiveness, and safety

A systematic review (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 SR was designed to search for up-to-date and high-quality evidence, according to current standards and clinical practice. The applied methodology follows international standards, such as the Cochrane Collaboration guidelines for performing SRs, and the reporting of the SR follows the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[41,42]

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 inclusion and exclusion criteria
4. Critical appraisal (quality and risk of bias assessment)
5. Data extraction
6. Data synthesis
7. Quality control

In addition, a stepwise approach could be implemented within the SR:

I. Search for original RCTs

II. Based on the data extraction of the selected RCTs it was discussed with the FOPH whether a systematic literature search would be conducted for comparative non-randomised studies. It was decided during the project not to proceed with this step.

The following sections describe the SR methodology of the efficacy, effectiveness, and safety of medical cannabis as applied to this HTA.

8.1 Methodology efficacy, effectiveness, and safety

8.1.1 Databases and search strategy

Search strategy

PubMed (MEDLINE) and Embase.com databases were searched for RCTs on medical cannabis use for chronic pain and spasticity 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 Chapter 6). 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 - 22th January 2020) and the language of publications (i.e. English, French, German, and Dutch). Since a large amount of medical cannabis studies was published in the eighties and nineties, a time horizon of forty years was chosen. Furthermore, animal studies and SRs were excluded with additional search strings. Two separate search strategies were developed for RCTs on medical cannabis use for chronic pain and spasticity (Appendix 15.1). 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 manually deleted.

Selection procedure

From the articles retrieved from PubMed (MEDLINE) and Embase.com the relevant references were selected by a three-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).
3. Screening during data extraction phase: further scrutiny of the article during the data extraction phase might lead to exclusion. To gain insight in the amount and quality of the available evidence on medical cannabis no strict criteria were applied yet for the quality of RCTs during the scoping phase. To avoid the inclusion of RCTs of very low quality, during the HTA phase more strict exclusion criteria were applied for a minimal treatment duration of two weeks[3] and for the sample size of RCTs: a. small sample size (n<50) without an a priori power calculation presented in the article; b. small sample size (n<25) with a priori power calculation presented in the article; and c. small sample size (n<50) while the presented a priori power calculation showed

that a higher number of patients was needed than actually included. In most of the additionally excluded RCTs due to these two exclusion criteria multiple quality issues were identified and sample size or treatment duration were considered as main reason for exclusion.

The process of selection and inclusion and exclusion of articles was registered in Excel and an Endnote library. The overall exclusion criteria applied are reported in PRISMA flow charts (Section 8.2.2) and in tables with an overview of the reasons for exclusion per excluded RCT (Appendix 15.2). 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 are presented in Table 4 .

Table 4. Inclusion and exclusion criteria for RCTs on medical cannabis use for chronic pain or spasticity

	Inclusion	**Exclusion**
Period of publication	1980-January 2020	Publications before 1980
Language of publication	English, German, French, Dutch	All other languages
Country of study	All countries	-
Study design/type	• RCT • Open-label extension study of an RCT	• Review • Phase I RCT (i.e. testing of drug on healthy volunteers) • (Irrelevant) post-hoc/subgroup analysis of an RCT included in the systematic literature search • Secondary analyses of an RCT excluded in the systematic literature search • Open-label extension study of an excluded RCT • Non-comparative extension trial • Experimental study (e.g. with pain stimuli) • Observational study • Case report • Study protocol • Abstract only • Non-pertinent publication type (e.g. expert opinion, letter, editorial, comment)
Study quality	Sufficient study quality and sample size	• 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)

		• Small sample size (n<50) without a power calculation presented in the article • Small sample size (n<25) with power calculation presented in the article • Small sample size (n<50) while the presented power calculation showed that a higher number of patients was needed than actually included • Studies only presenting preliminary/interim results • No extractable data, e.g. Figures only
Study population	Patients (all ages) with chronic pain or spasticity	• No population of interest • No or lacking information on study population • Patients with acute pain • Patients in whom medical cannabis is not primarily prescribed for the symptom chronic pain or spasticity • No or lacking definition of spasticity
Study intervention	• Medical cannabis, prescribed as standalone treatment or add-on treatment • Treatment duration of at least 2 weeks[3]	• Non-prescribed/recreational cannabis • Short treatment duration (<2 weeks) • No washout periods between study interventions in cross-over trial
Study comparison	• Placebo • No treatment for chronic pain or spasticity • Standard of care according to the treatment guidelines (i.e. conventional drugs for the chronic pain condition or spasticity)	• Comparisons with other treatments than standard of care • No comparison
Study outcomes	• See pre-specified outcomes in PICO table (Chapter 6) • The outcome measures must be in line with the reported definition for spasticity	• No efficacy outcomes or no useful results for efficacy

Keys: RCT= randomised-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 dif-

ferences between the two researchers regarding more than 2% of the articles selected as 'include 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 of the first 30% of titles and abstracts 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 regarding 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. During screening of the first 10% of the full-text articles there was less than 5% discrepancy between the two 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.

8.1.2 Other sources

During the full-text screening phase, 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 the efficacy, effectiveness, and safety systematic literature search no additional studies were included by this process.

8.1.3 Assessment of quality of evidence

Based on the key risk of bias criteria used in the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach, the risk of bias of the study designs of the included RCTs was assessed.[43] These key study limitations or risk of bias of RCTs include:

- Lack of allocation concealment (i.e. those enrolling patients are aware of the study arm or period to which the next enrolled patient will be allocated, e.g. based on birth date or chart number)

- Lack of 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 arm event rates, and differences between intervention and control arm, 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. use of unvalidated outcome measures; carryover effects in crossover trial)

Each risk of bias criterion of the included RCTs was rated as low risk of bias, moderate or unclear (i.e. not reported in the article) risk of bias, or high risk of bias. Based on the crucial limitations for one or more of these criteria, the risk of bias of the study design within the whole study was rated in one of the three categories: low risk of bias, moderate risk of bias, or high risk of bias. For outcomes for which it was possible to calculate pooled estimates, a GRADE assessment for the level the quality or certainty of the evidence on outcome level was implemented. Within GRADE, the risk of bias of the study design is one of the features on which the certainty of the evidence is assessed (see below). The risk of bias was assessed by two independent researchers. In case of discrepancy a third researcher was consulted to reach consensus.

The GRADE approach is a system for rating the certainty of a body of evidence in SRs, which for a specific outcome is rated across studies instead of a quality assessment of individual studies.[41] The certainty of the evidence is assessed by looking at the following features of the evidence found for each outcome:

- **Study limitations (risk of bias)** – the 'internal validity' of the evidence
- **Inconsistency** – the heterogeneity or variability in the estimates of treatment effect across studies
- **Indirectness** – the degree of differences between the population, intervention, comparator for the intervention, and outcome of interest across studies
- **Imprecision** (random error) – the extent to which confidence in the effect estimate is adequate to support a particular decision
- **Publication/other bias** – the degree of selective publication of studies

The certainty of the evidence is classified as high, moderate, low, or very low:

- **High** – further research is very unlikely to change our confidence in the estimate of effect
- **Moderate** – further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
- **Low** – further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
- **Very low** – any estimate of effect is very uncertain

8.1.4 Methodology data analyses efficacy, effectiveness, and safety

Different levels of heterogeneity in patient populations, outcomes, and outcome measures were observed for the RCTs on medical cannabis use for chronic pain and spasticity. After the full data extraction it was explored which level of data merging/stratification was possible and for which outcomes it was possible to calculate pooled estimates and implement a GRADE assessment for the certainty of the evidence on outcome level (see Section 8.1.3).

Data stratification

The options for clinically relevant data merging/stratification were discussed with clinical experts, based on the patient groups reported in the included RCTs. The clinical experts were blinded for the study results. Giving the differences in mechanisms underlying pain, the data on medical cannabis use for chronic pain was stratified in four groups:

- Cancer pain
- Neuropathic pain
- Musculoskeletal pain
- Nociceptive pain

The latter category, nociceptive pain, is reported here for a complete overview of the pain categories, however no RCTs were included for this specific chronic pain population.

The symptom spasticity arises from injury of upper motor neurons along the descending motor pathways. This damage can be caused by different pathologies, such as MS, stroke, or spinal cord injury. Since these diseases have identical origins of spasticity, the mechanisms of action of medical cannabis on spasticity symptoms are comparable, and the patient populations with spasticity could be merged. However, the conditions of the included RCTs differed largely regarding disease progression and life expectancy, therefore it was decided to stratify the data on medical cannabis use for spasticity in two populations:

- MS
- Motor neuron disease (i.e. amyotrophic lateral sclerosis (ALS) or primary lateral sclerosis (PLS))

Data synthesis

Pooled estimates were calculated and a GRADE assessment for the certainty of the evidence on outcome level was made, when 1) two or more studies within the above mentioned stratifications reported on the same outcome, and 2) sufficient data were reported in the studies (i.e. for efficacy data: mean change from baseline and standard deviation in the treatment arms; or number of patients with an outcome and total number of patients in the treatment arms; plus treatment difference between the treatment arms; for safety data: number of patients with an outcome and total number of patients in the treatment arms). This could be done for two outcomes: mortality and withdrawal of treatment due to adverse events. Pooling of data were done with the number of patients provided in the articles (i.e. for safety the data based on the number of randomised patients) and an unadjusted risk ratio (RR) was calculated. Considering the heterogeneity in the data, a random-effects model (DerSimonian & Laird) was used for the analyses. All analyses were conducted using the MetaXL (www.epigear.com) add-in for Microsoft Excel. The evidence on these outcomes was summarised in GRADE evidence profiles.

For most efficacy and safety outcomes it was, however, not possible to calculate pooled estimates and implement a GRADE assessment: for the efficacy outcomes clinically relevant patient-reported pain relief, improvement in a specific spasticity aspect, withdrawal due to lack of efficacy of medical cannabis, and improvement in HRQoL; and for the safety outcome occurrence of cannabis-associated SAEs. These outcomes were presented in summary tables and descriptively summarised per outcome measure.

8.2 Results efficacy, effectiveness, and safety

8.2.1 Evidence base pertaining to efficacy, effectiveness, and safety

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

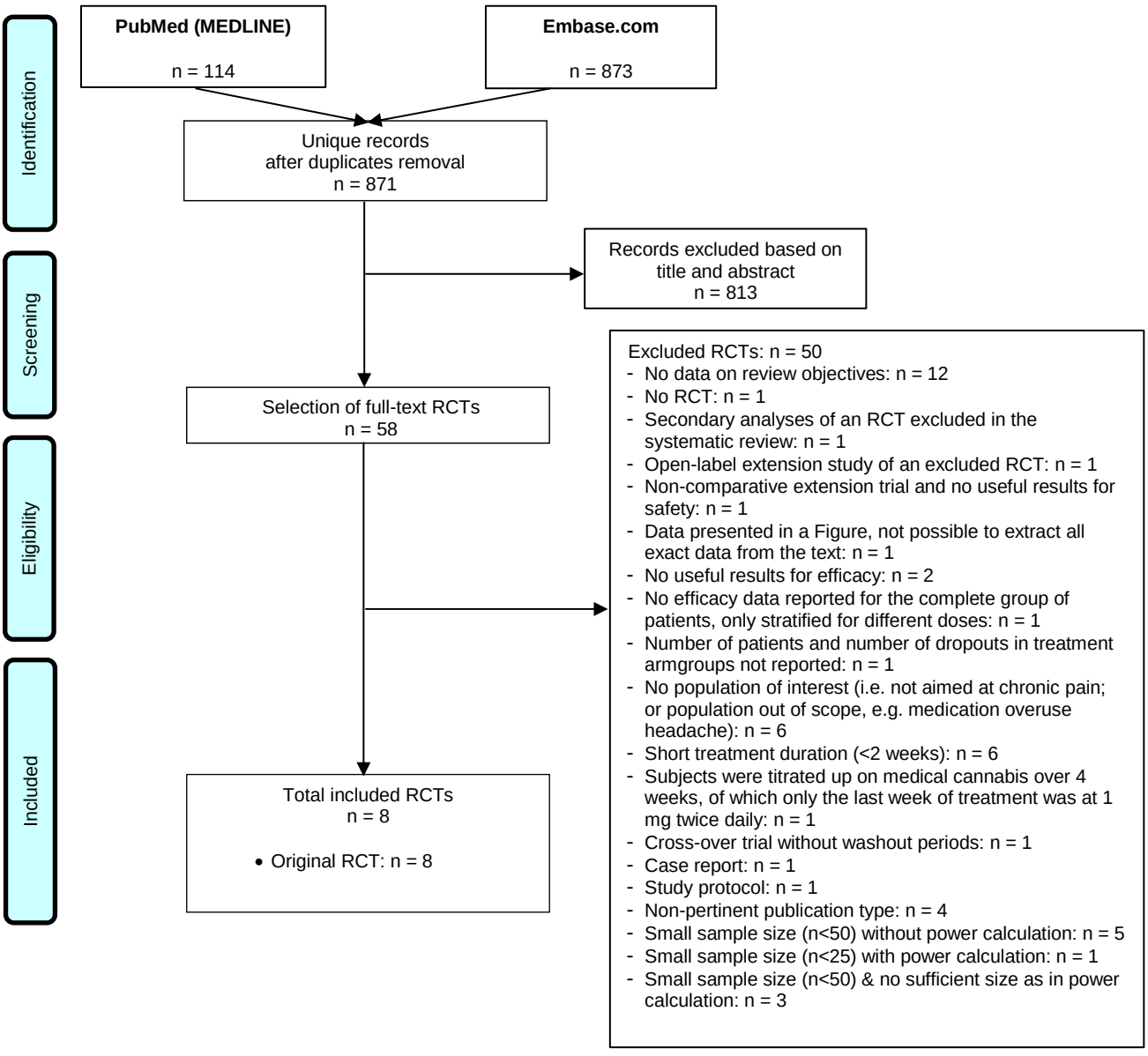
- Efficacy is the extent to which a specific health technology produces a beneficial, reproducible result under study conditions compared with alternative technologies (internal validity).
- Effectiveness is the extent to which a specific health technology, when applied in real world circumstances in 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 (SAEs).

8.2.2 PRISMA flow diagram

Chronic pain

In total, 871 unique records were identified in PubMed (MEDLINE) and Embase.com 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, eight original RCTs were finally included. The main reasons for exclusion were no data on review objectives (n=12 studies), different categories of a small sample size (n=9 studies, in total), no population of interest such as patients with non-chronic pain (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 given in the PRISMA flow chart (Figure 1). An overview of the reasons for exclusion per excluded RCT is enclosed in Appendix 15.2.

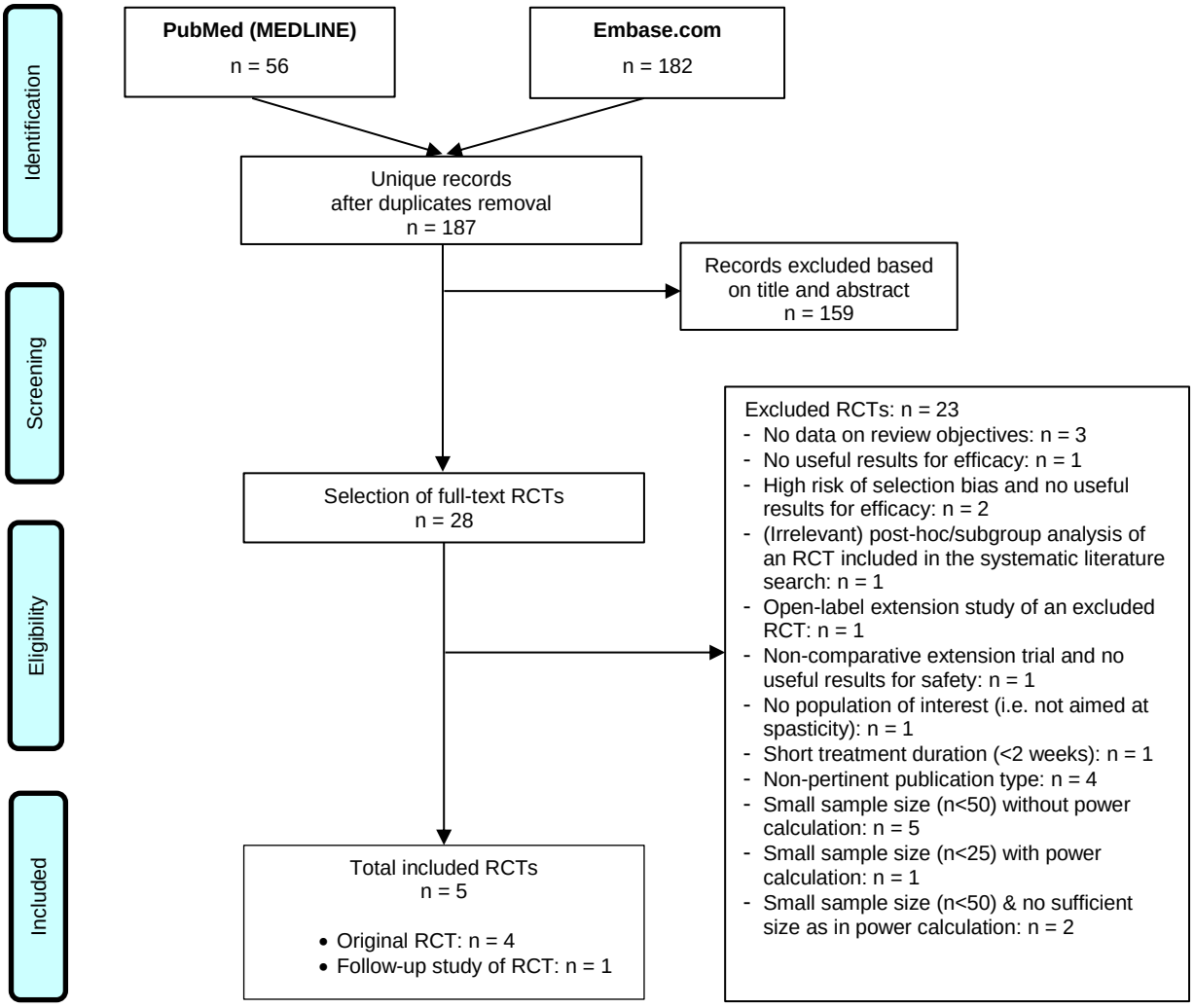
Figure 1. PRISMA flow chart of the efficacy, effectiveness, and safety systematic literature search on medical cannabis use for chronic pain symptoms



Spasticity

In the literature databases PubMed (MEDLINE) and Embase.com 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 23 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). In total, five studies were included: four original RCTs and one follow-up study of one of these original RCTs. An overview of the reasons for exclusion per excluded RCT is enclosed in Appendix 15.2.

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



8.2.3 Study characteristics and risk of bias of the included studies

Chronic pain

Eight original RCTs on medical cannabis use in adults with chronic pain were included in this HTA. All studies were RCTs with a parallel design, providing data on efficacy and safety outcomes. Two RCTs were conducted in patients with cancer pain[44,45]; five RCTs in a population with neuropathic pain (i.e. three RCTs in MS patients[46–48] and two RCTs in patients with allodynia[49,50]); and one RCT on medical cannabis use for musculoskeletal pain (i.e. rheumatoid arthritis[51]). THC:CBD spray (Sativex®) was the most frequently studied form of medical cannabis (in seven RCTs). A summary of the study characteristics is included in Table 5 and the risk of bias of the study designs of the individual RCTs in Table 6. In all RCTs bias arises for the study limitation blinding and subjective outcome measures. Unpredictable bias and uncertainty in the evidence base arise in research on medication with a characteristic well-known adverse event profile of medical cannabis (e.g. dizzy/light-headedness, fatigue, 'feeling high'), possibly leading to unblinding of patients to their treatment allocation. The patient-reported outcomes for chronic pain further increase this unpredictability and uncertainty, however, no fully objective measure is available for pain.

Cancer pain

Two multicentre RCTs were included on medical cannabis use in cancer patients, these studies were conducted in a mix of different countries (see Table 5). Fallon et al. described two RCTs, only the first study fulfilled our selection criteria. In Study I, patients were randomised to THC:CBD spray (n=200) or placebo (n=199), and then self-titrated study medication over a 2-week period, followed by a 3-week treatment period.[44] In the RCT of Lichtman et al., patients with advanced cancer and chronic pain were studied during 3 weeks of treatment with THC:CBD spray (n=199) or placebo (n=198).[45] The study designs of both RCTs had a moderate risk of bias (see Table 6).

Neuropathic pain

Three RCTs on chronic pain were included for the diagnosis MS in adults. The RCT of Langford et al.[46] was conducted in multiple countries (i.e. Canada, Czech Republic, France, Spain, and the UK) and the other RCTs[47,48] in a single European country (i.e. the UK and Germany). The total sample size ranged from 65 to 339 patients. THC:CBD spray (100 µl containing 2.7 mg THC and 2.5 mg CBD) was studied in two RCTs and the third RCT investigated dronabinol (THC). In all RCTs medical cannabis was compared to a placebo. The treatment duration ranged from 4 to 16 weeks. The study designs of these RCTs had a moderate risk of bias (see Table 6).

Allodynia is a condition where pain is caused by a stimulus that would not normally provoke pain. Nurmikko et al. conducted an RCT in Belgium and the UK and studied 63 patients in a THC:CBD spray arm and 62 patients in a placebo arm during a four-week treatment period.[49] The study design of this RCT had a moderate risk of bias. During 14 weeks, Serpell et al. compared 123 patients using THC:CBD spray with 117 patients receiving a placebo spray in a multicenter RCT (i.e. in Belgium, Canada, Czech Republic, Romania, and the UK).[50] The design of this RCT was assessed with a high risk of bias (see Table 6).

Musculoskeletal pain

One RCT, conducted in the UK, was included on chronic pain in rheumatoid arthritis. Treatment with THC:CBD spray (n=31) was compared to placebo (n=27) over the course of 5 weeks of treatment, including a titration phase of 2 weeks.[51] The risk of bias of the study design of this RCT was high (see Table 6).

Table 5. Study characteristics of the RCTs included on medical cannabis use for chronic pain

Reference Country	**Study design & period**	**Study population**	**Definition chronic pain**	**Intervention**	**Comparator**	**Sample size intention to treat & safety**	**Duration**
Cancer pain							
Fallon, 2017[44] Australia, Belgium, Bulgaria , Czech Republic, Estonia, Germany, Hungary, India, Israel, Italy, Latvia , Lithuania, Poland, Romania, Spain, Taiwan, UK	RCT - parallel NR	Adult patients with advanced cancer suffering from cancer-related pain, various types of cancer *Age (mean ± SD in y)* Study I: MC: 60.0 ± 11.0; P: 59.6 ± 11.0 *Sex (% female)* Study I: MC: 47.0%; P: 51.3%	Clinical diagnosis of cancer-related pain unalleviated by an optimised maintenance dose of Step 3 opioid therapy	**THC:CBD spray** 100 µl containing: 2.7 mg THC and 2.5 mg CBD; self-titration to optimal dose; max. of 10 sprays/day	**Placebo** Matching placebo	Study I, total: 399 / 399 THC:CBD spray: 200 / 200 Placebo: 199 / 199	- *Titration phase*: study I 2 weeks - *Study treatment*: study I 3 weeks - *Follow-up:* at end of treatment period
Lichtman, 2018[45] 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)* MC: 59.2 ± 12.0; P: 60.7 ± 11.1 *Sex (% female)* MC: 44.2%; P: 48.0%	Clinical diagnosis of cancer-related pain unallevi-ated by an optimised maintenance dose of Step 3 opioid therapy	**THC:CBD spray** 100 µl containing: 2.7 mg THC and 2.5 mg CBD; self-titration to optimal dose; max. of 10 sprays/day	**Placebo** Matching placebo	Total: 397 / 397 THC:CBD spray: 199 / 199 Placebo: 198 / 198	- *Titration phase*: 2 weeks - *Study treatment*: 3 weeks - *Follow-up:* at end of treatment period

Reference Country	Study design & period	Study population	Definition chronic pain	Intervention	Comparator	Sample size intention to treat & safety	Duration
Neuropathic pain							
Langford, 2013[46] Canada, Czech Republic, France Spain, UK	RCT - parallel NR	Adult patients with MS *Age (mean ± SD in y)* 48.97 ± 10.47 *Sex (% female)* 68%	Central neuropathic pain due to MS ≥3 months	**THC:CBD spray** 100 µl containing: 2.7 mg THC and 2.5 mg CBD; self-titration to optimal dose; max. of 12 sprays/day	**Placebo** Placebo delivered the excipient plus colorants	Total: 339 / 339 THC:CBD spray: 167 / 167 Placebo: 172 / 172	- *Titration phase*: 1 week - *Study treatment*: 14 weeks - *Follow-up:* at end of treatment period
Rog, 2005[47] UK	RCT - parallel March 2002-July 2002	Adult patients with MS *Age (mean ± SD in y)* 49.2 ± 8.3 *Sex (% female)* 78.8%	Central pain ≥3 months for which a nociceptive cause appeared unlikely	**THC:CBD spray** 100 µl containing: 2.7 mg THC and 2.5 mg CBD; self-titration to optimal dose; max. of 48 sprays/day	**Placebo** Matched the appearance, smell, and taste	Total: 65 / 66 THC:CBD spray: 33 / 34 Placebo: 32 / 32	- *Titration phase*: 1 week - *Study treatment*: 4 weeks - *Follow-up:* at end of treatment period
Schimrigk, 2017[48] 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 central neuropathic pain at maximal pain area for ≥3 months	**Dronabinol** THC; daily dose between 7.5 and 15.0 mg	**Placebo** NR	Total: 240 / 240 Dronabinol: 124 / 124 Placebo: 116 / 116	- *Titration phase*: first 4 weeks of treatment - *Study treatment*: 16 weeks - *Follow-up:* at end of treatment period
Nurmikko, 2007[49] Belgium, UK	RCT - parallel NR	Adult patients with a current history of unilateral peripheral neuropathic pain and allodynia *Age (mean ± SD in y)* MC: 52.4 ± 15.8; P: 54.3 ± 15.2 *Sex (% female)* MC: 55.6%; P: 62.9%	≥6 months pain due to a clinically identifiable nerve lesion	**THC:CBD spray** 100 µl containing: 2.7 mg THC and 2.5 mg CBD; self-titration to optimal dose; max. of 48 sprays/day	**Placebo** Identical in composition, appearance, odour and taste	Total: 125 / 125 THC:CBD spray: 63 / 63 Placebo: 62 / 62	- *Titration phase*: 1 week - *Study treatment*: 4 weeks - *Follow-up:* at end of treatment period
Serpell, 2014[50] Belgium, Canada, Czech Republic, Romania, UK	RCT - parallel Sept 2005-Oct 2006	Adult patients with allodynia *Age (mean ± SD in y)* 57.3 ± 14.2 *Sex (% female)*	≥6 months peripheral neuropathic pain	**THC:CBD spray** 100 µl containing: 2.7 mg THC and 2.5 mg CBD; self-titration to optimal dose;	**Placebo** Spray of placebo delivered the same excipients plus colorants	Total: 240 / 246 THC:CBD spray: 123 / 128 Placebo: 117 / 118	- *Titration phase*: 1 week - *Study treatment*: 14 weeks - *Follow-up:* at end of treatment period

Reference Country	Study design & period	Study population	Definition chronic pain	Intervention	Comparator	Sample size intention to treat & safety	Duration
		61%		max. of 24 sprays/day			
Musculoskeletal pain							
Blake, 2006[51] 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	**THC:CBD spray** 100 µl containing: 2.7 mg THC and 2.5 mg CBD; self-titration to optimal dose; max. of 6 sprays/day	**Placebo** NR	Total: 58 / 58 THC:CBD spray: 31 / 31 Placebo: 27 / 27	- *Titration phase*: 2 weeks - *Study treatment*: 3 weeks - *Follow-up:* at end of treatment period

Keys: CBD = cannabidiol, MC = medical cannabis, MS = multiple sclerosis, NR = not reported, P = placebo, RCT = randomised controlled trial, SD = standard deviation, THC = tetrahydrocannabinol, UK = United Kingdom, y = years.

Table 6. Risk of bias of the included RCTs on medical cannabis use for chronic pain

Reference	Allocation concealment	Blinding	Loss to follow-up	Intention to treat	Selective outcome reporting	Other limitations	RISK OF BIAS
Cancer pain							
Fallon, 2017[44]	NR	Double blind; not fully described; despite the double blind design, the risk of bias associated with unmasking as a result of treatment side-effects cannot be excluded	Intervention: 42%* Placebo: 33%*	Yes	No	Subjective outcome measures; differences between multi-country study centers NR; funded by industry	**Moderate**
Lichtman, 2018[45]	NR	Double blind; not fully described; despite the double blind design, the risk of bias associated with unmasking as a result of treatment side-effects cannot be excluded	Intervention: 29%* Placebo: 24%*	Yes	No	Subjective outcome measures; differences between multi-country study centers NR; funded by industry	**Moderate**
Neuropathic pain							
Langford, 2013[46]	NR	Double blind; not fully described; despite the double blind design, the risk of bias associated with unmasking as a result of treatment side-effects cannot be excluded	Intervention: 16% Placebo: 9%	Yes	No	Subjective outcome measures; differences between multi-country study centers NR; funded by industry	**Moderate**

Rog, 2005[47]	Reported	Despite the double blind design, the risk of bias associated with unmasking as a result of treatment side-effects cannot be excluded	Intervention: 6% Placebo: 0%	Yes	No	Subjective outcome measures; funded by industry	**Moderate**
Schimrigk, 2017[48]	NR	Double blind; not fully described; despite the double blind design, the risk of bias associated with unmasking as a result of treatment side-effects cannot be excluded	Intervention: 15% Placebo: 10%	Yes	No	Subjective outcome measures; funded by industry	**Moderate**
Nurmikko, 2007[49]	Reported	Double blind; not fully described; despite the double blind design, the risk of bias associated with unmasking as a result of treatment side-effects cannot be excluded	Intervention: 21% Placebo: 11%	Yes	No	Subjective outcome measures; funded by industry	**Moderate**
Serpell, 2014[50]	Reported	Despite the double blind design, the risk of bias associated with unmasking as a result of treatment side-effects cannot be excluded	Intervention: 40% Placebo: 21%	Yes	No	Subjective outcome measures; funded by industry	**High**
Musculoskeletal pain							
Blake, 2006[51]	NR	Double blind; not described; despite the double blind design, the risk of bias associated with unmasking as a result of treatment side-effects cannot be excluded	Intervention: 3% Placebo: 11%	Yes	No	Error and deviations in results table for primary outcomes; subjective outcome measures; funded by industry	**High**

Keys: NR = not reported. Low risk of bias; Moderate or unclear risk of bias; High risk of bias * Relative high percentage of loss to follow-up due to mortality in a population of patients with advanced cancer.

Spasticity

In total, five studies (four original RCTs and one randomised follow-up of an RCT) were included in this HTA on the efficacy of medical cannabis use for spasticity symptoms. Three RCTs were conducted in adults patients with MS and one RCT in a population of adult patients with motor neuron disease. THC:CBD spray was the most frequently studied form of medical cannabis (in three RCTs). A summary of the study characteristics is included in Table 7 and the risk of bias of the study designs of the individual RCTs in Table 8. In all RCTs bias arises for the study limitation blinding and subjective outcome measures. Unpredictable bias and uncertainty in the evidence base arise in research on medication with

a characteristic well-known adverse event profile like medical cannabis (e.g. dizzy/light-headedness, fatigue, 'feeling high'), possibly leading to unblinding of patients to their treatment allocation. The subjective outcomes for the symptom spasticity further increase this unpredictability and uncertainty, however, no fully objective measure is available.

Spasticity in patients with multiple sclerosis

Four studies were included on adult patients with spasticity caused by MS: three original RCTs with a parallel design[9,11,52] and one randomised follow-up of an RCT.[53] These RCTs were conducted in one western European country (UK) or a combination of western and eastern European countries (UK and Romania; UK and Czech Republic). The total sample size ranged from 184 to 630 patients. THC:CBD spray (100 µl actuation containing 2.7 mg THC and 2.5 mg CBD) was studied in three RCTs and one RCT investigated Dronabinol (delta-9-THC) and THC:CBD capsules (2.5 mg THC and 1.25 mg CBD). In all RCTs medical cannabis was compared with a placebo. The treatment duration ranged from 6 to 14 weeks and the follow-up study had a duration of 12 months. The study design of the RCTs and the follow-up study had a moderate risk of bias (see Table 8).

Spasticity in patients with motor neuron disease

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, ALS or PLS.[54] This multicentre Italian RCT included 59 adults for 4 weeks of study treatment, of whom 29 were randomly assigned to be treated with THC:CBD spray and 30 with a placebo. The risk of bias of the study design of this RCT was moderate (see Table 8).

Table 7. Study characteristics of the RCTs included on medical cannabis use for spasticity

Reference Country	**Study design & period**	**Study population**	**Definition spasticity**	**Intervention**	**Comparator**	**Sample size intention to treat & safety**	**Duration**
Multiple sclerosis							
Collin, 2007[52] Romania, UK	RCT - parallel April 2002-March 2004	Adult patients with MS, stable disease for ≥3 months before study entry, and significant spasticity in ≥2 muscle groups *Age (mean ± SD in y)* MC: 49.7 ± 10.2 / P: 47.8 ± 9.5	Significant spasticity in ≥2 muscle groups with an Ashworth score of ≥2	**THC:CBD spray** 100 µl containing: 2.7 mg THC and 2.5 mg CBD; self-titration to 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: 184 / 189 THC:CBD spray: 120 / 124 Placebo: 64 / 65	- *Titration phase*: 2 weeks - *Study treatment*: 6 weeks - *Follow-up:* at end of treatment period

Reference Country	Study design & period	Study population	Definition spasticity	Intervention	Comparator	Sample size intention to treat & safety	Duration
		Sex (% female) MC: 64.5% / P: 52.3%					
Collin, 2010[11] Czech Republic, UK	RCT - parallel Period NR	Adult patients with any disease subtype of MS of ≥6 months duration and ≥3 month history of spasticity *Age (mean ± SD in y)* MC: 48.0 ± 10.06 / P: 47.1 ± 9.15 *Sex (% female)* MC: 63% / P: 59%	Moderate spasticity: spasticity severity on a 0-10 NRS had to sum to ≥24 (i.e. minimum mean daily score of 4 out of 10)	**THC:CBD spray** 100 µl containing: 2.7 mg THC and 2.5 mg CBD; self-titration to 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: 305 / 337 THC:CBD spray: 150 / 167 Placebo: 155 / 170	- *Titration phase*: 1 week - *Study treatment*: 14 weeks - *Follow-up:* at end of treatment period
Zajicek, 2003[9] & Zajicek, 2005[53] UK	RCT - parallel & follow-up RCT Dec 2000 -Oct 2003	Adult patients with stable MS ≥6 months and problematic spasticity *Age (mean ± SD in y)* Dronabinol: 50.2 ± 8.2 / THC:CBD capsules: 50.5 ± 7.6 / P: 50.9 ± 7.6 *Sex (% female)* Dronabinol: 69.4% / THC:CBD capsules: 64.0% / P: 63.4%	Problematic spasticity: Ashworth score of ≥2 in ≥2 lower limb muscle groups	**Dronabinol** Synthetic delta-9-THC capsules **THC:CBD capsules (cannabis-extract)** Capsules with 2.5 mg THC, 1.25 mg CBD, <5% other cannabinoids; dose based on body-weight, max. of 25 mg daily	**Placebo** Capsules matched to either Dronabinol or THC:CBD capsules	**Original RCT** Total: 630 Dronabinol: 206 THC:CBD capsules: 211 Placebo: 213 **Follow-up of RCT** Total: 502 Dronabinol: 154 THC:CBD capsules: 172 Placebo: 176	- *Titration phase*: 5 weeks - *Study treatment*: 8 weeks - *Study treatment reduction to 0*: 2 weeks - *Follow-up:* • at end of treatment period • at 12 months follow-up
Motor neuron disease							
Riva, 2019[54] Italy	RCT - parallel Jan 2013-Dec 2014	Adult patients with MND (i.e. amyotrophic lateral sclerosis or primary lateral sclerosis) and spasticity for ≥3 months *Age (mean ± SD in y)* MC: 58.4 ± 10.6 / P: 57.2 ± 13.8 *Sex (% female)* MC: 38% / P: 47%	Spasticity score of ≥1 on the 5-point Modified Ashworth Scale in ≥2 muscle groups	**Nabiximols (THC:CBD spray not specifically reported)** 100 µl containing: 2.7 mg THC and 2.5 mg CBD; self-titration to optimal dose; max. of 12 sprays/day *Dose (mean ± SD):*	**Placebo** Placebo solutions were transparent and indistinguishable from intervention *Dose (mean ± SD):* 11.2 ± 1.4 sprays/day	Total: 59 / 59 Nabiximols: 29 / 29 Placebo: 30 / 30	- *Titration phase*: 2 weeks - *Study treatment*: 4 weeks - *Follow-up:* at end of treatment period

Reference Country	Study design & period	Study population	Definition spasticity	Intervention	Comparator	Sample size intention to treat & safety	Duration
				8.03 ± 2.9 sprays/day			

Keys: CBD = cannabidiol, MC = medical cannabis, MND = motor neuron disease, NR = not reported, NRS = numeric rating scale, P = placebo, RCT = randomised controlled trial, SD = standard deviation, THC = tetrahydrocannabinol, y = years.

Table 8. Risk of bias of the included RCTs on medical cannabis use for spasticity symptoms

Reference	Allocation concealment	Blinding	Loss to follow-up	Intention to treat	Selective outcome reporting	Other limitations	RISK OF BIAS
Multiple sclerosis							
Collin, 2007[52]	NR	Double blind, not fully described; despite the double blind design, the risk of bias associated with unmasking as a result of treatment side-effects cannot be excluded	Intervention: 10% Placebo: 5%	Yes	No	Subjective outcome measures; differences between multi-country study centers NR; funded by industry	**Moderate**
Collin, 2010[11]	NR	Double blind, not fully described; despite the double blind design, the risk of bias associated with unmasking as a result of treatment side-effects cannot be excluded	Intervention: 10% Placebo: 9%	Yes	No	Subjective outcome measures; differences between multi-country study centers NR; funded by industry	**Moderate**
Zajicek, 2003[9] & Zajicek, 2005[53]	Reported	Expected unmasking of both treating doctors and patients and known side-effects of cannabinoids, blinding was maintained in the assessing individuals	Dronabinol: 2% THC:CBD capsules: 4% Placebo: 3%	Yes	Ashworth scale assessed at 6 time points, but only reported for start and end of RCT	Subjective outcome measures	**Moderate**
Motor neuron disease							
Riva, 2019[54]	Reported	Despite the double blind design, the risk of bias associated with unmasking as a result	Intervention: 3% Placebo: 0%	Yes	No	Subjective outcome measures	**Moderate**

		of treatment side-effects cannot be excluded					

Keys: NR = not reported. Low risk of bias; Moderate or unclear risk of bias

8.2.4 Findings efficacy

Chronic pain

Clinically relevant patient-reported pain relief was presented in different ways. RCTs tended to report average pain scores or average changes in pain scores; a patient-reported pain score ranges from zero (no pain) to ten (being the worst pain). However, this outcome has been described as problematic, because amongst others small average pain differences between the intervention and placebo arm hide the fact that a substantial minority of the patients achieve extremely good levels of pain relief .[55] 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.[3,55] However, dichotomising continuous variables also has limitations.[56]

Cancer pain

Two RCTs on THC:CBD spray in patients with cancer pain reported efficacy results measured with the patient-rated numeric rating scale (NRS) pain score, NRS worst pain score, and median percentage change in average NRS pain score.[44,45] No statistically significant treatment differences were found in favour of THC:CBD spray (Table 9).

Table 9. Efficacy results on medical cannabis use for cancer pain: NRS pain (patient-rated)

Reference Risk of bias RCT	Intervention Comparator	Sample size (ITT)	NRS pain score (0-10)		NRS worst pain score (0-10)		Median % change in average NRS pain score	
			Adjusted mean (SD) change from baseline	Adjusted treatment difference (95% CI); p-value	Adjusted mean (SD) change from baseline	Adjusted treatment difference (95% CI); p-value	Median % (IQR) change from baseline	Median treatment difference (95% CI); p-value
Fallon, 2017[44] Moderate risk of bias	THC:CBD spray (2.7 mg THC/2.5 mg CBD)	200	NR	0.12 (-0.18–0.42) p=0.434	NR	0.11 (-0.21–0.44) p=0.496	7.2% (NR)	-1.84% (-6.19–1.50) p=0.274
	Placebo	199	NR		NR		9.5% (NR)	
Lichtman, 2018[45]	THC:CBD spray (2.7 mg THC/2.5 mg CBD)	199	NR	-0.16 (-0.45–0.12) p=0.253	NR	-0.06 (-0.36–0.24) p=0.678	10.7% (NR)	3.41% (0.00–8.16) p=0.0854

Moderate risk . . .	Placebo	198	NR		NR		4.5% (NR)	

Keys: CBD = cannabidiol, CI = confidence interval, IQR = interquartile range, ITT = intention to treat, NR = not reported, NRS = numeric rating scale, RCT = randomised controlled trial, SD = standard deviation, THC = tetrahydrocannabinol.

Neuropathic pain

In total, four RCTs were included which compared the efficacy of THC:CBD spray versus placebo in patients with neuropathic pain.[46,47,49,50] Efficacy results were reported for a range of outcomes (i.e. NRS pain score, NRS peripheral neural pain score, NRS neuropathic pain score, ≥30% reduction in NRS pain score, ≥50% reduction in NRS pain score, and ≥30% reduction in NRS peripheral neuropathic pain score), but only few statistically significant results were found. Two of the four RCTs reported statistically significant treatment differences in favour of THC:CBD spray, as measured with the NRS pain and NRS neuropathic pain scores (Table 10). Serpell et al. reported 28% treatment responders, as defined by a ≥30% reduction in NRS peripheral neuropathic pain score, in the THC:CBD spray arm versus 16% in patients receiving placebo treatment (OR=1.97; 95% CI 1.05–3.70; p=0.034; Table 10. Efficacy results on medical cannabis use for neuropathic pain: NRS pain score (patient-rated)Table 11). Furthermore, health-related quality of life (HRQoL) was measured with different methods, i.e. the EQ-5D health index, EQ-5D visual analogue scales (VAS) score, and pain disability index. Only Nurmikko et al. found a statistically significant change in HRQoL for patients receiving THC:CBD spray compared to placebo, with an improvement in the pain disability index (treatment difference -5.85; 95% CI -9.62– -2.09; p=0.003; Table 12).[49] The unadjusted pooled estimates for respectively a ≥30% and ≥50% reduction in NRS pain score were non-significant ORs of 1.36 (95% CI 0.92-2.00) and 1.59 (0.62-4.04).

Table 10. Efficacy results on medical cannabis use for neuropathic pain: NRS pain score (patient-rated)

Reference Risk of bias RCT	**Popu-lation**	**Intervention Comparator**	**Sam-ple size (ITT)**	**NRS pain score (0-10)**				**NRS peripheral neural pain (0-10)**		**NRS neuropathic pain (0-10)**	
				Mean change (SD) from baseline	**Treat-ment dif-ference (95% CI); p-value**	**Adjusted mean change (SD) from baseline**	**Adjusted treatment difference (95% CI); p-value**	**Adjusted mean change (SD) from baseline**	**Adjusted treatment difference (95% CI); p-value**	**Adjusted mean change (SD) from baseline**	**Adjusted treatment difference (95% CI); p-value**
Langford, 2013[46] Moderate risk of bias	MS	THC:CBD spray (2.7 mg THC/2.5	167	-1.93 (NR)	-0.17 (-0.62–0.29) p=0.47	-	-	-	-		
		Placebo	172	-1.76 (NR)		-	-	-	-		

Rog, 2005[47] Moderate risk of bias	MS	THC:CBD spray (2.7 mg THC/2.5 mg CBD)	33	-	-	NR	-1.25 (-2.11–-0.39) p=0.005	-	-	NR	-6.58 (-12.97–-0.19) p=0.044
		Placebo	32	-	-	NR		-	-	NR	
Nurmikko, 2007[49] Moderate risk of bias	Allo-dynia	THC:CBD spray (2.7 mg THC/2.5 mg CBD)	63	-	-	-1.48 (NR)	-0.96 (-1.59–-0.32) p=0.004	-	-		
		Placebo	62	-	-	-0.52 (NR)		-	-		
Serpell, 2014[50] High risk of bias	Allo-dynia	THC:CBD spray (2.7 mg THC/2.5	123	-	-	-	-	NR	-0.34 (-0.79–0.11) p=0.139	NR	-2.86 (-7.22–1.50) p=0.198
		Placebo	117	-	-	-	-	NR		NR	

Keys: CBD = cannabidiol, CI = confidence interval, ITT = intention to treat, MS = multiple sclerosis, NR = not reported, NRS = numeric rating scale, RCT = randomised controlled trial, SD = standard deviation, THC = tetrahydrocannabinol. Statistically significant results

Table 11. Efficacy results on medical cannabis use for neuropathic pain: treatment responders based on NRS pain

Reference Risk of bias RCT	**Population**	**Intervention Comparator**	**Sample size (ITT)**	**≥30% reduction in NRS pain score**		**≥50% reduction in NRS pain score**		**≥30% reduction in NRS peripheral neuropathic pain score**	
				n (%)	**OR (95% CI); p-value**	**n (%)**	**OR (95% CI); p-value**	**n (%)**	**OR (95% CI); p-value**
Langford, 2013[46] Moderate risk of bias	MS	THC:CBD spray (2.7 mg THC/2.5 mg CBD)	167	NR (50)	1.31 (0.84–2.04) p=0.234	NR (30)	NR (NR) p=0.714	-	-
		Placebo	172	NR (45)		NR (28)		-	-
Nurmikko, 2007[49] Moderate risk of bias	Allodynia	THC:CBD spray (2.7 mg THC/2.5 mg CBD)	63	NR (26)	NR	NR (20)	NR	-	-
		Placebo	62	NR (15)		NR (8)		-	-
Serpell, 2014[50] High risk of bias	Allodynia	THC:CBD spray (2.7 mg THC/2.5 mg CBD)	123	-	-	-	-	34 (28)	1.97 (1.05–3.70) p=0.034
		Placebo	117	-	-	-	-	19 (16)	

Keys: CBD = cannabidiol, CI = confidence interval, ITT = intention to treat, MS = multiple sclerosis, NR = not reported, NRS = numeric rating scale, OR = odds ratio, RCT = randomised controlled trial, THC = tetrahydrocannabinol. Statistically significant results

Table 12. Efficacy results on medical cannabis use for neuropathic pain: quality of life

Reference Risk of bias RCT	Popu-lation	Intervention Comparator	Sample size (ITT)	EQ-5D health index		EQ-5D VAS		Pain disability index	
				Mean change (SD) from baseline	Treatment difference (95% CI); p-value	Mean change (SD) from baseline	Treatment difference (95% CI); p-value	Mean change (SD) from baseline	Treatment difference (95% CI); p-value
Langford, 2013[46] Moderate risk of bias	MS	THC:CBD spray (2.7 mg THC/2.5 mg CBD)	167	0.05 (NR)	-0.01 (NR) p=0.396	7.20 (NR)	1.94 (NR) p=0.383	-	-
		Placebo	172	0.07 (NR)		5.26 (NR)		-	-
Nurmikko, 2007[49] Moderate risk of bias	Allo-dynia	THC:CBD spray (2.7 mg THC/2.5 mg CBD)	63	-	-	-	-	-5.61 (NR)	-5.85 (-9.62– -2.09) p=0.003
		Placebo	62	-	-	-	-	0.24 (NR)	
Serpell, 2014[50] High risk of bias	Allo-dynia	THC:CBD spray (2.7 mg THC/2.5 mg CBD)	123	-	-	NR	-0.75 (-5.60– 4.09) p=0.760	-	-
		Placebo	117	-	-	NR		-	-

Keys: CBD = cannabidiol, CI = confidence interval, ITT = intention to treat, MS = multiple sclerosis, NR = not reported, RCT = randomised controlled trial, SD = standard deviation, THC = tetrahydrocannabinol, VAS = visual analogue scale. Statistically significant results

The RCT on dronabinol versus placebo in MS patients with neuropathic pain reported limited efficacy on NRS pain scores and quality of life.[48] Schimrigk et al. did not find a statistically significant treatment difference for NRS pain score (mean change from baseline dronabinol and placebo: -1.92±2.01 vs. -1.81±1.94; treatment difference not reported; 95% CI not reported; p=0.676).[48] The quality of life assessment with the SF-36 showed improvement within both study arms (physical component summary for dronabinol -3.50 and placebo -3.18), however the treatment difference between study arms was not statistically significant (treatment difference, 95% CI, and p-value not reported).[48]

Musculoskeletal pain

Blake et al. compared the efficacy of THC:CBD spray with placebo in patients with chronic pain symptoms caused by rheumatoid arthritis.[51] A statistically significant treatment difference was found of -1.04 in favour of THC:CBD spray for the outcome NRS morning pain at rest (95% CI -1.90– -0.18; p=0.018; Table 13).

Table 13. Efficacy results on medical cannabis use for musculoskeletal pain: NRS pain (patient-rated)

Reference Risk of bias RCT	Intervention Comparator	Sample size (ITT)	NRS morning pain at rest (0-10)*	
			Median (IQR) change from base-line	Treatment difference (95% CI); p-value
Blake, 2006[51] High risk of bias	THC:CBD spray (2.7 mg THC/2.5 mg CBD)	31	-2.2 (NR)	-1.04 (-1.90– -0.18) p=0.018
	Placebo	27	-1.2 (NR)	

Keys: CBD = cannabidiol, CI = confidence interval, IQR = interquartile range, ITT = intention to treat, NR = not reported, NRS = numeric rating scale, RCT = randomised controlled trial, THC = tetrahydrocannabinol. * Data on the outcome 'NRS morning pain on movement (0-10)' was not extracted from the study of Blake, 2006, because it was not possible to recalculate their reported unadjusted difference between the THC:CBD spray and placebo arm. Statistically significant results

Spasticity

The most common assessments of spasticity in clinical practice and research are the Ashworth scale, modified Ashworth scale, and the spasticity 0-10 NRS. The original Ashworth Scale was published in 1964 and enables the evaluator to grade spasticity on a 5-point muscle tone numeric scale, ranging from 0 (normal) to 4 (severe spasticity in a limb rigid in flexion or extension).[57,58] In 1987, the Ashworth scale was modified by adding 1+ to the scale to increase sensitivity.[57,58] The usability of the Ashworth scale as an outcome for spasticity is complicated by these two versions and both have limitations, e.g. they only measure one aspect of spasticity and the grading is largely dependent on the evaluator, which influences the intra and interrater reliability.[57,58] As the reliability and sensitivity of the Ashworth scale to measure significant functional change in spasticity has been questioned, spasticity NRS scores or VAS scores have been used in spasticity studies. The NRS was developed to capture information from the patient's perspective and the severity of spasticity is rated on a scale ranging from 0 (no spasticity) to 10 (worst possible spasticity).[57] The test-retest reliability of the NRS is better than the Ashworth Scale, however quantitative evaluation methods of spasticity are still difficult and subjective and currently no ideal objective measure of this highly complex symptom is available.[57]

Spasticity in patients with MS

Two RCTs on THC:CBD spray in patients with spasticity caused by MS reported efficacy results measured with the Ashworth scale, modified Ashworth scale, and patient-rated NRS spasticity score. They also reported the treatment response based on the NRS spasticity score and quality of life.[11,52] Only statistically significant treatment differences were found in the RCT of Collin et al., 2007 for two outcomes: a treatment difference in favour of THC:CBD spray on the NRS spasticity score of -0.52 (95% CI -1.029– -0.004; p=0.048; Table 14) and 18.1% more treatment responders in the THC:CBD spray arm as defined by a ≥30% reduction in NRS spasticity (95% CI 4.73–31.52; p=0.014; Table 15). The

unadjusted pooled estimate for a ≥30% reduction in NRS spasticity for both studies of Collin et al. was an OR of 1.70 (95% CI 0.99-2.92).

Table 14. Efficacy results on medical cannabis use for spasticity symptoms in patients with MS: Ashworth scale (observer rated) and NRS spasticity (patient-rated)

Reference Risk of bias RCT	Intervention Comparator	Sample size (ITT)	Ashworth scale		Modified Ashworth scale		NRS spasticity score (0-10)	
			Adjusted mean change (SD) from baseline	Adjusted treatment difference (95% CI); p-value	Adjusted mean change (SD) from baseline	Adjusted treatment difference (95% CI); p-value	Adjusted mean change (SD) from baseline	Adjusted treatment difference (95% CI); p-value
Collin, 2007[52] Moderate risk of bias	THC:CBD spray (2.7 mg THC/2.5 mg	120	-0.64 (NR)	-0.11 (-0.29–0.07) p=0.218	-	-	-1.18 (NR)	-0.52 (-1.029–-0.004) p=0.048
	Placebo	64	-0.53 (NR)		-	-	-0.63 (NR)	
Collin, 2010[11] Moderate risk of bias	THC:CBD spray (2.7 mg THC/2.5 mg	150	-	-	-2.17 (NR)	-0.16 (NR) p=0.857	-1.05 (NR)	-0.23 (NR) p=0.219
	Placebo	155	-	-	-2.01 (NR)		-0.82 (NR)	

Keys: CBD = cannabidiol, CI = confidence interval, ITT = intention to treat, NR = not reported, NRS = numeric rating scale, RCT = randomised controlled trial, SD = standard deviation, THC = tetrahydrocannabinol. Statistically significant results

Table 15. Efficacy results on medical cannabis use for spasticity symptoms in patients with MS: treatment responders based on NRS spasticity

Reference Risk of bias RCT	Intervention Comparator	Sample size (ITT)	≥30% reduction in NRS spasticity			≥50% reduction in NRS spasticity	
			n (%)	Treatment difference (95% CI); p-value	OR (95% CI); p-value	n (%)	Treatment difference (95% CI); p-value
Collin, 2007[52] Moderate risk of bias	THC:CBD spray (2.7 mg THC/2.5 mg	120	48 (40.0%)	18.1% (4.73–31.52) p=0.014	-	21 (17.5%)	8.1% (-1.73–17.98) p=0.189
	Placebo	64	14 (21.9%)		-	6 (9.4%)	
Collin, 2010[11] Moderate risk of bias	THC:CBD spray (2.7 mg THC/2.5 mg	150	NR (31%)	5.9% (NR) p=0.231	1.34 (0.83–2.17) p=0.231	-	-
	Placebo	155	NR (25%)			-	-

Keys: CBD = cannabidiol, CI = confidence interval, ITT = intention to treat, NRS = numeric rating scale, OR = odds ratio, RCT = randomised controlled trial, THC = tetrahydrocannabinol. Statistically significant results

Table 16. Efficacy results on medical cannabis use for spasticity symptoms in patients with MS: quality of life

Reference Risk of bias RCT	Intervention Comparator	Sample size (ITT)	EQ-5D health state index		EQ-5D health status VAS	
			Adjusted mean change (SD) from baseline	Adjusted treatment difference (95% CI); p-value	Adjusted mean change (SD) from baseline	Adjusted treatment difference (95% CI); p-value
Collin, 2010[11] Moderate risk of bias	THC:CBD spray (2.7 mg THC/2.5 mg	150	0.03 (NR)	0.02 (NR) p=0.175	4.29 (NR)	1.42 (NR) p=0.538
	Placebo	155	0.01 (NR)		2.87 (NR)	

Keys: CBD = cannabidiol, CI = confidence interval, ITT = intention to treat, NR = not reported, RCT = randomised controlled trial, SD = standard deviation, THC = tetrahydrocannabinol, VAS = visual analogue scale.

Zajicek et al. studied three study arms of MS patients receiving Dronabinol, THC:CBD capsules, or placebo capsules for their spasticity symptoms and assessed the efficacy with the Ashworth scale.[9,53] A small statistically significant (p=0.01) treatment difference of 2.05 was found for the change in Ashworth score from baseline to 52 weeks' follow-up for Dronabinol compared to placebo and they did not find a statistically significant effect of treatment with THC:CBD capsules (Table 17).

Table 17. Efficacy results on medical cannabis use for spasticity symptoms in patients with MS: Ashworth scale (observer rated)

Reference Risk of bias RCT	Intervention Comparator	Sample size (ITT)	Ashworth scale	
			Mean change (SD) from baseline	Treatment difference (95% CI); p-value
Zajicek, 2003[9] & Zajicek, 2005[53] Moderate risk of bias	Dronabinol (100% THC)	206*	-1.86 (7.95)	0.94 (-0.44–2.31) NS‡
		156†	-1.82 (8.12)	2.05 (NR) S§
	THC:CBD capsules (2.5 mg THC/1.25 mg CBD)	211*	-1.24 (6.60)	0.32 (-1.04–1.67) NS‡
		172†	-0.10 (7.25)	-0.13 (NR) NS§
	Placebo	213*	-0.92 (6.56)	-
		176†	0.23 (7.87)	-

Keys: CBD = cannabidiol, CI = confidence interval, ITT = intention to treat, NR = not reported, NS = not significant, RCT = randomised controlled trial, S = significant, SD = standard deviation, THC = tetrahydrocannabinol. * At end of 5 weeks titration and 8 weeks of treatment period of the original RCT; † At end of 12 months follow-up; ‡ Comparison of the 3 groups using analysis of variance on the change in total Ashworth score showed no treatment effect with an unadjusted p-value of 0.40 and adjusted p-value of 0.29; § Comparison of the 3 study arms using analysis of variance on the change in total Ashworth score showed a small treatment effect with an unadjusted p-value of 0.04 and adjusted p-value of 0.01. Statistically significant results

Spasticity in patients with motor neuron disease

The RCT on THC:CBD spray for spasticity in ALS/PLS patients reported efficacy results measured with the modified Ashworth scale and patient-rated NRS spasticity score, and also reported the treatment

response based on the NRS spasticity score.[54] The mean change in Modified Ashworth Scale (assessed at baseline and after 6 weeks) improved with 0.11 in the THC:CBD spray arm and deteriorated with 0.16 in the placebo arm, resulting in a statistically significant treatment difference of -0.32 (95% CI -0.57– -0.07; p=0.013) (Table 18). However, no statistically significant difference was found between the THC:CBD spray and placebo arm for the change from baseline in spasticity as measured with the patient-rated NRS spasticity score (Table 18), nor a statistically significant reduction in the ≥30% or ≥50% reduction in NRS spasticity score (Table 19).

Table 18. Efficacy results on medical cannabis use for spasticity in patients with motor neuron disease: Ashworth scale (observer rated) and NRS spasticity score (patient-rated)

Reference Risk of bias RCT	Intervention Comparator	Sample size (ITT)	Modified Ashworth scale		NRS spasticity score (0-10)	
			Adjusted mean change (SD) from baseline	Adjusted treatment difference (95% CI); p-value	Mean change (SD) from baseline	Adjusted treatment difference (95% CI); p-value
Riva, 2019[54] Moderate risk of bias	THC:CBD spray (2.7 mg THC/2.5	29	-0.11 (0.48)	-0.32 (-0.57– -0.07) p=0.013	-0.32 (2.15)	-0.49 (-1.48–0.50) p=0.324
	Placebo	30	0.16 (0.47)		-0.12 (1.40)	

Keys: CBD = cannabidiol, CI = confidence interval, ITT = intention to treat, NRS = numeric rating scale, RCT = randomised controlled trial, SD = standard deviation, THC = tetrahydrocannabinol. Statistically significant results

Table 19. Efficacy results on medical cannabis use for spasticity symptoms in patients with motor neuron disease: treatment responders based on NRS spasticity score

Reference Risk of bias RCT	Intervention Comparator	Sample size (ITT)	≥30% reduction in NRS spasticity score		≥50% reduction in NRS spasticity score	
			n (%)	OR (95% CI); p-value	n (%)	OR (95% CI); p-value
Riva, 2019[54] Moderate risk of bias	THC:CBD spray (2.7 mg THC/2.5 mg CBD)	29	6 (21%)	1.70 (0.42–6.77) p=0.45	3 (10%)	1.61 (0.25–10.45) p=0.61
	Placebo	30	4 (13%)		2 (7%)	

Keys: CBD = cannabidiol, CI = confidence interval, ITT = intention to treat, NRS = numeric rating scale, OR = odds ratio, RCT = randomised controlled trial, THC = tetrahydrocannabinol.

8.2.5 Findings effectiveness

During the project it was decided not to proceed with an additional systematic literature search for comparative non-randomised studies, because sufficient data were found for the outcomes of interest on the highest possible level of evidence (i.e. from RCTs) and we do not expect that additional data from comparative non-randomised studies will have essential impact on the conclusions formulated in this

HTA. Therefore, no data is included on the effectiveness of medical cannabis for chronic pain or spasticity.

8.2.6 Findings safety

It was not possible to extract/synthesise data on individual SAEs of medical cannabis use from the included RCTs for a number of reasons: 1) the SAEs were mostly not clearly defined in the articles; 2) the events were reported incompletely (e.g. adverse events were reported only when they occurred in at least 5% or 10% of the participants); and 3) only numbers and/or percentages of adverse events were reported without statistical comparisons between the intervention and placebo arm or presenting risk ratios. The definitions of the safety outcomes deaths and withdrawal from treatment due to adverse events were in line between the RCTs and data were extracted and, if possible, pooled. In the individual RCTs only the number and percentages were reported for deaths and withdrawal from treatment, without a statistical comparison or risk ratio between the medical cannabis and placebo arm.

Chronic pain

Cancer pain

Two large multi-country RCTs compared the safety of THC:CBD spray versus placebo in patients with cancer pain. No statistically significant effects were found for treatment with THC:CBD spray on the occurrence of deaths (RR 0.90; 95% CI 0.62-1.30; high certainty; Table 20) and withdrawal from treatment due to adverse events (RR 1.21; 95% CI 0.90-1.63; moderate certainty; Table 20).[44,45]

Neuropathic pain

In two RCTs on THC:CBD spray, one in MS patients[47] and one in patients with allodynia [50], no deaths were reported in the THC:CBD spray and placebo arms. Two other RCTs, also in a population with MS and allodynia, did not report on the number of deaths.[46,49] Concerning the outcome withdrawal from treatment due to adverse events, the pooled analysis of these four RCTs showed that THC:CBD spray resulted in a statistically significant increase in withdrawals from treatment due to adverse events: 13.3% in the THC:CBD spray arm versus 5.5% in the placebo arm (RR 2.45; 95% CI 1.23-4.87; moderate certainty; Table 21). Another RCT compared the safety of dronabinol versus placebo in MS patients with neuropathic pain.[48] No deaths were reported during the 20-week study period and 12 subjects (9.7 %) in the dronabinol arm and 1 subject (0.9%) in the placebo arm withdrew from treatment due to adverse events.

Musculoskeletal pain

The RCT on THC:CBD spray for treatment of pain in patients with rheumatoid arthritis did not report on the number of deaths.[51] In the THC:CBD spray arm none of the subjects withdrew from treatment due to adverse events during five weeks of treatment versus 3 subjects (11.1%) in the placebo arm.

Table 20. GRADE evidence profile: safety of medical cannabis use in patients with cancer pain

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other consid-erations**	**THC:CBD spray**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**	
Deaths (in patients with cancer pain)											
2[Fallon, 2017[44]; Lichtman, 2018[45]]	randomised trials	not serious[a]	not serious	not serious	not serious	none	47/399 (11.8%)	52/397 (13.1%)	RR 0.90 (0.62 to 1.30)	14 fewer per 1,000 (from 32 fewer to 60 more)	⊕⊕⊕⊕ HIGH
Withdrawal from treatment due to adverse events (in patients with cancer pain)											
2[Fallon, 2017[44]; Lichtman, 2018[45]]	randomised trials	serious[b]	not serious	not serious	not serious	none	78/399 (19.5%)	64/397 (16.1%)	RR 1.21 (0.90 to 1.63)	34 more per 1,000 (from 19 fewer to 88 more)	⊕⊕⊕◯ MODERATE

[a] Not downgraded for risk of bias, since the risk of bias issues have little impact on the objective outcome death.
[b] Downgraded for serious risk of bias due to bias associated with unmasking as a result of treatment side-effects cannot be excluded in combination with a subjective outcome, and differences in inclusion/results between multi-country study centers not reported in Fallon et al., 2017 and Lichtman et al., 2018.

Table 21. GRADE evidence profile: safety of medical cannabis use in patients with neuropathic pain

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**THC:CBD spray**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**	
Withdrawal from treatment due to adverse events (in patients with neuropathic pain)											
4[Nurmikko, 2007[49]; Serpell, 2014[50]; Langford, 2013[46]; Rog, 2005[47]]	randomised trials	serious[a]	not serious	not serious	not serious	none	52/392 (13.3%)	21/384 (5.5%)	RR 2.45 (1.23 to 4.87)	79 more per 1,000 (from 39 fewer to 120 more)	⨁⨁⨁◯ MODERATE

[a] Downgraded for serious risk of bias due to bias associated with unmasking as a result of treatment side-effects cannot be excluded in combination with a subjective outcome in Nurmikko et al., 2007, Serpell et al., 2014, Langford et al., 2013, and Rog et al., 2005; and large and skewed loss to follow-up in the RCT of Serpell et al., 2014.

Spasticity

Spasticity in patients with MS

In two RCTs, Collin et al. studied THC:CBD spray in patients with spasticity caused by MS.[11,52] In the first RCT no deaths were reported in the THC:CBD spray and placebo arm during the 8-week study period.[52] The second 15-week RCT reported two deaths (i.e. due to gastrointestinal carcinoma with liver metastases and metastatic oesophageal carcinoma), considered not to be related to the study medication.[11] However, the authors did not report if these deaths occurred in the THC:CBD spray and/or placebo arm. The pooled analysis of both RCTs showed that THC:CBD spray did not result in a statistically significant increase in withdrawals from treatment due to adverse events: 5.2% in the THC:CBD spray arm versus 3.0% in the placebo arm (RR 1.75; 95% CI 0.72-4.23; moderate certainty; Table 22). Zajicek et al. studied three arms of MS patients receiving either Dronabinol, THC:CBD capsules, or placebo capsules.[9,53] One subject (0.6%), randomised to the Dronabinol arm, died from pneumonia during the 15-week RCT. Seven subjects (4.5%) in the Dronabinol arm, two subjects (1.2%) in the THC:CBD capsules arm, and none of the subjects receiving placebo withdrew from treatment due to adverse events. During the 12 month follow-up phase of the RCT there were six deaths, however not all details were reported in the article. Two subjects chose to continue medication during follow-up, two subjects chose to discontinue medication, and for two subjects this was not reported. The two subjects who continued medication died from pneumonia and seizure and were randomised to THC:CBD capsules treatment.

Spasticity in patients with motor neuron disease

The RCT on THC:CBD spray for spasticity in ALS/PLS patients did not report data on the number of deaths.[54] In both the THC:CBD spray and placebo arm none of the subjects withdrew from treatment due to adverse events.

Table 22. GRADE evidence profile: safety of medical cannabis use for spasticity in patients with MS

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**THC:CBD spray**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**	
Withdrawal from treatment due to adverse events (in patients with spasticity caused by MS)											
2[Collin, 2007[52]; Collin 2010[11]]	randomised trials	serious[a]	not serious	not serious	not serious	none	15/291 (5.2%)	7/235 (3.0%)	RR 1.75 (0.72 to 4.23)	21 more per 1,000 (from 16 fewer to 57 more)	⊕⊕⊕◯ MODERATE

[a] Downgraded for serious risk of bias due to bias associated with unmasking as a result of treatment side-effects cannot be excluded in combination with a subjective outcome, and differences in inclusion/results between multi-country study centers not reported in Collin et al., 2007 and Collin et al., 2010.

8.3 Summary statement efficacy, effectiveness, and safety

In this HTA, eight RCTs (moderate risk of bias n=6; high risk of bias n=2) were included on medical cannabis use in adults with chronic pain caused by cancer (n=2), neuropathic disease (n=5), and musculoskeletal disease (n=1). Four RCTs and one randomised follow-up of an RCT (all with moderate risk of bias) were included on medical cannabis use in adults with spasticity caused by MS (n=4) and motor neuron disease (n=1). THC:CBD spray (Sativex®) was the most frequently studied form of medical cannabis.

Heterogeneity between studies in outcomes and outcome measures, data skewness, and incompleteness of study results (i.e. studies omitting to report detailed results such as treatment effects in the intervention and placebo arms or measures of variability) precluded the calculation of pooled estimates for efficacy data for the stratified pain and spasticity populations. Overall, the efficacy data on medical cannabis use for chronic pain and spasticity was inconsistent (i.e. studies with comparable patient populations and similar type of medical cannabis did not show consistent results) and inconclusive (i.e. none of the studies was able to draw a definitive conclusion on the efficacy of medical cannabis). Furthermore, multiple factors increase the risk of bias in studies on medical cannabis, however the extent as well as the direction of the potential bias are difficult to comprehend. Although it was possible to calculate pooled estimates for part of the safety outcomes and some patient populations, the issues highlighted for efficacy also apply to safety, resulting in an incomplete safety profile of medical cannabis use for chronic pain and spasticity.

In studies on medical cannabis, an unpredictable bias and uncertainty in the evidence base arises caused by the risk of unblinding of patients to their treatment allocation in combination with the patient-reported outcomes for the symptoms chronic pain and spasticity. Given these considerations it is neither possible to conclude that medical cannabis is an efficacious and safe treatment option for chronic pain and spasticity, nor to conclude that medical cannabis is not efficacious and safe for the treatment of chronic pain and spasticity.

Future studies on medical cannabis in these symptoms will likely be exposed to similar challenges and limitations, of which only part can be solved with improved study designs and complete reporting of results.

9 Cost-effectiveness and budget impact

SRs were conducted to identify cost-effectiveness studies on medical cannabis use for chronic pain and spasticity. In addition, two cost-effectiveness models were developed to calculate the cost-effectiveness and budget impact of medical cannabis for the Swiss context specifically. In this chapter, the employed methods are further detailed starting with the SRs on medical cannabis use for chronic pain and spasticity, followed by a description of the conceptual cost-effectiveness models, additional searches for model inputs, and cost-effectiveness and budget impact analyses for the symptoms chronic pain and spasticity (Chapters 9.1.1 – 9.1.3). Finally, the results of the SRs, the cost-effectiveness models, and the budget impact analyses are presented (Chapter 9.2.1 – 9.2.3).

9.1 Methodology cost-effectiveness and budget impact

9.1.1 Databases and search strategy

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 use for chronic pain and spasticity. The methods of this systematic literature search will be discussed in this section.

Search strategy

PubMed (MEDLINE), Embase.com, and NHS Economic Evaluation Database (NHS EED) were searched for peer-reviewed scientific literature. The PICO method was used to specify the research questions. Chapter 6 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, French, German, and Dutch were included.

The search terms of the efficacy, effectiveness, and safety literature search were combined with search terms to find economic evaluations (e.g. cost-effectiveness, cost-utility, economic evaluation, budget impact). The search terms for economic evaluations were developed together with an information specialist of the Erasmus University Medical Centre. Two separate search strategies were developed, one on medical cannabis use in chronic pain and one on medical cannabis use in spasticity (Appendix 15.3).

The search for economic evaluations on medical cannabis use for chronic pain and spasticity was executed on January 27th, 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.

Inclusion and exclusion criteria

The inclusion and exclusion criteria applied during the selection processes for the economic evaluations are presented in Table 23. The list of excluded studies can be found in Appendix 15.4. The process of selection 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 9.2.1).

Table 23. Inclusion and exclusion criteria for economic evaluations of medical cannabis use for chronic pain and spasticity

	Inclusion	**Exclusion**
Period of publication	Start database - January 2020	
Language of publication	English, French, German, Dutch	All other languages
Country of study	All countries	-
Study design/type	Economic evaluations (CEA, CUA), Budget impact analyses	Other economic evaluations
Study quality	All economic evaluations	
Study population	Patients (all ages) with chronic pain or spasticity	No or lacking information on study population
	Patients (all ages) with chronic pain	• Patients without chronic pain • Patients in whom medical cannabis is not primarily prescribed for the symptom chronic pain
	Patients (all ages) with spasticity	• Patients in whom medical cannabis is not primarily prescribed for the symptom spasticity • No or lacking definition of spasticity
Study intervention	Medical cannabis, prescribed as standalone treatment or add-on treatment	Non-prescribed/recreational/non-medical cannabis

Study comparison	• Placebo • No treatment for chronic pain • Standard of care according to the treatment guidelines (i.e. conventional drugs for the chronic pain condition or spasticity condition)	Comparisons with other treatments than standard of care
Study outcomes	Incremental costs Incremental QALYs ICERs	No/other cost-effectiveness outcomes

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 relevance 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.

9.1.2 Other sources

Hand search of reference lists

During the full-text screening phase of the cost-effectiveness systematic literature search, reference lists of the included studies were checked to find any other studies that were not captured with our literature search.

HTA websites

Clinical guidelines and technology assessments from the major national HTA agency websites (e.g. EUnetHTA for Europe, National Institute for Health and Care Excellence (NICE) from the United Kingdom (UK), Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG) from Germany, Haute Autorité de santé (HAS) from France, National Health Care Institute (ZiN) from the Netherlands, Canadian Agency for Drugs and Technologies in Health (CADTH) from Canada, and Pharmaceutical Benefits Advisory Committee (PBAC) and Therapeutic Goods Administration (TGA) from Australia) were searched for documents addressing medical cannabis use for chronic pain and spasticity (i.e. search terms 'medical cannabis' in relevant language). The aim of this search was to check whether the search for economic evaluations possibly missed relevant evidence on the cost-effectiveness of medical cannabis. The initial search yielded NICE guidelines on the symptoms chronic pain[59] and spasticity[60], SRs on the CADTH webpage for the symptoms chronic pain[61] and spasticity[62], SRs on the TGA website for the symptoms chronic pain[63] and spasticity[64], one evaluation on the IQWiG website for the symptom spasticity[65], and a stance document on medical cannabis in various symptoms from ZiN[66]. No missed studies were identified in these clinical guidelines and technology assessments. However, as the NICE guidelines for chronic pain and spasticity included de novo cost-effectiveness models based on input from their own SRs, these were included for the cost-effectiveness systematic literature search.

9.1.3 Assessment of quality of evidence

The Consensus Health Economics Checklist (CHEC) was used for the appraisal of the methodological quality of the economic evaluations.[67] The CHEC was preferred over the Drummond checklist, because of the decreasing use of the Drummond checklist in the field[68] and the experienced feasibility of completing the checklist. The CHEC is one of the two most frequently used checklists in recent studies, the other checklist is the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist.[69] 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[67] with clear questions about the economic evaluation that will give insight into the general quality of the study for a preliminary critical appraisal of the quality of the included studies. The studies were judged on whether the criteria were fulfilled ("1"), not fulfilled ("0"), or inconclusive ("0.5").

9.1.4 Methodology cost-effectiveness modelling

Considering the lack of cost-effectiveness studies on medical cannabis in the Swiss context, cost-effectiveness models were developed that incorporated the most recent and (where possible) Switzerland-specific effectiveness, costs, and HRQoL (expressed in utilities on a scale from 0 to 1) evidence. However, cost-effectiveness models were available for the UK setting where the cost-effectiveness of medical cannabis in addition to standard of care (SOC) was compared to SOC alone in the indications of chronic pain and spasticity. These two UK models, which were developed by NICE, were used as starting point for the current cost-effectiveness models and adapted to better represent the Swiss context. First, the aspects that were equal for all Swiss cost-effectiveness models are described, including the model structure and the incorporation of discontinuation and SAE. Then, the input parameters specific for the chronic pain models will be described, followed by the input parameters specific for the spasticity models.

9.1.4.1 General model settings and assumptions

To model the cost-effectiveness of medical cannabis, a decision had to be made on the preferred outcome measure for efficacy. Based on previous cost-effectiveness models in spasticity and chronic pain populations, and taking into account data availability (for the efficacy measure itself as well as for relatable utility and resource use data), the absolute change in numeric rating scale (NRS) score was the preferred efficacy outcome measure in the chronic pain models, and the proportion of responders at ≥30% reduction in NRS score was the preferred efficacy outcome in the spasticity models. As a result, usable efficacy evidence for cost-effectiveness modelling was available for two chronic pain populations (neuropathic pain and musculoskeletal pain) and two spasticity populations (MS and motor neuron disease). No usable efficacy usable evidence was available for modelling the cost-effectiveness of medical cannabis in cancer pain as the efficacy data were not reported for both arms separately. All studies that reported efficacy using the preferred outcome measure compared THC:CBD spray (Sativex®) in addition to SOC to SOC alone. Consequently, as no usable efficacy data were available for other medical cannabis products or routes of administration, the Swiss models were developed comparing THC:CBD spray in addition to SOC to SOC alone. The standard of care is defined as any interventions that would usually be prescribed in these patient populations, including licensed oral anti-spasticity drugs or analgesics if appropriate.

The models adopted a cycle length of four weeks, following a lifetime horizon. The analyses were performed from a healthcare perspective (i.e. only including all direct medical costs). Costs were reported in Swiss franc (CHF) using the prices from the year 2020 from an insurance perspective. Health outcomes were

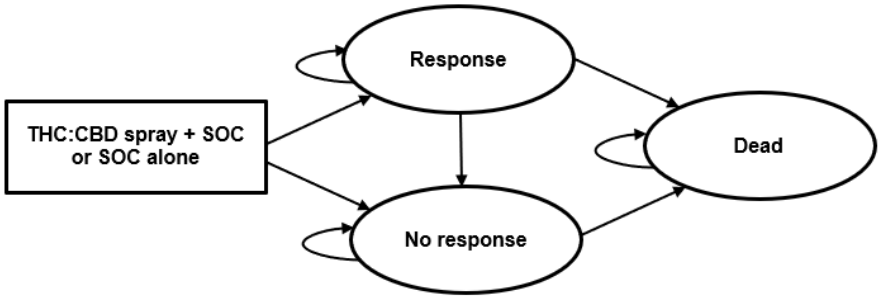
reported in quality-adjusted life years (QALYs). In the base case analysis, costs and effects were discounted with a factor of 3% from the second year onwards. The models were programmed in R 3.6.1 using RStudio 1.2.1335.

All subpopulations were investigated separately in the Swiss cost-effectiveness models as the cost-effectiveness results may differ depending on the underlying cause of the symptom. For chronic pain, the main cost-effectiveness model was developed using information on neuropathic pain as for this subpopulation the availability of model input was most comprehensive. For the same reason, information on MS served as a basis for the main spasticity cost-effectiveness model. For the other subpopulations the neuropathic pain and MS cost-effectiveness models were adapted using the efficacy data available for this population as identified during the SR on efficacy, effectiveness, and safety. If input for a certain parameter was not available for the specific subpopulation (i.e. utilities or resource use), the input from the neuropathic pain (for chronic pain subpopulations) and MS (for spasticity subpopulations) cost-effectiveness models were assumed.

Model structure

The Swiss cost-effectiveness models were designed as Markov models with three health states (Figure 3). The health states included treatment response, no treatment response and a dead health state. The model structure was the same for the THC:CBD spray in addition to SOC arm and the SOC alone arm (from here on the THC:CBD spray arm and the SOC arm). Treatment response was defined as ≥30% reduction in the NRS pain score for chronic pain indications, and as ≥30% reduction in the NRS spasticity score in the models for spasticity subpopulations in line with the assumptions made by the NICE expert committee.[60] It was assumed that patients who do not achieve the ≥30% response criterium will discontinue THC:CBD spray and hence transition to the SOC arm. The models adopted a cycle length of 4-weeks, meaning that each 4 weeks patients could either transition from one health state to another or remain in the current health state.

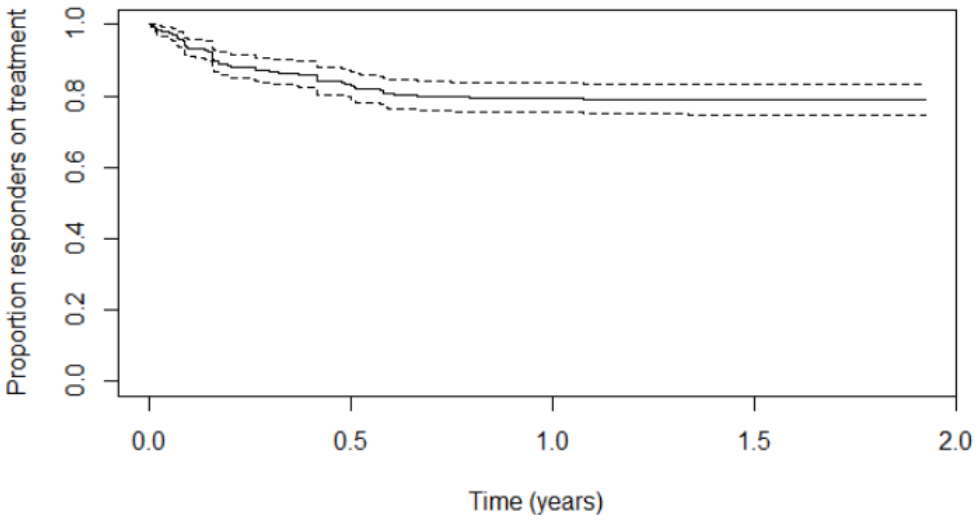
Figure 3. Model structure



Discontinuation

In both arms, patients could discontinue THC:CBD spray or placebo from the second cycle onwards (i.e. after a 4-week trial period). Patients could discontinue because they did not achieve the ≥30% reduction criterion or stopped achieving this criterion, or because of adverse events. Long-term discontinuation was derived from the SA.FE study which investigated discontinuation of THC:CBD spray using real-world data of an Italian sample of MS patients.[70] Using the data from this study, discontinuation for the THC:CBD spray arm is modelled using survival analyses. Similar to the NICE models, a Gompertz model was fitted to the curve. The long-term discontinuation is presented in Figure 4 (dashed lines represent upper and lower confidence limits). For the SOC arm, long-term discontinuation due to adverse events was not considered realistic, since patients do not receive an active treatment. Therefore, a competing risks model was estimated, separating discontinuation related to adverse events from discontinuation from other causes (mainly not maintaining response level of ≥30%). As a result, discontinuation rates were lower in the SOC arm than in the THC:CBD spray arm. The Gompertz model was used in concordance with the model used for discontinuation in the THC:CBD spray arm. To test the impact of the assumption of differential discontinuation on the results, discontinuation rates in the SOC arm was set equal to discontinuation in the THC:CBD spray arm in a scenario analysis.

Figure 4. Discontinuation for responders on THC:CBD spray



* the solid line represents the average proportion of treatment responders over the first 2 years of treatment. **dotted lines represent the upper and lower values for the 95% confidence interval.

Serious Adverse events

Only serious adverse events (SAEs) were considered in the Swiss cost-effectiveness models, since the prevalence, duration and effects (in terms of costs and effects) of non-serious adverse events were negligible. SAEs are events that result in death, are life-threatening, require inpatient hospitalisation, or cause prolongation of existing hospitalisation. SAE rates were derived from a published systematic literature review by Wang et al., in line with the models developed by NICE.[24] Yearly SAE rates were 0.37 for the THC:CBD spray arm and 0.25 for the SOC arm.[71] The disutilities associated with SAEs were taken from the study by Hagiwara et al. as no usable Swiss utility data were identified.[71] The disutility for a SAE was therefore set at 0.10 and was assumed to last for 3 days. SAEs were excluded in a scenario analysis.

Search for model input on utilities, resource use and unit costs

A comprehensive search was performed to identify the most recent Swiss utility and cost data available to use as input in the Swiss cost-effectiveness models. The search terms, methods, and results of this systematic literature search are provided in Appendix 15.5. The search aimed to identify the following utility, costs and resource use inputs for the Swiss context:

- Costs of treatment with THC:CBD spray;
- Resource use and related unit costs of treatment of patients with chronic pain or spasticity, stratified by NRS score;
- Resource use and related unit costs of patients with SAEs attributable to THC:CBD spray treatment
- Utilities in patients with chronic pain or spasticity, stratified by NRS score; and
- Disutilities in patients with SAEs attributable to THC:CBD spray.

As no relevant inputs were identified specifically for the Swiss context, expert opinion and public databases were used to derive Swiss cost inputs. For resource use and utilities, the inputs from the NICE models were assumed.

9.1.4.2 Model input chronic pain

Treatment effectiveness

In the chronic pain model, treatment effects were modelled using the mean change in NRS pain score from baseline. Baseline NRS pain scores were simulated using a beta distribution (n=10,000) with a mean NRS

pain score at baseline of 6.9 and an SE of 1.3 for the neuropathic pain model based on the pooled mean NRS pain scores at baseline in Langford et al. and Nurmikko et al..[46,49] The mean NRS pain score at baseline reported in the Blake et al. study was used for the musculoskeletal pain model (mean=5.3, SD=1.1).[51] The resulting density plot of baseline NRS pain scores are presented in Appendix 15.8.

The SR on the efficacy, effectiveness, and safety of medical cannabis identified two studies that provided the (adjusted) mean change in pain score for the neuropathic subpopulation of chronic pain patients. Langford et al. found mean changes in NRS pain score for chronic pain patients of -1.93 and -1.76 for patients receiving THC/CBD spray and placebo, respectively.[46] Nurmikko et al. reported an adjusted mean change in NRS pain score of -1.42 for the THC:CBD spray arm and -0.52 for the placebo arm.[49] In this study, patients remained on their existing stable analgesia regardless of the treatment arm. Neither study reported the associated SDs, which were needed for the cost-effectiveness model. However, the studies did report the proportion of patients that responded to treatment, defined as a reduction in NRS pain score of ≥30%. Assuming mean changes in NRS pain scores to be distributed normally, the SDs were determined for both studies. This resulted in SDs for THC:CBD spray and SOC of 2.0 and 1.5 in the study of Langford et al. and 1.0 and 1.5 in the Nurmikko et al. study, respectively.[46,49] Using the mean treatment effects, estimated SDs and studies' sample sizes, pooled estimates for the treatment effect were calculated, to be used in the base case analysis for neuropathic pain. The pooled estimates were -1.71 (SD=1.10) for the THC:CBD spray arm, and -1.17 (SD=1.5) for the SOC arm.

The SR on the efficacy, effectiveness, and safety of medical cannabis identified one study in patients with musculoskeletal pain. Blake et al. reported median changes in NRS pain score of -2.2 and -1.2 for THC:CBD spray and placebo in patients with musculoskeletal pain.[51] According to the authors, NRS pain scores were distributed nonparametrically, and median changes in NRS pain scores were reported rather than mean changes. In addition, the data provided by Blake et al. did not include the variation around the reported median treatment effect. Although the data from the Blake et al. study has several limitations, this study was the only study available for musculoskeletal pain and a significant (median) treatment effect of THC:CBD spray on morning pain at rest (on an NRS score) was reported. In absence of better-quality data, the study was nonetheless used to inform the cost-effectiveness model in musculoskeletal pain patients. Since the model required mean change in NRS pain score (and SD), the median value reported in Blake et al. was used as the mean value, ignoring the non-parametric distribution of change in NRS pain score in the trial. The SD was assumed 20% of the median change in NRS pain score.

The SR on the efficacy, effectiveness, and safety of medical cannabis identified two studies in (chronic) cancer pain patients. These studies provided an adjusted mean change in NRS pain score between THC:CBD spray and placebo as their main clinical outcome. However, as these studies did not report the mean changes in NRS pain score for each of the study arms separately (nor the associated SDs), we were unable to investigate cost-effectiveness of THC:CBD spray for cancer pain patients.

To calculate the NRS pain scores of the simulated patients after the first cycle in both models, the simulated change in NRS pain scores was added to the beta distribution of baseline NRS pain scores. The number of patients achieving the treatment response criteria of ≥30% change in NRS pain score was determined to be 0.49 and 0.46 in the neuropathic pain model for the THC:CBD spray arm and SOC arm, respectively. The response rates in the musculoskeletal pain model were 0.86 and 0.17 for THC:CBD spray and SOC, respectively.

If patients achieved the ≥30% change in NRS pain score criterion (i.e. responders), patients were assumed to retain the reduction in NRS pain score for patients' model lifetime or until patients discontinued treatment. If patient did not achieve the response criterion (i.e. non-responders), patients' NRS pain scores were assumed to revert to baseline values for the remainder of the patients' model lifetime.

Mortality

As there was no data on whether THC:CBD spray affects a patient's mortality risk and THC:CBD spray was not expected to fundamentally modify the patient's disease, mortality was assumed to be constant between both treatment arms. In line with Torrance et al., a standardised mortality ratio (SMR) of 1.32 (SD 0.08) was applied to Swiss population life tables published by mortality.org.[72,73]

Utility inputs

In the absence of usable Swiss utility estimates, health state utilities values were based on the study by Gu et al., which included adult patients with neuropathic pain from the United States of America (USA).[74] Gu et al. estimated utility values using regression techniques (ordered logistic models and ordinary least squares) with the different NRS pain score, age, and gender as independent variables.[74] The regression estimates and corresponding standard errors are reported in Table 24.

Table 24. Regression coefficients to determine utilities for chronic pain

	Mean	Lower CI	Upper CI
Constant	0.684	0.617	0.751
NRS 0	0.000		
NRS 1	-0.005	-0.62	0.052
NRS 2	-0.088	-0.143	-0.033
NRS 3	-0.098	-0.151	-0.045
NRS 4	-0.138	-0.191	-0.085
NRS 5	-0.152	-0.205	-0.099
NRS 6	-0.188	-0.239	-0.137
NRS 7	-0.260	-0.313	-0.207
NRS 8	-0.328	-0.381	-0.275
NRS 9	-0.398	-0.461	-0.335
NRS 10	-0.464	-0.525	-0.403
Age	0.003	0.001	0.005
Gender	-0.034	-0.048	-0.020

Keys: NRS = numeric rating scale, CI = confidence interval

The simulated NRS pain scores were used to determine mean utility scores for responders and non-responders. In accordance with the NICE model, we assumed the NRS pain scores of chronic pain patients did not increase over time. However, using the age coefficient from the Gu et al. study the utility values did increase over time.[74] Average utility values are presented in Table 25.

Table 25. Mean utility values for responders and non-responders

	THC:CBD spray responders	THC:CBD spray non-responders	SOC responders	SOC non-responders
Neuropathic pain	0.755	0.598	0.759	0.605
Musculoskeletal pain	0.803	0.689	0.807	0.720

Keys: THC = tetrahydrocannabinol, CBD = cannabidiol, SOC = standard of care, THC = tetrahydrocannabinol, CBD = cannabidiol

Cost and resource use inputs

As presented in Appendix 15.5, the non-systematic literature search did not yield usable Swiss data on resource use in chronic pain. Resource use was therefore derived from literature sources from other countries, details are described in the next paragraphs. To obtain Swiss cost estimates, the resource use was multiplied with unit costs provided by the FOPH (Table 26).

Treatment costs THC:CBD spray

A weighted pooled estimate of 9.79 daily doses of THC:CBD spray was used based on the Langford et al. and Nurmikko et al. studies.[46,49] This resulted in a per cycle cost of 659 CHF in the neuropathic pain model. The musculoskeletal model used a mean daily dose of 5.4 THC:CBD sprays as reported in the Blake et al. study[51], resulting in a per cycle cost of 363 CHF.

Health state costs

Resource use was calculated for different levels of pain in line with the modelled health states. As usable Swiss data on the resource use of chronic pain patients were not identified, the NICE committee's resource use estimates were used in the model. The NICE committee estimated the number of community-based visits, outpatient clinic visits, accident & emergency (A&E) visits, hospital admissions and home care visits associated with the following pain scores: NRS 0-2, NRS 3-4, NRS 5-6, NRS 7-8, and NRS 9-10. The overall management cost for a patient in each 4-week cycle was equal to the weighted average of their pain distribution multiplied by the corresponding resource use costs. Table 26 provides an overview of the resource use and costs applied in the Swiss cost-effectiveness models. Costs of background medication (i.e. analgesics or anti-spasticity drugs) were not included in the model as THC:CBD spray was evaluated as an add-on therapy to SOC and hence no significant differences between the THC:CBD spray arm and the SOC arm were anticipated. Furthermore, medication costs only account for a small proportion of the total treatment costs and excluding medication costs was therefore expected to only have a minor influence on the cost-effectiveness results.

Table 26. Unit costs, annual resource use per health state and associated costs per 4-week cycle per NRS pain score for chronic pain patients

	Community visits	**Outpatient visits**	**A&E visits**	**Hospitalisations**	**Home care (per hour)**	
Unit cost	140.00	240.00	995.00	3920.00	64.75	
NRS level	**Community visits (annual)**	**Outpatient visits (annual)**	**A&E visits**(annual)	**Hospitalisations (annual)**	**Home care hours (annual)**	**Total cost per 4-week cycle (CHF)**
NRS 0-2	0	0	0	0	0	0.00
NRS 3-4	0	1	0	0	0	18.46
NRS 5-6	0	2	1	0.5	0	264.31
NRS 7-8	0	4	2	1	0	528.62

NRS 9-10	12	8	4	2	52	1’220.89

Keys: NRS = numeric rating scale, A&E = accident & emergency, CHF = Swiss Franc

Serious adverse events costs

SAEs were assumed to be related to additional resource use. It was assumed that all patients experiencing an SAE would require an A&E visit, and 50% of patients require an ambulance transfer. Combined with Swiss unit costs, this resulted in an average cost of 1’245 CHF per SAE.

9.1.4.3 Model input spasticity

Treatment effectiveness

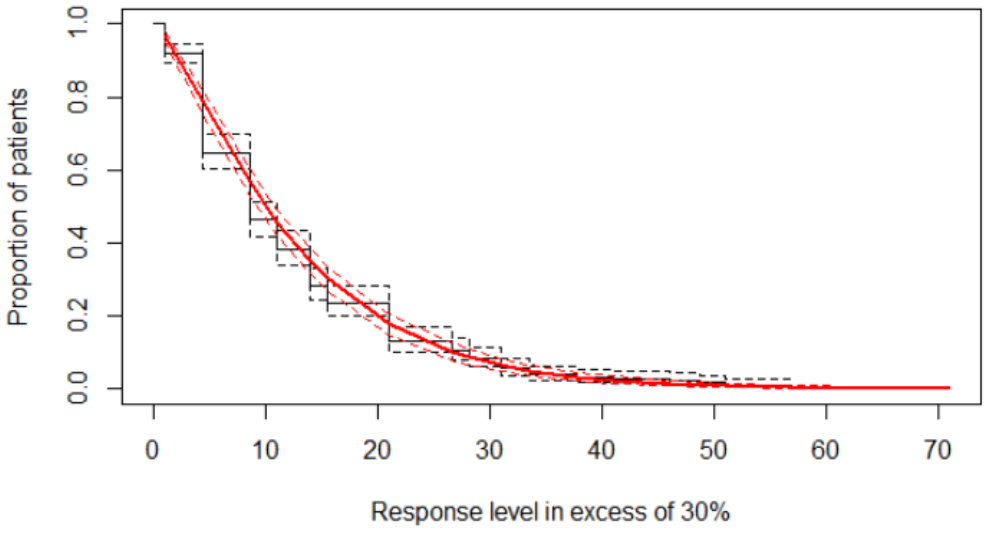
Treatment response was defined as an NRS spasticity score reduction of ≥30%. The proportion of responders was derived from the literature for each subpopulation. For MS spasticity, the SR on efficacy, effectiveness, and safety identified two studies that reported the proportion of responders based on this criterion. In one study, 40% of patients treated with THC:CBD spray obtained a reduction in NRS spasticity score of ≥30% or more, compared to 22% of patients treated with placebo.[52] In the other study, 31% of patients on THC:CBD spray had a ≥30% reduction in NRS spasticity score, versus 25% of SOC patients.[11] The pooled estimate of these two studies was used in the Swiss cost-effectiveness model for MS spasticity; base case values for response were 35% and 24% for THC:CBD spray arm SOC arm respectively. Both studies investigated the efficacy of THC:CBD spray in adults with advanced spasticity in MS who did not gain adequate relief using current therapy. In scenario analyses, alternative response rates were used.

For motor neuron disease spasticity, the SR on efficacy, effectiveness, and safety identified one study that reported the proportion of responders based on a ≥30% reduction in NRS spasticity score. In this study, 21% of patients treated with THC:CBD spray obtained treatment response, compared to 13% treated with placebo.[54] The study investigated the efficacy of THC:CBD spray in adults with spasticity due to motor neuron disease that was incompletely controlled by therapy.

Patients that obtained response according to the ≥30% criterion could have a reduction in NRS spasticity score anywhere between 30% and 100%. The response level (i.e. relative reduction in NRS spasticity score) was therefore simulated using long-term follow-up data on MS patients of a large observational study in Italy (SA.FE study).[70] All responders had a response of at least 30%. The proportion of patients reaching

higher response criteria diminished as the response criterion increased. This pattern is similar to a survival curve, in which 100% of patients have a survival of zero time and the proportion of patients decreased with increasing time. The analogy to survival analyses led to fitting a survival curve on the data to determine the treatment response level. For this purpose, the response levels were interpreted as survival time and observations were interpreted as an event. In line with the NICE model, the gamma curve was used to predict the level of response. Figure 5 provides a graphical presentation of the modelled response level, for MS patients that obtained at least a 30% reduction in NRS spasticity score.

Figure 5. Response levels for responders (≥30% reduction in NRS spasticity score)



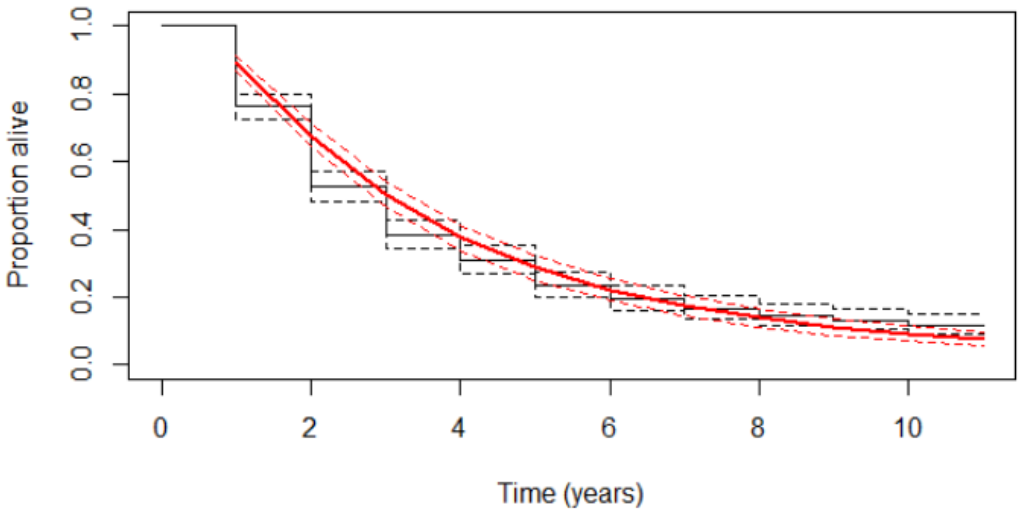
Mortality

Patients diagnosed with MS and motor neuron disease experience a higher mortality risk than the general population. For MS, SMRs were applied to Swiss mortality rates from the general population to correct for increased mortality. Background mortality was based on the all-cause mortality rates derived from Swiss lifetables.[73] The SMR for MS was obtained from a published meta-analysis.[75] Since an SMR was unavailable for Switzerland specifically, the overall SMR was used, which was determined at a level of 2.81 (95% CI 2.74-2.87) and based on cohorts of mostly Northern Europe and Canada.

For motor neuron disease, mortality data were retrieved from an Italian population-based study involving 483 patients.[76] Based on Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC), a lognormal model proved to best fit the survival data. The survival curve for motor neuron disease patients is provided in Figure 6. The SR on efficacy, effectiveness, and safety found no evidence for an impact of

THC:CBD spray on survival, therefore the same mortality risk was applied for both the THC:CBD spray arm and the SoC arm.

Figure 6. Survival for motor neuron disease patients



Utility inputs

In the absence of usable Swiss utility estimates, health state utilities were based on a published regression model of the EQ-5D in MS patients in Sweden, with EDSS (Expanded Disability Status Scale) scores and NRS spasticity scores as independent variables.[77] The mean EDSS score observed in the overall sample of the SA.FE study (i.e. 6.5) was used to estimate utility values for each NRS class.[70] This approach was also adopted by NICE, as their expert committee judged that it was unlikely that THC:CBD spray would affect EDSS scores. The regression coefficients and corresponding standard errors are reported in Table 27.

Table 27. Regression coefficients to determine utilities for spasticity

Parameter	Coefficient	Standard error
Constant	0.9229	0.2551
NRS	-0.0505	0.0109
EDSS 5	-0.0293	0.2779
EDSS 5.5	-0.3417	0.3020
EDSS 6	-0.1305	0.2532
EDSS 6.5	-0.2521	0.2520
EDSS 7	-0.3353	0.2656

EDSS 7.5	-0.5260	0.2673
EDSS 8	-0.8124	0.2542
EDSS 8.5	-0.9408	0.2849
EDSS 9	-0.7648	0.2853

Keys: NRS = numeric rating scale, EDSS = Expanded Disability Status Scale

To determine utility values for the responder and non-responder health state, NRS spasticity scores were simulated for both arms. The baseline NRS spasticity score for each health state was simulated by applying a beta distribution (n=10'000) on the baseline NRS spasticity scores in the SA.FE study (mean=7.5, SD=1.45).[70] The resulting density plot of baseline NRS spasticity scores is presented in 15.8.

For responders, these baseline NRS spasticity scores were combined with the simulated response levels (presented in Figure 5). In addition, for both responder and non-responder health states, NRS spasticity scores were assumed to progress over time. Progression in spasticity was calculated using data from a large registry, containing 35'000 patients, in which progression of several MS symptoms, including spasticity, was quantified over a period of 30 years.[78] Prevalence of symptoms as reported in the study was considered a proxy for severity, and was transformed into NRS spasticity scores. The calculated yearly progression in NRS spasticity scores was 0.07. In scenario analyses, alternative NRS progression rates were investigated. Due to the natural progression in both study arms, utilities decreased over time. Using the NRS spasticity scores for responders and non-responders, average utility values were estimated to be 0.39 for responders and 0.24 for non-responders.

For motor neuron disease, the same methodology was used, but the baseline values were based on average NRS spasticity scores obtained from a study with motor neuron disease patients (mean=5.7, SD=1.7, THC:CBD spray arm).[54] As a result, utility values were estimated to be 0.48 for responders and 0.37 for non-responders.

Cost and resource use inputs

As presented in Appendix 15.5, the non-systematic literature search did not yield usable Swiss data on resource use in spasticity. Resource use was therefore derived from literature sources from other countries, details are described in the next paragraphs. To obtain Swiss cost estimates, the resource use was multiplied with unit costs provided by the FOPH (Table 28).

Treatment costs THC:CBD spray

Treatment costs for THC:CBD spray were provided by FOPH and was equal to 0.89 CHF per milligram of THC (2.40 CHF per dose). Patients with MS were assumed to receive 6.3 doses per day[70], resulting in a per 4-week cycle treatment costs of 423.89 CHF. Patients with motor neuron disease were assumed to receive 5.5 doses per day[79] resulting in a per 4-week cycle costs of 370.06 CHF.

Health state costs

Background resource use was based on a study from the UK, in which health care specialists were asked to estimate health care consumption for various NRS classes.[80] Reported levels of resource use was multiplied with Swiss specific unit costs to obtain health state costs per NRS class. The NICE committee argued that resource use reported by Stevenson et al. (2015) was not attributable fully to spasticity, but was likely to be attributable to other symptoms as well, due to the methodology used to relate costs to NRS spasticity levels. This argument was further substantiated by evidence from the literature. Health state costs were therefore attributed to spasticity for 50% in the base case analyses. This proportion was varied in scenario analyses. The adapted resource use cost estimates were combined with the simulated NRS spasticity levels, similar to utilities. As with utilities, the natural progression of NRS spasticity affected health state costs; the increase in NRS spasticity scores over time resulted in an increase of health state costs over time. Average per 4-week cycle health state cost were estimated to be 935 CHF for responders and 2'714 CHF for non-responders. Table 28 provides the unit costs of the included cost categories and the cost estimates per NRS level.

Table 28. Unit costs, annual resource use per health state and associated costs per 4-week cycle per NRS spasticity score for spasticity patients

	Community visits	**Outpatient visits**	**A&E visits**	**Hospitalisations**	**Home care (per hour)**	
Unit cost	140.00	240.00	995.00	3920.00	64.75	
NRS level	**Community visits (annual)**	**Outpatient visits (annual)**	**A&E visits (annual)**	**Hospitalisations (annual)**	**Home care (annual)**	**Total cost per 4-week cycle (CHF)**
0-2	0.04	0.28	0.01	0.00	0.00	6.27
3-4	0.06	0.92	0.02	0.01	34.42	191.23

5-6	0.42	1.61	0.05	0.25	156.43	822.61
7-8	4.00	1.83	0.08	0.11	342.59	1’817.49
9-10	9.33	2.21	0.12	0.18	680.48	3’584.18

Keys: NRS = numeric rating scale, A&E = accident & emergency, CHF = Swiss Franc

The same methodology was used for motor neuron disease patients, assuming that the relation between NRS spasticity score and costs was equal in motor neuron disease and MS. However, since the baseline NRS spasticity score was different compared to MS patients, health state costs were different. Per 4-week cycle health state costs were estimated to be 343 CHF for responders and 1’242 CHF for non-responders.

Adverse event costs

SAEs were assumed to be related to additional resource use. It was assumed that all patients experiencing a SAE would require an A&E visit, 25% of patients require an ambulance transfer and 25% require an inpatient stay. Combined with Swiss unit costs, this resulted in a cost of 2’100 CHF per SAE.

9.1.4.4 Analytical methods

Base case analyses

The base case analyses were conducted using the settings for the input parameters and assumptions as described in the previous sections. This implies that the Swiss cost-effectiveness models were run using a lifetime time horizon and discounting of costs and effects with a discount factor of 3% from the second year onwards. For each patient population subgroup a separate base case analysis was performed. To show the impact of changing the assumptions and parameter uncertainty on the cost-effectiveness results, scenario and sensitivity analyses were run.

Scenario analyses

Several scenario analyses were performed to explore the impact of structural uncertainty on the cost-effectiveness outcomes. In these analyses, key model assumptions were varied. An overview of the scenario analyses is provided in Table 29.

Table 29. Description of base case and scenario analyses

Parameter	Base case analysis	Scenario analysis
Time horizon	Lifetime	• 5 years • 10 years

		• 20 years • 30 years
Discount rate	3% discount rate for costs and outcomes	• No discounting • 5% discount rate for costs and outcomes
Effect estimates	Chronic pain (neuropathic pain): weighted pooled estimate based on Langford 2013[46] and Nurmikko 2007[49]. Spasticity (MS): pooled estimate from Collin 2007[52] and Collin 2010[11] Spasticity (Motor neuron disease): Riva 2019[54]	Chronic pain (neuropathic): • estimate from Langford 2013[46] and Nurmikko 2007[49] separately. Spasticity (MS): • Collin 2007[52] only (THC:CBD spray: 40% vs SOC: 22%) • Collin 2010[11] only (THC:CBD spray: 31% vs SOC: 25%) • NICE estimate[60] (THC:CBD spray: 28% vs SOC: 24%) Spasticity (Motor neuron disease): • MC response increased by 50% • SOC response increased by 50%
Standard deviations effect estimates (chronic pain model only)	Chronic pain (neuropathic): pooled estimate of SDs provided by Langford 2013[46] and Nurmikko 2007[49].	Chronic pain (neuropathic): alternative SD equal to 20% of the mean change in NRS pain score. Chronic pain (musculoskeletal): varied SD to 10% and 50% of median change in NRS pain score.
Adverse events	Only serious adverse events	No adverse events
Natural progression (spasticity model only)	Spasticity: 0.073 NRS spasticity score reduction per year	Spasticity: • No natural progression • NICE estimates for natural progression (0.227 NRS spasticity score per year)
Discontinuation of THC:CBD spray and standard of care	Differential discontinuation: SOC only non-AE related discontinuation	Equal discontinuation: AE-related and non-AE related discontinuation in both arms
Proportion of costs attributable to spasticity (spasticity model only)	50%	• 100% • 25%

Keys: MS = multiple sclerosis, SOC = standard of care, SD = standard deviation, NRS = numeric rating scale, AE = adverse event, THC = tetrahydrocannabinol, CBD = cannabidiol

One-way sensitivity analyses

Parameter values included in the cost-effectiveness model are typically surrounded with uncertainty. Uncertainty of individual parameters was tested using one-way sensitivity analyses (OWSA); model parameters were systematically and independently varied using plausible ranges based on 95% confidence inter-

vals from appropriate distributions (also used in probabilistic sensitivity analysis) or a 20% increase/decrease of the parameter value used in the base case. Incremental costs and effects were recorded at the upper and lower limits to produce tornado diagrams.

Probabilistic sensitivity analysis

In probabilistic sensitivity analysis (PSA) the impact of parameter uncertainty on the incremental cost-effectiveness ratio was assessed. In this analysis, all parameters to which probability distributions were assigned were varied jointly. For this purpose, 1'000 model iterations were performed. Results were plotted on the cost-effectiveness plane (CE-plane). From these results, a cost-effectiveness acceptability curve (CEAC) was estimated. Table 30 and Table 31 provide the distributions, deterministic value and uncertainty surrounding the parameter values. Where standard errors were unknown, they were estimated as 20% of the mean.

Table 30. Input probabilistic sensitivity analysis chronic pain

Parameter	Distribution	Deterministic value	Uncertainty	Alpha	Beta	Source
Chronic pain input (general)						
Standardised mortality ratio	Normal	1.32	SD: 0.08			Torrance 2006[72]
SAE rate THC:CBD spray	Beta	0.370		164	281	Wang 2008[24]
SAE rate SOC	Beta	0.250		60	179	Wang 2008[24]
SAE duration	Gamma	3.0		25	0.12	Assumption
SAE disutility	Gamma	0.10		1.638	0.058	Assumption
Utility constant	Normal	6.84	SD: 0.034			Gu 2012[74]
Disutility NRS 1	Normal	-0.005	SD: 0.029			Gu 2012[74]
Disutility NRS 2	Normal	-0.088	SD: 0.028			Gu 2012[74]
Disutility NRS 3	Normal	-0.098	SD: 0.027			Gu 2012[74]
Disutility NRS 4	Normal	-0.138	SD: 0.027			Gu 2012[74]
Disutility NRS 5	Normal	-0.152	SD: 0.027			Gu 2012[74]
Disutility NRS 6	Normal	-0.188	Sd: 0.026			Gu 2012[74]
Disutility NRS 7	Normal	-0.260	SD: 0.027			Gu 2012[74]
Disutility NRS 8	Normal	-0.328	SD: 0.027			Gu 2012[74]
Disutility NRS 9	Normal	-0.398	SD: 0.032			Gu 2012[74]
Disutility NRS 10	Normal	-0.464	SD: 0.031			Gu 2012[74]
Disutility Gender	Normal	-0.034	SD: 0.007			Gu 2012[74]

Parameter	Distribution	Deterministic value	Uncertainty	Alpha	Beta	Source
Background medical consumption	Gamma			25	(Mean/5)^2/Mean	Assumption
Outpatient visit costs (CHF)	Uniform	240	Range: 180-300			FOPH
Emergency visit costs (CHF)	Uniform	995				FOPH
Hospitalisation per day costs (CHF	Uniform	6'469	Range: 5'431-7'507			FOPH
GP visit costs (CHF)	Uniform	140	Range: 105-173			FOPH
Home care per hour costs (CHF)	Uniform	64.75	Range: 52.60-76.90			FOPH
Ambulance transportation costs (CHF)	Gamma	500		25	(Mean/5)^2/Mean	Assumption
Neuropathic pain specific input						
Patient age	Normal	51.05	SD: 12.86			Pooled estimate Langford 2013[46], Nurmikko 2007[49]
NRS baseline	Beta	6.9	SD: 1.33	7.65	3.44	Pooled estimate Langford 2013[46], Nurmikko 2007[49]
Treatment effect THC:CBD spray	Normal	-1.7158	SD: 1.1			Pooled estimate Langford 2013[46], Nurmikko 2007[49]
Treatment effect SOC	Normal	-1.16976	SD: 1.5			Pooled estimate Langford 2013[46], Nurmikko 2007[49]
Number of doses THC:CBD spray	Gamma	9.79		25	1/0.3916	Pooled estimate Langford 2013[46], Nurmikko 2007[49]
Musculoskeletal pain specific input						
Patient age	Normal	62.8	SD: 9.8			Blake 2006[51]
NRS baseline	Beta	5.3	SD: mean/5	11.22	9.95	Blake 2006[51]
Treatment effect THC:CBD spray	Normal	-2.2	SD: mean/5			Blake 2006[51]
Treatment effect SOC	Normal	-1.2	SD: mean/5			Blake 2006[51]
Number doses THC:CBD spray	Gamma	5.4		41.37	1/0.131	Blake 2006[51]

Keys: SAE = serious adverse event, SOC = standard of care, GP = general practitioner, NRS = numeric rating scale, SE = standard error, SD= standard deviation, THC = tetrahydrocannabinol, CBD = cannabidiol

Table 31. Input probabilistic sensitivity analysis spasticity

Parameter	Distribution	Deterministic value	Uncertainty	Alpha	Beta	Source
Spasticity input (general)						
SAE rate THC:CBD spray	Beta	0.370		164	281	Wang 2008[24]
SAE rate SOC	Beta	0.250		60	179	Wang 2008[24]
SAE duration	Gamma	3.0		25	0.12	Assumption
NRS coefficient utility	Normal	-0.0505	SE: 0.0109			Svensson 2014[77]
SAE disutility	Gamma	0.10		1.638	0.058	Assumption
Proportion of costs attributable to spasticity	Beta	0.50	SE: 0.1	12	12	Assumption
Background medical consumption	Gamma			25	Mean/5)^2/Mean	Assumption
Outpatient visit costs (CHF)	Uniform	240	Range: 180-300			FOPH
Emergency visit costs (CHF)	Uniform	995				FOPH
Hospitalisation per day costs (CHF)	Uniform	3'920	Range: 3'216-5'032			FOPH
GP visit costs (CHF)	Uniform	140	Range: 105-173			FOPH
Home care per hour costs (CHF)	Uniform	64.75	Range: 52.60-76.90			FOPH
Ambulance transportation costs (CHF)	Gamma	500		25	(Mean/5)^2/Mean	Assumption
SAE – proportion pts ambulance	Beta	0.25		75	224	Assumption
SAE – proportion pts hospitalised	Beta	0.25		75	224	Assumption
Multiple sclerosis specific input						
Patient age	Gamma	48.4	SE: 0.41	16'133	0.003	Collin 2007[52] & Collin 2010[11]
NRS baseline	Beta	7.5		5.93	1.98	Messina 2017[70]
Response THC:CBD spray	Beta	40.0%		48	72	Pooled estimate Collin 2007[52], Collin 2010[11]
Response SOC	Beta	21.9%		14	50	Pooled estimate Collin 2007[52], Collin 2010[11]
NRS progress	Normal	0.073	SD: 0.121			Kister 2013[78]

Parameter	Distribu-tion	Determin-istic value	Uncer-tainty	Alpha	Beta	Source
Standardised mortality ratio	Normal	2.81	SD: 0.03			Manouchehrinia 2016[75]
Number of doses THC:CBD spray	Gamma	6.3	SE: 0.115	3.150	0.002	Messina 2017[70]
Motor neuron disease specific input						
Patient age	Gamma	58.0	SE: 1.97	865.672	0.067	Riva 2019[54]
NRS baseline	Beta	5.7		4.26	3.22	Riva 2019[54]
Response THC:CBD spray	Beta	20.7%		6	23	Riva 2019[54]
Response SOC	Beta	13.3%		4	26	Riva 2019[54]
NRS progress	Normal	0.073	SD: 0.121			Kister 2013[78]
Number of doses THC:CBD spray	Gamma	5.5	SE: 0.769	50.926	0.108	Meyer 2019[79]

Keys: SAE = serious adverse event, SOC = standard of care, GP = general practitioner, NRS = numeric rating scale, SE = standard error, SD= standard deviation, THC = tetrahydrocannabinol, CBD = cannabidiol

9.1.5 Methodology budget impact analysis

The budget impact (BI) model allowed the calculation of the projected population-level five-year overall costs of reimbursing THC:CBD spray for the Swiss chronic pain population and for the moderate to severe spasticity population. The BI model was built as an extension to the Swiss cost-effectiveness model, which was described previously. Hence, the core model characteristics for the BI model were largely the same as those used for the cost-effectiveness model (i.e. one-month cycle time, 3% discounting, same transition probabilities, discontinuation rates, same resource use, and unit costs). The time horizon of the BI model was restricted to five years. The BI was restricted to treatment-resistant adults, i.e. adults were assumed to be eligible for THC:CBD spray when first-line treatment (and if applicable second or third line treatment) did not work sufficiently or stopped working.

To perform the budget impact analyses, additional input was required (illustrated in Table 32). First, the current number of adults with treatment-resistant chronic pain or moderate to severe spasticity in the Swiss population was determined. Subsequently, these patient populations were differentiated for the different subpopulation groups according to the underlying cause of the chronic pain (i.e. cancer pain, neuropathic pain, musculoskeletal pain) or spasticity symptoms (i.e. MS, motor neuron disease). Finally, information was required on the expected proportion of the patient (sub)populations using THC:CBD spray over the course of the five-year time horizon of the BI model. To obtain the required input, a survey was constructed. Clinical experts were selected and contacted by FOPH and were invited to fill out the survey. The survey

responses were averaged and sent out to additional experts, who were asked to validate the retrieved values, or provide alternative estimates if deemed appropriate. The base case values were based on the combination of initial responses and responses from the validation procedure. In the base case, the average values of the clinical experts were used. All respondents were weighted equally. To reflect uncertainty around the input values of the budget impact estimates, sensitivity analyses were performed, in which minimum and maximum values of clinical expert input were used.

Table 32. Input for the budget impact analysis

Parameter	Source
Prevalence of treatment-resistant chronic pain and treatment-resistant moderate to severe spasticity in adults	Clinical expert opinion
Distribution of subpopulations over the total chronic pain / spasticity population	Clinical expert opinion
Proportion of the cohort of patients that are expected to be receiving THC:CBD spray (for the upcoming five years)	Clinical expert opinion, assumption: equal demand for all subpopulations

Keys: THC = tetrahydrocannabinol, CBD = cannabidiol

At each cycle, the BI model estimated the number of patients that were using THC:CBD spray. These population-level numbers were calculated from the specific input parameters of the BI model, informed by expert opinion as described above. Hereby the BI model could calculate the following results:

1. The projected (cumulative) population level budget impact estimates for up to five years, which incorporate the total amount of cumulative costs from the cost-effectiveness model, as well as the estimated number of patients using THC:CBD spray, at each year.

2. The difference between the budget impact estimate of a scenario where THC:CBD spray was to be reimbursed and the budget impact of the status quo, where THC:CBD spray is not generally reimbursed for patients with treatment-resistant chronic pain and moderate to severe spasticity. This difference reflects the projected increase in the overall budget spent on these patient populations in Switzerland, when THC:CBD spray would be reimbursed for (subgroups of) patients with treatment-resistant chronic pain and treatment-resistant moderate to severe spasticity.

9.2 Results cost-effectiveness and budget impact

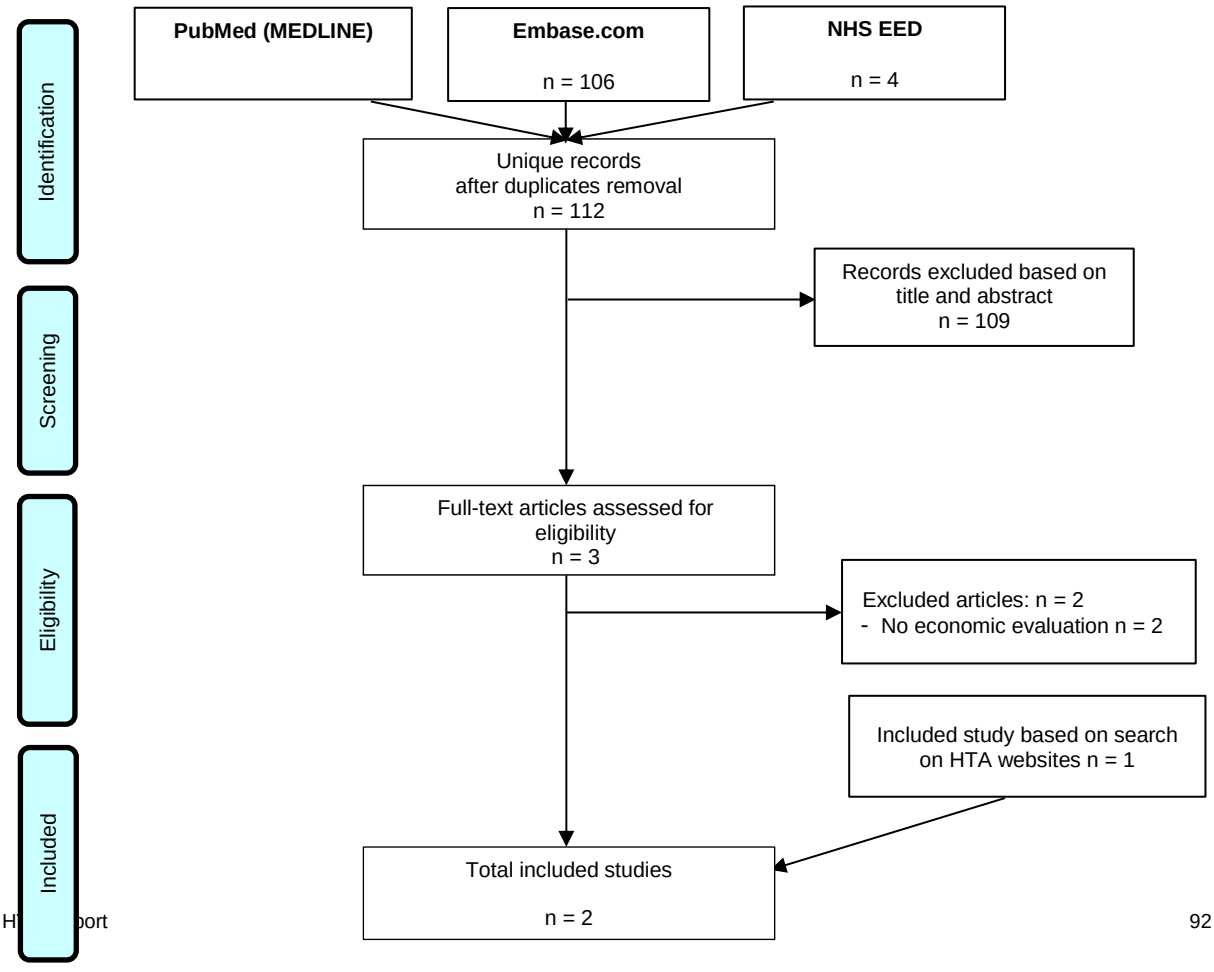
9.2.1 Findings cost-effectiveness SR

PRISMA flow diagram

Chronic pain

In total, 112 unique records were identified in PubMed (MEDLINE), Embase.com and NHS EED on the use of medical cannabis in chronic pain. Of those, 109 records were excluded based on their title and abstract, resulting in three studies to be screened in full-text. After applying the inclusion and exclusion criteria, one study was included. The other studies were no economic evaluations and where therefore excluded. 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 two studies. A complete overview of the selected literature is enclosed in the PRISMA flow chart (Figure 7).

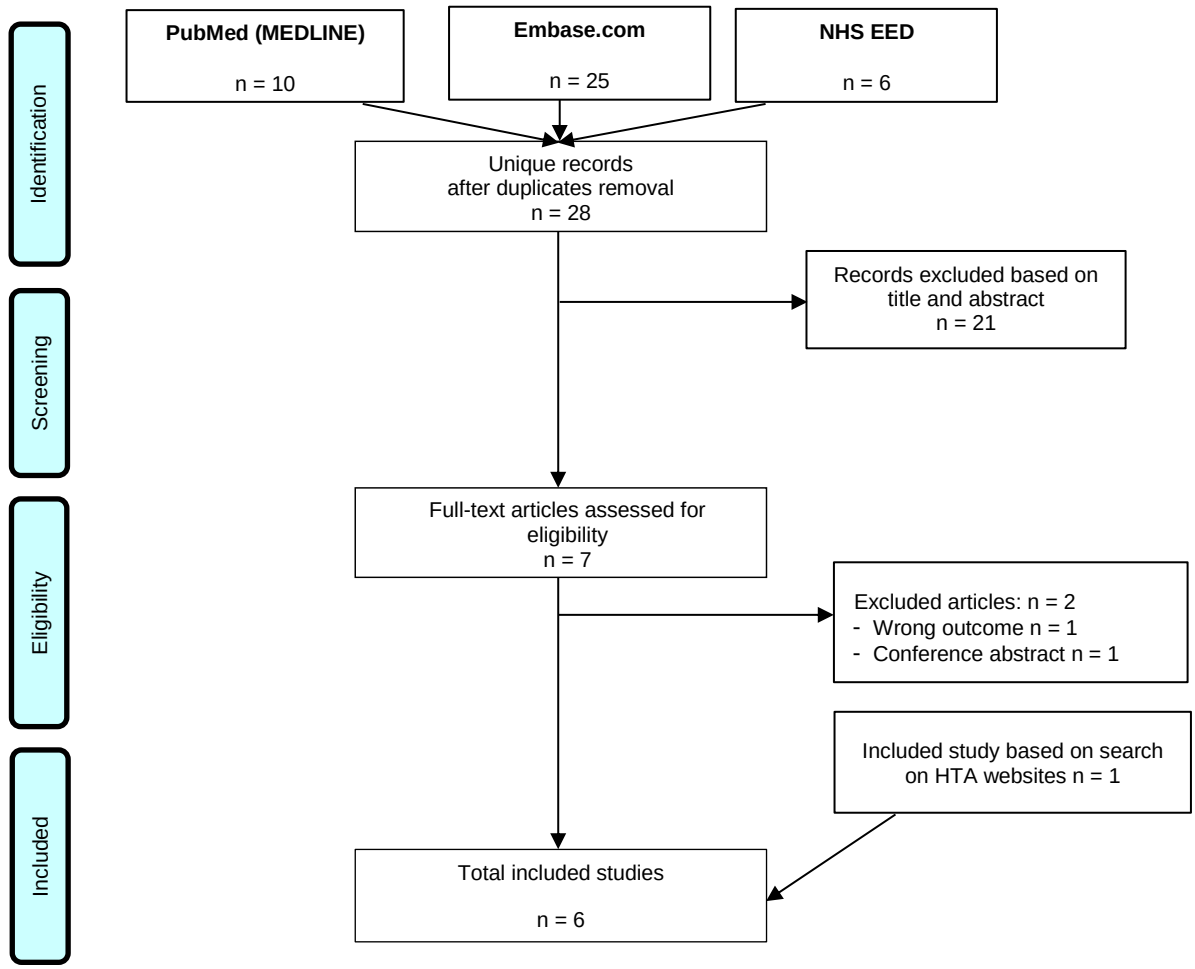
Figure 7. PRISMA flowchart of the cost-effectiveness systematic literature search on the use of medical cannabis for the symptom chronic pain



Spasticity

In total, 28 unique records were identified in PubMed (MEDLINE), Embase.com, and NHS EED on the use of medical cannabis in spasticity. Of those, 21 records were excluded based on their title and abstract, resulting in seven studies to be screened in full-text. After applying the inclusion and exclusion criteria, five economic evaluations were included. Two studies were excluded for 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 six studies. A complete overview of the selected literature is enclosed in the PRISMA flow chart (Figure 9).

Figure 9. PRISMA flowchart of the cost-effectiveness systematic literature search on the use of medical cannabis for the symptom spasticity



Study characteristics tables

The characteristics from the studies included on the cost-effectiveness of medical cannabis use in populations with the chronic pain and spasticity are presented in Table 33 and Table 34 respectively. The findings are described in more detail below.

Chronic pain

Two economic evaluations were included in the cost-effectiveness systematic literature search.[81,82] The study and model characteristics are presented in Table 33. 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.[81] The other study considered different 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 pain management.[82]

One economic evaluation was conducted for the USA[81] setting, and one was conducted for the UK.[82] Both economic evaluations were cost-utility analyses (CUAs), expressing outcomes in QALYs. One economic evaluation used a decision tree[81] and the other constructed a Markov model.[82] The decision tree employed a one-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, or death. The Markov model used the following health states: on treatment and responder, on treatment non-responder, discontinued and responder, discontinued non-responder, or death. Treatment response was defined as achieving ≥30% reduction in the NRS pain score. Both studies were published in 2019.

The ICERs were £24’474 for the UK model (lifetime horizon) and $48’594 for the USA model (1-year horizon), with incremental QALYs of 0.162 and 0.013 and incremental costs of $610 and £24’474 respectively.

Table 33. Study characteristics and main cost-effectiveness findings for the symptom chronic pain

Reference Country	Study design, type of model	Study population	Intervention	Comparator	Outcome measure used to model disease progress	Perspective	Time horizon	Discount rates (costs / effects)	ICER (incremental costs, incremental effects)
Neuropathic pain									
Tyree 2019[81], 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	USA healthcare sector perspective	1-year	3.0% / 3.0%	$48'594 / QALY ($610 ; 0,013 QALY)
Mixed aetiologies									
NICE 2019[82], 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: CUA = cost utility analysis, USA = Unites States of America, QALY = quality-adjusted life year, SOC = standard of care, NHS = national health service, PSS = personal social services, NRS = numeric rating scale, ICER = incremental cost-effectiveness ratio, THC = tetrahydrocannabinol, CBD = cannabidiol

Spasticity

Six economic evaluations were included in the cost-effectiveness systematic literature search.[82–87] The study and model characteristics are presented in Table 34. All studies compared THC:CBD spray 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 four weeks (according to the prescription requirement). The study design of all included studies was a CUA, expressing outcomes in QALYs. All

studies were model-based economic evaluations and adopted Markov models. 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 three or five levels. In the other study, health states were defined as either responders (≥30% reduction in NRS spasticity score) or non-responders.

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 5-year time horizon, one study used a time horizon of 30 years. One of the studies was conducted by NICE.[82] The most recent model-based study was from 2019.[82]

Among the models using a time horizon of 5 years, the ICERs ranged from £1'580 to £49'300. The incremental QALYs ranged from 0.081 to 0.443 for the same time horizon, and incremental costs ranged from £1'580 to £7'600.

Table 34. Study characteristics and main cost-effectiveness findings for the symptom spasticity

Reference Country	Study design, type of model	Study population	Intervention	Comparator	Outcome measure used to model disease progress	Perspective	Time horizon	Discount rates (costs / effects)	ICER (incremental costs, incremental effects)
Multiple sclerosis									
Gras 2016[83], 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 therapy lasting 4 weeks	THC:CBD spray + 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)
Slof 2015[85], Italy	CUA, Markov model	Patients with moderate to severe spasticity due to MS experiencing insufficient benefit from oral anti-spasticity	THC:CBD spray + SOC	SOC alone	Severity of MS-related spasticity, measured with the MS	Health-payer perspective	5 years	3.0% / 3.0%	€4'968 / QALY

Reference Country	Study design, type of model	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			Spasticity 0-1 NRS				(€2'152 ; 0.443 QALY)
Slof 2012[84], 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 + 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)
Lu 2012[86], 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 + 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[82], UK	CUA, Markov model	Patients with moderate to severe spasticity due to	THC:CBD spray + SOC	SOC alone	Severity of MS-related spasticity, measured	NHS and PSS perspective	5 years	3.5% / 3.5%	£19'512 / QALY

Reference Country	Study design, type of model	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			with the MS Spasticity 0-1 NRS (in terms of responders / non responders)				(£1'580 ; 0.081 QALY)
Flachenecker 2013[87], Germany	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 + 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)

Keys: SOC = standard of care, NRS = numeric rating scale, NHS = national health service, PSS = personal social services, ICER = incremental cost-effectiveness ratio, QALY = quality-adjusted life year, THC = tetrahydrocannabinol, CBD = cannabidiol

Input parameters

Chronic pain

An overview of the inputs reported in the included economic evaluations is displayed in Appendix 15.6. The economic evaluations used different sources for the efficacy data. NICE conducted an SR to identify model inputs (i.e. efficacy estimates, and adverse event parameters and costs).[82] 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..[88] More detailed input parameters were presented, which were based on several other 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 inputs reported in the included trial-based studies is displayed in Appendix 15.6. Five studies used efficacy data from the trial by Novotna et al..[12] NICE conducted a SR to identify model input (i.e. efficacy, adverse event parameters and costs, and costs of background spasticity management per health state).[82] 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 THC:CBD spray on mortality.

Quality appraisal

The results from the quality appraisal of the studies included on the cost-effectiveness of medical cannabis use in populations with chronic pain or spasticity are presented in Appendix 15.7. The economic evaluations that were included in the systematic literature search were assessed with the CHEC. The findings are described in more detail below.

Chronic pain

Overall, the study comparison was sufficiently described and the study design was appropriate for the stated objectives. Only the NICE model included a lifetime time horizon, which is generally the preferred option for economic evaluations.[82] 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.[81,82] The costs in the NICE model were based on the national tariff list.[82] Tyree et al. 2019 based their costs on the cost inputs of several other studies.[81] 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.[81] The NICE assessment included analyses using different treatment effects, discontinuation thresholds, QoL coefficients, dosing regimen, response values, and baseline pain scores amongst many more.[82] 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 15.7.

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. [17,82–85,87] In addition, two did not provide a clear description of the study population (e.g. mean age or age range, gender distribution).[83,85]

Only in the NICE model, the effectiveness and cost related model inputs were based on a systematic literature search.[82] 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.[82]

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.

9.2.2 Findings cost-effectiveness modelling

This paragraph describes the results of the cost-effectiveness analyses performed with the cost-effectiveness models developed for the symptoms chronic pain and spasticity.

9.2.2.1 Findings chronic pain models

Deterministic analysis

Table 35 presents the total costs, life years and QALYs for the THC:CBD spray arm and the SOC arm in the chronic pain models for the neuropathic and musculoskeletal pain etiologies. In the base case analysis for neuropathic pain (lifetime time horizon, starting age 51), patients lived on average for another 19.5 (31.6 undiscounted) years in both arms. THC:CBD spray resulted in a QALY loss of 0.020 at higher costs (50'883 CHF). Therefore, THC:CBD spray in addition to SOC was dominated by SOC alone (i.e. less effective and more costly than SOC alone). In contrast to the findings of the SR on the efficacy of medical cannabis, THC:CBD resulted in slightly lower QALYs in the cost-effectiveness model. This was attributable to different factors, in particular the difference in (long-term) discontinuation rates between the two treatment arms (discontinuation due to adverse events was only assumed to occur in the THC:CBD arm) and a minimal difference in utility values between the two arms resulting from the underlying simulated NRS scores. The impact of these model assumptions on the ICER values were assessed in the scenario analyses. The Markov traces in Appendix 15.8 show the patient flows over time.

For musculoskeletal pain, patients lived on average for another 15 (21 undiscounted) years in both groups in the base case analysis (lifetime time horizon, starting age 63 years). THC:CBD spray resulted in a QALY gain of 0.452 at higher costs (23'093 CHF) resulting in an ICER of 51'038 CHF per QALY. The Markov traces in Appendix 15.8 show the patient flows over time.

Table 35. Base case cost-effectiveness results chronic pain (discounted)

	Life years	Total QALYs	Incremental QALYs	Total costs (CHF)	Incremental costs (CHF)	ICER (CHF/ QALY)
Neuropathic pain						
SOC	19.490	12.570		153'709		
THC:CBD spray + SOC	19.490	12.550	-0.020[5]	204'593	50'883	Dominated
Musculoskeletal pain						
SOC	15.008	11.012		66'663		
THC:CBD spray + SOC	15.008	11.465	0.452	89'757	23'093	51'038

Keys: SOC = standard of care, ICER = incremental cost-effectiveness ratio, QALY = quality-adjusted life year, THC = tetrahydrocannabinol, CBD = cannabidiol

Probabilistic sensitivity analyses

The results of the PSA for the chronic pain models are presented in Table 36 and in the cost-effectiveness planes in Figure 10 and Figure 11. For neuropathic pain, the mean incremental costs and incremental QALYs were 82'471 CHF and -0.105, respectively. As a result, THC:CBD spray + SOC got dominated (i.e. less effective and more costly than SOC alone). In the probabilistic sensitivity analyses the incremental QALYs were relatively similar compared to the deterministic analyses. In contrast, the incremental costs were higher compared to the deterministic results. For musculoskeletal pain, the mean incremental costs and incremental QALYs were 32'691 CHF and 0.27, respectively. This resulted in a much higher ICER compared to the deterministic ICER of 51'038 CHF per QALY. The probabilistic results for musculoskeletal pain show a higher ICER compared to the deterministic ICER.

[5] * A QALY loss is counterintuitive based on the clinical efficacy, effectiveness and safety data presented in Chapter 8, however this can be explained through two main assumptions made for the neuropathic pain base case model. First, the pooled SD estimates were rather sizeable with 1.0 and 1.5 for THC:CBD spray and SOC, respectively. The difference in SD between the model arms, in conjunction with the relatively small difference in treatment effects, causes the SOC arm to have a slightly lower NRS score on average compared to the THC:CBD spray arm, despite the fact that there are more responders in the latter arm. Second, patients in the THC:CBD spray arm could discontinue treatment due to a loss of effectiveness and due to adverse events. Whereas in the SOC arm of the model, patients could only discontinue due to the loss of treatment effectiveness. These two assumptions were tested in scenario analyses to show their impact on the model outcomes – see Table 36.

Table 36. Results probabilistic sensitivity analysis – chronic pain

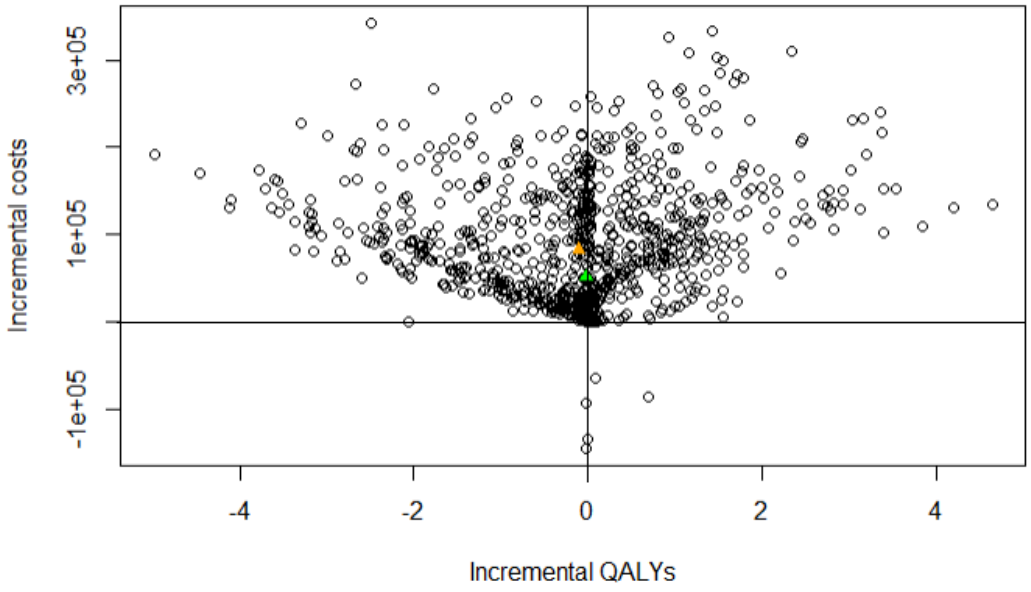
	Life years	Total QALYs	Incremental QALYs	Total costs (CHF)	Incremental costs (CHF)	ICER (CHF/QALY)
Neuropathic pain						
SOC	18.95	12.02		129'209		
THC:CBD spray + SOC	18.95	11.94	-0.105	155'461	82'471	Dominated
Musculoskeletal pain						
SOC	14.86	10.82		42'205		
THC:CBD spray + SOC	14.86	11.62	0.27	69'574	32'691	121'380

Keys: SOC = standard of care, ICER = incremental cost-effectiveness ratio, QALY = quality-adjusted life year, THC = tetrahydrocannabinol, CBD = cannabidiol.

Figure 10 and Figure 11 present the incremental costs and incremental effects of the PSA in a cost-effectiveness plane. Cost-effectiveness acceptability curves are presented in Appendix 15.10. The average probabilistic and deterministic values are indicated by the orange and green triangles, respectively. The results of the PSA for the neuropathic pain model shows that 46.8% of the iterations result in a positive incremental cost and incremental QALY, representing the north-east quadrant of the cost-effectiveness plane. Another 52.8% of the iterations resulted in positive incremental costs and negative incremental QALYs (dominated). A total of 0.3% of the iterations resulted in negative incremental costs and negative incremental QALYs.

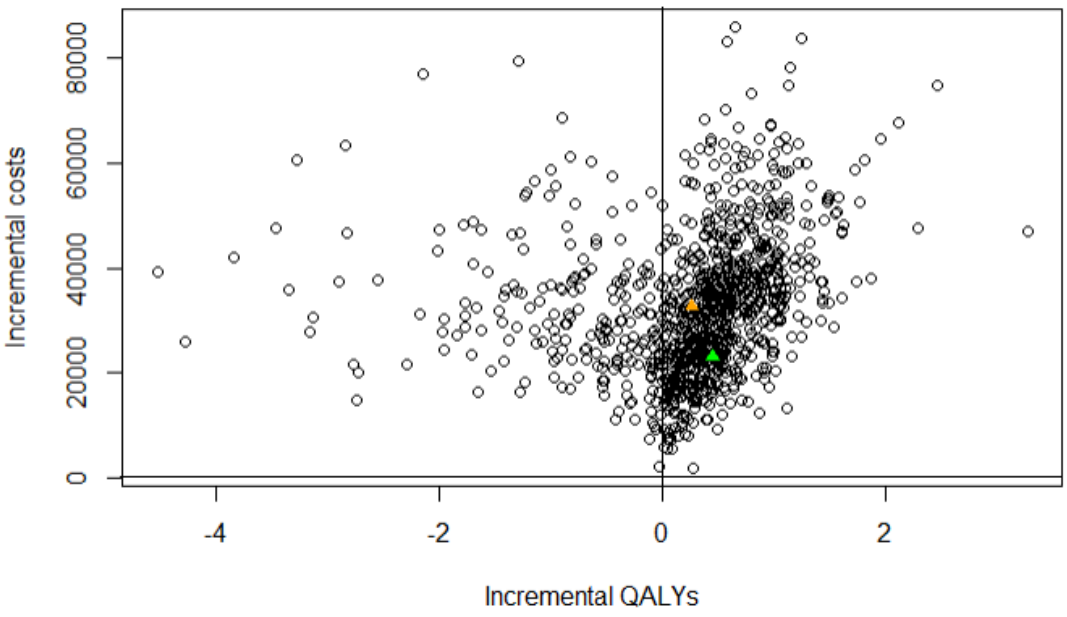
Approximately 79% of the PSA iterations for the musculoskeletal pain model resulted in positive incremental costs and incremental QALYs for THC:CBD spray in addition to SOC versus SOC alone, which represents the iterations in the north-eastern quadrant of the cost-effectiveness plane. None of the iterations resulted in negative incremental costs and negative incremental QALYs.

Figure 10. Cost-effectiveness plane – neuropathic pain



* Costs in CHF, average ICER displayed as a red triangle; deterministic ICER displayed as a green triangle.

Figure 11. Cost-effectiveness plane – musculoskeletal pain



* Costs in CHF, average ICER displayed as a red triangle; deterministic ICER displayed as a green triangle.

Scenario analyses

Various scenario analyses were conducted to assess the impact of structural uncertainty on the incremental cost-effectiveness ratio. In the first scenario analyses, the trials included in the pooled estimate for neuropathic pain were modelled separately using the treatment effects, patient characteristics (age, gender, NRS baseline score), and THC:CBD spray dosing reported in the individual trials. As a result, a small increase in the negative incremental QALYs and positive incremental costs was observed using the Langford et al.[46] input data, due to the smaller treatment effect compared to the base case analysis. The resulting ICER indicates that THC:CBD spray was still dominated by SOC (i.e. less effective and more costly than SOC alone). By using the input from Nurmikko et al.[49], with a larger treatment effect compared to the base case analysis, the model showed a small positive incremental QALY, as well as a small increase in incremental costs, resulting in an ICER of 827'166 CHF per QALY.

Table 37. Results scenario analyses chronic pain models

Scenario description	Incremental QALYs	Incremental costs (CHF)	ICER (CHF / QALY)
Neuropathic pain			
Base case	-0.020	50'883	Dominated
Apply 0% discount rates	-0.035	82'408	Dominated
Apply 5% discount rates	-0.015	39'422	Dominated
Apply 5 year time horizon	-0.001	12'297	Dominated
Apply 10 year time horizon	-0.006	22'392	Dominated
Apply 20 year time horizon	-0.014	37'424	Dominated
Apply 30 year time horizon	-0.018	46'575	Dominated
Efficacy data from Langford et al. 2013	-0.193	68'260	Dominated
Efficacy data from Nurmikko et al. 2007	0.066	32'617	493'583
Change SD of TE to 20% of TE	0.110	25'343	230'508
Apply same discontinuation rates for SOC and THC:CBD spray arms	0.101	44'250	439'990
Exclude SAEs	-0.020	50'029	Dominated
Mean utility and cost values for responders & non-responders	0.102	44'325	435'930
Increased THC:CBD cost (1.57 CHF per mg THC)	-0.020	88'414	Dominated
Musculoskeletal pain			
Base case	0.452	23'093	51'038

Apply 0% discount rates	0.638	32’672	51’175
Apply 5% discount rates	0.374	19’027	50’938
Apply 5 year time horizon	0.139	7’277	52’310
Apply 10 year time horizon	0.249	12’833	51’514
Apply 20 year time horizon	0.395	20’179	51’137
Apply 30 year time horizon	0.448	22’877	51’046
Change SD to 10% of median	0.365	28’569	78’333
Change SD to 50% of median	0.436	22’290	51’124
Apply same discontinuation rates for SOC and THC:CBD spray arms	0.483	21’393	44’247
Exclude SAEs	0.453	21’601	47’641
Mean utility and cost values for responders & non-responders	0.775	6’945	8’956
Increased THC:CBD spray cost (1.52 CHF per mg THC)	0.452	59’218	130’875

Keys: ICER = incremental cost-effectiveness ratio, QALY = quality-adjusted life year, SOC = standard of care, SD = standard deviation, TE = treatment effect, SAE = serious adverse event, THC = tetrahydrocannabinol, CBD = cannabidiol. Values represent rounded incremental QALYs, Costs and ICERs.

In the base case, the discount rate for costs and effects was 3%. Scenario analyses were conducted using discounts rates of 0% and 5%, for both costs and effects, respectively. In general, using a 0% discount rate increased the incremental QALYs and incremental costs. Conversely, using 5% discounting both the incremental QALYs and incremental costs decreased. Alternative discount rates did not change the ICERs for both the neuropathic and musculoskeletal pain models in a meaningful way.

A lifetime time horizon was used in the base case analysis. To test the influence of the time horizon on the model output scenario analyses were conducted for time horizons of 5, 10, 20 and 30 years. Although both incremental QALYs and incremental costs decreased for the shorter time horizons, the ICERs were not impacted in a meaningful way.

For the neuropathic pain model we tested the influence of using the treatment effect observed in the Langford et al. and Nurmikko et al. studies separately.[46,49] Using the treatment effect from the Langford et al. study did not change the ICER in a meaningful way as THC:CBD spray was still dominated by SOC. The treatment effect observed in the Nurmikko et al. study did change the ICER from dominated to 493’583 CHF per QALY.

In the base case, the SDs surrounding the treatment effect (for both THC:CBD spray and SOC) were determined using the response rates from the clinical studies, because the studies used for the treatment effect of THC:CBD spray for neuropathic pain (Langford et al.[46] and Nurmikko et al.[49]) and musculoskeletal pain (Blake et al.[51]) did not report SDs. The SDs were adjusted in scenario analyses. To test the assumption concerning SD, a scenario analysis was performed in which the SD was set equal to 20% of the pooled treatment effect for the neuropathic pain model. For THC:CBD spray this resulted in an SD of 0.34 (1.1 in base case) and of 0.23 (1.5 in base case) for SOC. The incremental QALYs increased and were positive for THC:CBD spray, while the incremental cost decreased. The ICER moved from SOC dominating THC:CBD spray to a positive ICER of 230'508 CHF per QALY in patients with neuropathic pain.

In the musculoskeletal pain model, the SD of the treatment effect was assumed 20% of the median change in NRS pain score reported in Blake et al..[51] In scenario analyses, SDs of 10% and 50% of the median change in NRS pain score were used. Using 10% of the median change in NRS pain score as input for the SD, incremental QALYs decreased and incremental costs increased. Consequently, the ICER increased to 78'333 CHF per QALY. Using the 50% of the median change in NRS pain score as input for the SD instead, resulted in a smaller decrease in incremental QALYs and a larger increase in incremental costs, and an ICER of 51'124 CHF per QALY.

In the base case analyses, differential discontinuation was used for the responders on THC:CBD spray in addition to SOC and responders on SOC alone: responders on THC:CBD spray in addition to SOC could discontinue because of lack of maintained response or because of adverse events, whereas responders on SOC alone were assumed to only discontinue because of lack of maintained response. When the same discontinuation rates were applied to both arms (i.e. SOC alone responders also discontinued due to adverse events), more patients using SOC alone switched from responder state to the non-responder state. This health state is associated with higher utilities and lower costs. Due to this change in discontinuation in the neuropathic pain model the ICER moved from THC:CBD spray being dominated by SOC (i.e. less effective and more costly than SOC alone) to a positive ICER of 439'990 CHF per QALY. The same change in discontinuation resulted in a slightly lower ICER in the musculoskeletal pain model of 44'247 CHF per QALY.

For the neuropathic pain model, not taking into account SAEs in the model did not change the results; because of the low prevalence and short duration of SAEs and limited associated disutilities and costs. For

this aetiology of chronic pain SOC remained dominant over THC:CBD spray. In contrast, for musculoskeletal pain a small decrease in incremental costs resulted in a lower ICER of 47’641 CHF per QALY.

In the base case, separate utility values are calculated for THC:CBD spray responders and non-responders and SOC responders and non-responders using an underlying micro-simulation model. In a simple Markov model, responders and non-responders would be assigned a utility value regardless of the treatment arm. We tested the effect of this assumption in a scenario by calculating a mean utility value for responders and non-responders. For the neuropathic pain model, using a mean utility value for responders and non-responders resulted in ICER of 435’930 CHF per QALY. For the musculoskeletal pain model, the ICER was 8’956 CHF per QALY.

Last, a scenario analysis was performed to assess the impact of the cost of THC:CBD spray on the outcomes of the models. In this analysis we increased the cost of THC:CBD spray from 0.89 CHF per mg THC to 1.57 CHF per mg THC, based on the cost of a pharmaceutical preparation which includes the same amount of THC and CBD. For the neuropathic pain model, this increased the incremental costs to 88’414 CHF, however, this did not impact the ICER in a meaningful way as THC:CBD spray remained dominated by SOC. For the musculoskeletal pain model, the incremental costs increased to 59’218 CHF, which is more than double the base case value. As a result, the ICER increased to 130’875 CHF per QALY.

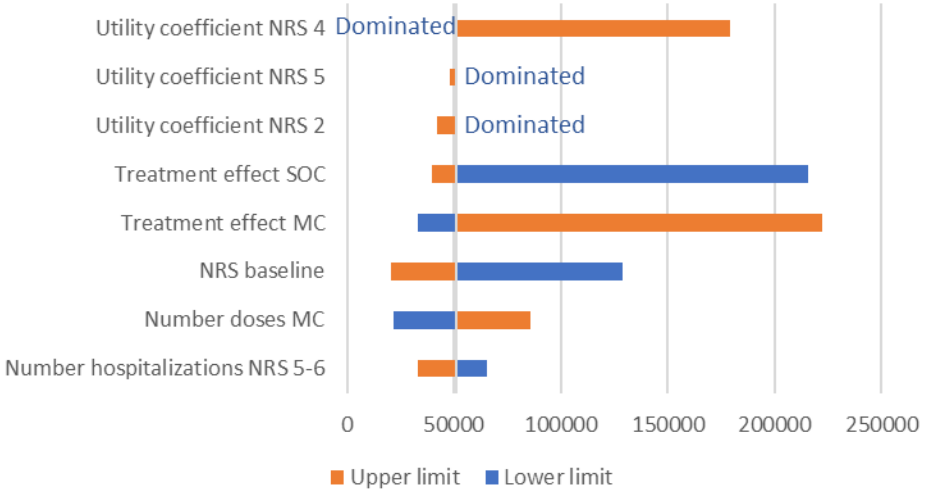
One-way sensitivity analyses

In one-way sensitivity analyses, uncertainty of individual parameters was assessed. For the neuropathic pain model only five parameters were able to change the ICERs in a relevant way. These parameters were the NRS baseline score, treatment effect of THC:CBD spray, treatment effect of SOC, the discontinuation shape parameter for THC:CBD spray, and the discontinuation rate parameter for SOC. For the other parameters, THC:CBD spray remained dominated by SOC for both the lower and upper limits of the one-way sensitivity analyses. In Appendix 15.11 15.11 separate tornado diagrams are presented for incremental QALYs and incremental costs.

In Figure 12 the results of the one-way sensitivity analyses for the eight most influential parameters for musculoskeletal pain model are presented. The three most influential parameters on the ICER were the utility values attached to the NRS pain scores 2, 4, and 5. Using the lower limit, the ICER changed from

51’093 CHF per QALY (base case) to an ICER where THC:CBD spray was dominated by SOC. Furthermore, the treatment effects of both THC:CBD spray and SOC had a large impact on the ICERs. In Appendix 15.11 tornado diagrams are presented for incremental QALYs and incremental costs separately.

Figure 12. Tornado diagram ICERs – Musculoskeletal pain



Keys: NRS = numeric rating scale, SOC = standard of care, MC = medical cannabis (THC:CBD spray)

9.2.2.2 Findings spasticity models

Deterministic analysis

Table 38 presents the total costs, life years and QALYs for the THC:CBD spray arm and the SOC arm in the MS and motor neuron disease models. In the base case analysis for MS (lifetime time horizon, starting age 48.4), patients lived on average for another 27.9 years (undiscounted; discounted 18.0 years) in both arms. THC:CBD spray resulted in a QALY gain of 0.135 at an additional costs of 7’401 CHF. The associated cost-effectiveness ratio was 54’675 CHF per QALY gained. The Markov traces in Appendix 15.8 show the patient flows over time.

For motor neuron disease, patients lived on average for another 4.5 years (undiscounted; discounted 4.0 years) in both arms in the base case analysis (lifetime time horizon, starting age 58). THC:CBD spray in addition to SOC resulted in a QALY gain of 0.019 at an additional cost of 1’598 CHF. The associated ICER was 84’628 CHF per QALY gained. The Markov traces in Appendix 15.8 show the patient flows over time.

Table 38. Base case cost-effectiveness results spasticity (lifetime time horizon; 3% discounting)

	Life years	Total QALYs	Incremental QALYs	Total costs (CHF)	Incremental costs (CHF)	ICER (CHF / QALY)
Multiple sclerosis						
SOC	17.961	4.924		552'369		
THC:CBD spray + SOC	17.961	5.059	0.135	559'770	7'401	54'675
Motor neuron disease						
SOC	3.991	1.523		60'516		
THC:CBD spray + SOC	3.991	1.542	0.019	62'114	1'598	84'628

Keys: SOC = standard of care, ICER = incremental cost-effectiveness ratio, QALY = quality-adjusted life year, CHF = Swiss Franc

Probabilistic sensitivity analysis

The results of the PSA for the spasticity models are presented in Table 39 and in the cost-effectiveness planes and CEAC Figure 13 and Figure 14. For MS, the mean incremental costs were 11'910 CHF and incremental QALYs were 0.122, resulting in an ICER of 97'375 CHF per QALY. For motor neuron disease, mean incremental costs were 1'565 CHF and incremental QALYs were 0.018, resulting in an ICER of 85;613 CHF per QALY. For MS, incremental QALYs were slightly lower and incremental costs were higher in the PSA compared to the deterministic analyses, leading in a higher ICER. For motor neuron disease, deterministic and probabilistic analyses yielded similar results. Deviations result from non-normal distributions of various parameters in the models.

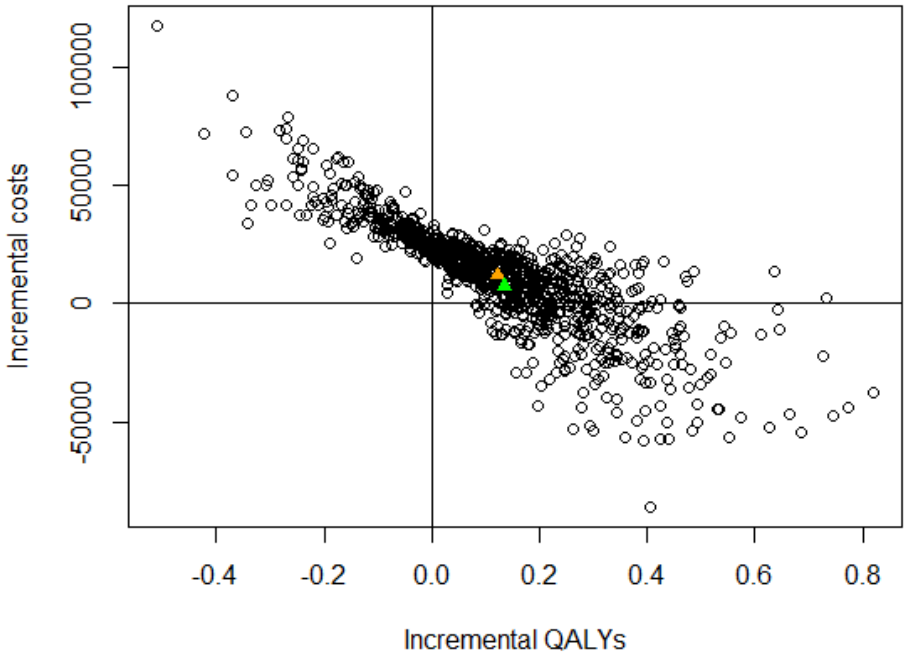
Table 39. Results probabilistic sensitivity analysis - spasticity

	Life years	Total QALYs	Incremental QALYs	Total costs (CHF)	Incremental costs (CHF)	ICER (CHF/QALY)
Multiple sclerosis						
SOC	17.970	5.269		515'326		
THC:CBD spray + SOC	17.970	5.391	0.122	527'236	11'910	97'375
Motor neuron disease						
SOC	4.000	1.529		61'443		
THC:CBD spray + SOC	4.000	1.548	0.018	63'009	1'565	85'613

Keys: SOC = standard of care, ICER = incremental cost-effectiveness ratio, QALY = quality-adjusted life year

Figure 13 and Figure 14 present the incremental costs and incremental effects of the PSA in a cost-effectiveness planes for MS and motor neuron disease, respectively. Cost-effectiveness acceptability curves are presented in Appendix 15.10. The average probabilistic and deterministic values are indicated by the orange and green triangles, respectively. The cost-effectiveness plane for MS spasticity shows that a large proportion of iterations (25%) resulted in positive incremental effects and cost savings, leading to dominant ICERs (southeast quadrant of the cost-effectiveness plane). On the other hand, 24% of iterations result in negative incremental effects and positive incremental costs, leading to a dominated ICER (northwest quadrant of the cost-effectiveness plane).

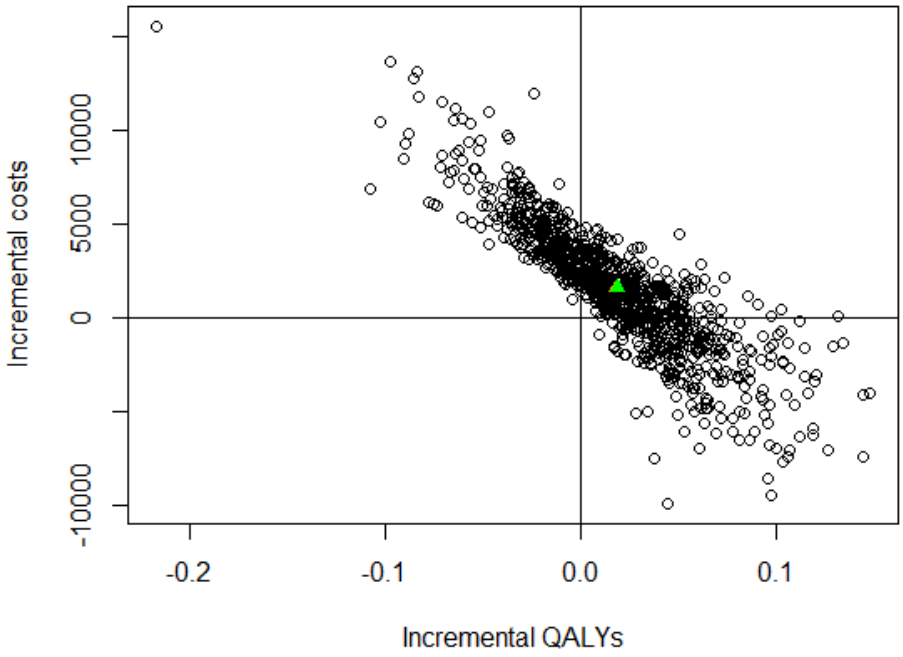
Figure 13. Cost-effectiveness plane – MS spasticity



*** Costs in CHF, average ICER displayed as a red triangle; deterministic ICER displayed as a green triangle**

For motor neuron disease, 29% of iterations resulted in a dominant ICER. In contrast, THC:CBD spray in addition to SOC was dominated by SOC alone in 31% of iterations. At a threshold of zero, 29% of iterations yielded cost-effective results. With a threshold of 100’000 CHF per QALY, 52% of iterations were cost-effective.

Figure 14. Cost-effectiveness plane – Motor neuron disease spasticity



* Costs in CHF, average ICER displayed as a red triangle; deterministic ICER displayed as a green triangle.

Scenario analyses

Various scenario analyses were conducted to assess the impact of structural uncertainty on the incremental cost-effectiveness ratio. Table 40 presents the outcomes for the scenario analyses for the multiple sclerosis and motor neuron disease models.

Table 40. Results scenario analyses spasticity models

Scenario description	Incremental QALYs	Incremental costs (CHF)	ICER (CHF/QALY)
Multiple sclerosis			
Base case	0.135	7'401	54'675
Apply 0% discount rates	0.209	11'536	55'129
Apply 5% discount rates	0.107	5'829	54'339
Apply 5 year time horizon	0.038	2'381	62'702
Apply 10 year time horizon	0.068	3'990	58'913
Apply 20 year time horizon	0.110	5'887	53'805
Apply 30 year time horizon	0.130	6'866	52'836
Efficacy data from Collin et al. 2007	0.280	-10'841	Dominant

Efficacy data from Collin et al. 2010	0.029	20’442	718’650
Efficacy data from NICE	0.265	-17’962	Dominant
Apply same discontinuation rates for SOC and THC:CBD spray arms	0.228	-6’817	Dominant
No spasticity progression	0.141	10’017	70’951
NRS progression 0.227/year	0.081	15’498	191’303
100% of resource use associated to spasticity	0.135	-13’376	Dominant
25% of resource use associated to spasticity	0.135	17’789	131’421
Exclude SAEs	0.136	6’168	45’408
Increased MC cost (1.57 CHF per mg THC)	0.135	27’988	206’768
Motor neuron disease			
Base case	0.019	1’598	84’628
Apply 0% discount rates	0.021	1’792	84’334
Apply 5% discount rates	0.018	1’501	84’807
Apply 5 year time horizon	0.014	1’319	92’534
Apply 10 year time horizon	0.017	1’539	88’678
Apply 20 year time horizon	0.019	1’602	85’966
Apply 30 year time horizon	0.019	1’601	85’005
Apply same discontinuation rates for SOC and THC:CBD spray arms	0.027	767	28’212
No spasticity progression	0.019	1’805	96’014
Spasticity progression 0.227 NRS per year	0.018	1’360	73’659
100% of resource use associated to spasticity	0.019	-248	Dominant
25% of resource use associated to spasticity	0.019	2’522	133’509
Exclude SAEs	0.019	1’427	75’267
Increased MC cost (1.57 CHF per mg THC)	0.019	4’099	217’035

Keys: ICER = incremental cost-effectiveness ratio, QALY = quality-adjusted life year, MC = medical cannabis, SOC = standard of care, SD = standard deviation, TE = treatment effect, SAE = serious adverse event. Values represent rounded incremental QALYs, Costs and ICERs.

In the first scenario analyses, the discount rates were changed. In the base case, the discount rate for costs and effects was 3%.In scenario analyses discounts rates of 0% and 5% were applied, for both costs and

effects. For both MS and motor neuron disease, when a discount rate of 0% was used (no discounting) both incremental QALYs and costs savings increased, and incremental QALYs and costs savings decreased with a discount rate of 5%. The effect on the ICER was limited, since the same discount rate was applied in both arms.

A lifetime time horizon was used in the base case analysis. For MS, shorter time horizons resulted in lower incremental QALYs and incremental costs. Shorter time horizons ignore differences in QALYs and costs that occur in later model cycles. Using a 5-year time horizon increased the ICER to 62'702 CHF per QALY; a 15% increase compared to the lifetime horizon used in the base case.

For motor neuron disease, shorter time horizons (i.e. 5 years, 10 years, 20 years, 30 years) resulted in a slight reduction in the number of QALYs gained and incremental costs. The impact on the ICER was modest. Effects of alternative time horizons was limited, because costs and effects incurred during the first years of the model were incorporated. Due to the high mortality rates, the effects of taking a shorter time horizon were modest, as most patients have died within the first years of the model.

In the base case analyses for MS, response rates from Collin et al. 2007[52] and Collin et al. 2010[11] were pooled to obtain one overall estimate. In scenario analyses, different response rates were used. Using the response rates reported by Collin et al. (2007)[52] only, resulted in larger QALY gains and cost savings (-10'841 CHF). This was due to the larger difference in response rates, compared to the base case. In this scenario, THC:CBD spray in addition to SOC was dominant (larger effects, lower costs) over SOC alone. Alternatively, using only the response rates from Collin et al. (2010)[11], incremental QALYs decreased to 0.029 and incremental costs increased to 20'442 CHF. This resulted in an ICER of 718'650 CHF per QALY. The ICER increased because differences in response rates in the Collin et al. (2010)[11] study were smaller than in the base case. Finally, when using the response rates used in the NICE submission[82], incremental QALYs increased and incremental costs were negative (-17'962 CHF). The associated ICER was dominant.

In the base case analyses, differential discontinuation was used for the responders on THC:CBD spray in addition to SOC and responders on SOC alone: responders on THC:CBD spray in addition to SOC could discontinue because of lack of maintained response or because of adverse events, whereas responders on SOC alone were assumed to only discontinue because of lack of maintained response. When the same discontinuation rates were applied to both arms (i.e. SOC alone responders also discontinued due to adverse events), more patients using SOC alone switched from responder state to the non-responder state,

which is associated with lower utilities and higher costs. For MS, incremental QALYs increased to 0.228 and incremental cost decreased to -6'817 CHF. THC:CBD spray in addition to SOC was dominant over SOC alone. For motor neuron disease, incremental QALYs increased to 0.027 and incremental cost decreased to 767 CHF, leading to a reduced ICER of 28'212 CHF per QALY.

NRS spasticity score was assumed to progress over time due to natural disease progression in both treatment arms. In the base case analyses, deterioration of 0.073 NRS points per year was used. In the NICE dossier submission, a much higher NRS spasticity progression was used (i.e. 0.227 points per year). With a lifetime time horizon used in the base case, this resulted in all patients eventually ending up in the most severe NRS spasticity score, which was not considered realistic. Nonetheless, the value used in the NICE submission[82] was tested in the scenario analysis. Using a higher NRS spasticity progression rate particularly impacted results. Incremental QALYs decreased to 0.081 and incremental costs more than doubled compared to the base case. The ICER increased to 191'303 CHF per QALY.

For motor neuron disease, natural progression of spasticity was assumed equal to the progression modelled in MS (i.e. 0.073 NRS points per year). Changing NRS progression only had a modest impact on the outcomes. Due to the high mortality in the motor neuron disease population, only a minority of patients progressed to more severe NRS spasticity states, limiting the impact on both incremental QALYs and costs.

Health state costs were calculated from resource use as identified by Stevenson et al. (2015)[80] multiplied by unit costs. In the base case analyses, 50% of resource use was assumed to be related to spasticity. Attributing more resource use to spasticity increased health state costs. As resource use costs were more than linearly related to NRS spasticity states, this particularly affected the SOC arm, in which NRS spasticity scores were higher. When resource use was assumed to be fully associated with spasticity in MS, incremental costs were negative (-13'376 CHF). In this scenario, THC:CBD spray in addition to SOC was dominant over SOC alone. The scenario which assumed that only 25% of resource use was attributed to spasticity resulted in incremental costs of 17'789 CHF. The ICER increased to 131'421 CHF per QALY.

The same pattern was observed in motor neuron disease. THC:CBD spray in addition to SOC resulted in costs savings of 248 CHF when all resource use costs were attributed to spasticity, resulting in dominance of THC:CBD spray in addition to SOC over SOC alone. When only 25% of resource was attributed to spasticity, incremental costs were 2'522 CHF, leading to an ICER of 133'509 CHF per QALY.

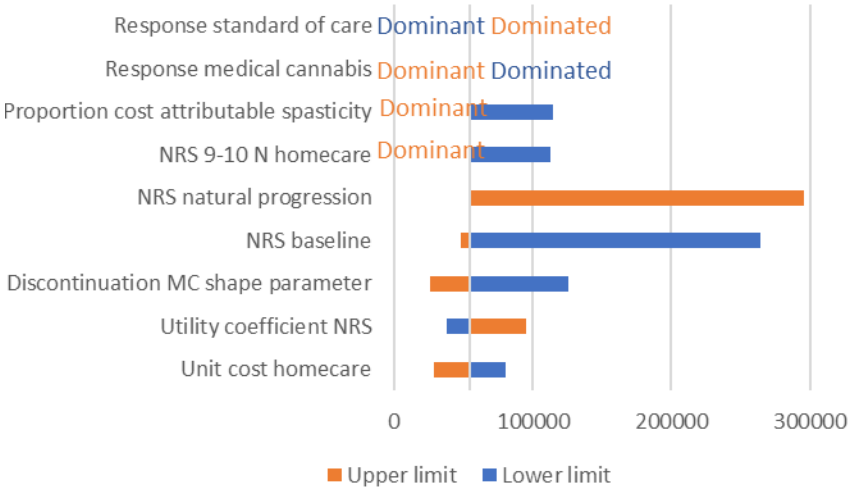
For both MS spasticity and motor neuron disease spasticity, not taking into account SAEs in the model resulted in lower incremental costs. Incremental QALYs were virtually unaffected because of the low prevalence and short duration of SAEs, and limited associated disutilities. In this scenario, the ICERs decreased to 45'408 CHF per QALY for MS and 75'267 CHF per QALY for motor neuron disease spasticity.

Last, a scenario analysis was performed to assess the impact of the cost of THC:CBD spray on the outcomes of the models. In this analysis we increased the cost of THC:CBD spray from 0.89 CHF per mg THC to 1.57 CHF per mg THC, based on the cost of a pharmaceutical preparation which includes the same amount of THC and CBD. For the MS spasticity model, this increased the incremental costs to 27'988 CHF and the ICER to 206'768 CHF per QALY. For the motor neuron disease model, the incremental costs increased to 4'099 CHF, and the ICER to 217'035 CHF per QALY.

One-way sensitivity analyses

In one-way sensitivity analyses, uncertainty of individual parameters was assessed. In Figure 15, the results of the one-way sensitivity analyses for the eight most influential parameters for the MS spasticity are presented. The response rates of THC:CBD spray and SOC were the most influential parameters for both incremental QALYs and incremental costs. In addition, the utility decrement per NRS spasticity state and the natural progression rate of NRS spasticity had an important impact on incremental QALYs. The amount of homecare patients received in the highest NRS spasticity states and the proportion of costs attributed to spasticity were major influencers of incremental costs.

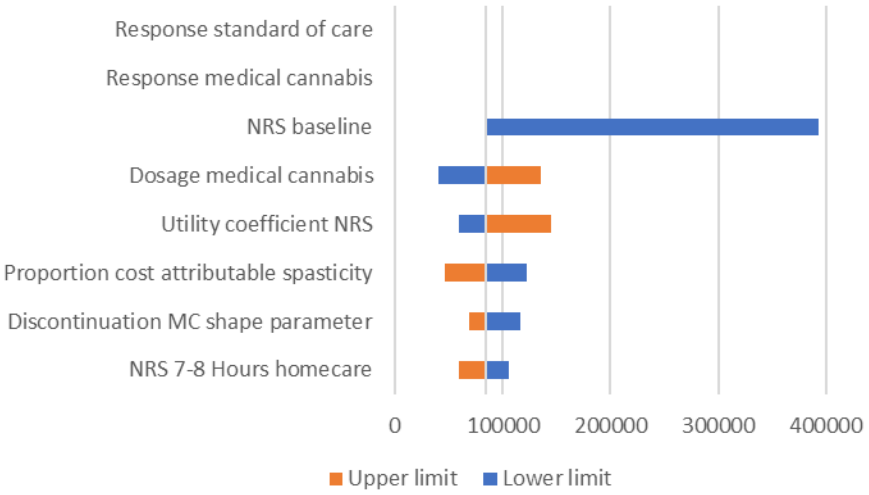
Figure 15. Tornado diagram ICERs – Multiple sclerosis



Keys: NRS = numeric rating scale, MC = medical cannabis (THC:CBD spray)

In Figure 16 the results of the one-way sensitivity analyses for the eight most influential parameters for motor neuron disease spasticity are presented. Treatment response rates were the parameters with the most impact on both incremental QALYs and incremental costs. Furthermore, the baseline NRS spasticity score and the utility decrement per NRS spasticity state had a large impact on incremental QALYs. The baseline NRS spasticity score and the dosage of THC:CBD spray were important variables with regards to incremental costs.

Figure 16. Tornado diagram ICERs – Motor neuron disease



Keys: NRS = numeric rating scale, MC = medical cannabis (THC:CBD spray)

9.2.3 Findings budget impact analysis

In the budget impact analysis, a situation in which THC:CBD spray is reimbursed is compared to the current situation for the years 2022 – 2026. The budget impact analysis was informed by data provided by Swiss experts, on eligible patients and uptake of THC:CBD spray. Data on the projected number of patients with chronic pain and spasticity were provided by three experts, and data on distribution over subpopulations were provided by five (chronic pain) and three (spasticity) experts. Data on uptake in chronic pain were provided by five experts, and data on uptake in spasticity were provided by four experts.

Table 41 presents the estimated number of patients projected to use THC:CBD spray in the period 2022-2026. Due to increasing uptake of THC:CBD spray, the number of users was expected to increase over time. In 2026, over 17’000 patients with chronic pain were expected to use THC:CBD spray if it were to be available on the Swiss market. In addition, over 3’000 patients with spasticity were expected to use

THC:CBD spray if reimbursed. The patient numbers reported indicate the total number of patients that initiated THC:CBD spray use, and thus comprise incidence and prevalence of THC:CBD spray users. For the proportion of patients who discontinue treatment and background medical costs, the cost-effectiveness model inputs were used.

Table 41. Estimated number of patients to use THC:CBD spray in years 2022 through 2026

	2022	2023	2024	2025	2026
Chronic pain					
Neuropathic pain	3'056	3'849	4'642	6'012	7'093
Musculoskeletal pain	4'428	5'577	6'726	8'711	10'277
Spasticity					
Multiple sclerosis	1'564	1'831	2'098	2'293	2'560
Motor neuron disease	304	356	408	446	498

All parameter values, including costs of THC:CBD spray treatment, health state costs, discontinuation and mortality, were derived from the cost-effectiveness model. Patients who discontinued THC:CBD spray treatment, regardless of underlying reason (i.e. death, reduced effectiveness, adverse events), did no longer incur costs of THC:CBD spray from the moment of discontinuation. A 3% discount rate was applied. Table 42 provides the estimated spending on for the THC:CBD spray arm of the model. These costs included costs of THC:CBD spray treatment and background medical costs. The proportion of costs associated to THC:CBD spray differed between the subpopulations and changed over the years (neuropathic pain: 24.8%-28.4%; musculoskeletal pain: 53.6%-58.1%; MS spasticity: 6.2%-7.6%; and motor neuron disease spasticity: 4.3%-6.4%). Background medical costs thus comprised the majority (neuropathic pain, MS spasticity and motor neuron disease spasticity) or a considerable proportion (musculoskeletal pain) of total costs. The majority of these background costs will also be incurred in the scenario without THC:CBD spray.

Table 42. Estimated total costs of THC:CBD spray use, including background medical costs (in CHF)

	2022	2023	2024	2025	2026
Chronic pain					
Neuropathic pain	31'841'461	37'921'329	43'391'721	53'763'994	60'430'582
Musculoskeletal pain	26'416'703	31'065'155	35'406'819	43'774'794	48'981'362
Spasticity					
Multiple sclerosis	103'618'160	129'554'567	153'851'817	194'802'660	225'266'478
Motor neuron disease	4'028'515	3'965'707	3'662'194	3'236'151	3'071'366

The results of the budget impact analysis are presented in Table 43. The budget impact for THC:CBD spray in neuropathic pain patients was estimated to be 8.6 million CHF in 2022, increasing to 15.2 million CHF in 2026. The budget impact for musculoskeletal pain patients increased from 8.3 million CHF in 2022 to 12.9 million CHF in 2026. The rising budget impact was caused by the increasing number of users.

For spasticity patients with MS, the budget impact in 2022 was estimated to be 2.8 million, and was estimated to increase to 4.5 million CHF in 2026. The budget impact for patients with motor neuron disease is expected to be 0.2 million CHF in 2022 and 0.1 million CHF in 2026. The budget impact for patients with spasticity due to motor neuron disease is estimated to decrease over time despite increasing numbers of patients, due to discontinuation and to limited life expectancy in this patient population.

Table 43. Estimated budget impact of THC:CBD spray in addition to SOC compared to SOC alone (in CHF)

	2022	**2023**	**2024**	**2025**	**2026**
Chronic pain					
Neuropathic pain	8'594'223	9'575'058	10'914'803	13'600'193	15'183'981
Musculoskeletal pain	8'253'084	8'231'119	9'338'521	11'722'143	12'888'973
Spasticity					
Multiple sclerosis	2'816'269	2'857'710	3'258'035	4'084'013	4'526'129
Motor neuron disease	173'572	118'900	106'713	89'728	86'231

The budget impact estimates were informed by data retrieved from a limited number of respondents. This resulted in highly uncertain outcomes of this budget impact analyses. Uncertainty existed around both the number of eligible patients and the projected uptake of THC:CBD spray. To assess this uncertainty, input data were varied in scenario analyses, using minimum and maximum values provided by experts (Table 44). Using the minimum values, projected budget impact of reimbursing THC:CBD spray decreased considerably, with reductions in 2026 between 91% (motor neuron disease) and 98% (musculoskeletal pain) compared to mean values. Using maximum values, the projected budget impact would be much larger compared to mean values, with increases of 122% (motor neuron disease) to 496% (neuropathic pain).

Table 44. Minimum and maximum estimated budget impact of THC:CBD spray in addition to SOC compared to SOC alone (in CHF)

	2022	**2023**	**2024**	**2025**	**2026**
Chronic pain					
Minimum BI neuropathic pain	516'694	445'519	417'640	391'627	366'994

Maximum BI neuropathic pain	53’145’647	58’724’240	66’603’527	85’824’579	90’420’809
Minimum BI musculoskeletal pain	489’209	364’686	342’061	318’884	296’715
Maximum BI musculoskeletal pain	36’126’197	35’699’164	40’309’567	52’555’867	53’926’437
Spasticity					
Minimum BI multiple sclerosis	166’937	127’346	120’224	112’202	105’934
Maximum BI multiple sclerosis	12’327’646	12’396’132	14’065’632	18’297’360	18’967’280
Minimum BI motor neuron disease	39’941	20’751	14’705	10’311	7’351
Maximum BI motor neuron disease	380’393	289’953	277’651	222’276	191’703

Keys: BI = budget impact

9.3 Summary statement cost-effectiveness and budget impact

The systematic literature search on the cost-effectiveness of medical cannabis use in chronic pain and spasticity did not provide evidence for Switzerland. Therefore, cost-effectiveness models were developed, characterising the natural history of the disease in a patient’s lifetime in Swiss clinical practice. The models were used to determine the cost-effectiveness of medical cannabis in addition to standard of care (SOC) to SOC alone for all subpopulations for which usable efficacy evidence was available. The absolute change in numeric rating scale (NRS) score was the preferred efficacy outcome measure in chronic pain models, and the proportion of responders at ≥30% reduction in NRS score was the preferred efficacy outcome in spasticity models. Usable efficacy evidence for cost-effectiveness modelling was available for two chronic pain populations (neuropathic pain and musculoskeletal pain) and two spasticity populations (MS and motor neuron disease). These studies reported the efficacy of THC:CBD spray (Sativex®). No usable efficacy data were available for modelling the cost-effectiveness of medical cannabis in cancer pain.

Separate, although similar, cost-effectiveness models were developed for chronic pain and spasticity. Two chronic pain populations (neuropathic pain and musculoskeletal pain) and two spasticity populations (MS and motor neuron disease) were modelled separately. A systematic review was conducted to identify Swiss cost and utility data, however, neither were identified. Instead, expert

opinion and public databases were used to derive Swiss cost inputs. In three models, the effects of THC:CBD spray in addition to SOC compared to SOC alone were modest. In the neuropathic pain model, a small negative effect was found. This negative effect can be explained through two model assumptions concerning the SDs of the treatment effects and the discontinuation of treatment due to adverse events. Furthermore, THC:CBD spray in addition to SOC was associated with increased costs compared to SOC alone in all four models. Incremental cost-effectiveness ratios were 51'038 CHF per QALY for musculoskeletal pain, 54'675 CHF per QALY for spasticity in MS, 84'628 CHF per QALY for motor neuron disease. For neuropathic pain, THC:CBD spray was dominated (i.e. less effective and more costly than SOC alone) due to the small QALY loss. In general, these findings (i.e. modest effects at increased costs) were in concordance with findings from the cost-effectiveness systematic literature search.

Uncertainty in the models was assessed in scenario analyses, one-way sensitivity analyses, and probabilistic sensitivity analyses. Treatment effects, utility values, and NRS baseline scores were important parameters in the cost-effectiveness models. If THC:CBD spray was to be reimbursed, it would be associated with a considerable budget impact for the chronic pain population. For spasticity, the budget impact would be relatively modest. Budget impact estimates were prone to considerable uncertainty. The generalisability of the cost-effectiveness and budget impact estimates to other populations, other medical cannabis products or other routes of administration is unknown.

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10 Legal, social, ethical, and organisational issues

10.1 Methodology legal, social, ethical, and organisational issues

To address the legal, social, ethical, and organisational aspects of medical cannabis in the treatment of chronic pain and spasticity, a grey literature search was conducted. The search was aimed at identifying clinical guidelines and HTA documents by health authorities on the topic of medical cannabis in at least one of the symptoms of interest for this HTA report (i.e. chronic pain and spasticity). Websites of HTA agencies were searched for potentially relevant web-pages and documents, using the websites' database or search bar using combinations of keywords relating to the intervention (cannabis, marijuana, cannabinoids, can-

nabidiol, nabiximols, dronabinol, tetrahydrocannabinol, nabilone, THC:CBD spray, THC, CBD, Sativex, Epidiolex, Cesamet, Marinol). Websites that did not have a database or search bar were searched manually. Reference lists of the included documents were checked to find any other clinical guidelines or HTA documents that were not captured with our web search. Documents identified during the targeted web search were included for data extraction if they met the eligibility criteria as described in Table 45. PRISMA flow charts are not provided given the non-systematic nature of the grey literature search. Each included report was screened for information on legal, social, ethical, and organisational issues or consequences regarding the prescription and reimbursement of medical cannabis. The EUnetHTA Core Model was used to conceptualise the four HTA domains, i.e. the description and questions provided in the EUnetHTA Core Model were used as framework for the screening of documents. The results of the literature searches were summarised using narrative synthesis.

Table 45. Inclusion and exclusion criteria applied during the grey literature search

Inclusion
Published by a government or non-governmental organisations (NGO) at either the regional, national or international level
Available in English, Dutch, German, or French
Evidence-based clinical guideline or HTA document on medical cannabis in at least one of the following symptoms: chronic pain, spasticity
Exclusion
Document was a draft or summary version or has been replaced with another document
Newsletters, news releases, or memoranda

10.2 Results legal, social, ethical, and organisational issues

Reports from 13 different institutes in Europe, Australia, Canada, and the USA were found with the grey literature search. A total of 16 documents were included. Seven reports covered a range of symptoms or diagnoses for which medical cannabis can be prescribed, whereas eight reports focused on a specific indication of medical cannabis. Medical cannabis use in chronic pain was addressed in 10 documents and 13 documents evaluated medical cannabis use in spasticity (Appendix 15.10). All included reports were published between 2016 and 2019. The findings on legal, social, ethical and organisational issues are described below. However, the issues identified in the documents were not specific to pain or spasticity populations, nor were they specific for THC:CBD spray. Hence, the results should be interpreted as general issues that may need to be considered when allowing the use of cannabis for medical purposes. The relevance of each issue may differ depending on the medical cannabis products and/or patient population

concerned. Furthermore, while the issues may provide valuable input beyond its original place of origin, it should be noted that issues can be specific to a particular context (i.e. law, culture, healthcare system, epidemiology) and transferability may be limited in these cases.

10.2.1 Findings legal issues

According to the EUnetHTA Core Model, the objective of the legal domain is to identify rules and regulations that need to be considered when evaluating the healthcare technology.[40] This information should provide insight into the areas of healthcare legislation in need of harmonisation, and delivers tools for legislative and policy reforms. As the Swiss medical cannabis legislation is currently being reviewed, the legal analysis will be targeted at identifying general legal barriers to reimbursing medical cannabis that are not specific to the Swiss context.

Four documents discussed legal issues or provided information on regulatory regimes in place to allow the use of medical cannabis in various countries. In July 2018, the FOPH announced its intention to broaden access to medical cannabis, and a new law was proposed in 2019.[89] Laws that may need to be considered when broadening patient access include laws on drugs and psychoactive substances, as well as regulations on quality control and marketing.

Drug laws

In general, national drug laws are in place to ensure that patients have access to high-quality, safe and effective medicines. As medical cannabis contains substances that may produce psychoactive effects, additional restrictions may apply under laws such as Controlled Substances Act (USA)[15], Opioid act (the Netherlands), or Misuse of Drugs act (Ireland).[90] If a country considers to permit the use of cannabis for medicinal purposes, such regulations need to be taken into account as these may affect the import, production, supply and possession of medical cannabis. The legal framework for allowing medical cannabis differs across countries, as can be observed from the overviews of regulatory regimes documented in the EMCDDA (European Monitoring Centre for Drugs and Drug Addiction) report and the HPRA (Health Products Regulatory Authority, Ireland) reports on medical cannabis.[89,90] Some countries restrict the products that can be used to pharmaceutical-quality cannabinoids or standardised plant extracts[89] which may be supplied through the regulated pharmacy system. Other countries initiated government-run programs to supply quality-controlled cannabis[91], and/or allow patients to grow their own cannabis. In many cases, growing, processing and supply of medical cannabis are controlled and operated under government tenders supervised by the Health Ministry.[90] The HPRA recommends that one should be careful with circumventing

the medicines regulatory system in order to prevent unintended consequences and lower standards of patient protection.

In Chapter 5, an outline is provided of different European countries which allow or consider allowing cannabis to be used for medical purposes. Information on the consequences of the various regimes on patients access to medical cannabis is described under the domain social issues.

Quality control of medical cannabis products

Regulations are required to ensure that the medical cannabis products supplied are of standardised quality. Questions that arise when cannabis is to be prescribed for medicinal purposes include what type of quality standards should be applied, if cannabis may be grown at home, for which products quality standards will be applicable and how these will be put into effect. Some countries restrict the cannabis products that can be used to pharmaceutical-quality cannabinoids or standardised plant extracts.[89] For these products, the APPG (All-Party Parliamentary Group, UK) advices that as a minimum requirement the proportion and dosage of CBD and THC should be clearly labelled, so that the prescriber can easily determine these doses.[22] Additional requirements that may be considered for medical cannabis products are listing any other minor cannabinoids and terpenes and presenting a Certificate of Analysis.

Marketing

Over the past few years, various cannabis-based products (i.e. tea, oils, gum, lotions) have been brought on the market.[89] As these products contain a very low level of THC (i.e. below the legal minimum level), they are not restricted under national drug laws as they would have little or no psychoactive effect. Rather, these products may claim to have a high level of CBD, which is not controlled under drug law in most countries. The suggestion may however be made that these low-THC / high-CBD products would be beneficial for treating a wide range of illnesses or symptoms for which there is currently insufficient evidence to make proper assessments. For example, marketing of these products could contain non-specific words or phrases, such as ‘health and well-being’, ‘wellness’, or ‘nutraceuticals’. More substantial claims, i.e. that the product prevents or treats disease or relieves symptoms, would bring these products under medicines law and a license for sale would then be required.[89] It should be clear to consumers that these products, which are readily available in a wide range of shops[22], have not been assessed for use for medical purposes. Food safety and other regulations may be required to regulate these products to ensure that they contain what it is claimed.[89] Advertising of unlicensed products can be prohibited.

10.2.2 Findings social issues

The EUnetHTA Core Model describes the social domain as involving issues relevant to the receivers of the healthcare technology and their caregivers (patient aspect) as well as issues related to broader social groups such as elderly, ethnic minorities, or people with learning disabilities (social aspect).[40] The social domain covers issues regarding experiences, expectations and perceptions of patients, as well as caregiver burden, accessibility of the intervention, and adherence.

Three documents addressed social issues that are relevant when considering reimbursement of medical cannabis. The discrepancy between scientific research and public perception is described, as patient experiences and patient expectations regarding the effectiveness of medical cannabis might not be substantiated by scientific evidence. Consequently, as scientific data are mandatory to determine the role of cannabis as a medicine, patients with an unmet medical need might not have access to medical cannabis even though they expect to benefit from it.

Patient aspects

The HPRA addressed a gap between *"the public perception of effectiveness and safety, and the position of many medical experts that further scientific research is required to determine the role of cannabis as a medical treatment"*.[90] While the public interest in medical cannabis is generally acknowledged, the patient demand may have been sparked by compelling anecdotal reports of effectiveness in individual patients rather than on scientific research. That is, while popular media refers to a growing body of evidence regarding the effectiveness of medical cannabis, the HPRA points to the limitations of the scientific data and notes that at the time of writing (2017) the effectiveness of medical cannabis has not yet been proven for a large number of medical conditions. After reviewing access programs for medical cannabis use, the HPRA concluded that changes in this field have been led by patient demand rather than requests from healthcare professionals. At the same time, the Medical Cannabis Clinicians Society (MCCS) (UK) points out it should not be lightly missed that cannabis has been used for centuries by many millions of people and that much is known about efficacy and side-effects from this accumulated experience.[22] In contrary, the EMCDDA report describes that while several pharmaceutical cannabinoids have been approved for medical use, these are generally not widely used because patients find it difficult to achieve the desired therapeutic benefits without also experiencing unwanted psychoactive side-effects.[89]

Social group aspects

The EMCDDA described that in Europe access to medical cannabis is usually granted for the treatment of a narrow range of medical conditions. As many governments are faced with demand from patients who want to use cannabis and cannabinoids to treat symptoms of illnesses for which there is currently little or no evidence of efficacy or safety, patients with these conditions may resort to black market cannabis products. In some countries this has led to the development of special access schemes to allow unauthorised medical cannabis products on prescription. However, the accessibility through these schemes may be hindered by physicians' reluctance to prescribe cannabis for ethical and medico-legal reasons. Furthermore, the access to medical cannabis can be influenced by the burden of the approval processes, the quality and the cost of the cannabis and cannabinoids that are available, and restrictions on the cannabis products that they are allowed to use.

10.2.3 Findings ethical issues

The ethical domain is described in the EUnetHTA Core Model as considering the consequences of implementing or not implementing a healthcare technology with regard to prevailing societal values (shaped by the socio-political, cultural, legal, religious, and economic context) and with regard to the unintended consequences that may arise in the use of the specific healthcare technology.[40] Ethically relevant issues and conflicts may include medicalisation, trade-offs between benefit and harms, distribution of health care resources, and impact on broader outcomes (i.e. wellbeing, working, social, and family life). The ethical domain may overlap with the evaluation of legal, patient's, and social aspects (legal and social domains). For this ethical analysis, the impact of medical cannabis on public health will be the main focus.

Illicit use

Cannabis is the most commonly used illicit drug in Europe with the prevalence of cannabis use being about five times higher than that of other substances among people entering addiction services.[89] The risk of abuse of medical cannabis should therefore be considered when intending to broaden access. More particularly, medical cannabis programmes have been reported as a major source for the drug's illicit use in the USA, particularly among young people.[90] According to the WHO, there is strong scientific support for concluding that cannabis has high potential for abuse and is addictive[90], and as such, normalisation of cannabis use might lead to unintended consequences. Citing a study from Volkow et al., the HPRA drew a comparison with alcohol and tobacco: it is not the increased toxicity, but rather the easy access and widespread availability that make these drugs account for the greatest burden to society. As broader access to

medical cannabis may lead to an increase in recreational use of cannabis through diversion to non-authorised individuals, the societal impact should be taken into account.

Black market

If patients with an unmet medical need find it difficult to legally obtain cannabis for medical purposes, they may resort to the black market.[89] A potential risk of resorting to the black market is that medical cannabis might turn into a 'gateway drug', as patients may have more opportunities to use other illicit drugs when these are supplied by the same black market as cannabis.[90] The risk of resorting to black market cannabis products should therefore be considered as an unintended consequence when patients cannot obtain cannabis for medicinal purposes legally.

Substitution for other drugs

It has been suggested that medical cannabis may substitute drugs with more severe side-effects, such as other analgesics (i.e. opioids) in people with chronic pain. While a study from the USA found indications that medical cannabis laws might be associated with a temporal lower rate of opioid overdose deaths, further research is needed to confirm these findings as it is uncertain whether other state-specific factors might have contributed.[89] Furthermore, rather than substituting other analgesics as fully, medical cannabis may be viewed as add-on to existing treatment, with the potential to lower the required dose of other analgesics.

Vulnerable populations

The HPRA warns that while increasing access to medical cannabis may benefit individual patients that have an unmet medical need, unintended consequences may arise including a negative impact on vulnerable populations who are at increased risk of both short-term and long-term side-effects, resulting in a negative impact on public health.[90] Adolescents have been identified as a vulnerable population, as a small number of studies investigating sustained (recreational) cannabis use in young adults suggest that the age of onset is a critical factor for potential adverse effects on brain development and cognitive function.[89,90] However, there are only few prospective studies on this matter, and the risks of recreational and/or chronic use of cannabis may not necessarily be transferable to the use of medical cannabis products by patients[90]. Another population that may be particularly vulnerable are people with pre-existing cognitive dysfunction, as cognitive impairment is considered to be one of the key safety issues with cannabis use outside the setting of clinical trials. Finally, people with a history of psychosis disorders (i.e. schizophrenia) or with a genetic predisposition to psychosis can be regarded a vulnerable population, as continued medical cannabis use

might be associated with a high number of relapses, hospital admission, and more severe positive symptoms (i.e. hallucinations or delusions).[90] The risk for relapse in patients with psychosis and for developing psychosis in people with a genetic predisposition, respectively, mainly depends on the frequency of use, the potency of the cannabis product (THC-rich) and the THC:CBD ratio.[92] However, for studies assessing impaired cognitive functioning and psychotic disorders in relation to cannabis, difficulties in accounting for important confounders occur and reverse causation is generally difficult to exclude. Nevertheless, when allowing medical cannabis for children or adolescents, patients with a (history of) psychiatric disorders or patients with a genetic predisposition to psychosis disorders, the pharmacological effects of the individual cannabinoids should be further considered given the potential effects on the development of psychosis disorder, worsening of symptoms, and effects on cognitive function.

Quality of scientific evidence

Preservation of blinding might be an issue in studies investigating medical cannabis. While placebo products are available that mimic the smell of medical cannabis, the psychoactive and vasoactive effects pose a considerable challenge for effective blinding, as study participants who experience these adverse events may surmise that they are receiving medical cannabis and not a placebo.[15] Strategies to promote effective blinding exist. For example, a higher ratio of CBD to the concentration of THC may reduce the psychoactive effects of THC. Furthermore, the effectiveness of blinding might be assessed by asking study participants to guess to which study arm they are randomised. However, by asking this question study participants might infer that attempts of blinding were ineffective which may in turn make the study results invalid. As the NASEM (National Academies of Sciences, USA) summarises, whether or not investigators applied these methods, study results of medical cannabis studies are at risk of being undermined. Asking study participants to guess their study-arm might uncover concerns on unmasking, while journal reviewers might discount study results if such tests were not conducted under the assumption that unmasking cannot be ruled out.

10.2.4 Findings organisational issues

The organisational domain of the EUnetHTA Core Model encompasses the ways in which different kinds of resources need to be mobilised and organised when implementing a technology, as well as the consequences the health technology implementation may have for the organisation and the health care system as a whole.[40] Organisational issues may include the process of health delivery (i.e. work processes, patient

flow, quality assurance, communication, co-operation) and organisation of the health care system (i.e. sustainability, centralisation, accessibility, allocation of resources). As the budget impact of technology implementation is described in Chapter 9, this will not be explored as part of the organisational domain.

Two organisations described organisational issues that may arise when cannabis is to be allowed for medicinal purposes. Aspects that need to be considered when organising medical cannabis on prescription include deciding on the access scheme, controlling the quality of medical cannabis products, and educating prescribing physicians.

Schemes for allowing patient access

There is considerable variation between countries in the approaches taken to organise access to cannabis for medicinal purposes, reflecting a variety of historical and cultural factors. In most countries, the provision of cannabis and cannabinoid products and preparations for medical purposes has evolved over time, often in response to patient demand or product developments, and the situation continues to change rapidly. In general three broad types of approach can be seen, however, often countries will use more than one of these in parallel: 1) Allowing the use of medicinal products containing cannabinoids, 2) Allowing the medical use of unauthorised products or preparations, 3) De novo stand-alone medical cannabis programmes.[89] Depending on how access to medical cannabis is organised, the issues described in this chapter might be of more or less relevance. For example, when unauthorised products or preparations are allowed, questions need to be answered on whether patients are allowed to grow their own cannabis for medical purposes, whether and how the quality of these products will be controlled, and how physicians may prescribe these products. When medicinal cannabis preparations are allowed, the distribution of products should be decided on (i.e. through any pharmacy, through specific pharmacies, or other distribution channels), and pharmacovigilance schemes need to be considered. In all cases, one should think of how medical cannabis fits into existing treatment, whether and how prescriptions should be limited, and whether, how and by whom monitoring of patients (i.e. effects and adverse events) should be carried out to strengthen the evidence base.[89]

Education of physicians

The EMCDDA and HPRA referred to studies which indicate that healthcare professionals are cautious of recommending cannabis for medical use. Physicians may be reluctant to prescribe cannabis for ethical reasons (i.e. concerns about the mental health consequences of cannabis use, and the potential for misuse

and abuse) or for medico-legal reasons (i.e. are they liable for any harms that the patient may experience).[89,90] Moreover, especially when prescribing cannabis preparations, physicians might be uncertain about for which clinical indications medical cannabis should be used, in what doses, and for how long.[89] Therefore, when allowing the prescription of medical cannabis, guidelines and training of physicians might be required to ensure medical cannabis is prescribed appropriately.

10.3 Summary statement legal, social, ethical, and organisational issues

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When considering reimbursement of medical cannabis for certain populations, relevant legal, social, ethical, and organisational issues should also be considered. For example, reimbursement of medical cannabis may provoke legal issues as the cultivation, consumption, distribution, and reimbursement of medical cannabis will be subject to different laws in Switzerland which are interconnected. In addition, it should be noted that a change in the reimbursement policy of medical cannabis may have social and ethical consequences including the gap between patient expectations and scientific evidence, accessibility restrictions, vulnerable populations at risk of unintended consequences, and illicit use. Furthermore, organisational challenges may arise in the supply and quality control of medical cannabis products. It should be noted that the applicability of the issues identified might differ depending on the context, for instance on the type of medical cannabis product, on the national laws, and on the organisation of the healthcare system.

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11 Additional issues

Due to our broad search for legal, social, ethical, and organisational issues related to medical cannabis, no additional issues were encountered that were not already covered in the previous chapters.

12 Discussion

The present HTA evaluated the efficacy, safety, cost-effectiveness, and budget impact of medical cannabis compared to placebo, no treatment, or standard of care, in patients of all ages with chronic pain or spasticity,

based on available scientific literature. In this section, the main strengths, limitations, and evidence gaps of this HTA are discussed.

12.1 Strengths

One of the main strengths of this HTA is the systematic literature search for studies on the efficacy, safety, and cost-effectiveness of medical cannabis for chronic pain and spasticity in multiple peer-reviewed scientific literature databases. A rigorous methodology, adhering to international methodological standards such as Cochrane and PRISMA, was applied to identify, critically appraise, analyse, and summarise pertinent evidence on predefined outcomes of interest in order to minimise bias. Another strength of this HTA is that the cost-effectiveness modelling was performed specifically for the Swiss context. This was an improvement compared to previous cost-effectiveness studies for numerous reasons, including the use of a lifetime horizon, using up-to-date and, where possible, Swiss-specific clinical and economic input parameters, model input provided by the SR on the efficacy and safety of medical cannabis for chronic pain and spasticity, and accompanied with extensive scenario and sensitivity analyses. Finally, this HTA provided an overview of relevant legal, social, ethical, and organisational issues regarding the use of cannabis for medical purposes.

12.2 Limitations

The efficacy and safety data reported in the included studies were heterogeneous (i.e. between studies in outcomes and outcome measures), incomplete (i.e. studies omitting to report detailed results such as treatment effects in the intervention and placebo arms or measures of variability), inconsistent (i.e. studies with comparable patient populations and similar type of medical cannabis did not show consistent results), and inconclusive (i.e. none of the studies were able to draw a definitive conclusion on the efficacy of medical cannabis).The incompleteness and heterogeneity of the data precluded the calculation of pooled estimates. Furthermore, unpredictable bias and uncertainty in the evidence base arise in research on medication with a characteristic well-known adverse event profile like medical cannabis (e.g. dizzy/light-headedness, fatigue, ‘feeling high’). Since these adverse events may occur in both the medical cannabis arm as well as in the SOC arm (e.g. these complaints may occur due to the underlying disease or as side-effect of other drugs patients use), this possibly leads to patients speculating about their treatment allocation. Adding to this, the SR on the efficacy of medical cannabis shows that up to half of the patients in the SOC group reaches the ≥30% response criterion which may suggest a considerable placebo effect. The patient-reported outcomes for the symptoms chronic pain and spasticity further increased this unpredictability and

uncertainty, however, no fully objective measures are available for these symptoms. Hence, future studies on medical cannabis in these symptoms will likely be exposed to similar challenges and limitations, of which only part can be solved with improved study designs and complete reporting of results. While the various factors described here increase the risk of bias, the extent as well as the direction of the potential bias are difficult to comprehend.

Due to the limited available data and other limitations, the cost-effectiveness model represents a simplification of the complex reality of the symptoms chronic pain and spasticity. Information on treatment response was based on the SR on the efficacy, and safety of medical cannabis for chronic pain and spasticity, and consequently was prone to the limitations described above. Furthermore, when input for a certain parameter was not available for the subpopulations musculoskeletal pain and motor neuron disease, the input from the neuropathic pain and MS cost-effectiveness models were assumed, respectively which introduces additional uncertainty. Finally, assumptions had to be made on various important model input parameters, particularly concerning (distribution of) treatment effects, discontinuation, disease progression, resource use, and utility estimates, which could not be based on input specific to the Swiss system. The most important assumptions were therefore assessed in scenario analyses and parameter uncertainty was assessed in sensitivity analyses.

The budget impact estimates had to be based on expert opinion, since other data sources were not available. Only a few experts who were approached for providing input for the budget impact analysis were able to provide estimates on the prevalence of the studied symptoms chronic pain and spasticity or on the expected uptake of THC:CBD spray. Furthermore, the legal, social, ethical, and organisational issues identified were not specific for the products and symptoms studied within this HTA report, nor where they specific for the Swiss situation. Hence, the applicability of each issue to the current research question is unknown. Furthermore, given the non-systematic approach of the literature search for these domains, not all relevant consequences might have been identified.

Finally, it should be noted that THC and CBD can trigger a variety of physiological actions and medical cannabis may therefore have a health effect beyond the dimensions of pain or spasticity alone (i.e. beneficial side-effects, for example on sleep). This HTA report was focused on the use of medical cannabis for treating pain and spasticity, and additional effects were therefore not investigated in the SR nor were they captured in the cost-effectiveness estimates.

12.3 Evidence gaps

The evidence base for the use of medical cannabis was lacking for the symptoms nausea and vomiting and unintentional weight loss, and therefore complete data extraction and cost-effectiveness modelling was not performed. Moreover, no studies were included in the SR on efficacy and safety of medical cannabis that examined botanical cannabis or its crude extract. Furthermore, to proceed with cost-effectiveness modelling a decision had to be made on the preferred outcome measure of efficacy and after selecting the articles with (complete) data on the specified outcome measure only studies evaluating THC:CBD spray remained. As a result, the cost-effectiveness model and budget impact analysis evaluated only one isolated medical cannabis product. Also, no other route of administering cannabis was explored apart from the oromucosal route. Thus, it is unknown if the findings of this HTA will be generalisable to patients who use different medical cannabis preparations or different routes of administration.

13 Conclusions

While the research question encompassed all chronic pain populations and all spasticity populations there was only sufficient evidence to assess the efficacy and safety of the use of medical cannabis for patients with neuropathic pain, musculoskeletal pain, cancer pain, spasticity in MS and spasticity in motor neuron disease. However, due to incomplete, inconclusive, and inconsistent study findings, no conclusions could be drawn on the efficacy and safety of medical cannabis in these patient populations. Cost-effectiveness modelling was performed for THC:CBD spray only (2.7mg THC / 2.5mg CBD), and resulted in a minimal QALY loss for neuropathic pain and only small QALY gains for musculoskeletal pain, MS spasticity, and motor neuron disease spasticity, combined with higher costs in all models compared to SOC alone. ICERs ranged from THC:CBD spray being dominated by SOC alone for neuropathic pain (i.e. more costly and less effective) to 51’038 CHF per QALY for musculoskeletal pain. The time horizon, discounting, discontinuation, effectiveness of THC:CBD spray in reducing NRS pain or spasticity scores, and the costs of THC:CBD spray had the largest impact on the cost-effectiveness estimates. If THC:CBD spray was to be reimbursed, the projected estimated budget impact would be substantial for neuropathic pain, whereas the budget impact for musculoskeletal pain, MS spasticity, and motor neuron disease would be limited. Besides the patient population for which THC:CBD spray is reimbursed, the budget impact depends on the uptake of THC:CBD spray in real-life (i.e. what proportion of eligible patients would be interested in getting THC:CBD spray prescribed). Data on these aspects is scarce and had to be based on projections from experts, which

increases the uncertainty surrounding the estimated budget impact. The generalisability of the cost-effectiveness and budget impact estimates to other medical cannabis products or other routes of administration is unknown.

When considering reimbursement of medical cannabis for certain patient populations, relevant legal, social, ethical, and organisational issues should also be considered. For example, reimbursement of medical cannabis will be subject to different and interconnected Swiss laws with regard to cultivation, consumption, distribution, and prescription. In addition, reimbursement of medical cannabis may have social and ethical consequences, for example as a result of a gap between patient expectations and scientific evidence. Other concerns include accessibility restrictions, vulnerable populations at risk of unintended consequences, and illicit use. Furthermore, organisational challenges may arise in the supply and quality control of medical cannabis products.

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

91. 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. Accessed from https://pubmed.ncbi.nlm.nih.gov/29119763/

92. Forti MD, Quattrone D, Freeman TP, et al. The contribution of cannabis use to variation in the incidence of psychotic disorder across Europe (EU-GEI): a multicentre case-control study. *The Lancet Psychiatry*. 2019;6(5):427-436. doi:10.1016/S2215-0366(19)30048-3

15 Appendices

15.1 Search strategy efficacy, effectiveness, and safety

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

	Medical cannabis for chronic pain	**Medical cannabis for spasticity**
Population	"Chronic Pain"[Mesh] OR "Analgesia"[Mesh] OR pain*[tiab] OR analgesia[tiab]	"Muscle Spasticity"[Mesh] OR spastic*[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 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 doubleblind*[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.com

	Medical cannabis for chronic pain	**Medical cannabis for spasticity**
Population	'chronic pain'/exp OR 'analgesia'/exp OR pain*:ti,ab OR analgesia:ti,ab	'spasticity'/exp OR spastic*: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 doubleblind*: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)

15.2 Excluded RCTs efficacy, effectiveness, and safety

Table I. Excluded RCTs found with the efficacy, effectiveness, and safety systematic literature search on medical cannabis use for 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
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.	Cross-over trial without washout periods
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
De Vries M, van Rijckevorsel DCM, Vissers KCP, Wilder-Smith OHG, van	Small sample size (n<50) & no sufficient size

Goor H. 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.	as in power calculation
Ellis RJ, Toperoff W, Vaida F, Van Den Brande G, Gonzales J, Gouaux B, et al. Smoked medical cannabis for neuropathic pain in HIV: A randomized, crossover clinical trial. Neuropsychopharmacology. 2009;34(3):672-80.	Short treatment duration (<2 weeks)
Frank B, Serpell MG, Hughes J, Matthews JNS, 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.	No useful results for efficacy
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 excluded 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)
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. J Pain Symptom Manage. 2014;47(1):166-73.	Small sample size (n<50) without power calculation

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 Esophagus. 2017;30(2).	No useful results for efficacy
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
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. Wien Klin Wochenschr. 2006;118(11-12):327-35.	Small sample size (n<50) without power calculation
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.	No efficacy data reported for the complete group of patients, only stratified for different doses
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 / Association of Academic Physiatrists. 2010;89(10):840-8.	Small sample size (n<50) without power calculation
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.	Non-comparative extension trial and no useful results for safety
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 arms 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.	Subjects were titrated up on medical cannabis over 4 weeks, of which only the last week of treatment was at 1 mg twice daily
Svendsen KB, Jensen TS, Bach FW. Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? Randomised double blind placebo controlled crossover trial. British Medical Journal. 2004;329(7460):253-7.	Small sample size (n<25) with power calculation
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.	Small sample size (n<50) & no sufficient size as in power calculation
Turcotte D, Doupe M, Torabi M, Gomori A, Ethans K, Esfahani F, et al. Nabilone as an adjunctive to gabapentin for multiple sclerosis-induced neuropathic pain: a randomized controlled trial. Pain Med. 2015;16(1):149-59.	No data on review objectives
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
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. Mult Scler. 2004;10(4):434-41.	Small sample size (n<50) & no sufficient size as in power calculation
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. Clin Rehabil. 2003;17(1):21-9.	Small sample size (n<50) without power calculation
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	No data on review objectives

Neuropathic Pain. Journal of Pain. 2008;9(6):506-21.	
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
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 : a double-blind placebo-controlled cross-over trial. J Neurol. 2006;253(10):1337-41.	Small sample size (n<50) without power calculation
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 efficacy, effectiveness, and safety systematic literature search on medical cannabis use for spasticity symptoms

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
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)
Farrar JT, Troxel AB, Stott C, Duncombe P, Jensen MP. Validity, reliability, and clinical importance of change in a 0-10 numeric rating scale measure of spasticity: a post hoc	No data on review objectives

analysis of a randomized, double-blind, placebo-controlled trial. Clinical Therapeutics. 2008;30(5):974-85.	
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. 2007;45(8):551-62.	No data on review objectives
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.	Small sample size (n<50) without power calculation
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. J Neurol. 2015;262(11):2520-7.	Small sample size (n<50) & no sufficient size as in power calculation
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. Int J Neurosci. 2019;129(2):119-28.	High risk of selection bias and no useful results for efficacy
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
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. Eur J Neurol. 2011;18(9):1122-31.	High risk of selection bias and 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.	Small sample size (n<50) without power calculation
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. Arch Phys Med Rehabil. 2010;91(5):703-7.	Small sample size (n<50) without power calculation
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.	Non-comparative extension trial and no useful results for safety
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.	Small sample size (n<25) with power calculation

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. Mult Scler. 2004;10(4):417-24.	Small sample size (n<50) without power calculation
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. Mult Scler. 2004;10(4):434-41.	Small sample size (n<50) & no sufficient size as in power calculation
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 excluded RCT
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. Clin Rehabil. 2003;17(1):21-9.	Small sample size (n<50) without power calculation
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)

15.3 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**
Population	"Chronic Pain"[Mesh] OR "Analgesia"[Mesh] OR pain*[tiab] OR analgesia[tiab]	"Muscle Spasticity"[Mesh] OR spastic*[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**
Population	'chronic pain'/exp OR 'analgesia'/exp OR pain*:ti,ab OR analgesia:ti,ab	'spasticity'/exp OR spastic*:ti,ab
Intervention:	'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-	

cannabis	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 III. 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"

15.4 Excluded economic evaluations cost-effectiveness

Table I. Excluded economic evaluations of medical cannabis use in 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 of medical cannabis use in 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

15.5 Non-systematic search of Swiss utility and resource use inputs

15.5.1 Methods search for Swiss resource use

To identify the most recent Swiss cost data available to use as input in the cost-effectiveness model, a comprehensive search for resource use and costs data of medical cannabis in Switzerland was performed. This Appendix provides more information on the methods and the results of this search. The tables below show the search strings that were utilised to conduct the systematic search.

Table I. Search string costing studies PubMed

PubMed (MEDLINE)	Costing studies
Medical 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]
Costing studies	((economics OR "economic aspect" OR cost OR "health care cost" OR "drug cost" OR "hospital cost" OR socioeconomics OR "health economics" OR "pharmacoeconomics" OR "fee" OR "budget" OR "eco-nomic evaluation" OR "hospital finance" OR "financial management" OR "health care financing") OR ("healthcare costs" OR (healthcare AND cost) OR fiscal OR funding OR financial OR finance) OR ((cost AND estimate*) OR "cost estimate" OR "cost variable" OR (unit AND cost)) OR (economic* OR pharmacoeconomic* OR price* OR pricing) OR ((healthcare OR "health care") AND (utilisation OR utilisation)) OR (cost* AND (treat* OR therap*)) OR ((direct OR indirect) AND cost*) OR ("resource use" OR "resource utilisation" OR "resource utilisation") OR ("treatment costs" OR "costs of treatment" OR "cost of treatment" OR "costs of therapy" OR "cost of therapy" OR "cost of treating"))
Country	Switzerland[tiab] OR Swiss[tiab]
Period	N/A
Hits	2

Table II. Search string costing studies Embase.com

EMBASE.com	**Costing studies**
Medical 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
Costing studies	Economics/exp OR Cost/exp OR 'Health Economics'/exp OR Budget/exp OR budget*:ab,ti OR (economic* OR cost OR costs OR costly OR costing OR price OR prices OR pricing OR pharmacoeconomic* OR pharmaco-economic* OR expenditure OR expenditures OR expense OR expenses OR financial OR finance OR finances OR financed):ab,ti OR (economic* OR cost OR costs OR costly OR costing OR price OR prices OR pricing OR pharmacoeconomic* OR pharmaco-economic* OR expenditure OR expenditures OR expense OR expenses OR financial OR finance OR finances OR financed):ab,ti OR (cost* adj2 (effective* OR utilit* OR benefit* OR minimi* OR analy* OR outcome OR outcomes)):ab,ti OR (value adj2 (money OR monetary)):ab,ti
Country	Switzerland:ab,ti OR Swiss:ab,ti

Period	N/A
Hits	256

15.5.2 Results search for Swiss resource use

The selection of studies is illustrated in Figure I. The references and decisions of the 4 studies that were included in the full-text screening are reported in Table III. None of the studies that were included in the full-text screening reported Swiss cost data. Hence, we did not extract any data from the identified studies.

Figure I. PRISMA flowchart studies on healthcare costs

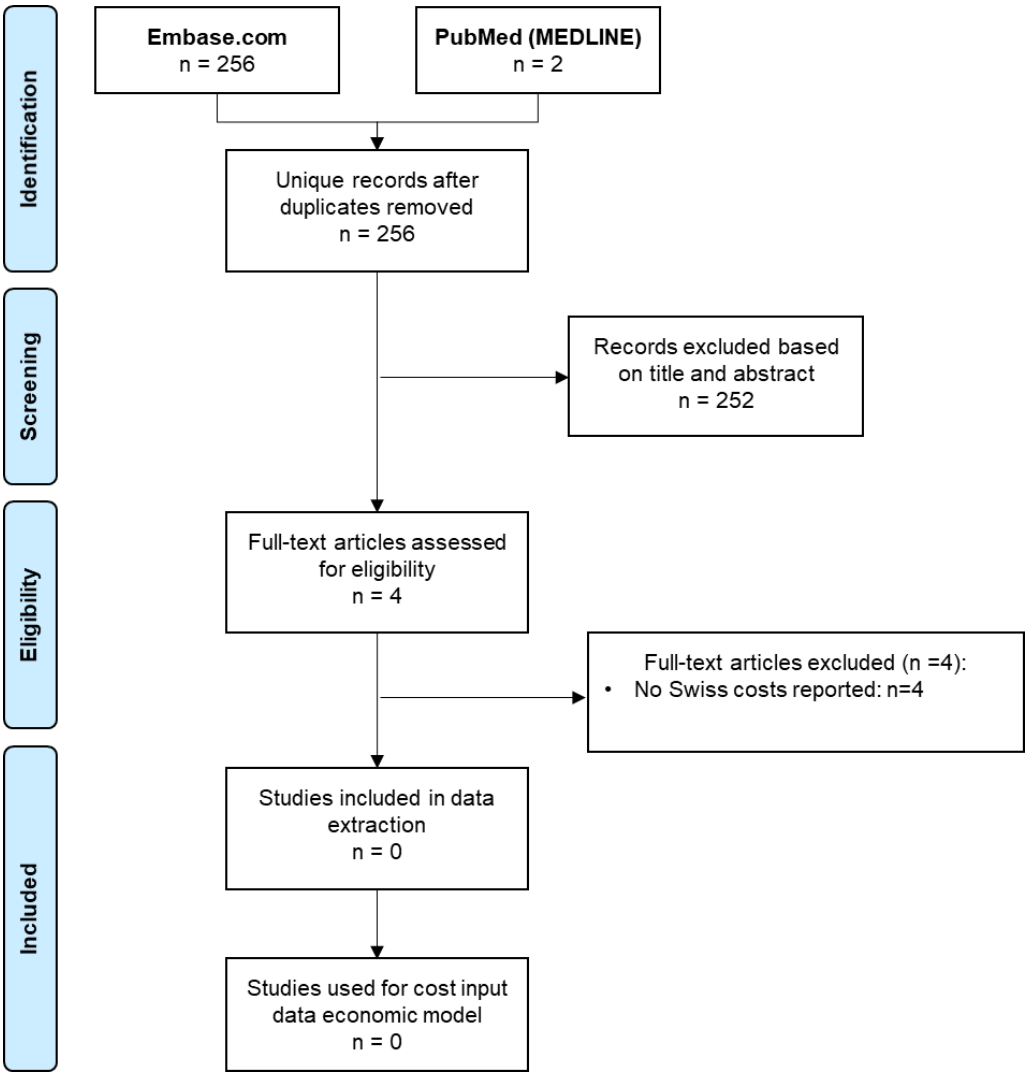


Table III. References and decisions of studies included in full-text screening of healthcare costs systematic literature search

Reference	Decision
Elliott, J., McCoy, B., Clifford, T., Potter, B. K., Wells, G. A., & Coyle, D. (2020). Economic Evaluation of Cannabinoid Oil for Dravet Syndrome: A Cost-Utility Analysis. *PharmacoEconomics*, 1-10.	Exclude: no Swiss specific cost data
Mantovani, L. G., Cozzolino, P., Cortesi, P. A., & Patti, F. (2020). Cost-Effectiveness Analysis of Cannabinoid Oromucosal Spray Use for the Management of Spasticity in Subjects with Multiple Sclerosis. *Clinical Drug Investigation*, 1-8.	Exclude: no Swiss specific cost data
Neuberger, E. E., Carlson, J. J., & Veenstra, D. L. (2020). Cost-Effectiveness of Cannabidiol Adjunct Therapy versus Usual Care for the Treatment of Seizures in Lennox-Gastaut Syndrome. *PharmacoEconomics*, *38*(11), 1237-1245.	Exclude: no Swiss specific cost data
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.	Exclude: no Swiss specific cost data

15.5.3 Methods search for Swiss utility values

To identify the most recent Swiss utility data available to use as input in the cost-effectiveness model, a comprehensive search for baseline utilities for patients receiving medical cannabis and disutilties associated with (serious) adverse events in Swiss patients was performed. The search terms are provided in Table IV and Table V. A search filter for utilities was added to the clinical search strings regarding medical cannabis. The search filter for utilities were based on the search string that was developed by CADTH to identify studies on the health utilities and/or quality of life of patients in Medline and Embase.[f]

Table IV. Search terms utilities PubMed

PubMed (MEDLINE)	HRQoL studies
Medical 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

[f] https://www.cadth.ca/resources/finding-evidence/strings-attached-cadths-database-search-filters#eco

	syndros[tiab] OR tetrahydrocannabivarin[tiab] OR THC:CBD spray[tiab]
HRQoL/Utilities	“Quality of Life"[Mesh] OR “Value of Life”[tiab] OR “Quality of Life”[tiab] OR utilit*[tiab] OR disutilit*[tiab] OR eq5d[tiab] OR “eq 5d”[tiab]
Country	Switzerland[tiab] OR Swiss[tiab]
Period	N/A
Hits	2

Table V. Search terms utilities Embase.com

EMBASE.com	**HRQoL studies**
Medical 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
HRQoL/Utilities	‘quality of life’/exp OR ‘Value of Life’:ab,ti OR ‘Quality of Life’:ab,ti OR utilit*:ab,ti OR disutilit*:ab,ti OR eq5d/exp OR eq5d:ab,ti OR ‘eq 5d’:ab,ti
Country	Switzerland:ab,ti OR Swiss:ab,ti
Period	N/A
Hits	223

15.5.4 Results search for Swiss utility values

The selection of studies is illustrated in Figure II. The references and decisions of the 4 studies that were included in the full-text screening are reported in Table VI. These 4 studies were the exact same studies that were identified in the cost search. None of these studies reported Swiss utilities for the relevant health states as defined by our model structure. Hence, we did not extract any data from the identified studies.

Figure II. PRISMA flowchart costs on health-related quality of life

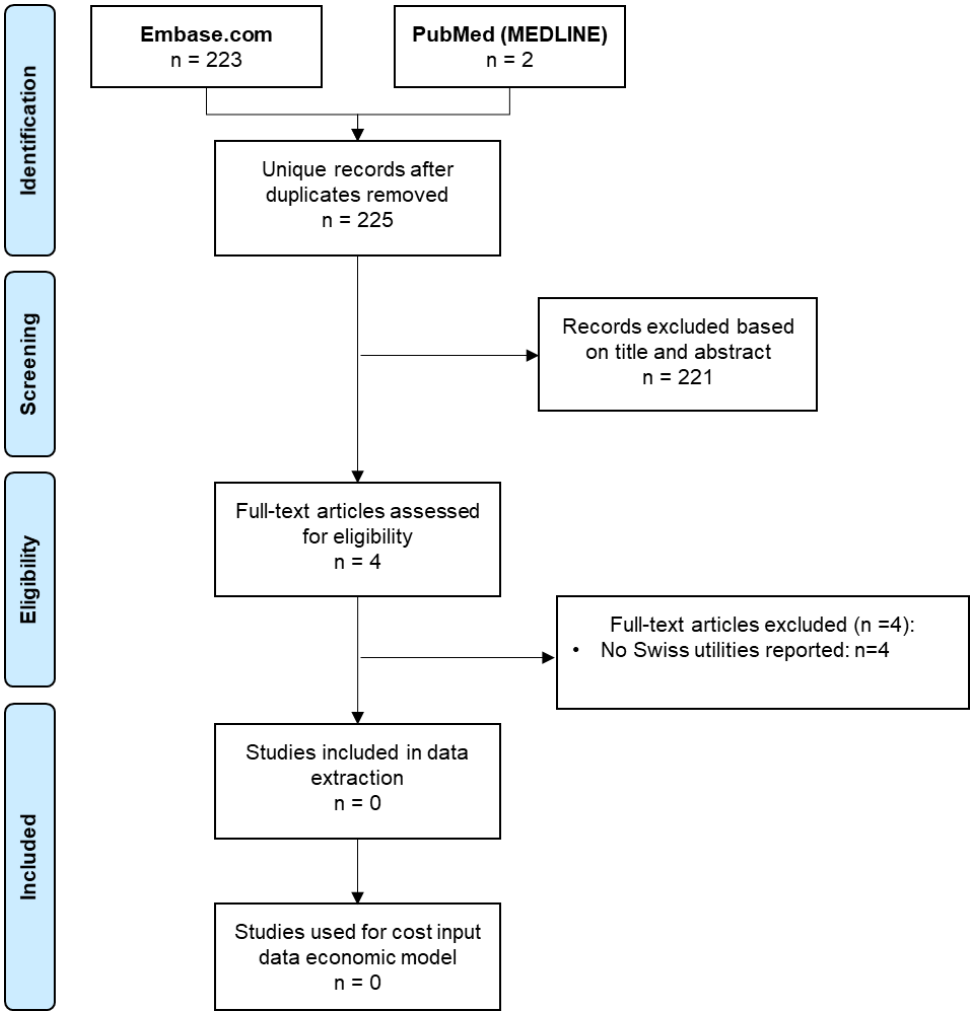


Table VI. References and decisions of studies included in full-text screening of health-related quality of life systematic literature search

Reference	Decision
Elliott, J., McCoy, B., Clifford, T., Potter, B. K., Wells, G. A., & Coyle, D. (2020). Economic Evaluation of Cannabinoid Oil for Dravet Syndrome: A Cost-Utility Analysis. *PharmacoEconomics*, 1-10.	Exclude: no Swiss specific utility data
Mantovani, L. G., Cozzolino, P., Cortesi, P. A., & Patti, F. (2020). Cost-Effectiveness Analysis of Cannabinoid Oromucosal Spray Use for the Management of Spasticity in Subjects with Multiple Sclerosis. *Clinical Drug Investigation*, 1-8.	Exclude: no Swiss specific utility data
Neuberger, E. E., Carlson, J. J., & Veenstra, D. L. (2020). Cost-Effectiveness of Cannabidiol Adjunct Therapy versus Usual Care for the Treatment of Seizures in Lennox-Gastaut Syndrome. *PharmacoEconomics*, *38*(11), 1237-1245.	Exclude: no Swiss specific utility data
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.	Exclude: no Swiss specific utility data

15.6 Input tables economic evaluations

Table I. Cost inputs reported in economic evaluations of medical cannabis use in chronic pain

	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. Cost inputs reported in economic evaluations of medical cannabis use in spasticity

	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
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 III. Effectiveness and utility inputs reported in economic evaluations of medical cannabis use in chronic pain

	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 IV. Effectiveness and utility inputs reported in economic evaluations of medical cannabis use in spasticity

	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

15.7 Quality appraisal economic evaluations

Table I. Critical appraisal of economic evaluations on medical cannabis use in 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?[g]	0.5	0.5
6	Is the actual perspective chosen appropriate?[h]	0.5	1
Costs			

[g] 0.5 if not lifetime
[h] 0.5 if not societal

7	Are all important and relevant costs for each alternative identified?	See table Appendix 15.6	
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 Appendix 15.6	
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
17	Does the study discuss the generalisability 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)?[i]	0	1
19	Are ethical and distributional issues discussed appropriately?	0	0

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

Table II. Critical appraisal of economic evaluations on medical cannabis use in 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

[i] 0.5 if a conflict of interest is stated

5	Is the chosen time horizon appropriate in order to include relevant costs and consequences?[j]	**0.5**	0.5	0.5	0.5	0.5	0.5
6	Is the actual perspective chosen appropriate?[k]	**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 Appendix 15.5					
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 Appendix 15.5					
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	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 generalisability 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)?[l]	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

[j] 0.5 if not lifetime
[k] 0.5 if not societal
[l] 0.5 if a conflict of interest is stated

15.8 Simulated NRS baseline values

Figure 1. Simulated NRS baseline values neuropathic pain (n=10’000, mean=0.690, SD=0.135)

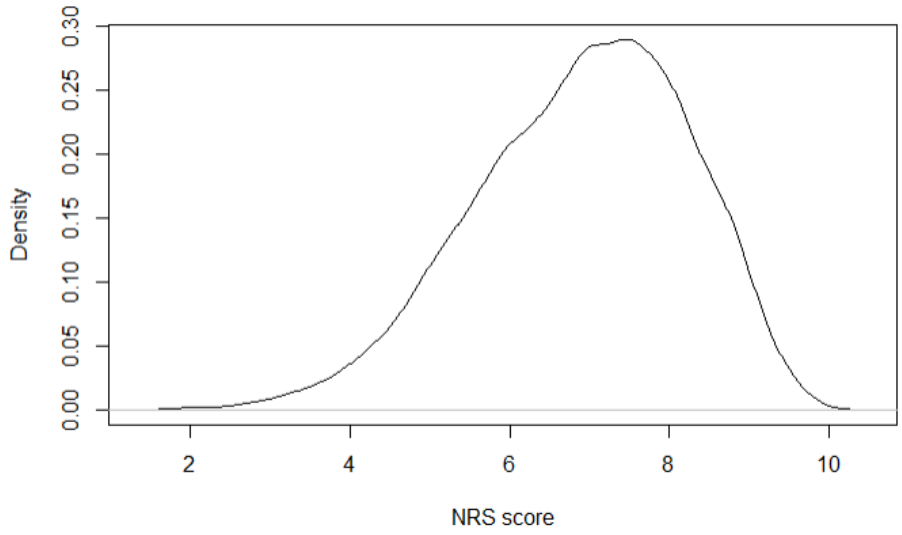


Figure 2. Simulated NRS baseline values musculoskeletal pain (n=10’000, mean=0.530, SD=0.106)

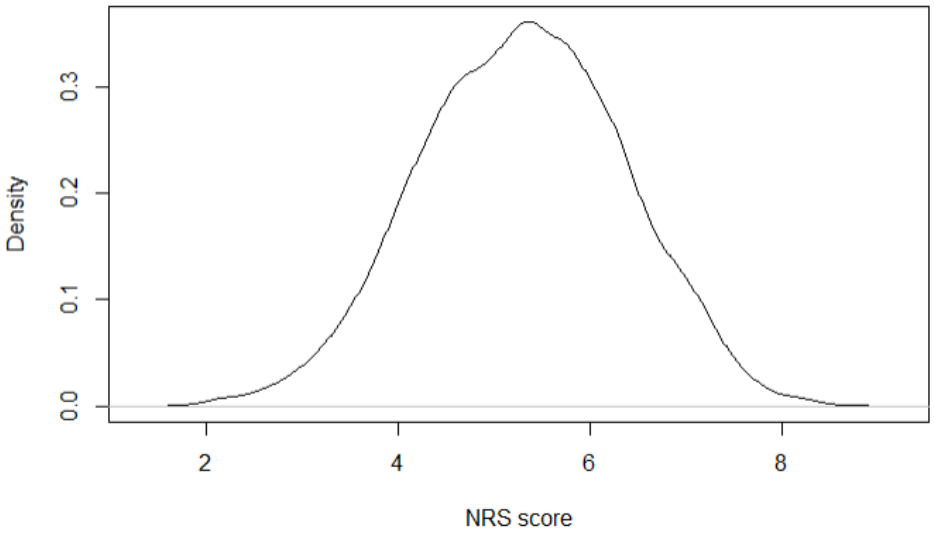
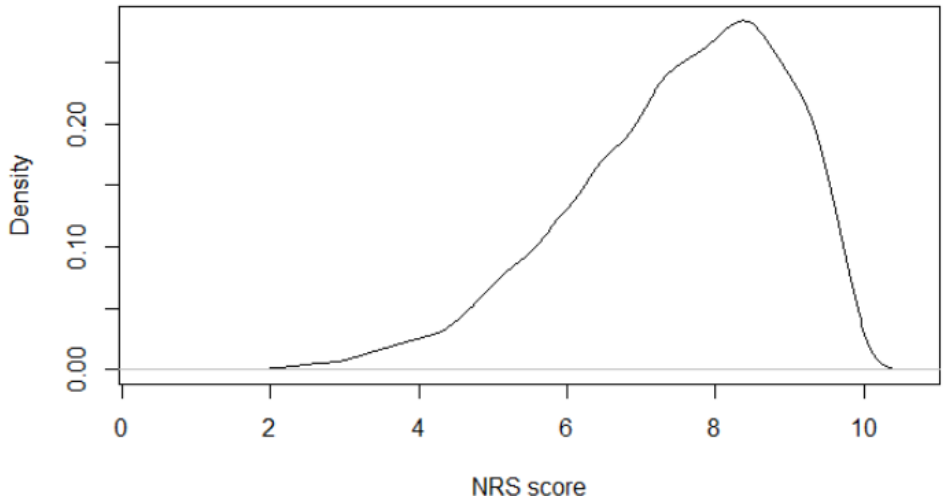


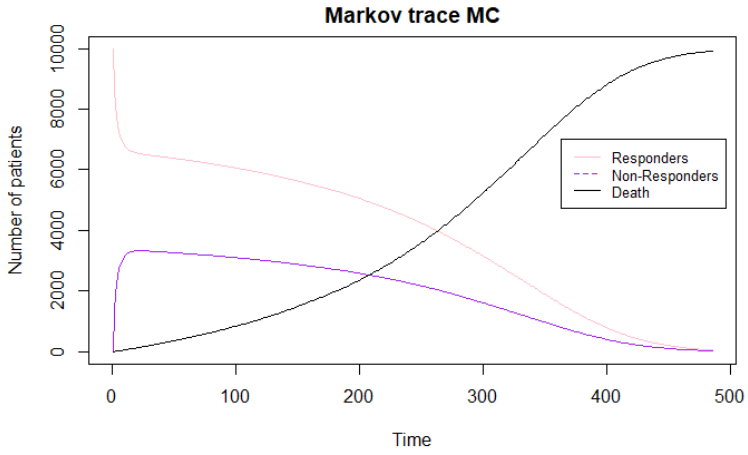
Figure 3. Simulated NRS baseline values MS spasticity (n=10’000)



* The NRS baseline values simulated for MS spasticity were also applied to the motor neuron disease model

15.9 Markov traces

Figure 1. Musculoskeletal pain



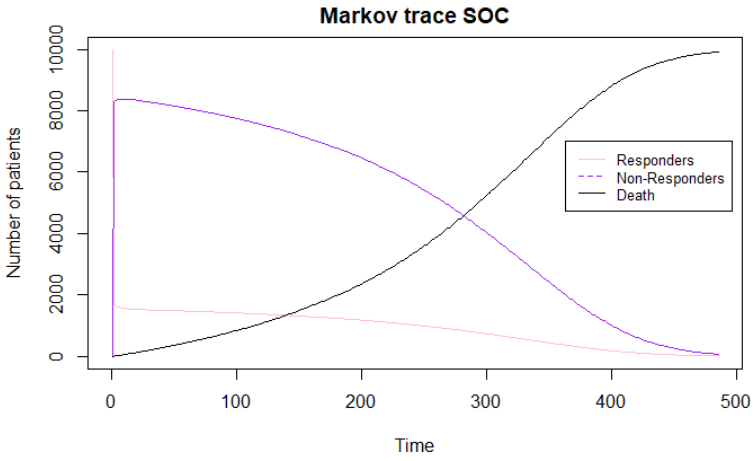


Figure 2. Neuropathic pain

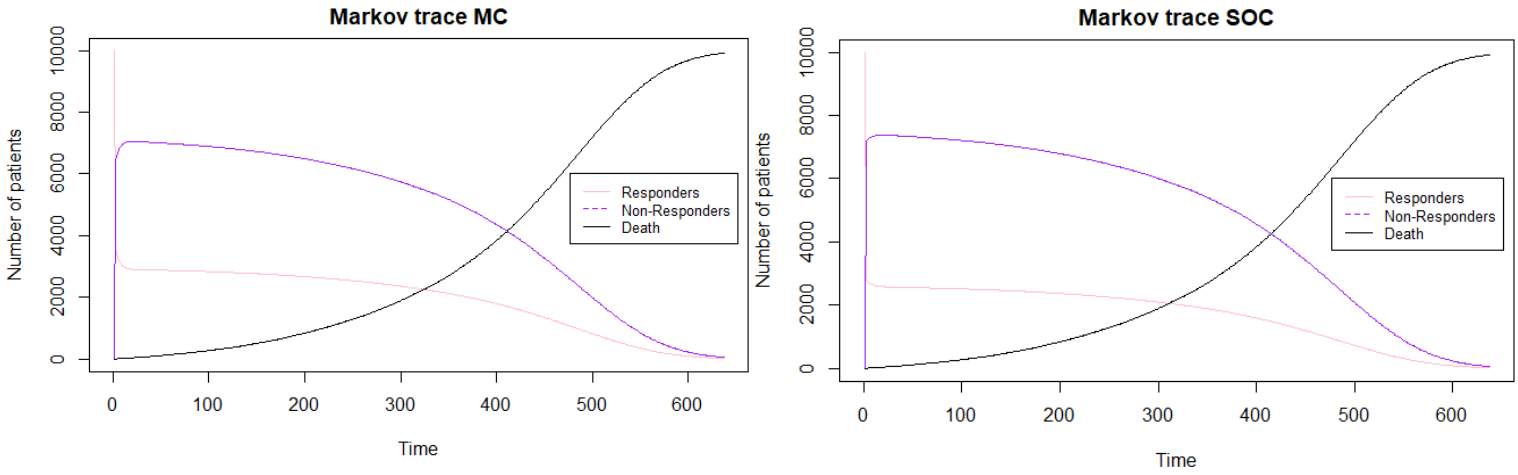


Figure 3. MS spasticity

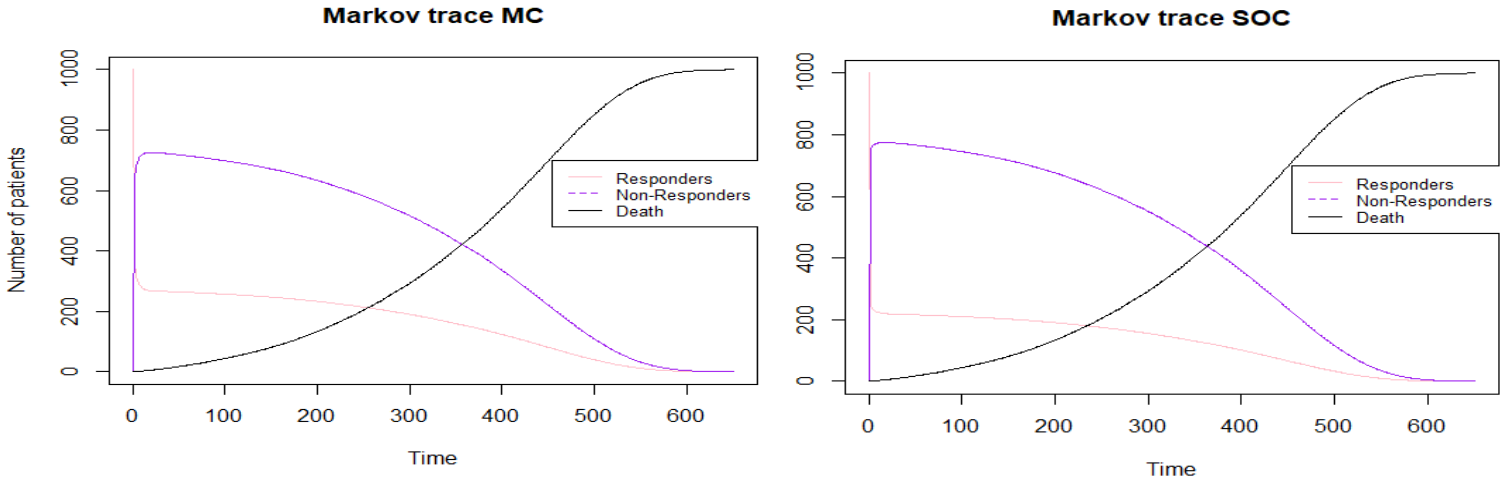
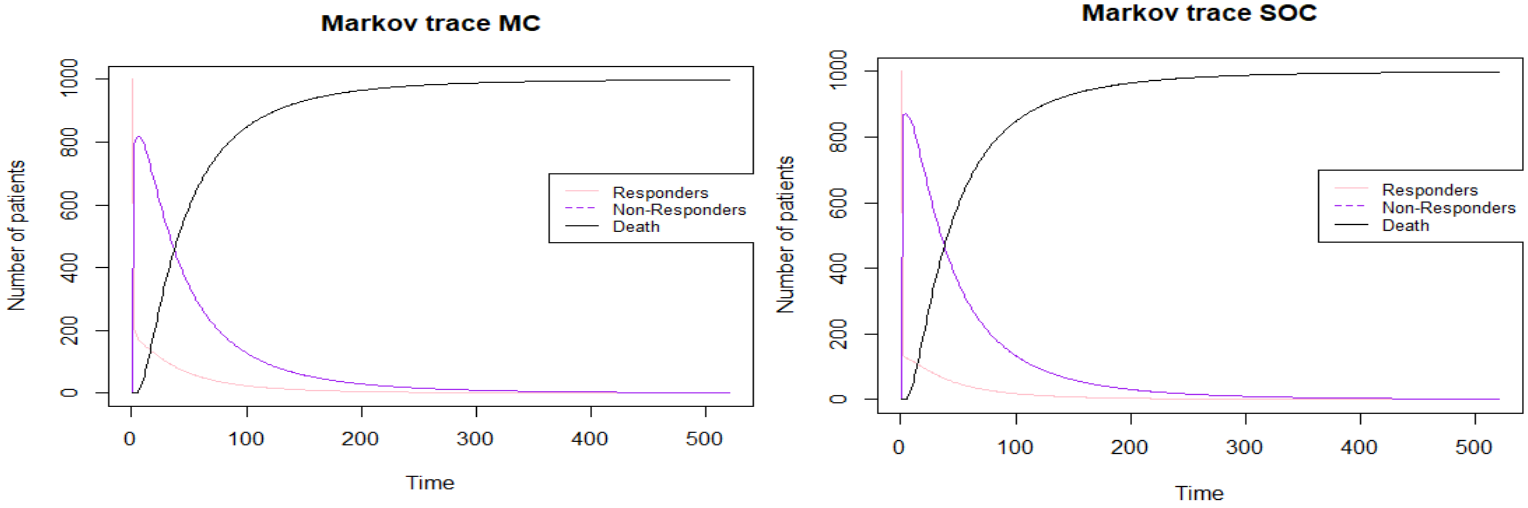


Figure 4. Motor neuron disease spasticity



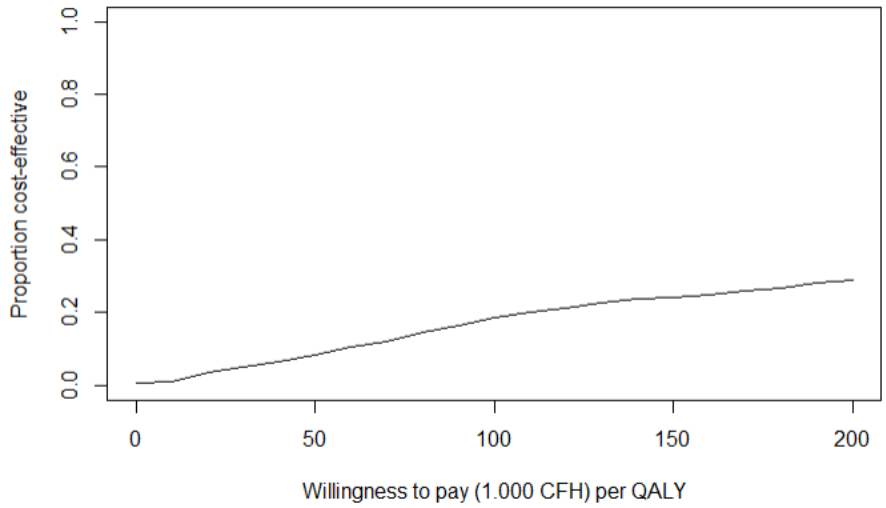
15.10 Cost-effectiveness acceptability curves

The cost-effectiveness acceptability curve presents the number of iterations that fall below a cost-effectiveness threshold (horizontal axis).

Neuropathic pain

At a threshold of zero, 0.7% of iterations yielded cost-effective results. As the threshold increases, the proportion of cost-effective iterations increase as well. With a threshold of 100'000 CHF per QALY, 18.6% of iterations were cost-effective.

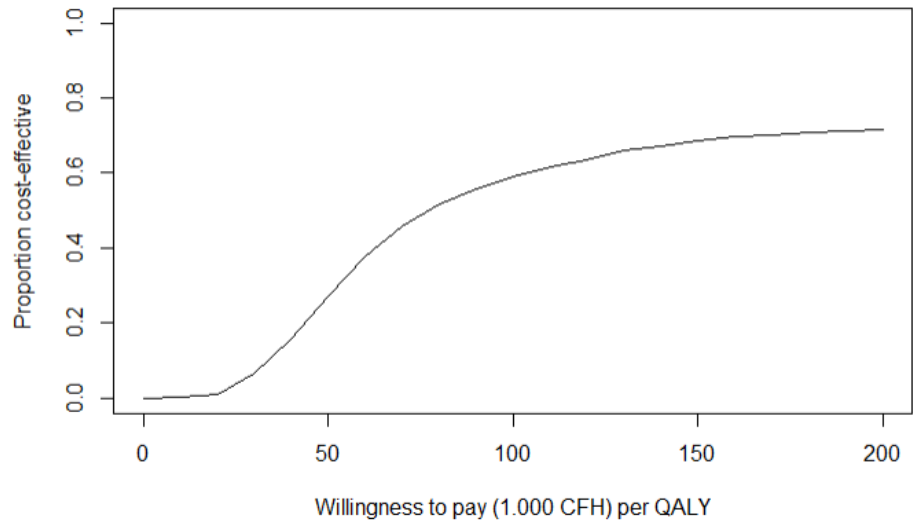
Figure 1. Cost-effectiveness acceptability curve – neuropathic pain



Musculoskeletal pain

At a cost-effectiveness acceptability threshold of zero, 0.0 % of iterations yielded cost-effective results. As the threshold increases, the proportion of cost-effective iterations increase as well. With a threshold of 100'000 CHF per QALY, 59.1% of iterations were cost-effective.

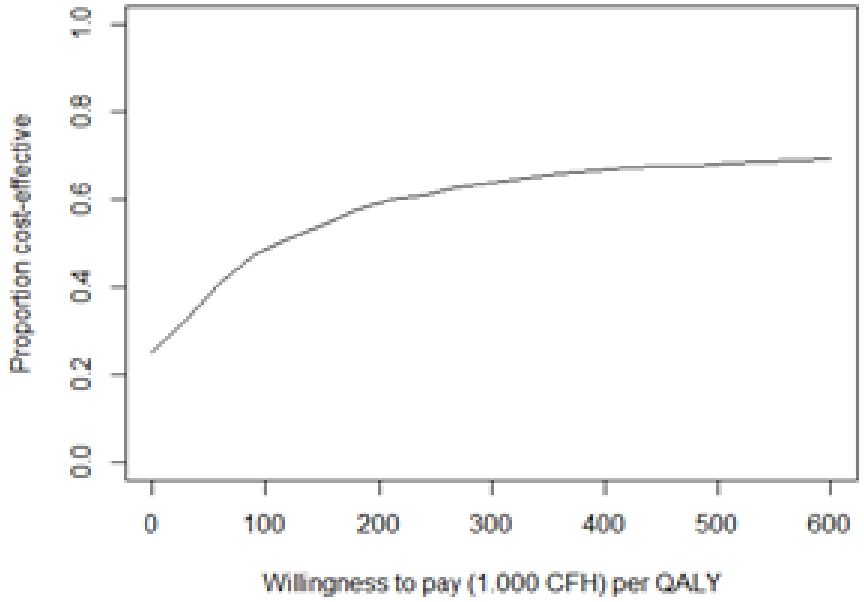
Figure 2. Cost-effectiveness acceptability curve – musculoskeletal pain



MS spasticity

At a threshold of zero, 25% of iterations yielded cost-effective results. This proportion is equal to the number of dominant ICERs. As the threshold increases, the proportion of cost-effective iterations increase as well. With a threshold of 100'000 CHF per QALY 48% of iterations were cost-effective.

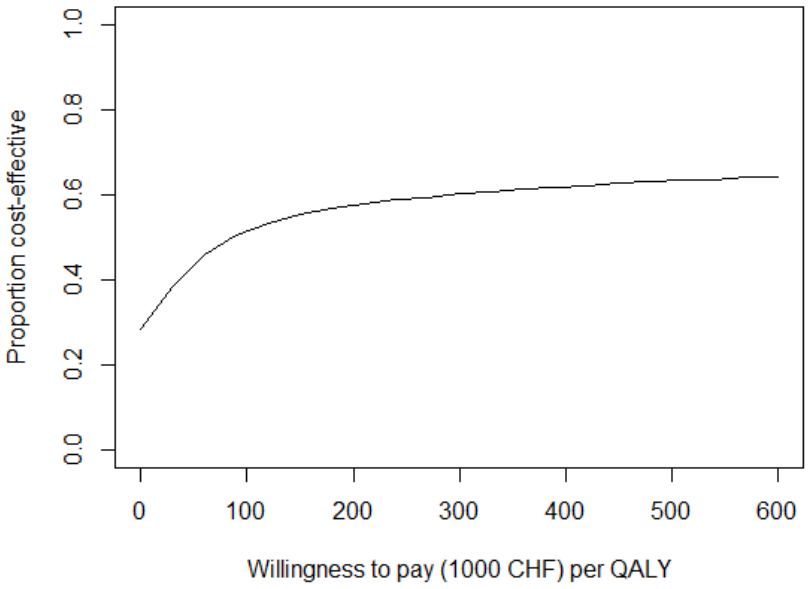
Figure 3. Cost-effectiveness acceptability curve – MS spasticity



Motor neuron disease spasticity

For motor neuron disease, 29% of iterations yielded cost-effective results at a threshold of zero CHF per QALY. With a threshold of 100'000 CHF per QALY, 52% of iterations were cost-effective.

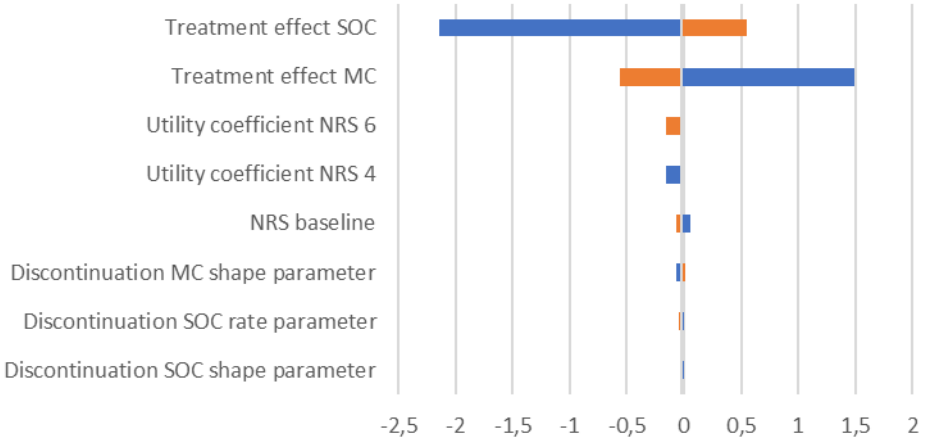
Figure 4. Cost-effectiveness acceptability curve – Motor neuron disease



15.11 One-way sensitivity analysis additional tornado diagrams

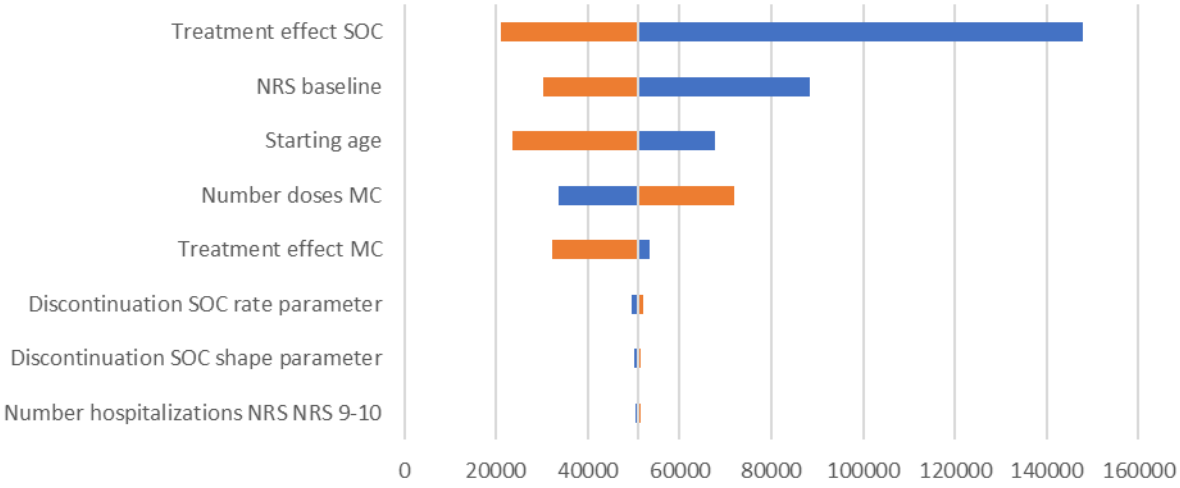
Neuropathic pain

Figure 1. Tornado diagram incremental QALYs



Keys: NRS = numeric rating scale, SOC = standard of care, MC = medical cannabis (THC:CBD spray)

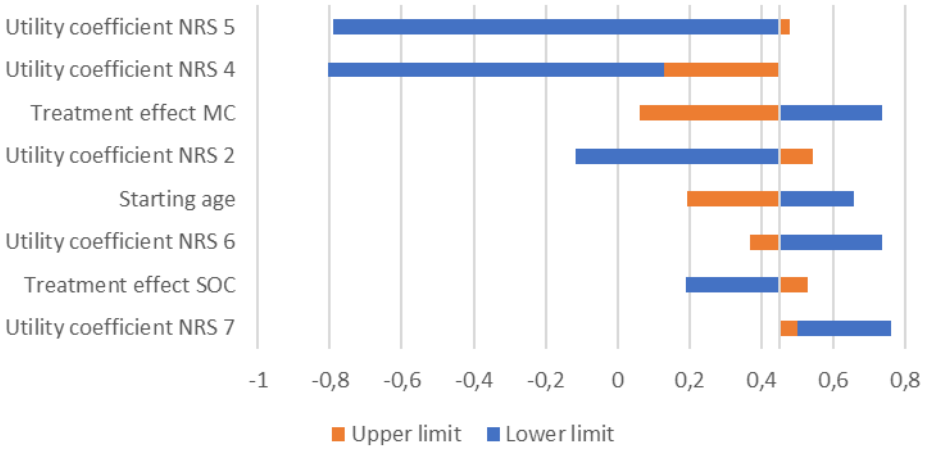
Figure 2. Tornado diagram incremental costs



Keys: NRS = numeric rating scale, SOC = standard of care, MC = medical cannabis (THC:CBD spray)

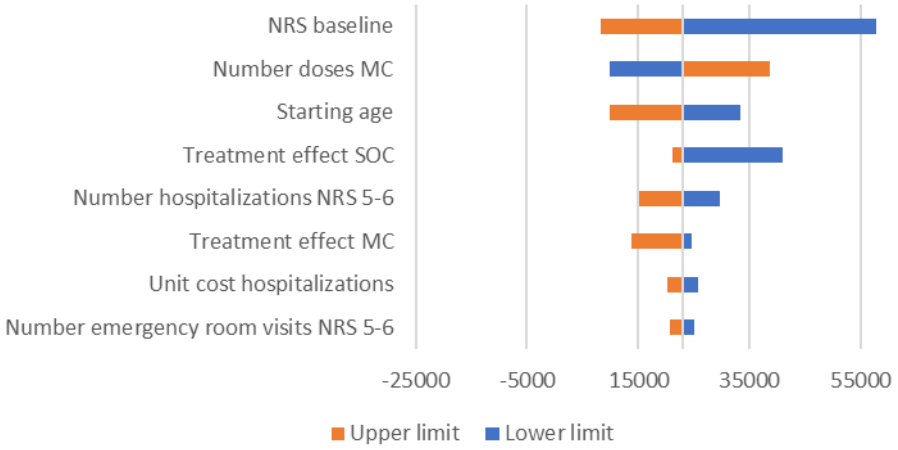
Musculoskeletal pain

Figure 3. Tornado diagram incremental QALYs



Keys: NRS = numeric rating scale, SOC = standard of care, MC = medical cannabis (THC:CBD spray)

Figure 4. Tornado diagram incremental costs



Keys: NRS = numeric rating scale, SOC = standard of care, MC = medical cannabis (THC:CBD spray)

Multiple sclerosis spasticity

Figure 5. Tornado diagram incremental QALYs

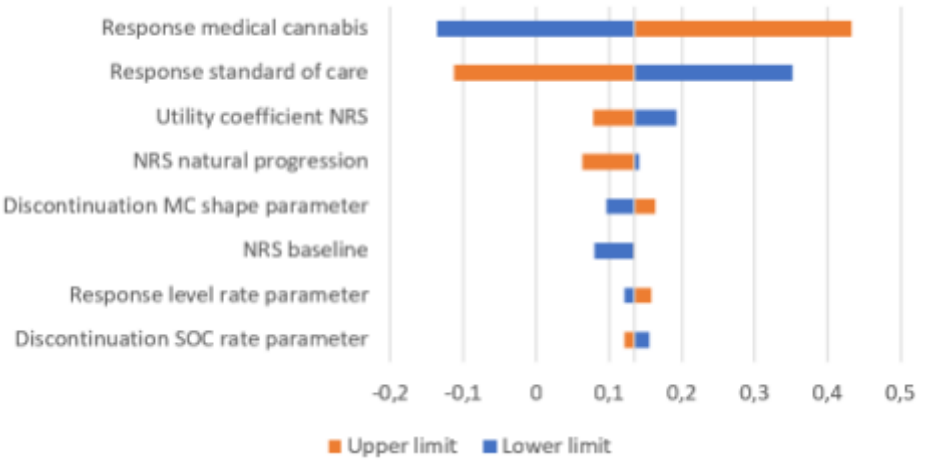
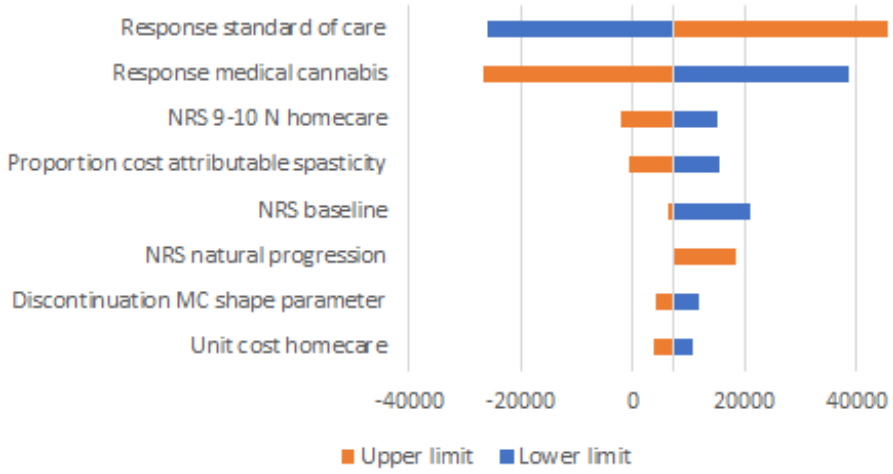


Figure 6. Tornado diagram incremental costs



Keys: NRS = numeric rating scale, SOC = standard of care, MC = medical cannabis (THC:CBD spray)

Motorneuron disease spasticity

Figure 7. Tornado diagram incremental QALYs

Keys: NRS = numeric rating scale, SOC = standard of care, MC = medical cannabis (THC:CBD spray)

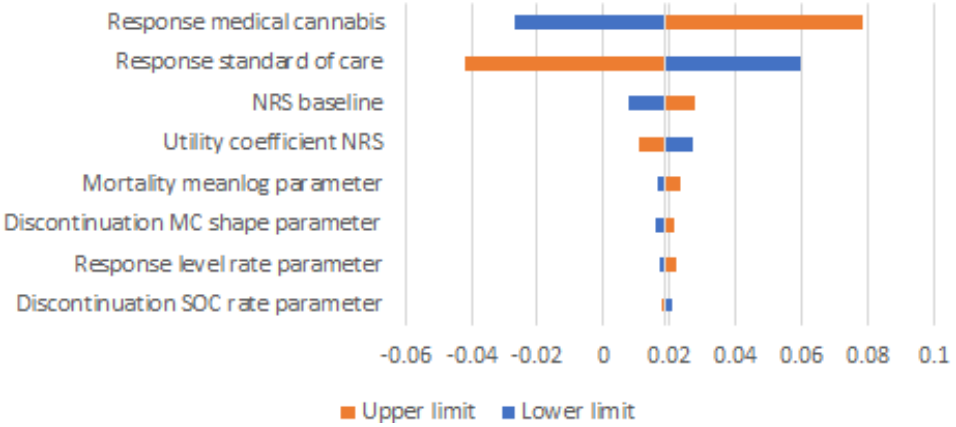
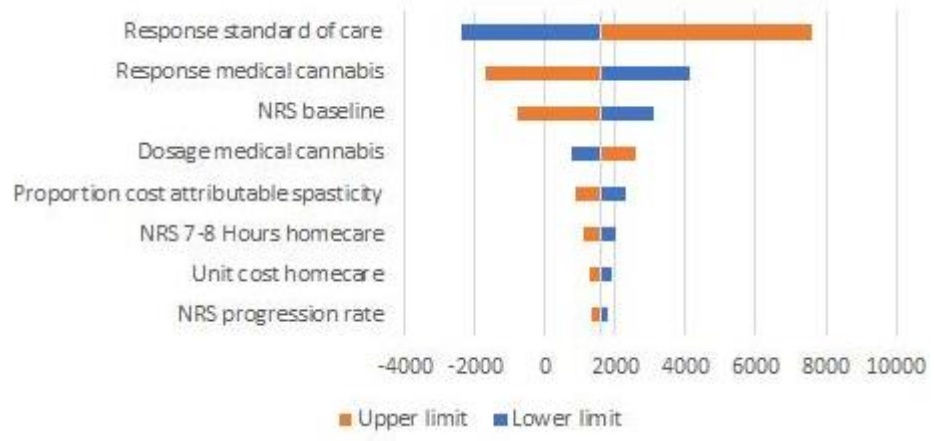


Figure 8. Tornado diagram incremental costs



Keys: NRS = numeric rating scale, SOC = standard of care, MC = medical cannabis (THC:CBD spray)

15.12 HTA reports and clinical guidelines

Organisation, year	Context	Type of document	Indication(s) evaluated	Product(s) evaluated
An Roinn Sláinte, 2019 (updated 2020)	Ireland	Clinical guidance	Treatment-resistant spasticity in multiple sclerosis, treatment-resistant intractable nausea and vomiting associated with cancer chemotherapy, severe treatment-resistant epilepsy	Multiple products
APPG, 2016	United Kingdom	Evidence review	A wide range of indications (including chronic pain and spasticity)	Multiple products
CADTH, 2019	Canada	Evidence review	Chronic pain	Multiple products
CADTH, 2019	Canada	Evidence review	Spasticity in multiple sclerosis	Sativex
DEP, 2016	Italy	Evidence review	A wide range of indications (including chronic pain and spasticity)	Multiple products
EMCDDA, 2018	European Union	Evidence review	A wide range of indications (including chronic pain and spasticity)	Multiple products
G-BA, 2018	Germany	Policy decision	Spasticity in patients with multiple sclerosis	Sativex
HPRA, 2017	Ireland	Evidence review with policy guidance	A wide range of indications (including chronic pain and spasticity)	Multiple products
iQWiG, 2018	Germany	Evidence review	Spasticity in patients with multiple sclerosis	Sativex
MCCS & APPG, 2019	United Kingdom	Clinical Guidance	A wide range of indications (including chronic pain and spasticity)	Multiple products
NASEM, 2017	United States of America	Evidence review	A wide range of indications (including chronic pain and spasticity)	Multiple products
NICE, 2019	United Kingdom	Evidence review with policy guidance	Chronic pain	Multiple products
NICE, 2019	United Kingdom	Evidence review with policy guidance	Spasticity	Multiple products
TGA, 2017	Australia	Evidence review with clinical guidance	Chronic non-cancer pain	Multiple products
TGA, 2017	Australia	Evidence review with clinical guidance	Multiple sclerosis	Multiple products
ZIN, 2017	The Netherlands	Evidence review with	A wide range of indications (including chronic pain and spasticity)	Multiple products

		policy decision		