National Institute for Health and Care Excellence

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Cannabis-based medicinal products

[C] Evidence review for spasticity

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Evidence review underpinning recommendations 1.3.1 and 1.3.2 in the NICE guideline

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Final

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Update information
September 2020: The average spasticity management cost of response was corrected from £138.72 to £207.18 (appendix M).

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Effectiveness of cannabis-based medicinal products for the treatment of spasticity

Introduction

Spasticity is a specific form of increased muscle tone (hypertonia) associated with a number of neurological disorders. The prevalence of lower limb spasticity reported in a systematic review was 28-37% in people with stroke, 41-69% in people with multiple sclerosis, 13% in people with traumatic brain injury and 75% moderate-severe spasticity in people with cerebral palsy. The impact of spasticity and co-existing disorders on the individual varies. Common problems include motor developmental delay (in children), pain from muscle spasms, impaired motor function affecting the person's ability to participate in society, and difficulties with daily care due to the onset of secondary complications of spasticity. Management should be tailored to meet the problems faced by the individual and achieve their goals.

The NICE guidelines on Spasticity in under 19s, Multiple sclerosis, Cerebral palsy in adults, Cerebral palsy in under 25s and Motor neurone disease, include recommendations on how to manage spasticity in these conditions.

The aim of this review is to examine the effectiveness of cannabis-based medicinal products (CBMP) for people with spasticity. This review also aims to identify adverse events, complications and contraindications associated with the use of CBMP. Additionally, this review will examine individual patient requirements, treatment durations, reviewing and stopping criteria with the use of CBMP.

Review question

What is the clinical and cost effectiveness of cannabis-based medicinal products for people with spasticity?

What are the adverse effects or complications of cannabis-based medicinal products for people with spasticity?

What are the contraindications, potential interactions and risks and cautions for use of cannabis-based medicinal products for people with spasticity?

What are the individual patient monitoring requirements, treatment durations, reviewing and stopping criteria, including how should treatment be withdrawn or stopped, for use of cannabis-based medicinal products for people with spasticity?

The review protocol for this review question is in Appendix A. The PICO table below formed part of the search strategy to identify studies associated with spasticity.

Table 1 PICO table

Population	Adults, young people, children and babies with spasticity. Specific considerations will be given to: • Young people, children and babies • Pregnant women and women who are breastfeeding • People with existing substance abuse • People with hepatic and renal failure

Interventions	Cannabis-based medicinal product
Comparator	• Placebo • Any relevant treatment (including physiotherapy, botulinum toxin, other management of symptoms) • Combination of treatments • Usual or standard care.
Outcomes	• 30% or greater improvement in spasticity • Change in spasticity using any validated scale which measures spasticity • Serious adverse events • Adverse events including but not limited to sleep problems, fatigue, road traffic accidents, psychological distress, dizziness, headache, confusion state, paranoia, psychosis, substance dependence, diarrhoea at the start of treatment • Withdrawals due to adverse events • Substance abuse due to the use of cannabis-based medicinal product • Misuse/diversion • Hepatic and renal failure Outcomes requiring a narrative synthesis: • Contraindications as listed in exclusion criteria • Monitoring requirements, treatment durations, reviewing and stopping criteria, including how treatment should be withdrawn and stopped in the methods of included studies

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual (2018). A review protocol was developed to encompass the 4 review questions around effectiveness, adverse events, contraindications and monitoring requirements. This review protocol can be found in Appendix A. Methods specific to the review questions are described in the review protocol in Appendix B.

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

A broad search strategy was used to identify all studies that examined the effectiveness of cannabis-based medicinal products (CBMP) in the treatment of intractable nausea and vomiting, chronic pain, spasticity and severe treatment-resistant epilepsy. Review protocol highlighted in Table 1 and Appendix A was used to identify studies associated with spasticity.

For the adult population, randomised controlled trials (RCTs) and systematic review of RCTs were considered. The committee noted that a minimum of 5 RCTs were required to provide adequate evidence. If fewer than 5 RCTs were identified, prospective cohort studies would also be considered for inclusion.

For children, RCTs and systematic reviews of RCTs were considered. The review protocol also specified that in the event of fewer than 5 RCTs being identified, prospective and retrospective cohort studies would also be considered for inclusion.

Additional information on safety concerns and contraindications will be obtained from the Summary of Product Characteristics and other relevant sources, such as the U.S Food and Drugs Administration.

Studies were also excluded if they examined the use of:

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

The review protocol also specifies that where possible, subgroup analyses would be conducted to explore the effectiveness of cannabis-based medicinal products in young people, children and babies, pregnant women and women who are breastfeeding, people with existing substance abuse and people with hepatic and renal failure.

For THC:CBD spray (THC:CBD spray), some studies used a dose greater than the maximum 12 sprays per day recommended in the product SPC. As the higher doses could have a different level of effectiveness or number of adverse events, the results for THC:CBD spray were split into subgroups: those within the recommended dose and those above the recommended dose. Two of the studies that used a dose within that recommended by the SPC were enriched enrolment trials. This design split the trials into two phases: Phase A where all participants were given THC: CBD spray and Phase B (RCT phase) where only those participants who responded to the treatment were included. This study design may result in more favourable outcomes for the intervention and fewer cases of adverse events. As a result, the studies that used an enriched enrolment design were highlighted in the forest plots and brought to the attention of the committee while they were discussing the evidence. There was not a large evidence base for any of the CBMP for spasticity and so it was decided not to group the results by length of follow-up period.

Some results were presented as the least squares mean. These results were included in the meta-analysis and a sensitivity analysis was used to assess their impact on the outcomes. Sensitivity analysis revealed that none of the least squares means changed the outcomes of the meta-analyses and so the results were included. Any results that were presented as least squares means have been identified in the footnotes of relevant forest plots.

Clinical evidence

The overall search for evidence of effectiveness of cannabis-based medicinal products for spasticity, nausea and vomiting, severe treatment resistant epilepsy and chronic pain returned a total of 19,491 results. After removing duplicates, 9,341 references were screened on their titles and abstracts. 75 studies were obtained for treatment of spasticity and reviewed against the inclusion criteria as described in the review protocol for spasticity (Appendix A). Overall, 15 RCTs (12 parallel and 3 crossover) were included (see Appendix E for evidence tables). The effectiveness and safety of CBMP was investigated for people with spasticity related to multiple sclerosis (13 studies), motor neurone disease (2 studies) and spinal cord injury (1 study). All studies investigated spasticity in adults (see Table 2). No studies were identified for any of the subgroup analyses. Observational studies were also incorporated into the literature search and no paediatric studies were identified.

See Appendix E for evidence tables and Appendix N for excluded studies.

Quality assessment of clinical studies included in the evidence review

In this review, parallel RCTs and crossover RCTs were identified. The quality of the evidence was initially graded as high. Most of the evidence identified was for the use of CBMP for people with multiple sclerosis. For crossover studies, the committee identified 1 week as an adequate washout period.

See Appendix H for full GRADE tables and Appendix F for forest plots in situations where data have been meta-analysed.

Interventions

Of the 15 studies included, 12 studies looked at management of spasticity in multiple sclerosis, 2 studies looked at spasticity in motor neurone disease and 1 investigated spasticity resulting from spinal cord injury. The included studies looked at the following interventions:

- Tetrahydrocannabinol: Cannabidiol (THC: CBD) spray
- THC capsules (synthetic THC)
- THC capsules (cannabis extract)
- Nabilone

At the time of writing this evidence review, with the exception of THC:CBD spray (Sativex), most CBMP such as tetrahydrocannabinol (a schedule 2 controlled drug) did not have a UK marketing authorisation for treating spasticity. Although Sativex has UK authorisation for the treatment of spasticity it does not currently have UK marketing authorisation for either motor neurone disease or spinal cord injury.

Summary of clinical studies included in the evidence review

Table 2: summary of included adult studies

Reference	Population	Intervention/ comparator	Outcomes	Limitations
Multiple sclerosis: THC: CBD spray versus placebo				
Collin 2007 (UK, Romania) Parallel RCT	Patients with spasticity due to MS in at least 2 muscle groups with an Ashworth score of 2 or more whose current therapy failed to provide adequate relief. Patients had stable disease for at least 3 months before the study. Follow-up: 2 and 6 weeks after beginning treatment	THC: CBD spray (Sativex: 2.7 mg: 2.5 mg) vs placebo (n=189) During a 2-week titration phase the initial dose (1 spray) was increased to a maximum 48 sprays per day. The maintenance dose was sustained for 4 weeks.	Change in spasticity from baseline (Ashworth) Change in spasticity from baseline (NRS) NRS responder (30% reduction in spasticity score)	Maximum dose was above the recommended maximum in the SPC for Sativex of 12 sprays per day
Collin 2010 (UK, Czech Republic) Parallel RCT	Patients who have had spasticity due to MS for at least 3 months and had a mean daily NRS spasticity score of at least 24 during the 6-day baseline period. Patients had to have stable treatment for at least 30 days before study entry. Follow-up: 14 weeks	THC: CBD spray (Sativex: 2.7 mg: 2.5 mg) vs placebo (n=337) During the titration phase patients self-titrated to their optimal dose with a maximum of 24 sprays per day. No information on length of the titration phase	Change in spasticity from baseline (NRS) NRS responder (30% reduction in spasticity score) Adverse events Serious adverse events	Maximum dose was above the recommended maximum in the SPC for Sativex of 12 sprays per day

Reference	Population	Intervention/ comparator	Outcomes	Limitations
Langford 2013 (UK, Czech Republic, Canada, Spain, France) Parallel RCT	Patients with central neuropathic pain due to MS for at least 3 months and a score of at least 24 on pain NRS in the 6 days before study entry. Follow up: 14 weeks	THC: CBD spray (Sativex: 2.7 mg: 2.5 mg) vs placebo (n=141) During the 1-week titration period patients self-titrated to their optimal dose using a pre-defined escalation scheme. The maximum dose was 12 sprays per day.	Change in spasticity from baseline (NRS) Treatment-related adverse events Treatment-related serious adverse events Withdrawal due to adverse events	
Leocani 2015 (Italy) Cross-over RCT	Patients with progressive primary or secondary MS for at least 12 months with moderate to severe spasticity as defined by a Modified Ashworth Scale score of at least 1+ in 1 limb. Patients were 18 years or older with an EDSS score of 3.0-6.5. Follow up: 2 weeks per study arm	THC: CBD spray (Sativex: 2.7 mg: 2.5 mg) vs placebo (n=34) During the 2-week titration phase the initial dose was increased by 1 spray per day until symptom relief was obtained with the minimum number of adverse events. The maximum does was 12 sprays per day.	Change in spasticity from baseline (Ashworth) Total adverse events Withdrawal due to adverse events	
Markova 2018 (Czech Republic, Austria) Parallel RCT	Patients with MS-related spasticity symptoms for at least 12 months with moderate to severe spasticity defined as an NRS score greater than 4. Patients were 18 years or older, had at least a 20% reduction in spasticity during Phase A. During the wash-out period from Phase A, at least 80% of this reduction had to be lost (i.e. an	THC: CBD spray (Sativex: 2.7 mg: 2.5 mg) vs placebo (n=106) Dose was titrated up during the single-blind 4-week trial period (Phase A) to a maximum of 12 sprays per day.	Change in spasticity from baseline (Modified Ashworth) Change in spasticity from baseline (NRS)	Enriched enrolment study. Patients were only included in the RCT phase of the trial if they showed a minimum 20% improvement in spasticity during the single-blind phase (Phase A) of the trial. This may increase

Reference	Population	Intervention/ comparator	Outcomes	Limitations
	increase in spasticity once treatment was stopped). Follow up: 12 weeks		NRS responder (30% reduction in spasticity score) Total adverse events Serious adverse events Withdrawal due to adverse events	efficacy and reduce the incidence of adverse events.
Novotna 2011 (UK, Spain, Poland, Czech Republic, Italy) Parallel RCT	Patients with a diagnosis of MS for at least 6 months and moderate to severe spasticity due to MS (defined by an NRS score of 4 or higher) for at least 3 months. Patients had to have at least a 20% reduction in spasticity during phase A. Follow up: 12 weeks	THC: CBD spray (Sativex: 2.7 mg: 2.5 mg) vs placebo (n=241) During the 10-day titration period patients self-titrated using a pre-defined escalation scheme to a maximum 12 sprays per day.	Change in spasticity from baseline (NRS) NRS responder (30% reduction in spasticity score)	Enriched enrolment study. Patients were only included in the RCT phase of the trial if they showed a minimum 20% improvement in spasticity during the single-blind phase (Phase A) of the trial. This may increase efficacy and reduce the incidence of adverse events. There was no evidence of a wash-out period between Phase A and Phase B.

Reference	Population	Intervention/ comparator	Outcomes	Limitations
Wade 2004 (UK) Parallel RCT	Patients with a diagnosis of MS and 1 of 5 target symptoms at a sufficient level of severity (spasticity, spasms, bladder problems, tremor, pain other than musculoskeletal). Follow up: 6 weeks	THC: CBD spray (Sativex: 2.7 mg: 2.5 mg) vs placebo (n=160) Patients were instructed to slowly self-titrate, aiming for an optimal balance of symptom relief and adverse events. Maximum dose was 120 mg THC and 120 mg CBD (approximately 44 sprays per day)	Change in spasticity from baseline (VAS) Change in spasticity from baseline (Modified Ashworth Scale) Withdrawal due to adverse events	Maximum dose was above the recommended maximum in the SPC for Sativex of 12 sprays per day
Multiple sclerosis: THC capsules versus placebo (synthetic THC)				
Ball 2015 (UK) Parallel RCT	Patients with a diagnosis of primary or secondary MS with evidence of disease progression in the year before study enrolment. Patients were aged 18-65 with an EDSS score of 4.0-6.5	Delta9-THC 3.5 mg capsules (synthetic THC - dronabinol) vs placebo (n=498) During the 4-week titration phase patients could increase the initial dose by 1 capsule twice daily until the maximum weight-related dose was achieved or adverse events developed	MSSS-88 score Adverse events	
Zajicek 2003 (UK) Parallel RCT	Patients who had a diagnosis of MS which was stable for 6 months before study entry and an Ashworth score of 2 or higher in 2 or more lower limb muscles. Patients were aged 18-64 years. Follow up: 15 weeks	2 intervention arms v placebo: 1. Delta9-THC 2.5 mg capsules (synthetic THC - dronabinol) 2. THC: CBD capsules (2.5 mg:1.25 mg) (cannabis extract) (n=657)	Change in spasticity from baseline (Ashworth Scale) Adverse events	

Reference	Population	Intervention/ comparator	Outcomes	Limitations
		During the 5-week titration phase patients could increase the initial dose each week by 1 capsule twice per day. Maximum dose was based on body weight	Serious adverse events	
Zajicek 2005 (UK) Parallel RCT	Long-term follow-up from Zajicek 2003 Follow up: 52 weeks	See Zajicek 2003 n=383	See Zajicek 2003	
Multiple sclerosis: THC capsules versus placebo (purified THC from cannabis extract)				
Van Amerongen 2018 (Netherlands) Parallel RCT	Patients with progressive primary or secondary MS according to revised McDonald criteria for more than 1 year. Patients had moderate spasticity defined by an Ashworth score of 2 or higher, stable treatment for at least 30 days before study enrolment and an EDSS score of 4.5-7.5 Follow up: 4 weeks	Delta9-THC capsules (Namisol - purified THC from cannabis extract) at doses of 3, 5 and 8 mg vs placebo The optimal dose was found during 2 clinic visits with a cross-over of 3, 5 and 8 mg THC and 100-minute interval between doses. No information on the timing of the clinic visits	Change in spasticity from baseline (Ashworth Scale) Change in spasticity from baseline (NRS) Adverse events	
Multiple sclerosis: THC:CBD cannabis extract capsules versus placebo (purified THC from cannabis extract)				
Zajicek 2003 (UK) Parallel RCT	See Zajicek 2003 (THC capsules)	See Zajicek 2003 (THC capsules)	See Zajicek 2003 (THC capsules)	
Zajicek 2005 (UK) Parallel RCT	See Zajicek 2003 (THC capsules)	See Zajicek 2003 (THC capsules)	See Zajicek 2003 (THC capsules)	

Reference	Population	Intervention/ comparator	Outcomes	Limitations
Zajicek 2012 (UK) Parallel RCT	Patients aged 18-64 years with a diagnosis of MS according to the McDonald criteria and stable symptoms for 6 months prior to study entry Follow up: 12 weeks	Delta9-THC capsules (extract from cannabis sativa L, standardised on cannabidiol (range 0.8–1.8 mg) and containing 2.5 mg Δ9- THC:1.25 mg CBD as the main cannabinoid vs placebo (n=279) During the 2-week titration phase the initial dose was increased by 5 mg per day every 3 days for up to 12 days to a maximum dose of 25 mg per day	MSSS-88 score (by category not overall score) Treatment-related adverse events Total serious adverse events Withdrawals due to adverse events	
Motor neurone disease: THC: CBD spray versus placebo				
Riva 2018 (Italy) Parallel RCT	Patients aged 18-80 with amyotrophic lateral sclerosis as defined by the revised El Escorial criteria or primary lateral sclerosis according to Pringle's criteria. Patients had a spasticity score of at least 1 on the Modified Ashworth scale in 2 or more muscle groups and had stable treatment for 30 days before study enrolment Follow up: 4 weeks	THC: CBD spray (2.7 mg: 2.5 mg) vs placebo (n=60) During the 2-week titration phase the initial dose was increased up to a maximum dose of 12 sprays per day. No information provided on how the dose was titrated	Change in spasticity from baseline (NRS) Change in spasticity from baseline (Ashworth) Total adverse events Treatment-related adverse events Total serious adverse events	

Reference	Population	Intervention/ comparator	Outcomes	Limitations
Motor neurone disease: Nabilone versus placebo				
Wissel 2006 (Austra, Germany, Switzerland) Cross-over RCT	Patients with chronic upper motor neurone syndrome and disabling spasticity-related pain. Passive stretch of the spastic muscles had to result in increased pain perception in the stimulated muscles	Delta9-THC capsules (nabilone – 0.5 mg) vs placebo (n=13) During the 1-week titration phase the initial dose (0.5 mg) could be increased to 1 mg per day	Change in spasticity from baseline (Ashworth)	
Spinal cord injury: Nabilone versus placebo				
Pooyania 2010 (Canada) Cross-over RCT	Patients aged 18-65 with spinal cord injury which occurred within the previous year at level C5 (ASIA grade A-D) or below. Patients had moderate spasticity with an Ashworth score of 3 or above, no change in ASIA neurologic level in the last 6 months and stable treatment for 30 days before study entry Follow up: 4 weeks per trial arm	Delta9-THC capsules (nabilone – 0.5 mg) vs placebo (n=12) During weeks 3 and 4 the initial dose (0.5 mg) could be increased to 0.5 mg twice per day depending on adverse events	Change in spasticity from baseline (Ashworth) Change in spasticity from baseline (VAS) Total serious adverse events	

See Appendix E for evidence tables and Appendix I for further information on adverse events.

As part of this evidence review, in addition to reviewing efficacy and safety data, studies were reviewed for information about patient monitoring and reviewing and stopping criteria when cannabis-based medicinal products were prescribed.

The interventions, doses, monitoring and stopping criteria are summarised in tables 4 and 5 below:

Table 4: summary of interventions and doses in the included studies with adult population

Intervention (number of studies, n)	Indication	Dose and duration	Patient monitoring	Stopping criteria
THC: CBD spray (n= 7)	Multiple sclerosis	Higher dose than recommended Maximum 24 - 48 sprays per day (1 spray = 2.7 mg THC:2.5 mg CBD) One study reported a titration phase of 2 weeks No information on timing of doses	Two RCTs included monitoring visits 2 weeks after the beginning of treatment. One study also included an additional follow-up at 6 weeks. Monitoring visits included a review of the doses used, use of concomitant medication, spasticity and adverse events.	One RCT reported that the development of adverse events could lead to medication being stopped. No information was provided on how the dose was reduced.
		Within recommended dose Maximum 12 sprays per day (1 spray = 2.7 mg THC:2.5 mg CBD) Titration phases were between 1 - 4 weeks. One study reported that the dose was increased by 1 spray	Two RCTs reported the timing of monitoring visits. One study included a visit 2 weeks after the start of treatment and the other reported visits at baseline followed by 4, 6 and 10 weeks after beginning medication.	One RCT reported that patients were monitored for adverse events and, if necessary, the dose was reduced until adverse events were resolved. No information was provided on how the dose was reduced.

Intervention (number of studies, n)	Indication	Dose and duration	Patient monitoring	Stopping criteria
		per day until symptom relief was achieved with minimum adverse events No information on timing of doses	Monitoring included a review of adverse events, spasticity and routine blood and urine analysis including a review of THC levels.	
THC capsules (synthetic THC) (n=3)	Multiple sclerosis	Maximum dose was based on body weight Titration phases were between 4 – 5 weeks during which time the dose could be increased each week by 1 capsule twice daily. Dose could be increased until maximum age-related dose was reached, or adverse events developed No information on timing of doses	One RCT included initial monitoring visits at 2 and 4 weeks after the beginning of treatment to allow for dose adjustment and monitoring of adverse events. Later follow-up visits were at 3 and 6 months and every 6 months from then on. Another RCT included monitoring visits at 2, 4, 8 and 12 weeks. Monitoring visits included a review of adverse events, spasticity, muscle spasms, walking ability, haematology, liver function and a general health questionnaire.	One RCT reported that patients were monitored for adverse events. If adverse events were considered intolerable then the dose was reduced. If necessary, medication was reduced by 1 capsule twice daily until the patient was off medication.
THC capsules (cannabis extract) (n=1)	Multiple sclerosis	Maximum dose 16 mg per day (initial dose of 3, 5 and 8 mg)	One RCT included a monitoring visit at 2 weeks.	One RCT reported that adverse events were monitored, and patients were

Intervention (number of studies, n)	Indication	Dose and duration	Patient monitoring	Stopping criteria
		Titration phase took place during 2 clinic visits No information on timing of doses	No information was provided for the timing of further follow up visits or what was reviewed during these visits.	returned to their initial dose if adverse events were intolerable. No information was provided on how the dose was reduced.
THC: CBD capsules (cannabis extract) (n=3)	Multiple sclerosis	Maximum dose was based on body weight for 1 study and was 25 mg THC for another (Initial dose was 1 capsule – 2.5 mg THC:1.25 mg CBD) Titration phase for 1 study was 5 weeks during which time the dose was increased each week by 1 capsule twice daily. Another study had a titration phase of 12 days during which the dose could be increased by 5 mg THC every 3 days No information on the timing of doses	One RCT included monitoring visits every 2 weeks for the first 6 weeks after the start of medication followed by visits every 2-4 weeks from week 7 onwards. Another study included monitoring visits at 2, 4, 8 and 12 weeks. Monitoring visits included a review of adverse events, spasticity, muscle spasms, walking ability and a general health questionnaire.	Not reported
THC: CBD spray (n=1)	Motor neurone disease	Maximum 12 sprays per day (1 spray = 2.7 mg THC:2.5 mg CBD)	One RCT included monitoring visits at baseline and 4 weeks after the beginning of medication	Medication was stopped if there was no improvement in symptoms. If patients experienced intolerable adverse events, they were advised not to increase the

Intervention (number of studies, n)	Indication	Dose and duration	Patient monitoring	Stopping criteria
		Titration phase of 2 weeks but no information on how dose was titrated No information on the timing of doses	in addition to a follow up phone call at 3 weeks. Monitoring included a review of adverse events, spasticity, pain, spasm frequency and sleep quality.	dose. Medication was temporarily stopped if nausea and anxiety were reported. No information was provided on how the dose was reduced.
THC capsules (synthetic THC) (n=1)	Motor neurone disease	Maximum 1 mg per day (initial dose 0.5 mg per day) During the 3rd week the dose could be increased to the maximum dose No information provided on the timing of doses	No information was provided on the timing of monitoring visits. Monitoring included a review of spasticity, motor performance, use of concomitant medication and adverse events.	Not reported
THC capsules (synthetic THC) (n=1)	Spinal cord injury	Maximum 0.5 mg twice per day initial dose 0.5 mg once per day) depending on adverse events No information provided on the timing of doses	No information was provided on the timing of monitoring visits. Monitoring included a review of side effects, vital signs and adverse events.	Patients were monitored for adverse events. If considered necessary, they could return to the initial dose at any time during treatment. No information was provided on how the dose was reduced.

See Appendix E for evidence tables.

Economic evidence

Included studies

A systematic review of the economic literature was conducted. 1,863 studies were retrieved by the search. Following review of titles and abstracts, 9 full-text studies were retrieved for detailed consideration. Two relevant cost–utility analyses were identified and included in this review.

The included studies were critically appraised using the economic evaluation checklist from NICE guideline manual 2018 Appendix H.

THC: CBD spray plus standard of care vs. standard of care alone for the treatment of spasticity in multiple sclerosis

Gras et al. 2016

Gras et al. (2016) conducted a cost-utility analysis in the UK, from the perspective of the NHS in Wales and Personal Social Services. This study was funded by the manufacturer of THC: CBD spray. The model was a Markov model comparing THC: CBD spray plus standard of care (SoC) with SoC alone for the treatment of moderate to severe spasticity in multiple sclerosis (NRS score ≥ 4, measured using the spasticity 0–10 NRS). Patients had not responded adequately to other anti-spasticity medication.

Treatment effects were taken from the pivotal trial (Novotna et al. 2011), an enriched design randomised controlled trial. (n=572 at the enrichment phase, n=241 RCT phase). Patients were only included in the RCT phase of the trial if they showed a minimum 20% improvement in spasticity during the single-blind enrichment phase of the trial. The utility was measured using the EQ-5D data from the same trial.

Resource use was based on a published clinical expert survey (Stevenson et al. 2015), including community-based visits, outpatient clinic visits, A&E visits, hospital admissions, home care visits, equipment costs (such as wheelchairs, walking aids). The model assumed all resource use from Stevenson et al. 2015 were attributed to spasticity alone while some of the costs might overlap with the management costs of MS patients.

Costs were taken from the Department of Health (DoH) NHS reference costs 2012-2013 and Unit costs of health and social care (PSSRU 2013).

Base care results showed that compared to SoC alone, THC: CBD spray plus SoC was £3,836 more expensive and produced 0.35 more QALYs over a 30-year time horizon. Probabilistic sensitivity analysis showed a 100% probability that THC: CBD spray plus SoC was a cost-effective strategy compared to SoC alone at the £20,000-£30,000 per QALY threshold.

Parameter uncertainty was explored on the unit cost, resource utilisation rates, resource quantities, utility values, and discount rate. The uncertainty of the transition probabilities or the discontinuations remained unclear as the model did not explore these in the sensitivity analysis.

This study was judged as directly applicable but with very serious limitations (see Appendix L).

Lu et al. 2012

Lu et al. (2012) conducted a cost-utility analysis in the UK, from the UK NHS perspective. The model was a Markov model comparing Sativex (THC: CBD spray) plus standard treatment with standard treatment alone for patients with spasticity due to MS and not responding adequately to oral anti-spasticity medication.

Treatment withdrawal rates were taken from the pivotal trial (Novotna et al. 2011. The utility was measured using the EQ-5D data from a conference presentation (Montalban et al. 2009 based on the RCT by Novotna et al. 2011). The utility of response and no response were 0.57 and 048, respectively.

Resource use was based on expert opinions and only consisted of clinical visits. Costs were taken from the NHS reference costs 2009. The model assumed no other resource use associated with spasticity due to MS. Costs were taken from the NHS reference costs 2009.

Base care results showed that compared to standard treatment alone, THC: CBD spray plus standard treatment was £7,627 more expensive and produced 0.1548 more QALYs over a 5-year time horizon. Probabilistic sensitivity analysis showed a 10.2% probability that THC: CBD spray plus standard treatment was a cost-effective strategy compared to standard treatment alone at £30,000 per QALY threshold.

Parameter uncertainty was explored on the transition probabilities, utilities, THC: CBD average daily sprays, cost of clinic visits. Several scenario analyses (e.g. time horizon) were also conducted.

This study was judged as directly applicable but with potentially serious limitations (see Appendix L).

Excluded studies

Seven studies were excluded following the full-text review. The list of excluded studies can be found in Appendix J.

Economic model

A de-novo cost-utility analysis was developed for this guideline (see Appendix M for full details). The analysis was a Markov model comparing the standard of care (SoC) plus cannabis to the standard of care alone over the 5-year time horizon. The target population are patients with spasticity who had not responded adequately to any standard spasticity treatment. The standard of care is defined as any interventions that would usually be used in this patient group, including licensed oral anti-spasticity medications if appropriate.

Cohorts of patients were followed from the initiation of the treatment. In the cannabis strategy, patients who did not achieve a response may discontinue cannabis. Responders remained on treatment but were subject to treatment discontinuation, after which they transitioned to the non-responder state. In the SoC strategy, the model assumed that a proportion of responders would lose the treatment benefit and become non-responders. This was modelled as discontinuation of the treatment benefit. The model assumed that all patients would always receive SoC in the background.

The treatment effects of THC: CBD spray, derived from the meta-analysis of four relevant RCTs of THC: CBD spray in patients with MS spasticity (see Appendix F for details), were presented as odds ratios (ORs) compared to the placebo from the

RCTs (Collin et al., 2007, 2010; Novotna et al., 2011; Markova et al., 2019). The treatment response for the THC: CBD spray strategy]) was based on a large observational study (Messina et al. 2017).

Baseline characteristics of the model cohort and discontinuation in patients achieving a treatment response are based on the same observational study (N=1,597) of THC: CBD spray in multiple sclerosis spasticity. Treatment response was defined as a reduction of ≥30% on the numerical rating scale (NRS) for spasticity.

Health state utilities in the model were based on a published utility regression model of EQ-5D, spasticity NRS and EDSS (Svensson, Borg and Nilsson, 2014). The committee agreed that medicinal cannabis was unlikely to have an impact on EDSS scores, but that mean EDSS should be reflected, based on their experience and published evidence. We simulated 10,000 hypothetical patients with NRS and EDSS scores based on the baseline NRS (mean 7.5; SD 1.45) and mean EDSS (mean 6.4; SD 1.2) data from Messina et al. (2017). We used data on the patients who had improved by at least 30% from the Messina et al. (2017) dataset and estimated the proportion of patients achieving greater levels of response (for example, 45-49% response). The weighted average utility of response and no response were 0.44 and 0.288, respectively. The utility difference between response and no response was much greater compared with the ones applied in Lu et al. 2012 (response and no response utility were 057 and 0.48, respectively), which were based on data observed in the underpinning trial.

Drug acquisition costs were estimated using pack/vial costs and the number of doses required per 4-week model cycle. The model applied the Sativex (THC: CBD spray) discount: NHS Pay for Responder scheme that first 3 x 10ml vial (90 doses per vial) for free and pay for responder only. The background management costs associated with spasticity were taken from a published UK study (Stevenson, Gras, Bardos, & Broughton, 2015), which reported spasticity management costs by NRS categories. Some of the reported resource use from Stevenson et al. (2015) might not be spasticity specific, such as wheelchair use. The model assumed that 50% of the resource use costs from Stevenson et al. (2015) were attributed to spasticity alone and therefore could be influenced by the treatment effect, based on a suggestion from the committee.

The model incorporated adverse events (AEs), based on the estimated incidence rate of serious and non-serious AEs for cannabinoid and control (placebo) (Wang et al., 2008). Costs and disutility associated with AEs were incorporated into the model.

Base-case results showed that, compared with standard of care alone, THC: CBD spray plus SoC was £1,580 more expensive and produced 0.081 more QALYs over a 5-year time horizon. The ICER was £19,512 per QALY gained. Probabilistic sensitivity analysis showed a 47.7% probability that, compared with standard treatment alone, THC: CBD spray plus SoC is associated with an ICER of £20,000/QALY or better and a 66.0% probability of an ICER of £30,000/QALY or better.

Parameter uncertainty was explored on the baseline characteristics, treatment effects, adverse events, discontinuation, mortality, utilities, THC: CBD average daily sprays, cost of spasticity management. Several scenario analyses, particularly on the assumptions on discontinuation, treatment response and utility estimation, were also conducted. The model was most sensitive to treatment effects. When varied over their plausible ranges, a large number of the examined parameters had the potential to change model outputs to one side or the other of a £20,000 / QALY threshold. However, the model was relatively robust if QALYs are valued at £30,000 each: only

the main effectiveness parameter (relative likelihood of response to THC:CBD spray), the probability of adverse events, and the proportion of costs that are attributable to spasticity had sufficient impact that the ICER could exceed £30,000/QALY.

Summary of evidence

The summary of evidence in this section reflects the evidence on effectiveness of cannabis-based medicinal products. Evidence statements are stratified by population and reflect evidence that was statistically significant. Further information on adverse events is also provided. The format of the evidence summary table is explained in the methods in Appendix B. Further information on adverse events is provided in Appendix I.

Clinical evidence

THC: CBD spray (dose higher than recommended) versus placebo

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Reduction in patient-reported spasticity from baseline (Numerical rating scale)					
3 (Collin 2007, Collin 2010, Wade 2004)	Parallel RCTs	558	MD -0.76 (-1.50, -0.01)	Very low	Favours THC:CBD spray
Number of people reporting 30% or greater reduction in spasticity (Numerical rating scale)					
2 (Collin 2007, Collin 2010)	Parallel RCTs	521	RR 0.71 (0.53, 0.94)	Moderate	Favours THC:CBD spray
Total adverse events					
1 (Collin 2010)	Parallel RCT	288	RR 1.20 (1.10, 1.32)	Moderate	Favours placebo

Commonly reported adverse events

- Commonly reported adverse events in studies included dizziness, somnolence, fatigue, nausea, dry mouth and asthenia

THC: CBD spray (within recommended dose) versus placebo

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Reduction in patient-reported spasticity from baseline (Numerical rating scale)					
4 (Langford 2013, Leocani 2015, Markova 2018, Novotna 2011)	3 Parallel RCTs 1 cross-over RCT	754	MD -0.78 (-1.51, -0.06)	Very low	Favours THC: CBD spray
Number of people with 30% or greater reduction in clinician-measured spasticity (Ashworth scale)					
1 (Novotna 2011)	Parallel RCTs	241	RR 0.69 (0.56, 0.85)	Low	Favours THC: CBD spray
Number of people reporting 30% or greater reduction in spasticity (Numerical rating scale)					
2 (Markova 2018, Novotna 2011)	Parallel RCTs	347	RR 0.55 (0.33, 0.92)	Very low	Favours THC: CBD spray
Treatment-related adverse events					
2 (Langford 2013, Markova 2018)	Parallel RCTs	445	RR 1.20 (1.03, 1.40)	High	Favours placebo
Withdrawal due to adverse events					
3 (Langford 2013, Leocani 2015, Novotna 2011)	2 Parallel RCTs 1 cross-over RCT	650	RR 2.02 (1.05, 3.87)	High	Favours placebo

Commonly reported adverse events

- Commonly reported adverse events in studies included dizziness, somnolence, nausea, vertigo and fatigue

THC capsules (synthetic THC) versus placebo

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Reduction in clinician-measured total body spasticity from baseline (Ashworth scale)					
2 (Zajicek 2003, Zajicek 2005)	Parallel RCTs	749	MD -1.38 (-2.47, -0.29)	Moderate	Favours THC capsules
Withdrawals due to adverse events					
2 (Zajicek 2003, Zajicek 2005)	Parallel RCTs	823	RR 3.55 (1.82, 6.91)	Moderate	Favours placebo

Commonly reported adverse events

- Commonly reported adverse events in studies included dizziness, sleep problems, balance problems, dissociative or perception disorders and somnolence.

THC capsules (purified THC from cannabis extract) versus placebo

No significant results were found for purified THC capsules v placebo

Commonly reported adverse events

- Commonly reported adverse events in studies included dizziness, muscular weakness, headache, euphoric mood and dry mouth.

THC: CBD cannabis extract capsules versus placebo

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Effect of spasticity on muscle stiffness (MSSS-88 subscale)					
1 (Zajicek 2012)	Parallel RCT	277	MD 3.70 (1.77, 5.63)	Moderate	Favours THC:CBD capsules
Effect of spasticity on muscle spasms (MSSS-88 subscale)					
1 (Zajicek 2012)	Parallel RCT	277	MD 3.10 (0.85, 5.35)	Moderate	Favours THC:CBD capsules
Effect of spasticity on ability to walk (MSSS-88 subscale)					
1 (Zajicek 2012)	Parallel RCT	277	MD 1.60 (0.43, 2.77)	Moderate	Favours THC:CBD capsules
Effect of spasticity on body movement (MSSS-88 subscale)					
1 (Zajicek 2012)	Parallel RCT	277	MD 2.10 (0.26, 3.94)	Moderate	Favours THC:CBD capsules
Treatment-related adverse events					
1 (Zajicek 2012)	Parallel RCT	277	RR 1.25 (1.12, 1.39)	Moderate	Favours placebo
Withdrawals due to adverse events					
3 (Zajicek 2003, Zajicek 2005, Zajicek 2012)	Parallel RCTs	1115	RR 2.96 (1.81, 4.83)	Moderate	Favours placebo

Commonly reported adverse events

- Commonly reported adverse events in studies included dizziness, sleep problems, gastrointestinal problems, bladder problems and fatigue

Motor neurone disease

THC: CBD spray versus placebo

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Reduction in clinician-measured spasticity from baseline (Modified Ashworth scale)					
1 (Riva 2019)	Parallel RCT	59	MD -0.27 (-0.51, -0.03)	High	Favours THC:CBD spray
Total adverse events					
1 (Riva 2019)	Parallel RCT	59	RR 2.84 (1.52, 5.33)	High	Favours placebo
Treatment-related adverse events					
1 (Riva 2019)	Parallel RCT	59	RR 5.43 (2.12, 13.90)	High	Favours placebo

Commonly reported adverse events

- Commonly reported adverse events in studies included asthenia, somnolence, vertigo, nausea and syncope.

THC capsules (purified THC from cannabis extract) versus placebo

No significant results were found for purified THC capsules v placebo

Commonly reported adverse events

- Commonly reported adverse events in studies included drowsiness and slight weakness in lower limbs.

Spinal cord injury

THC capsules (purified THC from cannabis extract) versus placebo

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Reduction in clinician-measured spasticity from baseline (Ashworth scale)					
1 (Pooyania 2010)	Cross-over RCT	22	MD -2.55 (-3.84, -1.26)	Moderate	Favours THC capsules

Commonly reported adverse events

- Commonly reported adverse events in studies included drowsiness, dry mouth and asthenia, mild vertigo, mild ataxia, and headache and lack of motivation.

Health economics evidence statements

Two published, directly applicable, UK-based cost–utility analyses compared oromucosal THC: CBD spray plus standard of care with standard of care alone for the treatment of spasticity in multiple sclerosis. An independently produced study with potentially serious limitations found that THC: CBD spray is associated with an ICER of £49,300 per QALY, with 10.2% probability that the ICER is £30,000 per QALY or better. The other, a manufacturer-sponsored analysis with very serious limitations, found that THC: CBD spray is associated with an ICER of £11,000 per QALY, with 100% probability that the ICER is £30,000 per QALY or better.

One directly applicable UK cost–utility analysis with minor limitations conducted for this guideline compared THC: CBD spray plus standard treatment with standard treatment alone for the treatment of spasticity. THC: CBD spray plus standard treatment compared to standard treatment alone was £1,580 more expensive and produced 0.081 more QALYs over five years (ICER = £19,512/QALY). Probabilistic sensitivity analysis showed a 47.7% probability that that the ICER is £20,000 per QALY or better.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The committee decided that outcomes including reduction in spasticity from baseline and the proportion of patients achieving 30% or greater improvement in spasticity were key outcomes for assessing effectiveness. The number of adverse events was also considered important to evaluate the safety of cannabis-based medicinal products. Other outcomes considered by the committee included the dose, treatment duration, contraindications, monitoring requirements and stopping criteria.

The quality of the evidence

Most of the evidence examined the use of THC:CBD spray for people with multiple sclerosis. However, the outcomes for these were low quality and had short follow up periods. Only 2 studies examined the use of cannabis-based medicinal products for people with motor neurone disease and 1 evaluated their use for people with spinal cord injury. The committee therefore agreed that they only had sufficient evidence to assess the effectiveness and adverse events for the use of THC:CBD spray for people with spasticity due to multiple sclerosis. Additionally, no paediatric studies were identified. Seven studies examined the use of THC:CBD spray for spasticity in people with multiple sclerosis. All were directly applicable, but some were downgraded for risk of bias, most commonly because of an enriched enrolment design or limited information on randomisation, allocation concealment and blinding. Three of these studies used maximum doses of between 24-48 sprays per day, higher than the maximum dose of 12 sprays per day recommended in the SPC, although the mean dose in two of these was similar to that in the dose-capped studies. The effectiveness and adverse events associated with allowing higher doses could differ to those which would be experienced when in the maximum dose is restricted, as in current clinical practice. Consequently, we conducted subgroup analysis on the studies that did and did not have their maximum daily dose restricted to 12 doses per day.

Two of the studies that used THC:CBD spray within the recommended dose used an enriched-enrolment study design (Markova 2018, Novotna 2011). This design split the trials into two phases: Phase A where all participants were given THC:CBD spray and Phase B (RCT phase) where only those participants who responded to the treatment were included. Both studies classified responders as people who showed a 20% reduction in spasticity during Phase A. The Markova trial also specified that patients who experienced a 20% improvement had to show an 80% reduction in that improvement during a 4-week washout period before the RCT began. The committee discussed the risk of bias of these studies, with some stating that, in comparison to a standard RCT, this study design is more similar to the process that would be followed in clinical practice. However, others highlighted that this design may favour responders and result in more positive outcomes and fewer adverse events once the RCT phase is reached. Given these potential effects on the outcomes, the studies were downgraded for risk of bias but were evaluated as directly applicable.

The committee highlighted potential issues with the sensitivity of some of the outcomes used to assess spasticity. Clinician-measured spasticity was assessed using the 5-point Ashworth or 6-point Modified Ashworth scale and although these are commonly used to measure spasticity in research they are not often used in clinical practice and can be insensitive to change that would be considered

meaningful to individual patients. As a result, improvements in spasticity may not register on the Ashworth or Modified Ashworth scales but this change may still be considered an improvement by the patient. A bigger treatment effect may therefore be seen in other outcomes, such as patient-reported change in spasticity, which is often scored using a 10-point numerical rating scale or 100-point visual analogue score.

Although there were limitations to some of the studies, most of the evidence for THC:CBD spray was from recent studies. The committee were therefore satisfied that the treatments used in the trials before the addition of cannabis-based medicinal products reflected current practice.

Benefits and harms

The committee agreed that there were benefits for the use of THC:CBD spray for the treatment of spasticity in multiple sclerosis. The clinical evidence showed improvements in patient-reported spasticity and could not differentiate between adverse events for THC:CBD spray and placebo. Also, economic modelling showed that THC:CBD spray would offer sufficient QALY gains if reduction in spasticity led to a halving of management costs and acquisition cost of THC:CBD spray (Sativex) was also reduced (in addition to the existing pay-for-responders scheme). Therefore, the committee agreed that under these conditions Sativex could be recommended to treat moderate to severe spasticity in adults with multiple sclerosis if other pharmacological treatments had not been effective.

There was limited evidence for the use of other cannabis-based medicinal products for the treatment of spasticity in other conditions. As a result, the committee could not confidently assess either the benefits or harms associated with these treatments and could not recommend them for use. The committee therefore made a research recommendation designed to help improve the understanding of the effects of cannabis-based medicinal products other than Sativex. The committee also highlighted that it is important to understand the effects of these products for people with conditions other than multiple sclerosis. People with cerebral palsy are a group that could particularly benefit from treatments that may help to reduce spasticity and so were included as a consideration for subgroup analysis.

Although one of the main concerns over the use of cannabis-based medicinal products is the potential for adverse events, the evidence could not differentiate between THC:CBD spray and placebo for the majority of the adverse event-related outcomes. However, it was suggested that the number of adverse events in the meta-analysis may have been reduced due to the studies which used enriched enrolment designs. The committee decided that despite the potential effect of the enriched enrolment studies, adverse events may not be a major concern. This decision was based on reports from some of the studies that many of the adverse events occurred near the beginning of treatment and could often be resolved during the dose titration phase. This was supported by the clinical experience of the committee, suggesting that the longer-term benefits of THC:CBD spray may outweigh the potential harms.

Cost effectiveness and resource use

The committee considered the evidence from two published economic evaluations that had been included in the clinical review. One manufacturer funded study (Gras 2016) found that THC: CBD spray was associated with an incremental cost-effectiveness ratio (ICER) of around £10,000/QALY gained over standard care (SoC) in the MS population. This study found that THC: CBD spray was associated with a

QALY gain of 0.35 over 30 years and an incremental cost of £3,836 which was derived from £98,501 costs in the SoC arm and £102,337 in the THC: CBD spray arm. The relatively small incremental (and high absolute) costs arise in this model because it uses estimates of resource use associated with different spasticity NRS scores that reflect the totality of background MS management costs and then makes the assumption that use of these resources is entirely related to NRS. Because of the wide variety of reasons that a patient might receive more or less intense management, the committee found this assumption highly implausible and so considered this study had overestimated the resource savings associated with reducing spasticity and therefore had serious limitations for decision-making. The other study included in the review was Lu 2012. This study was funded by the National Institute for Health Research and concluded that THC: CBD spray was associated with an additional 0.15 QALYS over 5 years at an additional £7,627, leading to an ICER of £49,257/QALY gained. This was the economic evaluation that underpinned the 2014 MS guideline committee's decision not to recommend THC: CBD spray on the grounds of cost-ineffectiveness. This study's clinical evidence is based solely on the Novotna 2011 RCT and had a number of other potential limitations including the sources of utility and cost data, not considering costs associated with adverse events and a different threshold for treatment response. Overall the committee considered this study relevant but with potentially serious limitations for decision-making.

A *de novo* economic model was produced for this review question which aimed to improve upon the published analyses by including evidence from all the relevant RCTs in the area along with recently published longer term patient registry data, adverse event data and the flexibility to conduct sensitivity and scenario analyses.

The committee noted that despite THC: CBD spray being found to be clinically effective at reducing spasticity, no studies found any significant differences in health-related quality of life (HRQoL) measures whether using the EQ-5D, SF-36 or VAS 0-100 instruments. Additionally, differences in point estimates between the two arms of all trials collecting HRQoL measures were very small. They considered that this might be because HRQoL measures have some level of insensitivity to changes in spasticity NRS and are therefore not capturing the benefits of the treatment appropriately. Another contributory factor could be condition severity in the population in the trials, as patients with advanced MS typically have many other important symptoms that can influence their HRQoL and reducing spasticity might not change their self-reported scores by much. The economic model estimated a fairly large difference in HRQoL between responders and non-responders of 0.15, which may therefore have been an overestimate. This difference was 0.09 in data that Lu et al report was observed in the Novotna trial, but using a lower response cut-off, which might also explain the discrepancy.

The economic model was mostly based on short term data from the RCTs and single arm discontinuation data from a registry of advanced MS patients treated with THC: CBD spray. The short-term response data was extrapolated over a 5 year time horizon, making use of the discontinuation data as well as estimated spasticity management costs and adverse event data. The committee discussed these limitations and requested a series of scenario analyses that examined discontinuation from response in both arms of the model over time.

The model only included data on >30% responders but the committee felt that THC:CBD spray might be prescribed on an ongoing basis for >20% responders in clinical practice, who would receive all of the treatment cost but less of the benefit. It's results may therefore be biased in favour of THC:CBD spray.

Over 5 years, the model produced costs of £30,630 in the SoC arm and £32,210 in the SoC + cannabis arm with incremental QALYs of 0.081, leading to an ICER of £19,512/QALY gained. A large number of sensitivity and scenario analyses were conducted on the model and, in most of the plausible analyses, the ICER remained in the range normally considered cost-effective by NICE's advisory committees. The committee discussed the use of the SoC + THC: CBD spray and SoC + placebo arms of the RCTs to model the THC: CBD spray and SoC arms of the economic analysis. While this method is standard for Health Technology Assessment, they noted that the response levels were reasonably high in both arms of the RCTs although the economic model, which combined the RCT with patient registry data predicted this value at ~13%. Some element of this response would be attributable to regression to the mean and some to the placebo effect, the latter of which they suspected would wane over time. They noted that without longer term data on differential response rates it was difficult to be confident that the extrapolations used in the model represented clinical reality. Nevertheless, most plausible variations in parameters and assumptions led to ICERs that were within or below the normal range of cost-effectiveness of £20-30,000/QALY gained, following a change of the list price of THC: CBD spray from £375 to £300. The model's most important limitations were likely to overestimate the cost-effectiveness rather than underestimate it. A scenario analysis using 20% instead of 30% as the cut-off for treatment response and continuation produced an ICER of £24,992/QALY.

There was little direct evidence and no cost-effectiveness data on the quality of life improvements and resource savings associated with using other CBMPs in spasticity in general so the committee decided to make a recommendation against using them outside the context of a clinical trial.

Other factors the committee took into account

It was highlighted that one of the difficulties faced when trying to determine the effects of a treatment in multiple sclerosis is that it is a progressive disease. Most studies appeared to control for this by stating that patients must have had stable treatment for a specified period before the beginning of the trial. This may have helped to identify treatment effects rather than changes due to disease progression. However, it was suggested that this criterion may have meant that the people included in these trials had less severe spasticity than some of those who might be prescribed cannabis-based medicinal products. Many studies also specified that people should have an Ashworth or Modified Ashworth score of 2 or above. This suggests that many participants had less severe spasticity than those who may be prescribed cannabis-based medicinal products, who often have more severe spasticity categorised by an Ashworth score or 3 or 4. Taking this limitation into consideration along with the clinical and cost effectiveness evidence, the committee agreed that there was scope for THC: CBD spray to be offered as part of a 4-week trial to treat moderate to severe spasticity in adults with multiple sclerosis if other pharmacological treatments are not effective and the company provides THC:CBD (Sativex) according to its pay-for-responders scheme.

The committee noted that there was a lack of evidence for the use of cannabis-based medicinal products for children with spasticity. Additionally, THC: CBD spray (Sativex) is not currently licensed in children. Due to this, the committee were unable to make recommendations for the use of THC: CBD spray (Sativex) in children. However, the committee did identify this as an area where further research was needed. Therefore, the committee drafted a research recommendation to explore the clinical and cost effectiveness of cannabis-based medicinal products other than Sativex for people with spasticity which includes children as a subgroup.

The committee also discussed the need for improved tools to assess outcomes for people with spasticity. This was particularly important for quality of life, where a reduction in spasticity is not always accompanied by improvements in quality of life scores. Although there are a number of questionnaires available to assess quality of life, such as the EQ-5D, none of these are specifically designed for people with spasticity. The committee thought that this was an important factor to consider when assessing treatment effectiveness and so this was included as part of the research recommendation.

This evidence review supports recommendations 1.3.1 and 1.3.2 and the research recommendation on spasticity.

Glossary

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

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

Appendix A Review protocols

Review protocol for clinical effectiveness, cost effectiveness, contraindications, potential interactions, individual patient monitoring requirements, treatment durations, reviewing and stopping criteria for cannabis based medicinal products

Field (based on PRISMA-P	Content
Review question	What is the clinical and cost effectiveness of cannabis-based medicinal products for people with spasticity? What are the adverse effects or complications of cannabis-based medicinal products for people with spasticity? What are the contraindications, potential interactions and risks and cautions for use of cannabis-based medicinal products for people with spasticity? What are the individual patient monitoring requirements, treatment durations, reviewing and stopping criteria, including how should treatment be withdrawn or stopped, for use of cannabis-based medicinal products for people with spasticity?
Type of review question	Intervention
Objective of the review	To determine the effectiveness, harms and cost-effectiveness of cannabis based medicinal products in reducing spasticity
Eligibility criteria – population/disease/condition/issue/domain	Adults, young people, children and babies. Specific considerations will be given to: • Young people, children and babies • Pregnant women and women who are breastfeeding • People with existing substance misuse • People with hepatic and renal failure The following definition of spasticity was used: A specific form of increased muscle tone (hypertonia) where one or more of the following are present:

Field (based on PRISMA-P	Content
	• The resistance to externally imposed movement increases with increasing speed of stretch and varies with the direction of joint movement. • The resistance to externally imposed movement increases rapidly beyond a threshold speed or joint angle
Eligibility criteria – intervention	Cannabis-based products for medicinal use (as per government definition): A cannabis-based product for medicinal use that is a preparation or other product, other than one to which paragraph 5 of part 1 of schedule 4 applies, which: is or contains cannabis, cannabis resin, cannabinol or a cannabinol derivative (not being dronabinol or its stereoisomers) is produced for medicinal use in humans; and is a medicinal product, or a substance or preparation for use as an ingredient of, or in the production of an ingredient of, a medicinal product (MDR 2018 regulations) Synthetic compounds which are identical in structure to naturally occurring cannabinoids such as delta-9-tetrahydrocannabinol (THC) for example dronabinol Licensed products Sativex and nabilone Plant-derived cannabinoids such as pure cannabidiol For the purpose of this guideline, all the interventions above will be classed as cannabis-based medicinal products.
Eligibility criteria – comparator	Placebo Any relevant treatment (including physiotherapy, botulinum toxin, other management of symptoms) Combination of treatments Usual or standard care.
Outcomes	30% or greater improvement in spasticity Change in spasticity measured using any validated scale which measures spasticity. Serious adverse events Adverse events including but not limited to: sleep problems, fatigue, road traffic accidents, psychological distress, dizziness, headache, confusion state, paranoia, psychosis, substance dependence, diarrhoea at the start of treatment

Field (based on PRISMA-P	Content
	Withdrawals due to adverse events Substance abuse due to the use of cannabis-based medicinal product. Misuse/diversion Hepatic or renal failure Outcomes requiring a narrative synthesis: Contraindications as listed in exclusion criteria Monitoring requirements, treatment durations, reviewing and stopping criteria, including how should treatment be withdrawn stopped as discussed in the methods of included studies.
Eligibility criteria – study design	For adults: RCTs Systematic reviews of RCTs The committee noted that a minimum of 5 RCTs were required to provide adequate evidence. If less than five RCTs identified, prospective cohort studies will be used. For children: RCTs Systematic reviews of RCTs If less than five RCTs identified, prospective and retrospective cohort studies will be used. Additional information on safety concerns and contraindications will be obtained from the Summary of Product Characteristics and other relevant sources, such as the U.S Food and Drugs Administration.
Other inclusion/exclusion criteria	Inclusion Cannabis-based products for the medicinal use when other treatments haven't helped or have been discounted. Exclusion Synthetic cannabinoids In schedule 1 of the 2001 regulations, Smoked cannabis-based products Studies which do not report the doses or the concentration of cannabinoid constituents. For randomised crossover studies, washout periods of less than 1 week.

Field (based on PRISMA-P	Content
	Rigidity due to Parkinson's disease. The committee noted that studies for Parkinson's disease may be measuring rigidity rather than spasticity.
sub-group analysis	Subgroups, where possible, will include: Young people, children and babies Pregnant women and women who are breastfeeding People with existing substance abuse Spasticity in relation to multiple sclerosis (MS) People with hepatic and renal failure
Selection process – duplicate screening/selection/analysis	10% of the abstracts will be reviewed by two reviewers, with any disagreements will be resolved by discussion or, if necessary, a third independent reviewer. If meaningful disagreements are found between the different reviewers, a further 10% of the abstracts will be reviewed by two reviewers, with this process continuing until agreement is achieved between the two reviewers. From this point, the remaining abstracts will be screened by a single reviewer.
Data management (software)	See Appendix B.
Information sources – databases and dates	Sources to be searched Clinical searches - Medline, Medline in Process, Medline EPub Ahead of Print, Embase, Cochrane CDSR, CENTRAL, DARE (legacy records), HTA, MHRA. Economic searches - Medline, Medline in Process, Medline EPub Ahead of Print, Embase, Econlit, NHS EED (legacy records) and HTA, with economic evaluations and quality of life filters applied. Supplementary search techniques None identified Limits Studies reported in English Study design RCT, SR and Observational filter will be applied (as agreed) Animal studies will be excluded from the search results Conference abstracts will be excluded from the search results No date limit will be set.
Identify if an update	N/A

Field (based on PRISMA-P	Content
Author contacts	Guideline updates team
Highlight if amendment to previous protocol	This is a new protocol.
Search strategy – for one database	For details please see Appendix C of relevant chapter.
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as Appendix D (clinical evidence tables) or H (economic evidence tables).
Data items – define all variables to be collected	For details please see evidence tables in Appendix D (clinical evidence tables) or H (economic evidence tables).
Methods for assessing bias at outcome/study level	Study checklists were used to critically appraise individual studies. For details please see Appendix H of Developing NICE guidelines: the manual The following checklists will be used: Risk of bias of intervention studies - systematic reviews and meta-analyses will be assessed using the Risk of Bias in Systematic Reviews (ROBIS) checklist Risk of bias of intervention studies – randomised controlled trials (individual or cluster) will be assessed using the Cochrane risk of bias (RoB) 2.0 tool Risk of bias of cohort studies will be assessed using Cochrane ROBINS-I The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis	For details please see section 6 of Developing NICE guidelines: the manual
Methods for quantitative analysis – combining studies	For details please see the methods and process section of the main file.

Field (based on PRISMA-P	Content
and exploring (in)consistency	
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6 of Developing NICE guidelines: the manual.
Confidence in cumulative evidence	For details please see sections 6 of Developing NICE guidelines: the manual
Rationale/context – what is known	For details please see the introduction to the evidence review in the main file.
Describe contributions of authors and guarantor	A multidisciplinary committee [add link to history page of the guideline] developed the evidence review. The committee was convened by NICE Guideline Updates Team and chaired by Steve Pilling in line with section 3 of Developing NICE guidelines: the manual. Staff from NICE undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the evidence review in collaboration with the committee. For details please see Developing NICE guidelines: the manual.
Sources of funding/support	The NICE Guideline Updates Team is an internal team within NICE.
Name of sponsor	The NICE Guideline Updates Team is an internal team within NICE.
Roles of sponsor	The NICE Guideline Updates Team is an internal team within NICE.

Appendix B Methods

Priority screening

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

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

Evidence synthesis and meta-analyses

Where possible, meta-analyses were conducted to combine the results of quantitative studies for each outcome. For continuous outcomes analysed as mean differences, where change from baseline data were reported in the trials and were accompanied by a measure of spread (for example standard deviation), these were extracted and used in the meta-analysis. Where measures of spread for change from baseline values were not reported, the corresponding values at study end were used and were combined with change from baseline values to produce summary estimates of effect. These studies were assessed to ensure that baseline values were balanced across the treatment groups; if there were significant differences at baseline these studies were not included in any meta-analysis and were reported separately. For continuous outcomes analysed as standardised mean differences, where only baseline and final time point values were available, change from baseline standard deviations were estimated, assuming a correlation coefficient of 0.5.

Evidence of effectiveness of interventions

Quality assessment

Parallel RCTs and crossover RCTs were quality assessed using the Cochrane Risk of Bias Tool 2.0.

Each individual study was classified into one of the following three groups:

- Low risk of bias – The true effect size for the study is likely to be close to the estimated effect size.
- Some concern around risk of bias – There is a possibility the true effect size for the study is substantially different to the estimated effect size.
- High risk of bias – It is likely the true effect size for the study is substantially different to the estimated effect size.

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

- Direct – No important deviations from the protocol in population, intervention, comparator and/or outcomes.

- Partially indirect – Important deviations from the protocol in one of the population, intervention, comparator and/or outcomes.
- Indirect – Important deviations from the protocol in at least two of the following areas: population, intervention, comparator and/or outcomes.

Methods for combining intervention evidence

Meta-analyses of interventional data were conducted with reference to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011).

A pooled relative risk was calculated for dichotomous outcomes (using the Mantel–Haenszel method) reporting numbers of people having an event. Both relative and absolute risks were presented, with absolute risks calculated by applying the relative risk to the pooled risk in the comparator arm of the meta-analysis (all pooled trials).

Fixed- and random-effects models (der Simonian and Laird) were fitted for all syntheses, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence. Fixed-effects models were the preferred choice to report, but in situations where the assumption of a shared mean for fixed-effects model were clearly not met, even after appropriate pre-specified subgroup analyses were conducted, random-effects results are presented. Fixed-effects models were deemed to be inappropriate if one or both of the following conditions was met:

- Significant between study heterogeneity in methodology, population, intervention or comparator was identified by the reviewer in advance of data analysis. This decision was made and recorded before any data analysis was undertaken.
- The presence of significant statistical heterogeneity in the meta-analysis, defined as $I^2 \geq 50\%$.

Meta-analyses were performed in Cochrane Review Manager V5.3

Minimal clinically important differences (MIDs)

The Core Outcome Measures in Effectiveness Trials (COMET) database was searched to identify published minimal clinically important difference thresholds relevant to this guideline. Identified MIDs were assessed to ensure they had been developed and validated in a methodologically rigorous way, and were applicable to the populations, interventions and outcomes specified in this guideline. In addition, the Guideline Committee were asked to prospectively specify any outcomes where they felt a consensus MID could be defined from their experience. In particular, any questions looking to evaluate non-inferiority (that one treatment is not meaningfully worse than another) required an MID to be defined to act as a non-inferiority margin.

One study [Farrar 2008] determined the clinical importance of change on a 0-10 numerical rating scale (NRS). The study estimated the level of change from baseline on the 0-10 NRS spasticity scale that constituted a minimal clinically important difference as anchored to the patient's global impression of change (PGIC). The findings showed that 'minimally improved' or better on the PGIC produced cut-off point of -0.9 for the raw score change. Therefore, -0.9 was used as a MID for the NRS scale.

No MIDs were identified for other outcomes. Therefore, line of no effect was used to assess imprecision.

When decisions were made in situations where MIDs were not available, the 'Evidence to Recommendations' section of that review should make explicit the committee's view of the expected clinical importance and relevance of the findings. In particular, this includes

consideration of whether the whole effect of a treatment (which may be felt across multiple independent outcome domains) would be likely to be clinically meaningful, rather than simply whether each individual sub outcome might be meaningful in isolation.

GRADE for pairwise meta-analyses of interventional evidence

GRADE was used to assess the quality of evidence for the selected outcomes as specified in 'Developing NICE guidelines: the manual (2018)'. Data from all study designs was initially rated as high quality and the quality of the evidence for each outcome was downgraded or not from this initial point, based on the criteria given in Table 1

Table 1: Rationale for downgrading quality of evidence for intervention studies

GRADE criteria	Reasons for downgrading quality
Risk of bias	Not serious: If less than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from studies at high risk of bias, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies at high and low risk of bias.
Indirectness	Not serious: If less than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from indirect studies, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between direct and indirect studies.
Inconsistency	Concerns about inconsistency of effects across studies, occurring when there is unexplained variability in the treatment effect demonstrated across studies (heterogeneity), after appropriate pre-specified subgroup analyses have been conducted. This was assessed using the I^2 statistic. N/A: Inconsistency was marked as not applicable if data on the outcome was only available from one study. Not serious: If the I^2 was less than 33.3%, the outcome was not downgraded. Serious: If the I^2 was between 33.3% and 66.7%, the outcome was downgraded one level. Very serious: If the I^2 was greater than 66.7%, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies with the smallest and largest effect sizes.
Imprecision	If the line of no effect was defined as an MID for the outcome, it was downgraded once if the 95% confidence interval for the effect size crossed the line of no effect (i.e. the outcome was not statistically significant), and twice if the sample size of the study was sufficiently small that it is not plausible any realistic effect size could have been detected.

GRADE criteria	Reasons for downgrading quality
	Outcomes meeting the criteria for downgrading above were not downgraded if the confidence interval was sufficiently narrow that the upper and lower bounds would correspond to clinically equivalent scenarios.

The quality of evidence for each outcome was upgraded if any of the following three conditions were met:

- Data from non-randomised studies showing an effect size sufficiently large that it cannot be explained by confounding alone.
- Data showing a dose-response gradient.
- Data where all plausible residual confounding is likely to increase our confidence in the effect estimate.

Summary of the evidence

The evidence is presented in the form of a table because the committee agreed in advance that effect sizes would be an important consideration. Summary of evidence is stratified by comparison and reflects evidence that was statistically significant.

Where the data are only consistent, at a 95% confidence level, with an effect in one direction (i.e. one that is 'statistically significant'), and the magnitude of that effect is most likely to meet or exceed the MID (i.e. the point estimate is not in the zone of equivalence). In such cases, we state that the evidence showed that there is an effect. In all other cases, we state that the evidence could not differentiate between the comparators.

Quality assessment

Single arm studies were also included in this review. These studies were quality assessed using the Institute of Health Economics (IHE) Quality Appraisal Checklist. Studies were assessed on the methods of participant recruitment, retention and outcome measurement (as appropriate), with each individual study classified into one of the following three groups:

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

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

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

Appendix C Literature search strategies

A single systematic search was conducted for all of the questions within this evidence review between 19th December 2018 and 21st January 2019. The following databases were searched MEDLINE, MEDLINE in Process, MEDLINE e pub Ahead of print, Embase, (all via the Ovid platform), Cochrane Database of Systematic Reviews CENTRAL (all via the Wiley platform), and the HTA and DARE databases (both via the CRD platform). NICE inhouse RCT, systematic review, and observational filters were attached where appropriate.

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

1 Medical Marijuana/

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

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

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

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

6 (nabilone or cesamet).tw.

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

8 Dronabinol/

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

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

11 (THC or tetrahydrocannabinol*).tw.

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

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

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

15 THCa.tw.

16 CBDa.tw.

17 cannabinol*.tw.

18 cannabigerol*.tw.

19 cannabichromene*.tw.

20 (tetrahydrocannabivarin* or THCV).tw.

21 (cannabidivarin* or CBDV).tw.

22 or/1-21

23 animals/ not humans/

24 22 not 23

25 limit 24 to english language

26 Randomized Controlled Trial.pt.

27 Controlled Clinical Trial.pt.

28 Clinical Trial.pt.

29 exp Clinical Trials as Topic/

30 Placebos/

31 Random Allocation/

32 Double-Blind Method/

33 Single-Blind Method/

34 Cross-Over Studies/

35 ((random$ or control$ or clinical$) adj3 (trial$ or stud$)).tw.

36 (random$ adj3 allocat$).tw.

37 placebo$.tw.

38 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw.

39 (crossover$ or (cross adj over$)).tw.

40 or/20-33

41 Meta-Analysis.pt.

42 Network Meta-Analysis/

43 Meta-Analysis as Topic/

44 Review.pt.

45 exp Review Literature as Topic/

46 (metaanaly$ or metanaly$ or (meta adj3 analy$)).tw.

47 (review$ or overview$).ti.

48 (systematic$ adj5 (review$ or overview$)).tw.

49 ((quantitative$ or qualitative$) adj5 (review$ or overview$)).tw.

50 ((studies or trial$) adj2 (review$ or overview$)).tw.

51 (integrat$ adj3 (research or review$ or literature)).tw.

52 (pool$ adj2 (analy$ or data)).tw.

53 (handsearch$ or (hand adj3 search$)).tw.

54 (manual$ adj3 search$).tw.

55 or/35-48

56 34 or 49

57 19 and 50

58 Observational Studies as Topic/

59 Observational Study/

60 Epidemiologic Studies/

61 exp Case-Control Studies/

62 exp Cohort Studies/

63 Cross-Sectional Studies/

64 Controlled Before-After Studies/

65 Historically Controlled Study/

66 Interrupted Time Series Analysis/

67 Comparative Study.pt.

68 case control$.tw.

69 case series.tw.

70 (cohort adj (study or studies)).tw.

71 cohort analy$.tw.

72 (follow up adj (study or studies)).tw.

73 (observational adj (study or studies)).tw.

74 longitudinal.tw.

75 prospective.tw.

76 retrospective.tw.

77 cross sectional.tw.

78 or/26-45

79 25 and 46

80 57 or 79

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

Economic evaluations

Economics/
exp "Costs and Cost Analysis"/
Economics, Dental/
exp Economics, Hospital/
exp Economics, Medical/
Economics, Nursing/
Economics, Pharmaceutical/
Budgets/
exp Models, Economic/
Markov Chains/
Monte Carlo Method/
Decision Trees/
econom$.tw.
cba.tw.
cea.tw.
cua.tw.
markov$.tw.
(monte adj carlo).tw.
(decision adj3 (tree$ or analys$)).tw.
(cost or costs or costing$ or costly or costed).tw.
(price$ or pricing$).tw.
budget$.tw.
expenditure$.tw.
(value adj3 (money or monetary)).tw.
(pharmacoeconomic$ or (pharmaco adj economic$)).tw.
or/1-25

Quality of Life

"Quality of Life"/
quality of life.tw.

"Value of Life"/

Quality-Adjusted Life Years/

quality adjusted life.tw.

(qaly$ or qald$ or qale$ or qtime$).tw.

disability adjusted life.tw.

daly$.tw.

Health Status Indicators/

(sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.

(sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.

(sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.

(sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.

(sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.

(euroqol or euro qol or eq5d or eq 5d).tw.

(qol or hql or hqol or hrqol).tw.

(hye or hyes).tw.

health$ year$ equivalent$.tw.

utilit$.tw.

(hui or hui1 or hui2 or hui3).tw.

disutili$.tw.

rosser.tw.

quality of wellbeing.tw.

quality of well-being.tw.

qwb.tw.

willingness to pay.tw.

standard gamble$.tw.

time trade off.tw.

time tradeoff.tw.

tto.tw.

or/1-30

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

Sativex

Dronabinol

Epidiolex

Nabiximols

Abalone

Tetrabinex

Nabidiolex

Cesamet

Tilray

Bedrocan

Bedrobinol

Bedica

Bediol

Bedrolite

Marinol

Syndros

THC

Tetrahydrocannabinol

Cannabinol

Cannibigerol

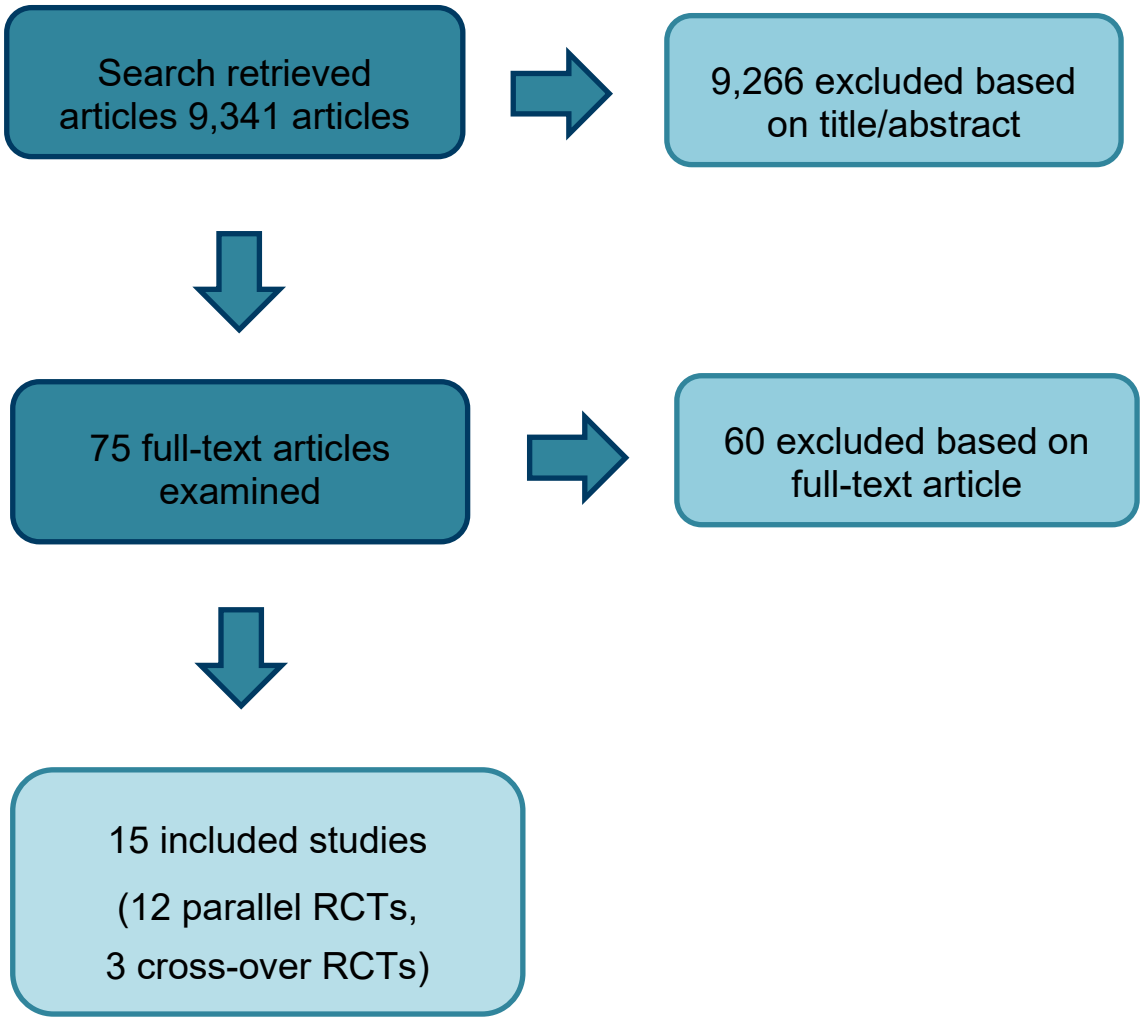
Cannabichromene

Tetrahydrocannabivarin

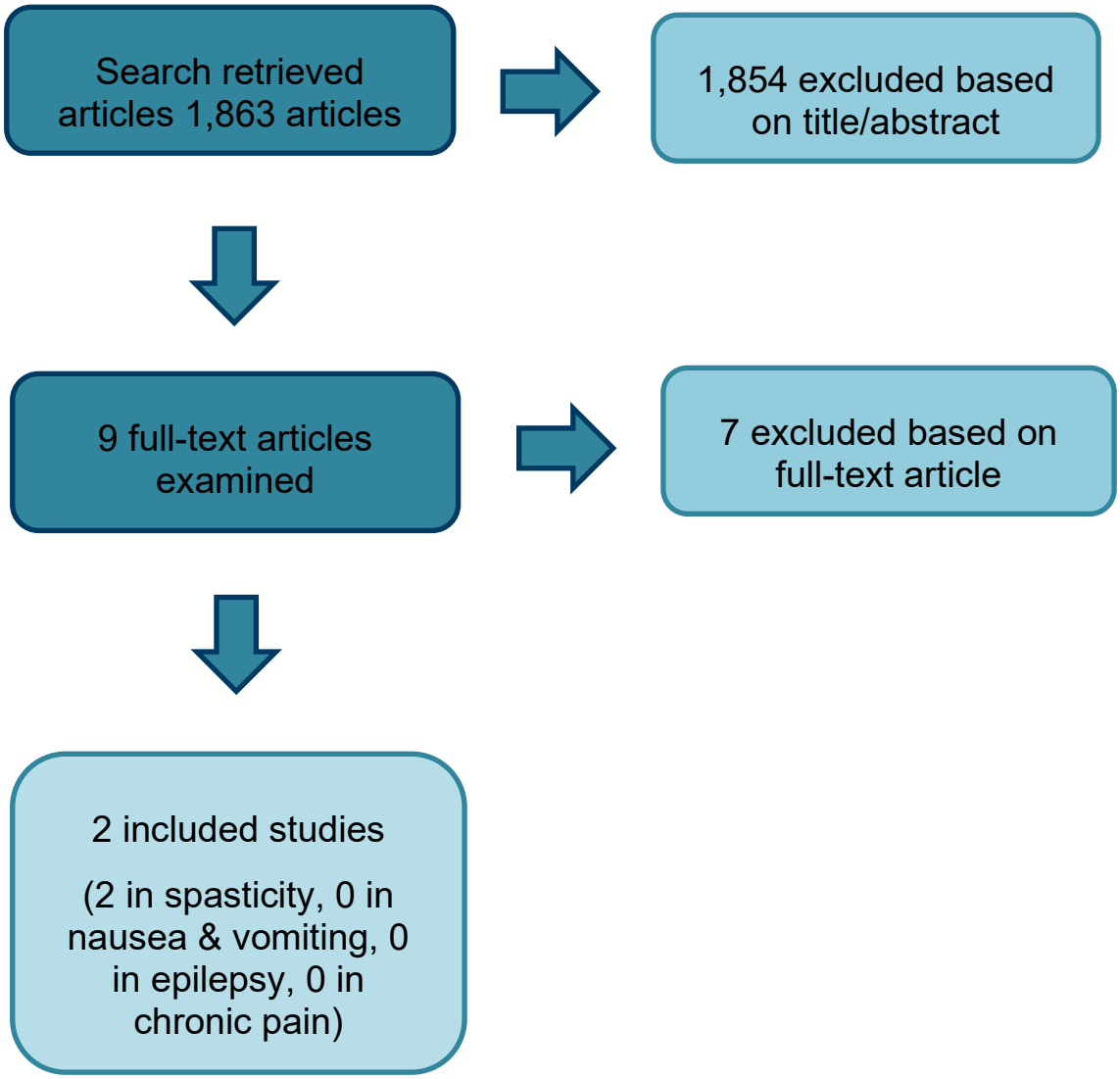
Cannabidivarin

Appendix D Clinical evidence study selection

RCTs and systematic reviews of RCTs search



Health economics search



Appendix E Clinical evidence tables

Parallel RCTs

Ball 2015

Bibliographic Reference	Ball, Susan; Vickery, Jane; Hobart, Jeremy; Wright, Dave; Green, Colin; Shearer, James; Nunn, Andrew; Cano, Mayam Gomez; MacManus, David; Miller, David; Mallik, Shahrukh; Zajicek, John; The Cannabinoid Use in Progressive Inflammatory brain Disease (CUPID) trial: a randomised double-blind placebo-controlled parallel-group multicentre trial and economic evaluation of cannabinoids to slow progression in multiple sclerosis; Health technology assessment (Winchester, England); 2015; vol. 19 (no. 12); vii-187

Study details

Study type	Randomised controlled trial (RCT)
Study location	27 NHS sites - England, Wales, Scotland
Study setting	25 hospital neurology departments 2 rehabilitation departments
Study dates	May 2006 - July 2008
Duration of follow-up	36 months
Sources of funding	MRC NIHR
Inclusion criteria	Age 18 - 65 years Diagnosis of MS Primary or secondary progressive MS Evidence of disease progression

	In previous year Expanded Disability Status Scale score 4.0 - 6.5 Willing to abstain from other cannabis use during trial
Exclusion criteria	Immunosuppressive/immunomodulatory therapy Previous 12 months Taking corticosteroids Previous 3 months Significant MS relapse Previous 6 months Serious illness/medical condition likely to interfere with study assessment History of psychotic illness Sesame seed allergy Pregnancy Prior cannabinoid use Including nabilone. In 4 weeks before study (identified by positive urinary cannabinoid test prior to study entry)
Sample size	498
Condition specific characteristics	Mean EDSS score Δ9-THC: 5.83 (0.69) Placebo: 5.88 (0.67)
Intervention 1	Δ9-THC capsules 3.5 mg Δ9-THC (dronabinol) gelatin capsules, 2-4 times per day (weight dependent)
Intervention 2	Placebo Identical sesame oil capsules
Outcome measures	Incidences of adverse events Quality of life

	MS Spasticity Scale-88 score Mean annual change

Study arms

	Δ9-THC capsules (N = 332)
Loss to follow-up	62
% Female	59.6%
Mean age (SD)	52.29 (7.6)
Condition specific characteristics	Mean EDSS score 5.83 (0.69)
Formulation	3.5 mg Δ9-THC (dronabinol) gelatin capsules, administered orally
How dose was titrated up	4 week titration phase. Could increase dose by 1 capsule twice daily until reached maximum weight-related dose or development of adverse events.
What the maintenance dose was	Maximum 2-4 capsules per day (weight dependent). Mean (SD) number of capsules: 5 weeks - 5 (1.91) 31 months - 3.91 (1.93)
How long the maintenance dose was sustained for	36 months

Monitoring/reviewing procedure	Initially monitored at 2 and 4 weeks after start of treatment to allow for dose adjustment and monitoring of adverse events. If adverse events developed, advised not to increase dose. If adverse events intolerable then dose reduced. Follow-up at 3 and 6 months followed by every 6 months. Monitoring included review of seizure diary, adverse events, depression, vital signs, haemotology and liver function.
Stopping criteria	No information provided

Placebo (N = 166)

Identical capsules

% Female	59.2%
Mean age (SD)	51.97 (8.2)
Condition specific characteristics	Mean EDSS score 5.88 (0.67)
Formulation	Placebo sesame seed oil capsules which appeared identical to active treatment
What the maintenance dose was	Mean (SD) number of capsules: 5 weeks - 6.32 (1.57) 31 months - 5.85 (1.92)

Risk of bias

Domain 1: Bias arising from the randomization process

Risk of bias judgement for this domain

Low

Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)

Risk of bias for this domain

Low

Domain 3. Bias due to missing outcome data

Risk-of-bias judgement for this domain

Some concerns

(19% of patients allocated CBD and 9% of patients allocated placebo lost to follow-up)

Domain 4. Bias in measurement of the outcome

Risk-of-bias judgement for this domain

Low

Domain 5. Bias in selection of the reported result

Risk-of-bias judgement domain

Low

Overall bias and Directness

Risk of bias judgement

Some concerns

(19% of patients allocated CBD and 9% of patients allocated placebo lost to follow-up)

Overall Directness

Partially directly applicable

(study aimed at slowing disease progression rather than reducing spasticity)

Collin 2007

Bibliographic Reference	Collin, C.; Davies, P.; Mutiboko, I. K.; Ratcliffe, S.; Sativex Spasticity in, M. S. Study Group; Randomized controlled trial of cannabis-based medicine in spasticity caused by multiple sclerosis; European journal of neurology; 2007; vol. 14 (no. 3); 290-6

Study details

Study type	Randomised controlled trial (RCT)
Study location	UK and Romania
Study setting	Eight centres
Study dates	April 2002 - March 2004
Duration of follow-up	6 weeks
Sources of funding	GW Pharma Ltd
Inclusion criteria	Age >18 years Diagnosis of MS Stable disease for at least 3 months before study entry Willing to abstain from other cannabis use during trial For at least 7 days before study entry and throughout the study Spasticity

	In at least 2 muscle groups with Ashworth score of 2 or more Current therapy failed to provide adequate relief Stable treatment For at least 30 days before study entry and during the study Use of effective contraception
Exclusion criteria	Known history of alcohol or substance abuse Known hypersensitivity to cannabinoids History of psychotic illness Psychosis or severe psychiatric disorder other than depression Pregnancy or lactation Severe cardiovascular disorder Including poorly controlled hypertension History of seizures
Sample size	189
Outcome measures	Change in spasticity from baseline (NRS) Weekly, up to 6 weeks Change in spasticity from baseline (Ashworth) Baseline to 4 weeks NRS responder (30% reduction in spasticity score) NRS responder (50% reduction in spasticity score)

Study arms

	2.7 mg Δ9-THC : 2.5 mg CBD oromucosal spray (Sativex) (N = 120)

Inclusion criteria	Current therapy failed to provide adequate relief
Split between study groups	120
Loss to follow-up	1
% Female	64.5%
Mean age (SD)	49.7 (10.2)
Condition specific characteristics	Duration of MS - years (SD) 13.6 (8.6)
Formulation	2.7 mg Δ9-THC : 2.5 mg CBD (Sativex)
How dose was titrated up	2 week titration phase - increased from initial dose to maximum 48 sprays/day. Other medications & therapies maintained
What the maintenance dose was	Maximum 48 sprays per day Mean sprays per day (SD): 9.4 (6.4)
How long the maintenance dose was sustained for	4 weeks
Monitoring/reviewing procedure	Monitored at 2 and 6 weeks. Monitoring included review of adverse events, other medication use and diary entries
Stopping criteria	No information provided

Placebo (N = 64)

Split between study groups	64
Loss to follow-up	1
% Female	52.3%
Mean age (SD)	47.8 (9.5)
Condition specific characteristics	Duration of MS - years (SD) 12.2 (7.7)
Formulation	Identically flavoured placebo
What the maintenance dose was	Mean sprays per day (SD): 14.7 (8.4)

Risk of bias

Domain 1: Bias arising from the randomization process

Risk of bias judgement for this domain

Low

Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)

Risk of bias for this domain

Low

Domain 3. Bias due to missing outcome data

Risk-of-bias judgement for this domain

Some concerns

(19% of patients allocated CBD and 9% of patients allocated placebo lost to follow-up)

Domain 4. Bias in measurement of the outcome

Risk-of-bias judgement for this domain

Low

Domain 5. Bias in selection of the reported result

Risk-of-bias judgement domain

Low

Overall bias and Directness

Risk of bias judgement

Some concerns

(19% of patients allocated CBD and 9% of patients allocated placebo lost to follow-up)

Overall Directness

Directly applicable

Collin 2010

Bibliographic Reference	Collin, C.; Ehler, E.; Waberzinek, G.; Alsindi, Z.; Davies, P.; Powell, K.; Notcutt, W.; O'Leary, C.; Ratcliffe, S.; Novakova, I.; Zapletalova, O.; Pikova, J.; Ambler, Z.; A double-blind, randomized, placebo-controlled, parallel-group study of Sativex, in subjects with symptoms of spasticity due to multiple sclerosis; Neurological research; 2010; vol. 32 (no. 5); 451-9

Study details

Study type	Randomised controlled trial (RCT)
Study location	UK, Czech Republic
Study setting	UK: 15 centres Czech Republic: 8 centres
Study dates	Not reported
Duration of follow-up	14 weeks
Sources of funding	GW Pharma Ltd
Inclusion criteria	Diagnosis of MS For at least 6 months Spasticity At least 3 month history of spasticity due to MS Current therapy failed to provide adequate relief NRS score Spasticity score of at least 24 during last 6 days of baseline period (min mean daily score of 4 - moderate spasticity) Stable treatment At least 30 days before study entry
Exclusion criteria	Spasticity not due to MS History of seizures History of psychotic illness Severe cardiovascular disorder History of renal or hepatic disorder
Sample size	337

Outcome measures	Change in spasticity from baseline (NRS) Mean NRS score over the last 14 days of treatment NRS responder (30% reduction in spasticity score) Incidences of adverse events Serious adverse events

Study arms

2.7 mg THC / 2.5 mg CBD oromucosal spray (Sativex) (N = 167)

Split between study groups	167
Loss to follow-up	1
% Female	63%
Mean age (SD)	48.0 (10.06)
Condition specific characteristics	Mean EDSS score 6.0 (1.56) Duration of MS - years (SD) 14.4 (8.29) Duration of spasticity symptoms 7.5 (5.14)
Formulation	2.7 mg THC / 2.5 mg CBD
How dose was titrated up	Self-titrated to optimal dose. No information on length of titration phase provided

What the maintenance dose was	Maximum 24 sprays per day Mean (range) sprays per day: 8.5 (1 - 22)
How long the maintenance dose was sustained for	15 weeks
Monitoring/reviewing procedure	No information on timing of reviews. Monitoring included review of medication usage, spasticity, timed 10 m walk test, pain, fatigue, tremor, bladder symptoms & sleep quality
Stopping criteria	Adverse events

Placebo (N = 170)

Split between study groups	170
Loss to follow-up	2
% Female	59%
Mean age (SD)	47.1 (9.15)
Condition specific characteristics	Mean EDSS score 6.0 (1.50) Duration of MS - years (SD) 16.0 (8.48) Duration of spasticity symptoms 16.0 (8.48)

	Formulation	Oromucosal spray
	What the maintenance dose was	Mean (range) sprays per day: 15.4 (2 - 23)

Risk of bias

Domain 1: Bias arising from the randomization process

Risk of bias judgement for this domain

Some concerns

(No information about randomisation or concealment of allocation sequence)

Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)

Risk of bias for this domain

Some Concerns

(No information about whether people delivering the intervention were aware of the assigned intervention)

Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)

Risk of bias judgement for this domain

This question has not yet been answered.

Domain 3. Bias due to missing outcome data

Risk-of-bias judgement for this domain

Some concerns

(21% of people assigned to CBD and 12% of people assigned to placebo withdrew from the trial)

Domain 4. Bias in measurement of the outcome

Risk-of-bias judgement for this domain

Some concerns

(No information about whether outcome assessors were blinded to intervention)

Domain 5. Bias in selection of the reported result

Risk-of-bias judgement domain

Low

Overall bias and Directness

Risk of bias judgement

Some concerns

(All outcomes: No information about the randomisation process, allocation concealment or whether outcome assessors were blinded to the intervention. Higher % of people withdrew from the active arm than placebo)

Overall Directness

Directly applicable

Langford 2013

Bibliographic Reference	Langford, R. M.; Mares, J.; Novotna, A.; Vachova, M.; Novakova, I.; Notcutt, W.; Ratcliffe, S.; A double-blind, randomized, placebo-controlled, parallel-group study of THC/CBD oromucosal spray in combination with the existing treatment regimen, in the relief of central neuropathic pain in patients with multiple sclerosis; Journal of neurology; 2013; vol. 260 (no. 4); 984-97

Study details

Study type	Randomised controlled trial (RCT)

Study location	33 study sites - UK (12), Czech republic (7), Canada (5), Spain (5), France (4)
Study setting	Not disclosed
Study dates	Not disclosed. Study was submitted for publication in 2012.
Duration of follow-up	Phase A (standard RCT): 14 weeks Phase B (withdrawal RCT): 14 weeks
Sources of funding	GW Pharma LTD
Inclusion criteria	Central neuropathic pain due to multiple sclerosis for at least 3 months Sum score of at least 24 on a pain 0-10 point NRS on the last 6 days Stable analgesia regimen for at least 2 weeks prior to study entry
Exclusion criteria	Pain from other concomitant conditions Other pain that was not central neuropathic pain Patients with a history of significant pychiatric conditions (other than depression) Patients with history of renal, hepatic, cardiovascular, convulsive disorder, or with sensitivity to cannabis
Sample size	Phase A (standard RCT): At start: 339; Completed: 297 Phase B (withdrawal RCT): At start: 42; Completed: 41
Split between study groups	Phase A (standard RCT): THC + CBD: 141; placebo: 156 Phase B (withdrawal RCT): THC + CBD: 21; placebo: 20
Loss to follow-up	Phase A (standard RCT): THC + CBD: 26; placebo: 16 Phase B (withdrawal RCT): THC + CBD: 0; placebo: 1

% Female	Phase A (standard RCT): THC + CBD: 68%; placebo: 68% Phase B (withdrawal RCT): THC + CBD: 52%; placebo: 67%
Mean age (SD)	Phase A (standard RCT): THC + CBD: 48.42 (10.43); placebo: 49.51 (10.50) Phase B (withdrawal RCT): THC + CBD: 46.20 (10.39); placebo: 49.82 (9.75)
Outcome measures	Response to treatment - an improvement of 30% or more in patient's mean pain NRS from baseline Incidences of adverse events Response to treatment - an improvement of 50% or more in patient's mean pain NRS from baseline Opioid dose Global Impression of Change Quality of life

Study arms

Oromucosal spray THC 2.7 mg and CBD 2.5 mg per 100 microlitre actuation (Sativex) (N = 141)	
Formulation	Oromucosal spray THC 2.7 mg and CBD 2.5 mg per 100 microlitre actuation.
How dose was titrated up	1-week baseline period allowing for dosing optimization preceded the 14-week treatment phase. During the baseline period, patients self-titrated, titrating upwards via a pre-defined escalation scheme to reach their optimal dose depending on efficacy, tolerability, and maximum permitted dose.
What the maintenance dose was	Patients were restricted to a maximum of 12 sprays per 24-h period.

How long the maintenance dose was sustained for	14 days
Monitoring/reviewing procedure	Review at 14 days
Stopping criteria	None described

Placebo (N = 156)

Formulation	Placebo delivered the excipient plus colorants.
How dose was titrated up	The same protocol was used for the placebo as for the medicinal cannabis.
How long the maintenance dose was sustained for	14 days
Monitoring/reviewing procedure	Reviewed at 14 days.

Withdrawal arm: Oromucosal spray THC 2.7 mg and CBD 2.5 mg per 100 microlitre actuation (N = 21)

Inclusion criteria	Criteria 1 French and Czech patients who had completed phase A of the study were invited to take part in phase B. Patients were required to have received an average of three or more sprays of THC: CBD per day in the 7 days prior to completion of phase A, shown tolerability to the study medication, and maintained a stable treatment regimen throughout the study for all neuropathic pain medications.
Formulation	Oromucosal spray THC 2.7 mg and CBD 2.5 mg per 100 microlitre actuation
How dose was titrated up	To escalate the dose to a maximum of 12 daily sprays during the phase B

What the maintenance dose was	Maximum dose of 12 daily sprays.
How long the maintenance dose was sustained for	28 days
Monitoring/reviewing procedure	No details provided
Stopping criteria	No details provided

Withdrawal arm: Placebo (N = 20)

Inclusion criteria	Criteria 1 French and Czech patients who had completed phase A of the study were invited to take part in phase B. Patients were required to have received an average of three or more sprays of THC: CBD per day in the 7 days prior to completion of phase A, shown tolerability to the study medication, and maintained a stable treatment regimen throughout the study for all neuropathic pain medications.
Formulation	Placebo delivered the excipient plus colorants.
How dose was titrated up	Same as intervention arm
How long the maintenance dose was sustained for	28 days
Monitoring/reviewing procedure	No details provided

Risk of bias

Domain 1: Bias arising from the randomization process

Risk of bias judgement for this domain

Low

Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)

Risk of bias for this domain

Low

Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)

Risk of bias judgement for this domain

Low

Domain 3. Bias due to missing outcome data

Risk-of-bias judgement for this domain

Low

Domain 4. Bias in measurement of the outcome

Risk-of-bias judgement for this domain

Low

Domain 5. Bias in selection of the reported result

Risk-of-bias judgement domain

Low

Overall bias and Directness

Risk of bias judgement

Low

Overall Directness

Directly applicable

Markova 2018

Bibliographic Reference	Markova, Jolana; Essner, Ute; Akmaz, Bulent; Marinelli, Marcella; Trompke, Christiane; Lentschat, Arnd; Vila, Carlos; 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; The International journal of neuroscience; 2018; 1-10

Study details

Study type	Randomised controlled trial (RCT)
Study location	Czech Republic and Austria
Study setting	15 sites (14 Czech Republic, 1 Austria)
Study dates	Not reported
Duration of follow-up	12 weeks
Sources of funding	Almirall Hermal GmbH and Almirall S.A.
Inclusion criteria	Age 18 years or over Diagnosis of MS MS spasticity symptoms for at least 12 months

	Moderate to severe spasticity defined as a score ≥4 on MS spasticity NRS scale Previous treatment with at least 2 different optimised oral MS spasticity therapies, including oral baclofen and/or oral tizanidine Receiving optimised treatment with one or more oral antispasticity drugs for at least 3 months before screening without adequate relief of MS spasticity symptoms At least 80% reduction in NRS spasticity score in Phase A
Exclusion criteria	Use of botulinum toxin In 6 months prior to study entry Prior use of THC:CBD spray Use of cannabis herb or other cannabinoid-based drugs within 30 days before study entry Known history of alcohol or substance abuse Pregnancy Possibility of pregnancy or lactation Family history of major psychiatric disorders other than depression History of myocardial infarction or clinically significant cardiac dysfunction Clinically significant impaired renal function or impaired hepatic function
Sample size	106
Outcome measures	NRS responder (30% reduction in spasticity score) Change in spasticity from baseline (NRS) Change in spasticity from baseline (Ashworth) Modified Ashworth scale Expanded Disability Status Scale Change from baseline Incidences of adverse events

	Serious adverse events Withdrawals due to adverse events

Study arms

THC:CBD Oromucosal spray (N = 53)	
Split between study groups	53
Loss to follow-up	3
% Female	Baseline characteristics n
Formulation	THC:CBD oromucosal spray (Sativex)
How dose was titrated up	During single-blind 4 week trial period (Phase A)
What the maintenance dose was	Maximum 12 sprays per day (based on optimal dose)
How long the maintenance dose was sustained for	12 weeks
Monitoring/reviewing procedure	Not reported
Stopping criteria	Not reported

	Placebo (N = 53)	
	Formulation	Placebo

Risk of bias

Domain 1: Bias arising from the randomization process

Risk of bias judgement for this domain

Some concerns

(Limited information on randomisation and allocation concealment. Baseline data for each arm in phase B not reported)

Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)

Risk of bias for this domain

Low

Domain 3. Bias due to missing outcome data

Risk-of-bias judgement for this domain

Low

Domain 4. Bias in measurement of the outcome

Risk-of-bias judgement for this domain

Some concerns

(No information on blinding of outcome assessors)

Domain 5. Bias in selection of the reported result

Risk-of-bias judgement domain

Low

Overall bias and Directness

Risk of bias judgement

High

(RCT phase was an enriched enrolment design which only included patients who showed a positive response to the active treatment. Limited information for randomisation and blinding. No baseline information for each arm of phase B.)

Overall Directness

Directly applicable

Novotna 2011

Bibliographic Reference	Novotna, A.; Mares, J.; Ratcliffe, S.; Novakova, I.; Vachova, M.; Zapletalova, O.; Gasperini, C.; Pozzilli, C.; Cefaro, L.; Comi, G.; Rossi, P.; Ambler, Z.; Stelmasiak, Z.; Erdmann, A.; Montalban, X.; Klimek, A.; Davies, P.; Sativex Spasticity Study, Group; A randomized, double-blind, placebo-controlled, parallel-group, enriched-design study of nabiximols* (Sativex()), as add-on therapy, in subjects with refractory spasticity caused by multiple sclerosis; European journal of neurology; 2011; vol. 18 (no. 9); 1122-31

Study details

Study location	Europe
Study setting	51 sites (18 UK, 11 Spain, 10 Poland, 8 Czech Republic, 5 Italy)
Study dates	Not reported
Duration of follow-up	12 weeks
Sources of funding	GW Pharma Ltd

Inclusion criteria	Diagnosis of MS for at least 6 months Spasticity due to MS for at least 3 months which was not fully relived with current antispasticity medication Antispasticity agents and/or disease-modifying medications were maintained at a stable dose for 30 days prior to and throughout the study Moderate to severe spasticity defined as a score ≥4 on MS spasticity NRS scale At least 20% reduction in NRS spasticity score in Phase A
Exclusion criteria	Concomitant disease or disorder that has spasticity-like symptoms Medical history that suggested relapse or remission was likely to recur during the study which could affect spasticity Use of cannabis herb or other cannabinoid-based drugs within 30 days before study entry History of psychiatric, renal, hepatic, cardiovascular or convulsive disorders Known history of alcohol or substance abuse Current non-prescribed use of any prescription drug
Sample size	241
% Female	60% (results not separated by study arm)
Mean age (SD)	48.6 (9.33) (results not separated by study arm)
Outcome measures	Change in spasticity from baseline (NRS) NRS responder (30% reduction in spasticity score) NRS responder (50% reduction in spasticity score)

Study arms

THC:CBD oromucosal spray (Sativex) (N = 124)

Split between study groups	92
Loss to follow-up	15
Formulation	THC:CBD oromucosal spray. 2.7 mg THC:2.5 mg CBD
How dose was titrated up	10 day titration period. Patients self-titrated through a pre-defined escalation scheme to a maximum 12 sprays per day
What the maintenance dose was	Maximum dose 12 sprays per day
How long the maintenance dose was sustained for	12 weeks
Monitoring/reviewing procedure	Spasticity NRS was recorded each day using interactive voice recognition system.
Stopping criteria	Not reported

Placebo (N = 117)

Split between study groups	60
Loss to follow-up	2
Formulation	Placebo

Risk of bias

Domain 1: Bias arising from the randomization process

Risk of bias judgement for this domain

Some concerns

(Limited information on randomisation and allocation concealment. Baseline data not reported separately for each study arm in phase B)

Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)

Risk of bias for this domain

Low

Domain 3. Bias due to missing outcome data

Risk-of-bias judgement for this domain

Low

Domain 4. Bias in measurement of the outcome

Risk-of-bias judgement for this domain

Some concerns

(Limited information about blinding of outcome assessors)

Domain 5. Bias in selection of the reported result

Risk-of-bias judgement domain

Some concerns

(Secondary end-points not stated in the methods)

Overall bias and Directness

Risk of bias judgement

High

(RCT phase was enriched enrollment design which only included patients who showed a positive response to active treatment. Limited information on randomisation and blinding, Baseline characteristics not reported for each study arm. Secondary end-points not stated in the methods)

Overall Directness

Directly applicable

Riva 2018

Bibliographic Reference	Riva, Nilo; Mora, Gabriele; Soraru, Gianni; Lunetta, Christian; Ferraro, Ottavia E.; Falzone, Yuri; Leocani, Letizia; Fazio, Raffaella; Comola, Mauro; Comi, Giancarlo; Group, Canals Study; Safety and efficacy of nabiximols on spasticity symptoms in patients with motor neuron disease (CANALS): a multicentre, double-blind, randomised, placebo-controlled, phase 2 trial; The Lancet. Neurology; 2018

Study details

Study type	Randomised controlled trial (RCT)
Study location	Italy
Study setting	4 tertiary centres for motor neurone disease
Study dates	January 2013 - December 2014
Duration of follow-up	4 weeks
Sources of funding	Fondazione Italiana di Ricerca per la Sclerosi Laterale Amiotrofica (AriSLA) Fondazione Vialli e Mauro

Inclusion criteria	Age 18-80 Amyotrophic lateral sclerosis As defined by revised El Escorial criteria Primary lateral sclerosis According to Pringle's criteria Spasticity Spasticity score of 1 or greater on 5-point Modified Ashworth Scale in 2 or more muscle groups Current therapy failed to provide adequate relief Current therapy for at least 3 months for spasticity due to motor neurone disease Stable treatment 30 days before study and throughout treatment Optimised any physiotherapy or medication likely to affect spasticity In 3 weeks before start of treatment
Exclusion criteria	Spasticity from other concomitant conditions Prior cannabinoid use In 30 days before study entry Use of botulinum toxin In 6 months before study entry History of renal or hepatic disorder History of psychotic illness Known history of alcohol or substance abuse Being bedridden or tracheotomised
Sample size	60
Outcome measures	Change in spasticity from baseline (Ashworth) Incidences of adverse events

	Sleep disruption

Study arms

	2.7 mg Δ9-THC / 2.5 mg CBD oromucosal spray (N = 30)
	Split between study groups: 30
	Loss to follow-up: 1
	% Female: 38%
	Mean age (SD): 58.4 (10.6)
	Condition specific characteristics: Duration of spasticity symptoms 2.9 (2.1); Duration of motor neurone disease 4.8 (2.8); Score on Modified Ashworth Scale 2.3 (0.6); Spasticity NRS score 5.7 (1.7)
	Formulation: 2.7 mg Δ9-THC / 2.5 mg CBD oromucosal spray (Sativex)
	How dose was titrated up: 2-week titration phase. Increased initial dose up to maximum 12 sprays/day

What the maintenance dose was	Maximum 12 sprays per day Mean (SD) sprays per day: 8.03 (2.9)
How long the maintenance dose was sustained for	4 week maintenance phase Followed by 6 week open-label (optional)
Monitoring/reviewing procedure	Follow-up at baseline, 3 weeks (phone call) and 4 weeks Monitoring included review of adverse effects, spasticity, pain, spasm frequency and sleep
Stopping criteria	No improvement in symptoms. Adverse events. Advised not to increase dose if intolerable adverse events occurred. Temporarily discontinued for nausea & anxiety

Placebo (N = 30)

Split between study groups	30
Loss to follow-up	0
% Female	47%
Mean age (SD)	57.2 (13.8)
Condition specific characteristics	Duration of spasticity symptoms 3.6 (3.9) Duration of motor neurone disease 4.6 (4.79) Score on Modified Ashworth Scale 2.4 (0.6)

		Spasticity NRS score 6.1 (1.8)
	Formulation	Identical oromucosal spray
	What the maintenance dose was	Mean (SD) sprays per day: 11.2 (1.4)

Risk of bias

Domain 1: Bias arising from the randomization process

Risk of bias judgement for this domain

Low

Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)

Risk of bias for this domain

Low

Domain 3. Bias due to missing outcome data

Risk-of-bias judgement for this domain

Low

Domain 4. Bias in measurement of the outcome

Risk-of-bias judgement for this domain

Low

Domain 5. Bias in selection of the reported result

Risk-of-bias judgement domain

Low

Overall bias and Directness

Risk of bias judgement

Low

Overall Directness

Directly applicable

van Amerongen 2018

Bibliographic Reference	van Amerongen, Guido; Kanhai, Kawita; Baakman, Anne Catrien; Heuberger, Jules; Klaassen, Erica; Beumer, Tim L.; Strijers, Rob L. M.; Killestein, Joep; van Gerven, Joop; Cohen, Adam; Groeneveld, Geert Jan; Effects on Spasticity and Neuropathic Pain of an Oral Formulation of DELTA9-tetrahydrocannabinol in Patients WithProgressive Multiple Sclerosis; Clinical therapeutics; 2018; vol. 40 (no. 9); 1467-1482

Study details

Study type	Randomised controlled trial (RCT)
Study location	Netherlands
Study setting	Centre for Human Drug Research VU University Medical Centre
Study dates	August 2011 - January 2013
Duration of follow-up	4 weeks
Sources of funding	Echo Pharmaceuticals

Inclusion criteria	Diagnosis of MS Progressive primary or secondary MS according to revised McDonald criteria for more than 1 year Stable treatment At least 30 days before study enrollment Spasticity Moderate spasticity defined by Ashworth score ≥2 Expanded Disability Status Scale score 4.5 - 7.5 at baseline
Exclusion criteria	Prior cannabinoid use Current use of Δ9-THC, confirmed by urine drugs screen
Sample size	24
Outcome measures	Sleep disruption Symbol digit substitution test (to assess visual perception, attention and working memory) Expanded Disability Status Scale Change in spasticity from baseline (Ashworth) Weeks 2 and 4 Change in spasticity from baseline (NRS) Weeks 2 and 4 Incidences of adverse events

Study arms

	Δ9-THC tablets (N = 12)	
	Split between study groups	12

Loss to follow-up	1
% Female	66.7%
Mean age (SD)	57.3 (9.0)
Condition specific characteristics	Mean EDSS score 6.2 (1.2) Duration of MS - years (SD) 10.3 (6.5)
Formulation	THC tablets (Namisol - purified THC extracted from cannabis extract). 3, 5 and 8 mg
How dose was titrated up	2 clinic visits with cross-over with 3, 5 and 8 mg with 100 min interval between doses. 7-14 day washout period between two visits
What the maintenance dose was	16 mg Range in daily dose: 15 mg - 28.5 mg
How long the maintenance dose was sustained for	4 weeks (dose increased after 2 weeks where appropriate)
Monitoring/reviewing procedure	Follow up at 2 weeks No information provided for monitoring procedure
Stopping criteria	Adverse events monitored. Patient returned to initial dose if adverse events intolerable

Placebo (N = 12)

Split between study groups	12

	Loss to follow-up	0
	% Female	66.7%
	Mean age (SD)	51.4 (8.0)
	Condition specific characteristics	Mean EDSS score 6.3 (0.5) Duration of MS - years (SD) 12.6 (4.9)
	Formulation	Identical placebo tablets

Risk of bias

Domain 1: Bias arising from the randomization process

Risk of bias judgement for this domain

Some concerns

(Limited information for randomisation and allocation concealment)

Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)

Risk of bias for this domain

Some Concerns

(No information on blinding of participants or people delivering the interventions)

Domain 3. Bias due to missing outcome data

Risk-of-bias judgement for this domain

Low

Domain 4. Bias in measurement of the outcome

Risk-of-bias judgement for this domain

Some concerns

(No information on blinding of outcome assessors)

Domain 5. Bias in selection of the reported result

Risk-of-bias judgement domain

Low

Overall bias and Directness

Risk of bias judgement

Some concerns

(All outcomes: Limited information for randomisation, allocation concealment and blinding)

Overall Directness

Directly applicable

Wade 2004

Bibliographic Reference	Wade, Derick T.; Makela, Petra; Robson, Philip; House, Heather; Bateman, Cynthia; Do cannabis-based medicinal extracts have general or specific effects on symptoms in multiple sclerosis? A double-blind, randomized, placebo-controlled study on 160 patients; Multiple sclerosis (Houndmills, Basingstoke, England); 2004; vol. 10 (no. 4); 434-41

Study details

Study type	Randomised controlled trial (RCT)

Study location	UK
Study setting	3 clinical centres
Study dates	Not reported. This study was submitted for publication in 2014.
Duration of follow-up	6 weeks
Sources of funding	GW Pharmaceuticals
Inclusion criteria	Diagnosis of MS of any type Stable symptoms Over previous 4 weeks with no relapse Stable treatment Unchanged in 4 weeks before study entry Willing to abstain from other cannabis use during trial 7 days before screening and throughout study 1 of 5 target symptoms at a sufficient level of severity Spasticity, spasms, bladder problems, tremor, pain (not musculoskeletal). If more than 1, patients nominated most troublesome
Exclusion criteria	Primary symptom rated less than 50% maximal severity using VAS Known history of alcohol or substance abuse Patients with a history of significant pychiatric conditions (other than depression) Other than depression associated with MS Severe cardiovascular disorder History of renal or hepatic disorder History of seizures Planned travel abroad during study

Sample size	At start: 160 Completed: 154
Split between study groups	At start: THC: CBD spray: 80 (20 with spasticity primary symptom; 18 with pain) Placebo: 80 (19 with spasticity primary symptom; 19 with pain) Completed: intervention: 77; placebo 77
Loss to follow-up	THC: CBD spray: 3 Placebo: 3
% Female	THC: CBD spray: 58.7% Placebo: 65%
Mean age (SD)	THC: CBD spray: 51.0 (9.4) Placebo: 50.4 (9.3)
Outcome measures	Mean average pain intensity Visual Analogue Scale (0-100) Incidences of adverse events

Study arms

	Oromucosal spray THC 2.7 mg and CBD 2.5 mg per 100 microlitre actuation (Sativex) (N = 77)
	Formulation: Oromucosal spray THC 2.7 mg and CBD 2.5 mg per 100 microlitre actuation

How dose was titrated up	Supervision of the first dose, given in the clinic, was followed by instructions to titrate slowly during home dosing, aiming for optimal balance of symptom relief and unwanted effects. Guidelines were given for increments up to a maximum of 120 mg THC and 120 mg CBD per day with no more than 20 mg of each in any 3-hour period.
What the maintenance dose was	This study exceeded the SPC's advice of a maximum of 12 actuations per day. The mean number of actuations was 17.5 per day.
How long the maintenance dose was sustained for	6 weeks
Monitoring/reviewing procedure	During the initial dose titration phase, patients recorded the time and number of actuations per day, in a dosing diary. Regular telephone contact was maintained according to individual patient requirements and a brief safety visit was conducted after two weeks, to review dosing and adverse events.
Stopping criteria	None
Placebo (N = 77)	
Formulation	The placebo spray contained excipients only. All preparations incorporated a peppermint flavour and colouring to disguise the taste and appearance of medicinal cannabis.
How dose was titrated up	Same as the medicinal cannabis
What the maintenance dose was	Same as the medicinal cannabis
How long the maintenance dose was sustained for	6 weeks
Monitoring/reviewing procedure	Same as the medicinal cannabis

	Stopping criteria	None

Risk of bias

Domain 1: Bias arising from the randomization process

Risk of bias judgement for this domain

Some concerns

(Limited information for randomisation and allocation concealment)

Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)

Risk of bias for this domain

Some Concerns

(No information on blinding of participants or people delivering the interventions)

Domain 3. Bias due to missing outcome data

Risk-of-bias judgement for this domain

Low

Domain 4. Bias in measurement of the outcome

Risk-of-bias judgement for this domain

Some concerns

(No information on blinding of outcome assessors)

Domain 5. Bias in selection of the reported result

Risk-of-bias judgement domain

Low

Overall bias and Directness

Risk of bias judgement

Some concerns

(Alll outcomes: Limited information for randomisation, allocation concealment and blinding)

Overall Directness

Directly applicable

Zajicek 2003

Bibliographic Reference	Zajicek, John; Fox, Patrick; Sanders, Hilary; Wright, David; Vickery, Jane; Nunn, Andrew; Thompson, Alan; Group, Uk Ms Research; Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomised placebo-controlled trial; Lancet (London, England); 2003; vol. 362 (no. 9395); 1517-26

Study details

Study type	Randomised controlled trial (RCT) Associated studies Zajicek 2005 (12 month follow up study)
Study location	UK
Study setting	33 neurology and rehabilitation centres
Study dates	December 2000 - October 2002
Duration of follow-up	Zajikec 2003: 15 weeks

	Zajikec 2005: 52 weeks
Sources of funding	Medical Research Council
Inclusion criteria	Age 18 - 64 Diagnosis of MS Stable for 6 months before study entry Spasticity Ashworth score ≥2 in 2 or more lower limb muscles Optimised any physiotherapy or medication likely to affect spasticity Not altered during 30 days before study entry
Exclusion criteria	Severe cardiovascular disorder Taking medication which could affect spasticity Unable to stop driving throughout study period Cognitive impairment History of psychotic illness Pregnancy Prior cannabinoid use Use of Δ9-THC at any point or use of cannabis in 30 days before entering study
Sample size	2003 study: 657 2005 study: 383
Outcome measures	Change in spasticity from baseline (Ashworth) United Kingdom Neurological Disability Score

	Barthel Index GHQ-30 Incidences of adverse events Serious adverse events

Study arms

	Δ9-THC capsules (N = 216)	
	Split between study groups	2003 study: 216 2005 study: 125
	Loss to follow-up	2003 study:9 2005 study: 8
	% Female	69.4%
	Mean age (SD)	50.2 (8.2)
	Condition specific characteristics	Score on Ashworth scale - mean (SD) 22.6 (10.1)
	Formulation	2.5 mg ΔTHC capsules (Dronabinol)
	How dose was titrated up	5 week titration phase. Increase initial dose by 1 capsule (2.5 mg THC), twice per day every week

What the maintenance dose was	Mean (SD) dose based on bodyweight: 30 - 49 kg: 3.22 (1.12) mg 50 - 69 kg: 4.58 (1.80) mg 70 - 89 kg: 6.30 (2.10) mg >89 kg: 6.56 (3.27) mg
How long the maintenance dose was sustained for	8 weeks
Stopping criteria	Adverse events monitored. If developed, didn't increase the dose. If intolerable, dose was reduced. Medication reduced by 1 capsule twice daily until off medication

THC:CBD capsules (N = 219)

Split between study groups	2003 study: 219 2005 study: 138
Loss to follow-up	2003 study: 4 2005 study: 11
% Female	63.9%
Mean age (SD)	50.5 (7.6)
Formulation	Cannabis extract (2.5 mg Δ9-THC : 1.25mg CBD) capsules (Cannador)

How dose was titrated up	5 week titration phase. Increase initial dose by 1 capsule (2.5 mg THC), twice per day every week
What the maintenance dose was	Mean (SD) dose based on bodyweight: 30 - 49 kg: 2.34 (1.44) mg 50 - 69 kg: 4.78 (1.78) mg 70 - 89 kg: 5.79 (2.33) mg >89 mg: 7.99 (2.86) mg
How long the maintenance dose was sustained for	8 weeks
Monitoring/reviewing procedure	Follow up in first 6 weeks: Every 2 weeks Follow up weeks 7-16: Every 2-4 weeks Monitoring included review of adverse events, spasticity, 10 m timed walk, general health questionnaire, Barthel index, depression, sleep, tiredness, tremor, and muscle spasms
Stopping criteria	Adverse events monitored. If developed, didn't increase the dose. If intolerable, dose was reduced. Medication reduced by 1 capsule twice daily until off medication

Placebo (N = 222)

Split between study groups	2003 study: 222 2005 study: 120
Loss to follow-up	2003 study: 6

	2005 study: 9
% Female	63.3%
Mean age (SD)	50.9 (7.6)
Condition specific characteristics	Score on Ashworth scale - mean (SD) 21.4 (8.5)
Formulation	Placebo matched to THC or plant extract capsule
What the maintenance dose was	Mean (SD) dose based on bodyweight: 30 - 49 kg: 3.57 (1.24) mg 50 - 69 kg: 5.21 (1.46) mg 70 - 89 kg: 7.11 (1.89) mg >89 mg: 8.47 (2.23) mg

Risk of bias

Domain 1: Bias arising from the randomization process

Risk of bias judgement for this domain

Low

Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)

Risk of bias for this domain

Low

Domain 3. Bias due to missing outcome data

Risk-of-bias judgement for this domain

Low

Domain 4. Bias in measurement of the outcome

Risk-of-bias judgement for this domain

Low

Domain 5. Bias in selection of the reported result

Risk-of-bias judgement domain

Some concerns

(Ashworth scale recorded at multpile time points but only reported for end of the trial)

Overall bias and Directness

Risk of bias judgement

Some concerns

(Ashworth scale recorded at multpile time points but only reported for end of the trial)

Overall Directness

Directly applicable

Zajicek 2005

Bibliographic Reference	Zajicek, J. P.; Sanders, H. P.; Wright, D. E.; Vickery, P. J.; Ingram, W. M.; Reilly, S. M.; Nunn, A. J.; Teare, L. J.; Fox, P. J.; Thompson, A. J.; Cannabinoids in multiple sclerosis (CAMS) study: safety and efficacy data for 12 months follow up; Journal of neurology, neurosurgery, and psychiatry; 2005; vol. 76 (no. 12); 1664-9

Study details

Study type	Associated studies Follow-up study from Zajikec 2003 Randomised controlled trial (RCT)

Zajicek 2012

Bibliographic Reference	Zajicek, John Peter; Hobart, Jeremy C.; Slade, Anita; Barnes, David; Mattison, Paul G.; Group, Musec Research; Multiple sclerosis and extract of cannabis: results of the MUSEC trial; Journal of neurology, neurosurgery, and psychiatry; 2012; vol. 83 (no. 11); 1125-32

Study details

Study type	Randomised controlled trial (RCT)
Study location	UK
Study setting	22 centres
Study dates	June 2006 - September 2008
Duration of follow-up	12 weeks
Sources of funding	Society for Clinical Research, Berlin, Germany, and Weleda AG, Arlesheim, Switzerland
Inclusion criteria	Age 18 - 64 Diagnosis of MS According to the McDonald criteria Stable symptoms For 6 months prior to study entry Stable treatment For 30 days before study entry

Exclusion criteria	Taking immunomodulatory drugs that might affect spasticity Cognitive impairment History of psychotic illness Pregnancy Fixed tendon contractures Prior cannabinoid use Within 30 days of study entry
Sample size	279
Outcome measures	MS Spasticity Scale-88 score By category, not overall score Sleep disruption category rating scale; 0 - 10

Study arms

Δ9-THC capsules (cannabis extract) (N = 144)

Split between study groups	144
Loss to follow-up	34
% Female	61.5%
Mean age (SD)	51.9 (7.7)
Condition specific characteristics	Duration of MS - years (SD)

	Cannabis extract: 14.5 (9.5)
Formulation	Extract from Cannabis sativa L (extraction medium ethanol 96%) in soft gelatine capsules, standardised on cannabidiol (range 0.8–1.8 mg) and containing 2.5 mg Δ9- THC:1.25 mg CBD as the main cannabinoid
How dose was titrated up	2 week titration phase Initial dose increased by 5 mg/day every 3 days for up to 12 days. Maximum dose 25 mg THC/day
What the maintenance dose was	Maximum 25 mg per day. Range of doses: 2.5 mg - 25.0 mg (47% of participants using 25 mg at end of titration period, 25% at end of study period). Optimal dose determined by adverse events. If intolerable, reduced by one capsule until side effects were resolved. After resolution, dose was escalated again. If side effects returned, dose was reduced again
How long the maintenance dose was sustained for	10 weeks
Monitoring/reviewing procedure	Follow up at 2, 4, 8 and 12 weeks. Monitoring included review of adverse events, muscle stiffness, pain, spasms, sleep disturbance, spasticity and walking ability
Stopping criteria	No information provided

Placebo (N = 135)

Split between study groups	135
Loss to follow-up	19
% Female	64.9%

	Mean age (SD)	52.0 (7.9)
	Condition specific characteristics	Duration of MS - years (SD) 15.1 (8.4)
	Formulation	Identical placebo capsules
	What the maintenance dose was	Range of doses: 2.5 mg - 25.0 mg (87% of participants using 25 mg at end of titration period, 69% at end of study period).

Risk of bias

Domain 1: Bias arising from the randomization process

Risk of bias judgement for this domain

Low

Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)

Risk of bias for this domain

Low

Domain 3. Bias due to missing outcome data

Risk-of-bias judgement for this domain

High

(High percentage of participants did not complete the trial. The percentage was higher for CBD which may be a result of the intervention)

Domain 4. Bias in measurement of the outcome

Risk-of-bias judgement for this domain

Low

Domain 5. Bias in selection of the reported result

Risk-of-bias judgement domain

Low

Overall bias and Directness

Risk of bias judgement

Some concerns

(All outcomes: High percentage of participants did not complete the trial. The percentage was higher for CBD which may be a result of the intervention)

Overall Directness

Directly applicable

Cross-over RCTs

Leocani 2015

Bibliographic Reference	Leocani, L.; Nuara, A.; Houdayer, E.; Schiavetti, I.; Del Carro, U.; Amadio, S.; Straffi, L.; Rossi, P.; Martinelli, V.; Vila, C.; et al.; Sativex and clinical-neurophysiological measures of spasticity in progressive multiple sclerosis; Journal of neurology; 2015; vol. 262 (no. 11); 2520-2527

Study details

Study type	Cross-over randomised controlled trial
Study location	Italy

Study setting	Not reported
Study dates	April 2012 - June 2013
Duration of follow-up	2 weeks
Sources of funding	Laboratorios Almirall S.A
Inclusion criteria	Age >18 years Diagnosis of MS Progressive primary or secondary MS for at least 12 months Stable symptoms Relapse-free for at least 3 months prior to screening Expanded Disability Status Scale score 3.0 - 6.5 Spasticity Moderate to severe. Defined by Modified Ashworth score of at least 1+ in 1 limb Stable treatment At least 2 months prior to screening. No modifications in 6 months prior to study
Exclusion criteria	Spasticity from other concomitant conditions Use of botulinum toxin In 4 months prior to screening History of psychotic illness Known history of alcohol or substance abuse Known hypersensitivity to cannabinoids History of seizures History of renal or hepatic disorder

	Severe cardiovascular disorder Pregnancy or lactating or unwilling to use contraception for study period
Sample size	44
Split between study groups	34 completed both study arms
Loss to follow-up	10
% Female	46%
Mean age (SD)	48 (8)
Condition specific characteristics	Duration of MS - years (SD) 17.3 (8.4) Mean EDSS score 5.7 (0.9) Score on Modified Ashworth Scale 9.7 (5.4) Spasticity NRS score 7.1 (1.4)
Outcome measures	Change in spasticity from baseline (Ashworth) Overall and lower limb. Baseline to 4 weeks Modified Ashworth Scale responder (>20% improvement from baseline) Change in spasticity from baseline (NRS) NRS responder (20% reduction in spasticity score) Incidences of adverse events

Study arms

2.7 mg THC / 2.5 mg CBD oromucosal spray (Sativex) (N = 34)

34 completed both study arms

Formulation	2.7 mg THC / 2.5 mg CBD oromucosal spray (Sativex)
How dose was titrated up	2-week titration phase. Increased initial dose by 1 spray/day until symptom relief obtained with minimum adverse events
What the maintenance dose was	Maximum 12 sprays per day Mean (SD) sprays per day: 7 (3)
How long the maintenance dose was sustained for	2 weeks
Monitoring/reviewing procedure	Follow up at baseline and weeks 4, 6 and 10 Monitoring included review of side effects and routine blood and urine analysis including THC level
Stopping criteria	Monitored for adverse events but most appeared during titration phase and were resolved after reducing the number of sprays

Placebo (N = 34)

34 completed both study arms

Formulation	Placebo oromucosal spray

	What the maintenance dose was	Mean (SD) sprays per day: 10 (3)

Risk of bias

Domain 1: Bias arising from the randomisation process

Risk of bias judgement for the randomisation process

Some concerns

(No analysis of period effects and limited information on randomisation and allocation concealement)

Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)

Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)

Some concerns

(No information about blinding of participants and trial personnel)

Domain 3. Bias due to missing outcome data

Risk of bias judgement for missing outcome data

Low

Domain 4. Bias in measurement of the outcome

Risk of bias judgement for measurement of the outcome

Some concerns

(No information on whether outcome assessors were blinded to intervention)

Domain 5. Bias in selection of the reported result

Risk of bias judgement for selection of the reported result

Low

Overall bias and Directness

Risk of bias judgement

Some concerns

(All outcomes: No analysis of period effects and limited information on randomisation, allocation concealment and blinding)

Overall Directness

Directly applicable

Pooyania 2010

Bibliographic Reference	Pooyania, Sepideh; Ethans, Karen; Szturm, Tony; Casey, Alan; Perry, Daryl; A randomized, double-blinded, crossover pilot study assessing the effect of nabilone on spasticity in persons with spinal cord injury; Archives of physical medicine and rehabilitation; 2010; vol. 91 (no. 5); 703-7

Study details

Study type	Cross-over randomised controlled trial
Study location	Canada
Study setting	Outpatient clinic
Study dates	Not reported
Duration of follow-up	4 weeks per trial (2 week washout period between trials)
Sources of funding	Not reported

Inclusion criteria	Age 18-65 Spinal cord injury Injury occurred within the previous year at level C5 (ASIA grade A–D) or below Stable neurologic level no change in ASIA neurologic level in the last 6 months Spasticity Moderate spasticity with Ashworth score ≥3 Stable treatment Spasticity medication unchanged for at least 30 days before study entry
Exclusion criteria	Severe cardiovascular disorder History of psychotic illness Cognitive impairment Pregnancy or breastfeeding Known history of alcohol or substance abuse Prior cannabinoid use Smoked cannabis less than 30 days before study entry or unwilling not to smoke during study Fixed tendon contractures Use of botulinum toxin During 4 months before study entry
Sample size	12
Split between study groups	Cross-over study - all participants completed both arms
Loss to follow-up	1

% Female	0%
Mean age (SD)	42.36

Study arms

Δ9-THC capsules (N = 12)

12 participants completed both study arms

Formulation	0.5 mg Nabilone
How dose was titrated up	First 2 weeks: 0.5 mg nabilone once per day Final two weeks: option to increase to 0.5 mg twice per day, depending on adverse events
What the maintenance dose was	0.5 mg nabilone
How long the maintenance dose was sustained for	2 weeks
Monitoring/reviewing procedure	No information on timing of follow up Monitoring included review of side effects, vital signs and adverse events
Stopping criteria	Monitored for adverse events. Could return to initial dose if necessary at any time

Placebo (N = 12)

	12 participants completed both study arms	
	Formulation	Placebo capsule

Risk of bias

Domain 1: Bias arising from the randomisation process

Risk of bias judgement for the randomisation process

Some concerns

(Period effects not included in analysis)

Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)

Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)

Low

Domain 3. Bias due to missing outcome data

Risk of bias judgement for missing outcome data

Low

Domain 4. Bias in measurement of the outcome

Risk of bias judgement for measurement of the outcome

Some concerns

(No about of blinding of outcome assessors)

Domain 5. Bias in selection of the reported result

Risk of bias judgement for selection of the reported result

Low

Overall bias and Directness

Risk of bias judgement

Some concerns

(All outcomes: Period effects not included and no information on blinding of outcome assessors)

Overall Directness

Directly applicable

Wissel 2006

Bibliographic Reference	Wissel, Jorg; Haydn, Tanja; Muller, Jorg; Brenneis, Christian; Berger, Thomas; Poewe, Werner; Schelosky, Ludwig D.; Low dose treatment with the synthetic cannabinoid Nabilone significantly reduces spasticity-related pain : a double-blind placebo-controlled cross-over trial; Journal of neurology; 2006; vol. 253 (no. 10); 1337-41

Study details

Study type	Cross-over randomised controlled trial
Study location	Austria, Germany, Switzerland
Study setting	Not reported
Study dates	Not reported
Duration of follow-up	4 weeks per treatment (1 week washout period)
Sources of funding	Not reported
Inclusion criteria	Chronic upper motor neuron syndrome

	Spasticity Disabling spasticity-related pain Current therapy failed to provide adequate relief Passive stretch of the spastic muscles had to result in increased pain perception in the stimulated muscles
Sample size	13
Split between study groups	Cross-over trial (all 13 patients completed both trials)
Loss to follow-up	None reported
% Female	69.2%
Mean age (SD)	44.8 (14.3)
Outcome measures	11-point box test (pain rating) Change in spasticity from baseline (Ashworth) Barthel Index A change from baseline on a numerical rating scale (NRS) of mean intensity of global neuropathic pain, where 0 = ‘‘No Pain’’ and 10 = ‘‘Worst Possible Pain’’.

Study arms

	Δ9-THC capsules (N = 13) Cross-over trial: all participants completed both trial arms

Outcome measures	Change in spasticity from baseline (Ashworth) Barthel Index 11-point box test (pain rating)
Formulation	Nabilone capsules
How dose was titrated up	1 week titration phase Week 1: 0.5 mg per day Week 3: 1 mg per day
What the maintenance dose was	1 mg per day
How long the maintenance dose was sustained for	3 weeks
Monitoring/reviewing procedure	No information on timing of clinic visits Monitoring included review of spasticity, motor performance, Barthel Index, other medication usage, adverse events
Stopping criteria	No information provided

Placebo (N = 13)

Cross-over trial: all participants completed both trial arms

Formulation	Identical placebo capsules

Risk of bias

Domain 1: Bias arising from the randomisation process

Risk of bias judgement for the randomisation process

High

(No information provided on randomisation, blinding nor baseline characteristics.)

Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)

Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)

Some concerns

Domain 3. Bias due to missing outcome data

Risk of bias judgement for missing outcome data

Low

Domain 4. Bias in measurement of the outcome

Risk of bias judgement for measurement of the outcome

Some concerns

Domain 5. Bias in selection of the reported result

Risk of bias judgement for selection of the reported result

Low

Overall bias and Directness

Risk of bias judgement

High

(No information provided on randomisation, blinding nor baseline characteristics.)

Overall Directness

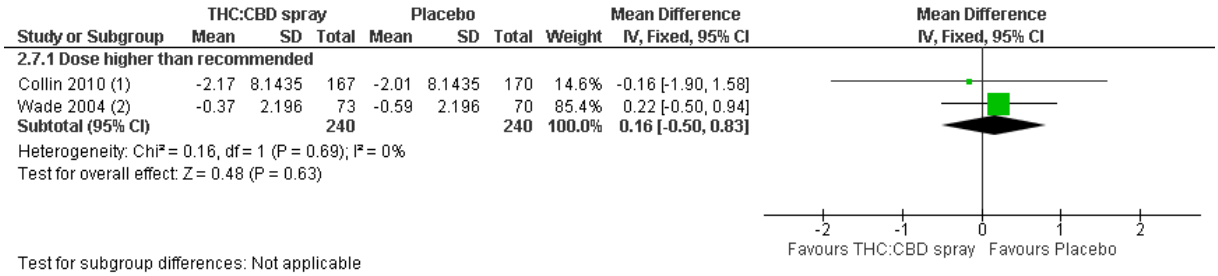
Directly applicable

Appendix F Forest plots

Multiple sclerosis

THC: CBD oromucosal spray versus placebo

Spasticity: Modified Ashworth Scale – change from baseline

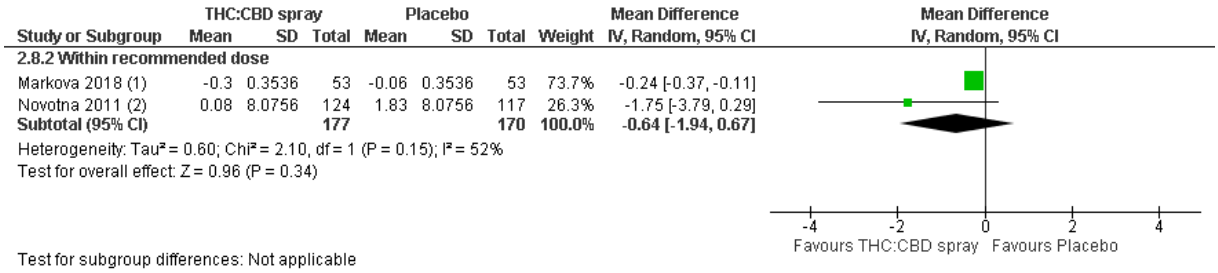


Test for subgroup differences: Not applicable

Footnotes

(1) 14 weeks follow up

(2) 6 weeks follow up



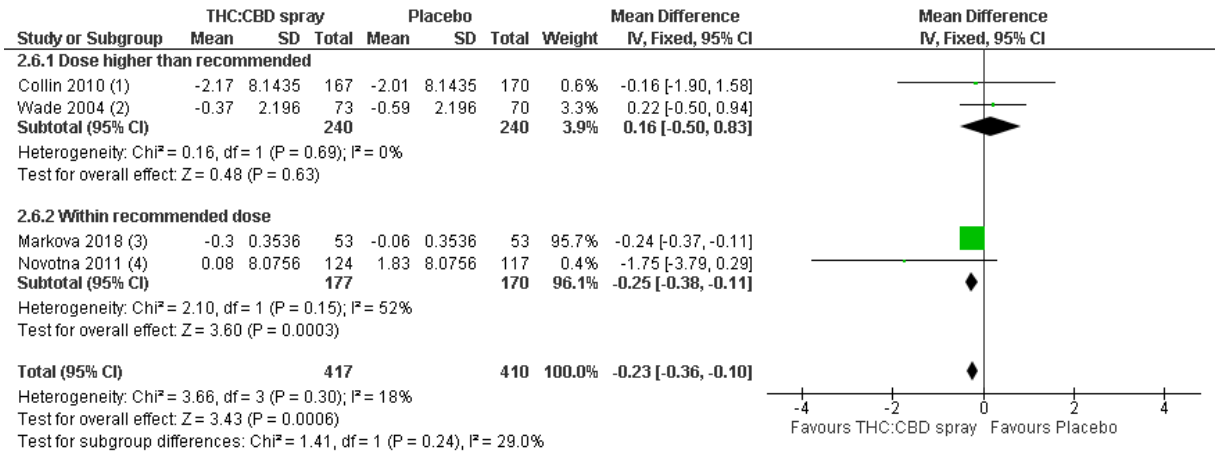
Test for subgroup differences: Not applicable

Footnotes

(1) 12 weeks follow up. LSM; Enriched enrolment study design

(2) 12 weeks follow up; Enriched enrolment study design

Pooled estimates



Footnotes

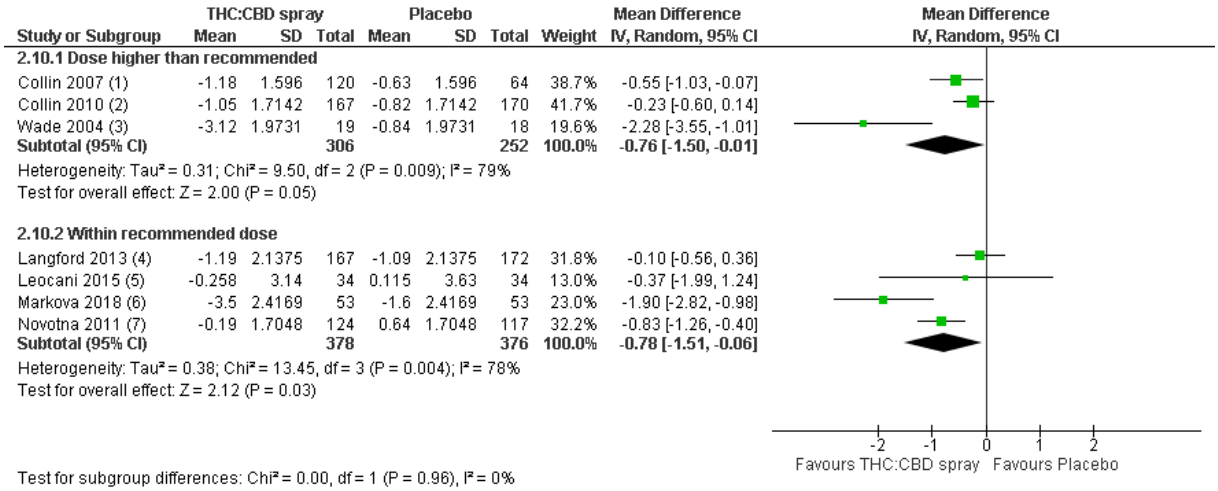
(1) 14 weeks follow up

(2) 6 weeks follow up

(3) 12 weeks follow up. LSM; Enriched enrolment study design

(4) 12 weeks follow up; Enriched enrolment study design

Spasticity: Numerical rating Scale- change from baseline

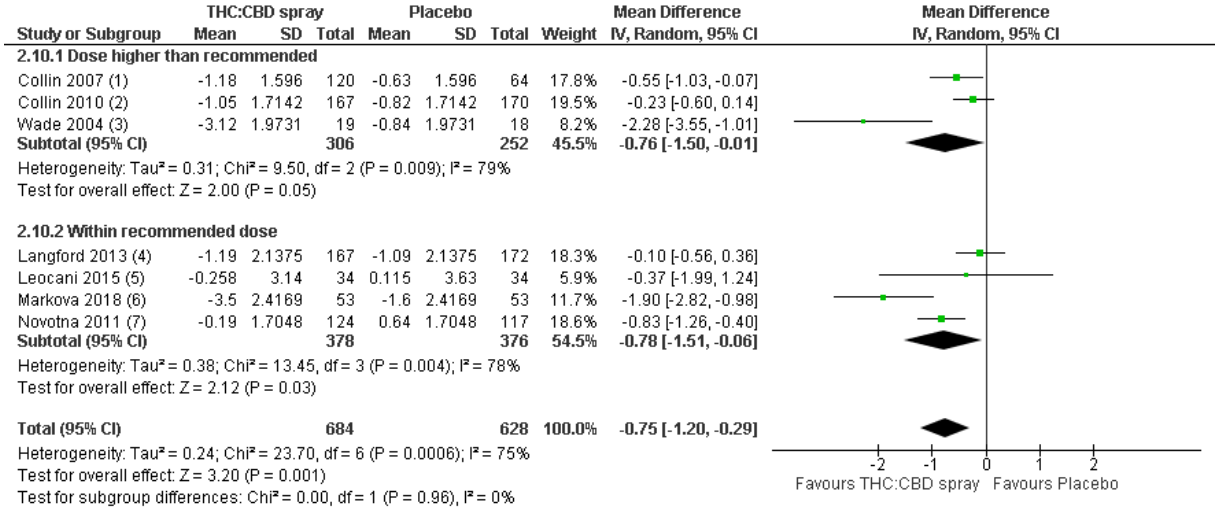


Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.96), I² = 0%

Footnotes

(1) 6 weeks follow up
(2) 14 weeks follow up
(3) 6 weeks follow up. VAS converted to NRS
(4) 14 weeks follow up
(5) 4 weeks follow up
(6) 12 weeks follow up; Enriched enrolment study design
(7) 12 weeks follow up; Enriched enrolment study design

Pooled estimates

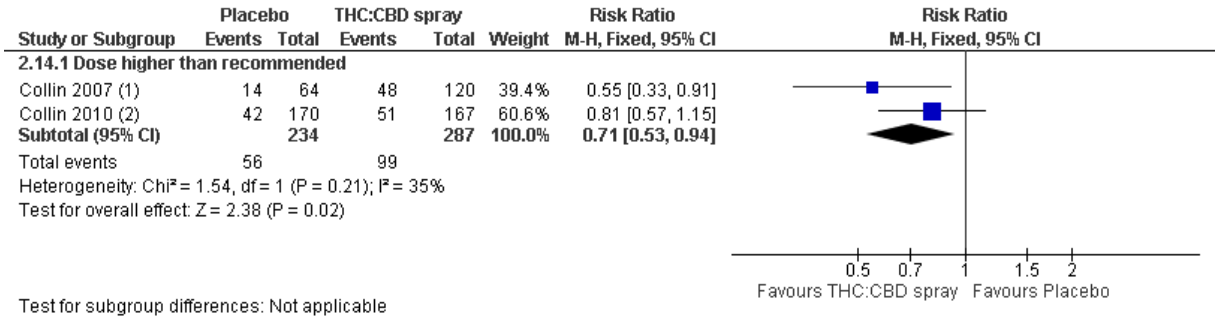


Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.96), I² = 0%

Footnotes

(1) 6 weeks follow up
(2) 14 weeks follow up
(3) 6 weeks follow up. VAS converted to NRS
(4) 14 weeks follow up
(5) 4 weeks follow up
(6) 12 weeks follow up; Enriched enrolment study design
(7) 12 weeks follow up; Enriched enrolment study design

Spasticity: Numerical rating scale responder (>30% improvement in spasticity)

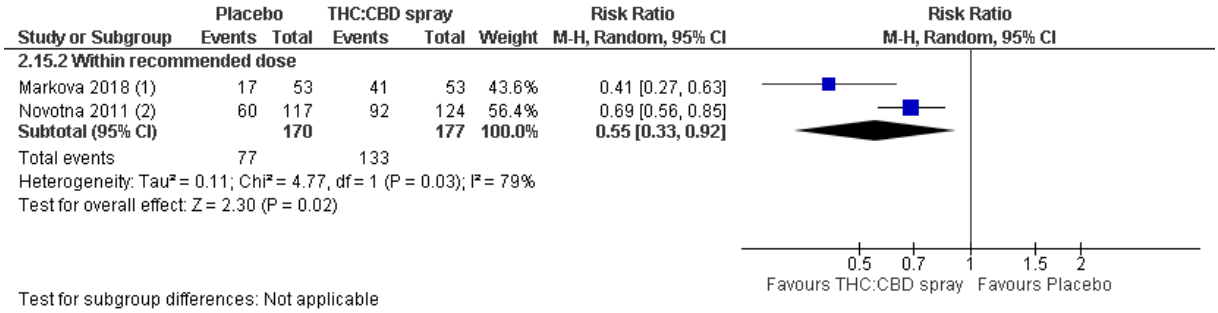


Test for subgroup differences: Not applicable

Footnotes

(1) 6 weeks follow up

(2) 14 weeks follow up



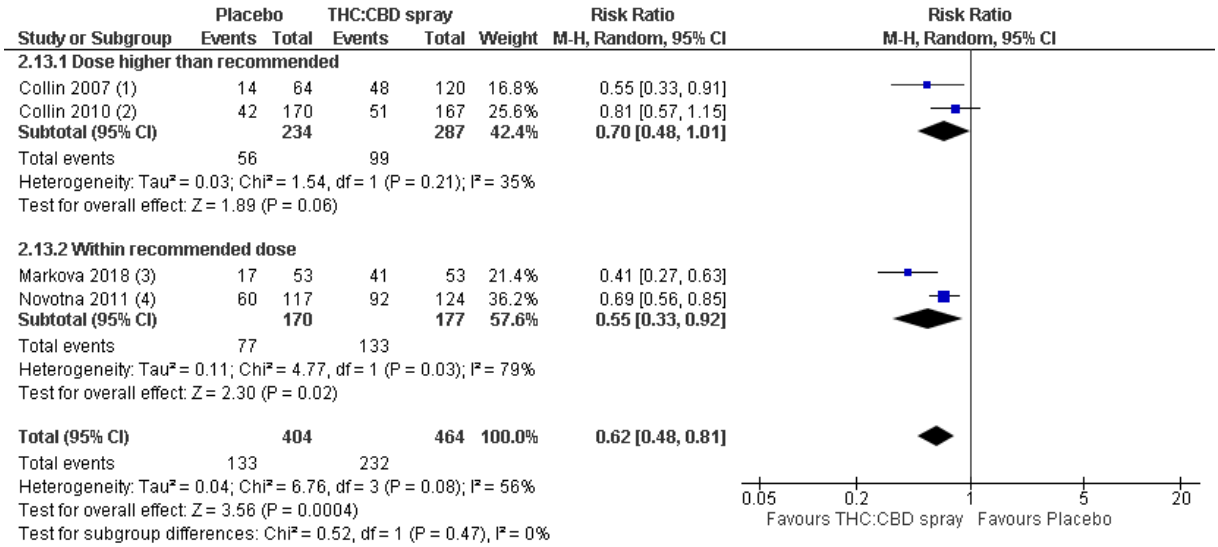
Test for subgroup differences: Not applicable

Footnotes

(1) 12 weeks follow up; Enriched enrolment study design

(2) 12 weeks follow up; Enriched enrolment study design

Pooled estimates



Footnotes

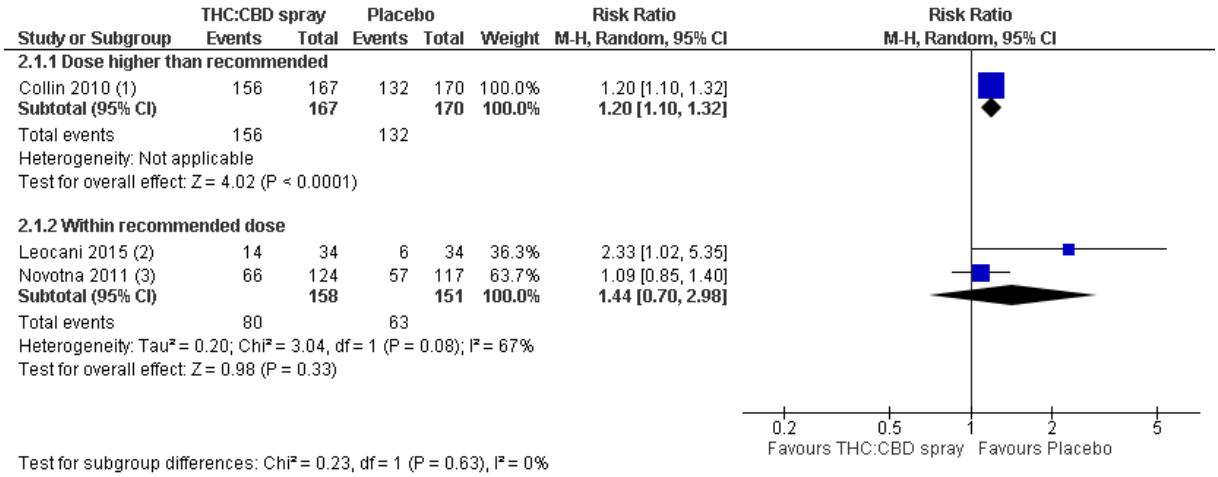
(1) 6 weeks follow up

(2) 14 weeks follow up

(3) 12 weeks follow up; Enriched enrolment study design

(4) 12 weeks follow up; Enriched enrolment study design

Total adverse events



Test for subgroup differences: Chi² = 0.23, df = 1 (P = 0.63), I² = 0%

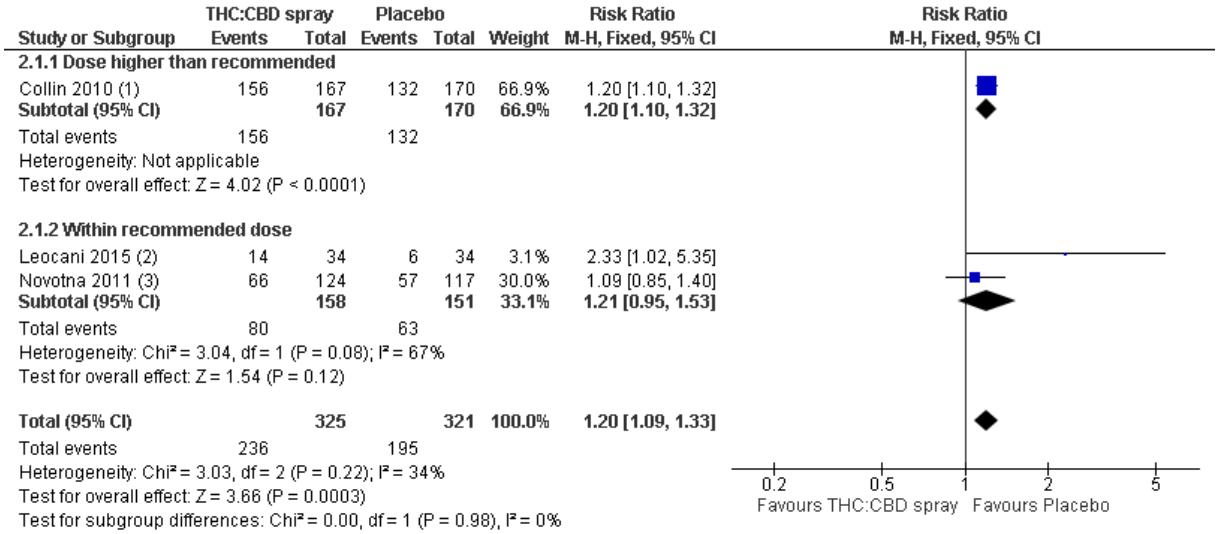
Footnotes

(1) 14 weeks follow up

(2) 4 weeks follow up

(3) 12 weeks follow up; Enriched enrolment study design

Pooled estimates



Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.98), I² = 0%

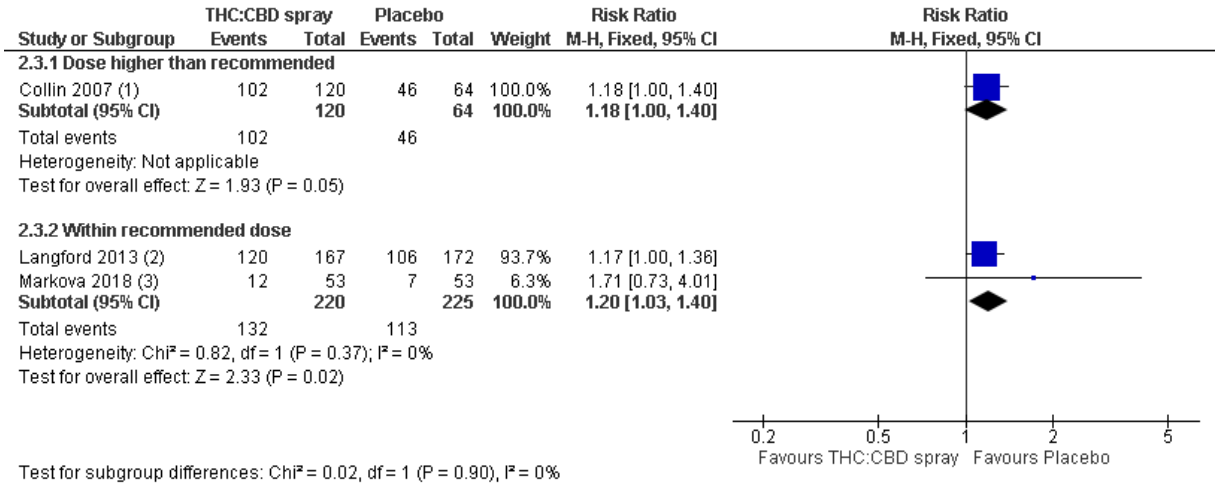
Footnotes

(1) 14 weeks follow up

(2) 4 weeks follow up

(3) 12 weeks follow up; Enriched enrolment study design

Treatment-related adverse events



Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.90), I² = 0%

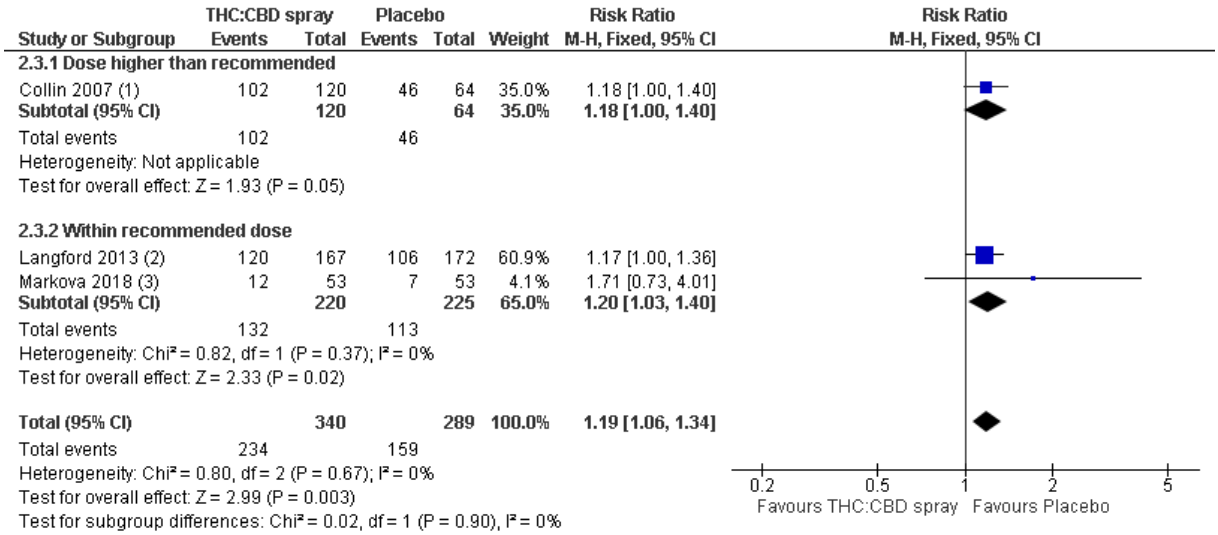
Footnotes

(1) 6 weeks follow up

(2) Phase B. 14 weeks follow up

(3) 12 weeks follow up; Enriched enrolment study design

Pooled estimates



Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.90), I² = 0%

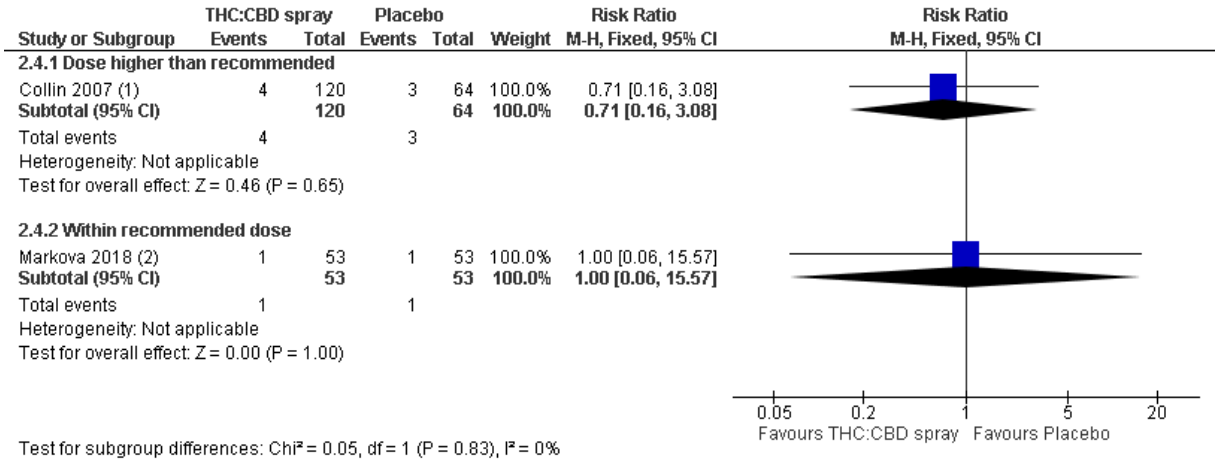
Footnotes

(1) 6 weeks follow up

(2) Phase B. 14 weeks follow up

(3) 12 weeks follow up; Enriched enrolment study design

Total serious adverse events



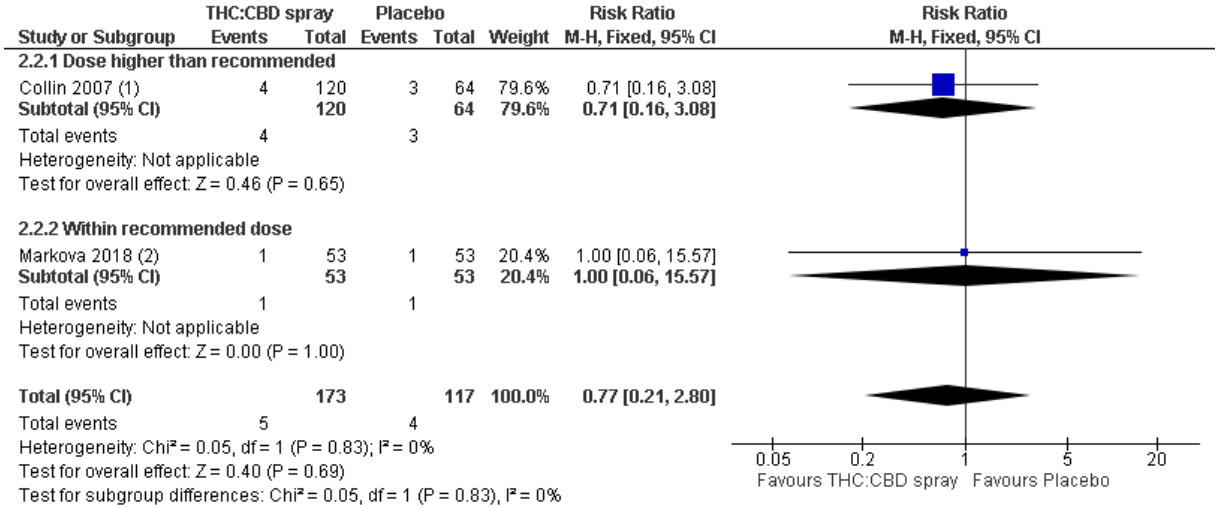
Test for subgroup differences: Chi² = 0.05, df = 1 (P = 0.83), I² = 0%

Footnotes

(1) 6 weeks follow up

(2) 12 weeks follow up; Enriched enrolment study design

Pooled estimates



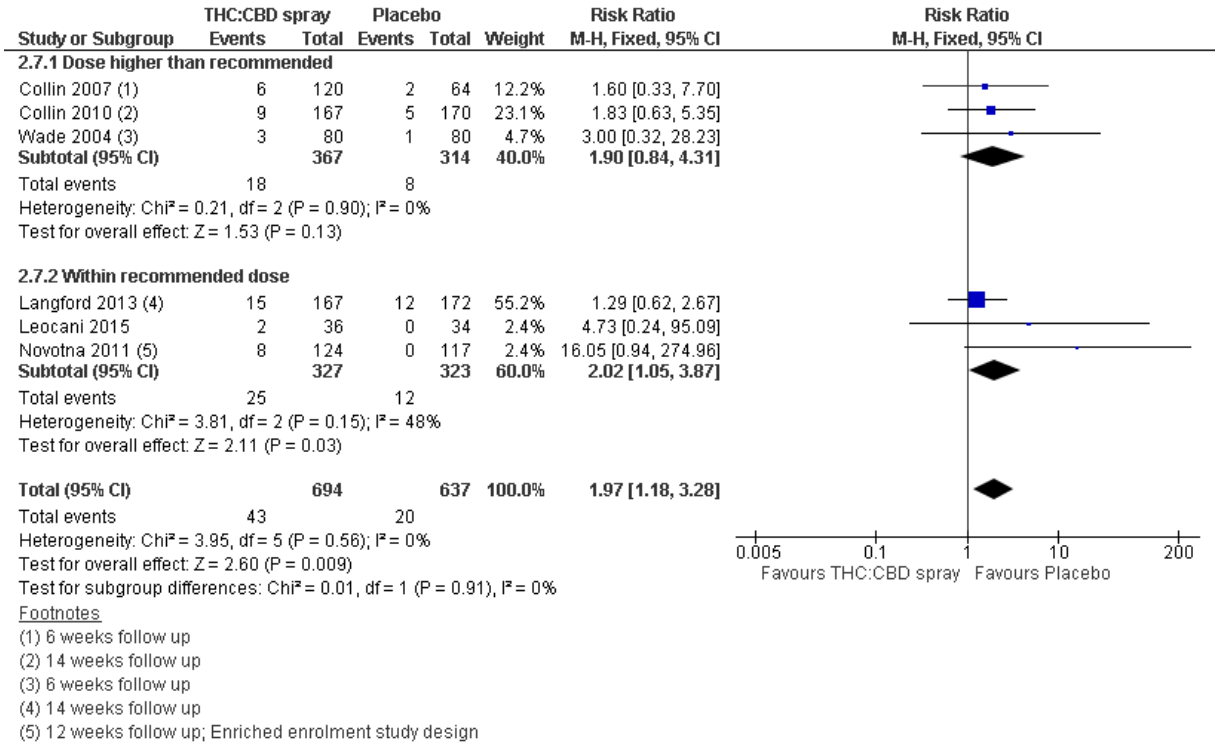
Test for subgroup differences: Chi² = 0.05, df = 1 (P = 0.83), I² = 0%

Footnotes

(1) 6 weeks follow up

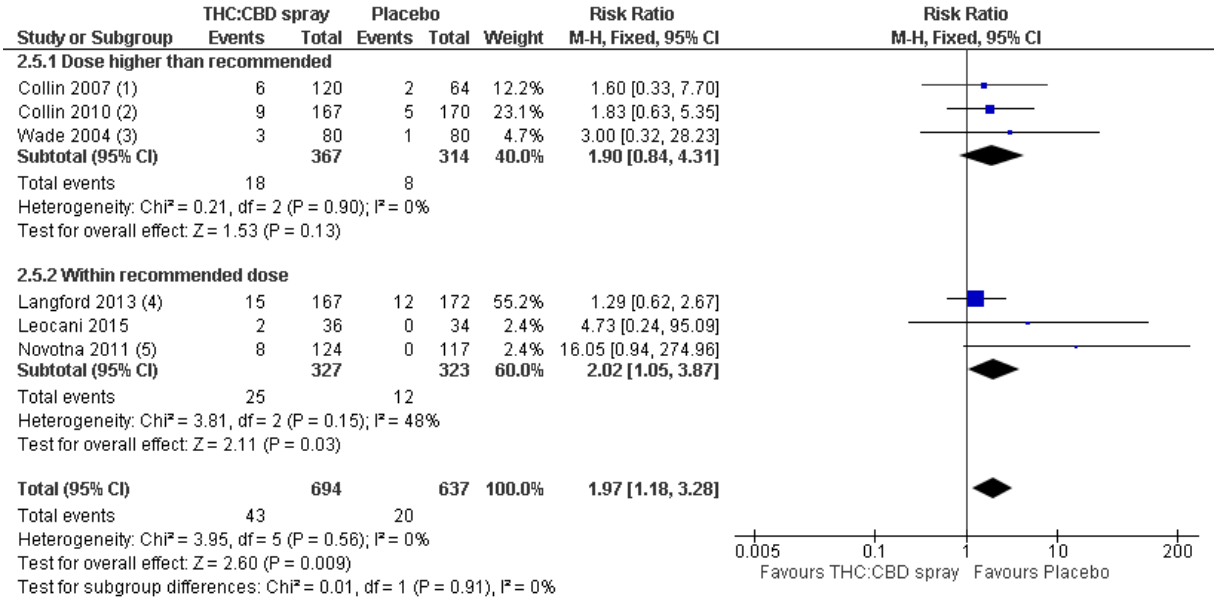
(2) 12 weeks follow up; Enriched enrolment study design

Withdrawal due to adverse events



Footnotes
(1) 6 weeks follow up
(2) 14 weeks follow up
(3) 6 weeks follow up
(4) 14 weeks follow up
(5) 12 weeks follow up; Enriched enrolment study design

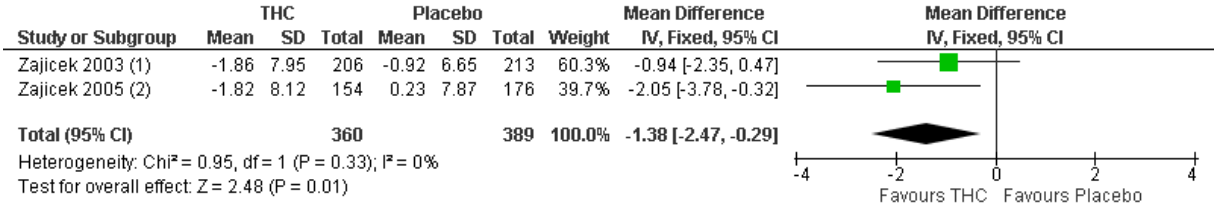
Pooled estimates



Footnotes
(1) 6 weeks follow up
(2) 14 weeks follow up
(3) 6 weeks follow up
(4) 14 weeks follow up
(5) 12 weeks follow up; Enriched enrolment study design

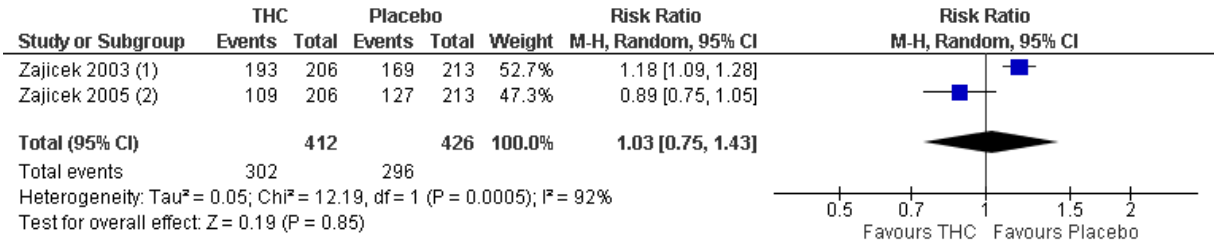
THC capsules (synthetic THC)

Spasticity: Ashworth Scale – change from baseline (total score)



Footnotes
(1) 8 weeks follow up
(2) 52 weeks follow-up

Total adverse events

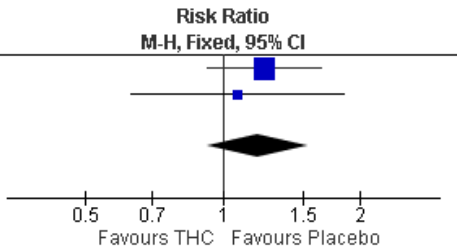


Footnotes
(1) 8 weeks follow up
(2) 52 weeks follow up

Total serious adverse events

Study or Subgroup	THC Events	THC Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ball 2015 (1)	114	329	46	164	73.1%	1.24 [0.93, 1.65]
Zajicek 2005 (2)	24	206	23	213	26.9%	1.08 [0.63, 1.85]
Total (95% CI)		**535**		**377**	**100.0%**	**1.19 [0.93, 1.54]**
Total events	138		69			

Heterogeneity: Chi² = 0.19, df = 1 (P = 0.66); I² = 0%
Test for overall effect: Z = 1.36 (P = 0.17)

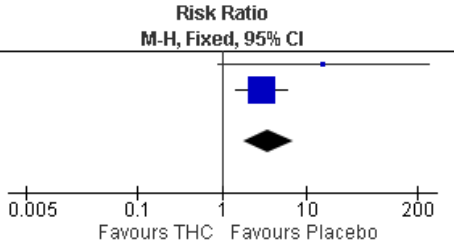


Footnotes
(1) 36 months follow up
(2) 52 weeks follow up

Withdrawals due to adverse events

Study or Subgroup	THC Events	THC Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Zajicek 2003 (1)	7	206	0	213	4.8%	15.51 [0.89, 269.79]
Zajicek 2005 (2)	28	197	10	207	95.2%	2.94 [1.47, 5.90]
Total (95% CI)		**403**		**420**	**100.0%**	**3.55 [1.82, 6.91]**
Total events	35		10			

Heterogeneity: Chi² = 1.30, df = 1 (P = 0.25); I² = 23%
Test for overall effect: Z = 3.72 (P = 0.0002)



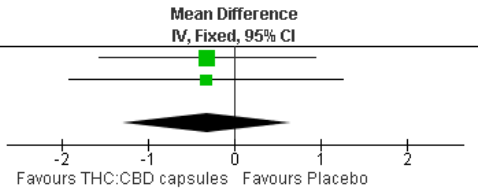
Footnotes
(1) 8 weeks follow up
(2) 52 weeks follow up

THC:CBD cannabis extract capsules

Spasticity: Ashworth Scale – change from baseline (total score)

Study or Subgroup	THC:CBD capsules Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Zajicek 2003 (1)	-1.24	6.6	211	-0.92	6.56	213	61.7%	-0.32 [-1.57, 0.93]
Zajicek 2005 (2)	-0.1	7.25	172	0.23	7.87	176	38.3%	-0.33 [-1.92, 1.26]
Total (95% CI)			**383**			**389**	**100.0%**	**-0.32 [-1.31, 0.66]**

Heterogeneity: Chi² = 0.00, df = 1 (P = 0.99); I² = 0%
Test for overall effect: Z = 0.65 (P = 0.52)

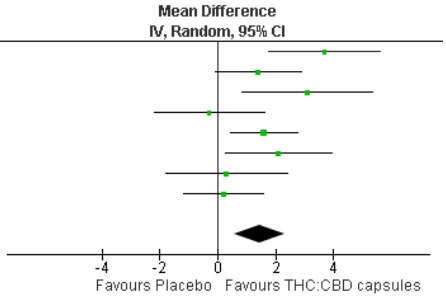


Footnotes
(1) 8 weeks follow up
(2) 52 weeks follow up

Effects of spasticity: MSSS-88 – change from baseline (subscales)

Study or Subgroup	THC:CBD capsules Mean	SD	Total	Cannabis-based products Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Zajicek 2012 (1)	-1.3	7.9	134	-5	8.5	143	11.2%	3.70 [1.77, 5.63]
Zajicek 2012 (2)	-1.6	6.2	134	-3	6.4	143	14.3%	1.40 [-0.08, 2.88]
Zajicek 2012 (3)	-2.1	9.2	134	-5.2	9.9	143	9.4%	3.10 [0.85, 5.35]
Zajicek 2012 (4)	-1.6	8.2	134	-1.3	8	143	11.3%	-0.30 [-2.21, 1.61]
Zajicek 2012 (5)	-1.4	4.2	134	-3	5.7	143	16.8%	1.60 [0.43, 2.77]
Zajicek 2012 (6)	-1.8	7.9	134	-3.9	7.7	143	11.8%	2.10 [0.26, 3.94]
Zajicek 2012 (7)	-1.8	9.1	134	-2.1	8.9	143	10.1%	0.30 [-1.82, 2.42]
Zajicek 2012 (8)	-1	5.6	134	-1.2	6.2	143	15.1%	0.20 [-1.19, 1.59]
Total (95% CI)			**1072**			**1144**	**100.0%**	**1.45 [0.56, 2.34]**

Heterogeneity: Tau² = 0.86; Chi² = 15.25, df = 7 (P = 0.03); I² = 54%
Test for overall effect: Z = 3.20 (P = 0.001)

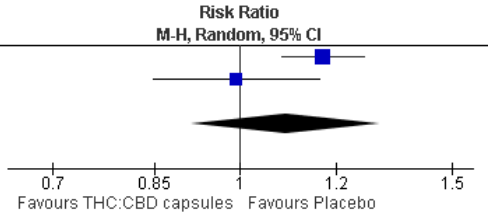


Footnotes
(1) Muscle stiffness
(2) Pain/discomfort
(3) Muscle spasms
(4) Daily activities
(5) Ability to walk
(6) Body movement
(7) Feelings
(8) Social functioning

Total adverse events

Study or Subgroup	THC:CBD capsules Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Zajicek 2003 (1)	196	211	169	213	57.0%	1.17 [1.08, 1.27]
Zajicek 2005 (2)	125	211	127	213	43.0%	0.99 [0.85, 1.16]
Total (95% CI)		**422**		**426**	**100.0%**	**1.09 [0.91, 1.31]**
Total events	321		296			

Heterogeneity: Tau² = 0.01; Chi² = 4.30, df = 1 (P = 0.04); I² = 77%
Test for overall effect: Z = 0.95 (P = 0.34)

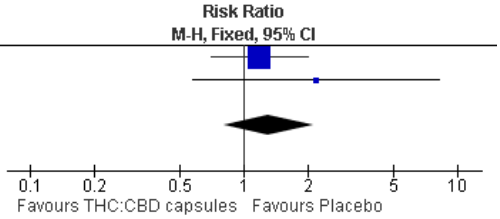


Footnotes
(1) 8 weeks follow up
(2) 52 weeks follow up

Total serious adverse events

Study or Subgroup	THC:CBD capsules Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Zajicek 2005 (1)	27	211	23	213	88.1%	1.19 [0.70, 2.00]
Zajicek 2012 (2)	7	143	3	134	11.9%	2.19 [0.58, 8.28]
Total (95% CI)		**354**		**347**	**100.0%**	**1.30 [0.80, 2.12]**
Total events	34		26			

Heterogeneity: Chi² = 0.71, df = 1 (P = 0.40); I² = 0%
Test for overall effect: Z = 1.08 (P = 0.28)

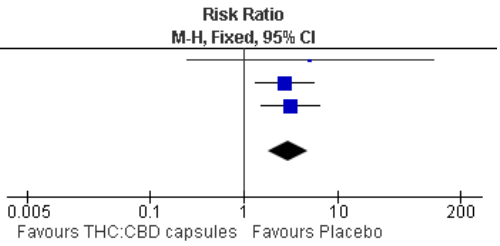


Footnotes
(1) 52 weeks follow up
(2) 12 weeks follow up

Withdrawals due to adverse events

Study or Subgroup	THC:CBD capsules Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Zajicek 2003 (1)	2	211	0	213	2.5%	5.05 [0.24, 104.51]
Zajicek 2005 (2)	27	207	10	207	50.5%	2.70 [1.34, 5.43]
Zajicek 2012 (3)	30	143	9	134	47.0%	3.12 [1.54, 6.33]
Total (95% CI)		**561**		**554**	**100.0%**	**2.96 [1.81, 4.83]**
Total events	59		19			

Heterogeneity: Chi² = 0.21, df = 2 (P = 0.90); I² = 0%
Test for overall effect: Z = 4.34 (P < 0.0001)



Footnotes
(1) 8 weeks follow up
(2) 52 weeks follow up
(3) 12 weeks follow up

Appendix H GRADE tables

Multiple sclerosis

THC:CBD spray

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Spasticity: Modified Ashworth scale (6 point scale) - Change from baseline (MD <0 favours THC:CBD spray)										
Dose higher than recommended										
2	Parallel RCTs	480	MD 0.16 (-0.50, 0.83)	-	-	Very serious[1]	Not serious	Not serious	Serious[6]	Very low
Within recommended dose										
2	Parallel RCTs	347	MD -0.64 (-1.94, 0.67)	-	-	Very serious[1]	Serious[3]	Not serious	Serious[6]	Very low
Spasticity: Ashworth scale (5 point scale) - Change from baseline (MD <0 favours THC:CBD spray)										
Dose higher than recommended										
1 (Collin 2007)	Parallel RCT	184	MD -0.11 (-0.29, 0.07)	-	-	Serious[7]	N/A[5]	Not serious	Serious[6]	Low
Spasticity: Numerical rating scale (11 point scale) - Change from baseline (MD <0 favours THC:CBD spray)										
Dose higher than recommended										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
3	Parallel RCTs	558	MD -0.76 (-1.50, -0.01)	-	-	Serious[2]	Very serious[4]	Not serious	Serious[9]	Very low
Within recommended dose										
4	3 Parallel RCTs 1 cross-over RCT	754	MD -0.78 (-1.51, -0.06)	-	-	Very serious[1]	Very serious[4]	Not serious	Serious[9]	Very low
Spasticity: Ashworth scale responder: >30% improvement in spasticity (RR <1 favours THC:CBD spray)										
Within recommended dose										
1 (Novotna 2011)	Parallel RCT	241	RR 0.69 (0.56, 0.85)	50 per 100	73 per 100 (60, 90)	Very serious[8]	N/A[5]	Not serious	Not serious	Low
Spasticity: Numerical rating scale responder: >30% improvement in spasticity (RR <1 favours THC:CBD spray)										
Dose higher than recommended										
2	Parallel RCTs	521	RR 0.71 (0.53, 0.94)	24 per 100	17 per 100 (13, 22)	Serious[2]	Not serious	Not serious	Not serious	Moderate
Within recommended dose										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
2	Parallel RCTs	347	RR 0.55 (0.33, 0.92)	45 per 100	82 per 100 (49, 137)	Very serious[1]	Very serious[4]	Not serious	Not serious	Very low
Total adverse events (RR<1 favours THC:CBD spray)										
Dose higher than recommended										
1 (Collin 2010)	Parallel RCT	288	RR 1.20 (1.10, 1.32)	78 per 100	93 per 100 (85, 100)	Serious[7]	N/A[5]	Not serious	Not serious	Moderate
Within recommended dose										
2	1 Parallel RCT 1 cross-over RCT	143	RR 1.44 (0.70, 2.98)	42 per 100	60 per 100 (29, 124)	Very serious[1]	Very serious[4]	Not serious	Serious[6]	Very low
Treatment-related adverse events (RR<1 favours THC:CBD spray)										
Dose higher than recommended										
1 (Collin 2007)	Parallel RCT	184	RR 1.18 (1.00, 1.40)	72 per 100	85 per 100 (72, 101)	Serious[7]	N/A[5]	Not serious	Serious[6]	Low

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Within recommended dose										
2	Parallel RCTs	445	RR 1.20 (1.03, 1.40)	50 per 100	60 per 100 (52, 70)	Not serious	Not serious	Not serious	Not serious	High
Total serious adverse events (RR<1 favours THC:CBD spray)										
Dose higher than recommended										
1 (Collin 2007)	Parallel RCT	184	RR 0.71 (0.16, 3.08)	5 per 100	3 per 100 (1, 14)	Serious[7]	N/A[5]	Not serious	Serious[6]	Low
Within recommended dose										
1 (Markova 2018)	Parallel RCT	106	RR 1.00 (0.06, 15.57)	2 per 100	2 per 100 (0, 29)	Very serious[8]	N/A[5]	Not serious	Serious[6]	Very low
Treatment-related serious adverse events (RR<1 favours THC:CBD spray)										
Within recommended dose										
1 (Langford 2013)	Parallel RCT	339	RR 1.54 (0.81, 2.94)	8 per 100	13 per 100 (7, 24)	Not serious	N/A[5]	Not serious	Serious[6]	Moderate

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Withdrawal due to adverse events (RR<1 favours THC:CBD spray)										
Dose higher than recommended										
3	Parallel RCTs	681	RR 1.90 (0.84, 4.31)	3 per 100	5 per 100 (2, 11)	Serious[2]	Not serious	Not serious	Serious[6]	Low
Within recommended dose										
3	2 Parallel RCTs 1 cross-over RCT	650	RR 2.02 (1.05, 3.87)	4 per 100	8 per 100 (4, 14)	Not serious	Not serious	Not serious	Not serious	High

1. > 33.3% of the weight in a meta-analysis came from studies at high risk of bias. Downgraded 2 levels
2. > 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias. Downgraded 1 level
3. I^2 between 33.3% and 66.7%. Downgraded one level
4. I^2 > 66.7%. Downgraded two levels
5. Inconsistency N/A as only 1 study
6. 95% confidence interval crosses line of no effect. Downgraded 1 level
7. Single study at moderate risk of bias. Downgraded 1 level
8. Single study at high risk of bias. Downgraded 2 levels
9. 95% confidence interval crosses one end of the defined MID (-0.9).

THC capsules (synthetic THC)

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Spasticity: Ashworth scale (5 point scale) - Change from baseline: Total score (MD <0 favours THC capsules)										
2	Parallel RCTs	749	MD -1.38 (-2.47, -0.29)	-	-	Serious[6]	Not serious	Not serious	Not serious	Moderate
Spasticity: Ashworth scale (5 point scale) - Change from baseline: Upper body score (MD <0 favours THC capsules)										
1 (Zajicek 2003)	Parallel RCT	419	MD -0.59 (-1.43, 0.25)	-	-	Serious[1]	N/A[3]	Not serious	Serious[4]	Low
Spasticity: Ashworth scale (5 point scale) - Change from baseline: Lower body score (MD <0 favours THC capsules)										
1 (Zajicek 2003)	Parallel RCT	419	MD -0.35 (-1.26, 0.56)	-	-	Serious[1]	N/A[3]	Not serious	Serious[4]	Low
Spasticity: MSSS-88 - Change from baseline: Subscales 1-3 (Muscle stiffness/spasms, pain & discomfort; 52 items, 5 point scale) (MD >0 favours THC capsules)										
1 (Ball 2015)	Parallel RCT	493	MD 0.34 (-0.98, 1.66)	-	-	Serious[1]	N/A[3]	Serious[5]	Serious[4]	Very low
Spasticity: MSSS-88 - Change from baseline: Subscales 4-6 (Activity, walking & body movements; 50 items, 5 point scale) (MD >0 favours THC capsules)										
1 (Ball 2015)	Parallel RCT	493	MD 0.03 (-1.20, 1.26)	-	-	Serious[1]	N/A[3]	Serious[5]	Serious[4]	Very low

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Spasticity: MSSS-88 - Change from baseline: Subscales 7-8 (Feelings & social functioning; 42 items, 5 point scale) (MD >0 favours THC capsules)										
1 (Ball 2015)	Parallel RCT	493	MD -0.63 (-1.56, 0.30)	-	-	Serious[1]	N/A[3]	Serious[5]	Serious[4]	Very low
Total adverse events (RR<1 favours THC capsules)										
2	Parallel RCTs	838	RR 1.03 (0.75, 1.43)	69 per 100	72 per 100 (52, 99)	Serious[6]	Very serious[2]	Not serious	Serious[4]	Very low
Total serious adverse events (RR<1 favours THC capsules)										
2	Parallel RCTs	912	RR 1.19 (0.93, 1.54)	18 per 100	22 per 100 (17, 28)	Serious[6]	Not serious	Serious[7]	Serious[4]	Very low
Withdrawals due to adverse events (RR<1 favours THC capsules)										
2	Parallel RCTs	823	RR 3.55 (1.82, 6.91)	2 per 100	8 per 100 (4, 16)	Serious[6]	Not serious	Not serious	Not serious	Moderate

1. Single study at moderate risk of bias. Downgraded 1 level
2. I^2 > 66.7%. Downgraded two levels
3. Inconsistency N/A as only 1 study
4. 95% confidence interval crosses line of no effect. Downgraded 1 level
5. Single study which was partially indirect. Downgraded 1 level
6. > 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias. Downgraded 1 level
7. > 33.3% of the weight in a meta-analysis came from studies which were partially indirect. Downgraded 1 level
8.

THC capsules (purified THC from cannabis extract)

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Spasticity: Numerical rating scale (11 point scale) - Change from baseline (MD <0 favours THC capsules)										
1 (van Amerongen 2018)	Parallel RCT	24	MD -0.38 (-1.30, 0.54)	-	-	Serious[1]	N/A[2]	Not serious	Serious[3]	Low
Total adverse events (RR<1 favours THC capsules)										
1 (van Amerongen 2018)	Parallel RCT	24	RR 1.43 (0.83, 2.45)	58 per 100	83 per 100 (48, 100)	Serious[1]	N/A[2]	Not serious	Serious[3]	Low
Withdrawals due to adverse events (RR<1 favours THC capsules)										
1 (van Amerongen 2018)	Parallel RCT	24	RR 3.00 (0.13, 67.06)	4 per 100	13 per 100 (1, 100)	Serious[1]	N/A[2]	Not serious	Serious[3]	Low

1. Single study at moderate risk of bias. Downgraded 1 level
2. Inconsistency N/A as only 1 study
3. 95% confidence interval crosses line of no effect. Downgraded 1 level

THC:CBD cannabis extract capsules

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Spasticity: Ashworth scale (5 point scale) - Change from baseline: Total score (MD <0 favours THC:CBD capsules)										
2	Parallel RCTs	772	MD -0.32 (-1.31, 0.66)	-	-	Serious[5]	Not serious	Not serious	Serious[3]	Low
Spasticity: Ashworth scale (5 point scale) - Change from baseline: Upper body score (MD <0 favours THC:CBD capsules)										
1 (Zajicek 2003)	Parallel RCT	424	MD -0.06 (-0.84, 0.72)	-	-	Serious[1]	N/A[2]	Not serious	Serious[3]	Low
Spasticity: Ashworth scale (5 point scale) - Change from baseline: Lower body score (MD <0 favours THC:CBD capsules)										
1 (Zajicek 2003)	Parallel RCT	424	MD -0.25 (-1.07, 0.57)	-	-	Serious[1]	N/A[2]	Not serious	Serious[3]	Low
Spasticity: MSSS-88 - Change from baseline: Subscale 1 (Muscle stiffness; 19 items, 5 point scale)) (MD >0 favours THC:CBD capsules)										
1 (Zajicek 2012)	Parallel RCT	277	MD 3.70 (1.77, 5.63)	-	-	Serious[1]	N/A[2]	Not serious	Not serious	Moderate
Spasticity: MSSS-88 - Change from baseline: Subscale 2 (Pain/discomfort; 10 items, 5 point scale) (MD >0 favours THC:CBD capsules)										
1 (Zajicek 2012)	Parallel RCT	277	MD 1.40 (-0.08, 2.88)	-	-	Serious[1]	N/A[2]	Not serious	Serious[3]	Low
Spasticity: MSSS-88 - Change from baseline: Subscale 3 (Muscle spasms; 23 items, 5 point scale) (MD >0 favours THC:CBD capsules)										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
1 (Zajicek 2012)	Parallel RCT	277	MD 3.10 (0.85, 5.35)	-	-	Serious[1]	N/A[2]	Not serious	Not serious	Moderate
Spasticity: MSSS-88 - Change from baseline: Subscale 4 (Daily activities; 14 items, 5 point scale) (MD >0 favours THC:CBD capsules)										
1 (Zajicek 2012)	Parallel RCT	277	MD -0.30 (-2.21, 1.61)	-	-	Serious[1]	N/A[2]	Not serious	Serious[3]	Low
Spasticity: MSSS-88 - Change from baseline: Subscale 5 (Ability to walk; 15 items, 5 point scale) (MD >0 favours THC:CBD capsules)										
1 (Zajicek 2012)	Parallel RCT	277	MD 1.60 (0.43, 2.77)	-	-	Serious[1]	N/A[2]	Not serious	Not serious	Moderate
Spasticity: MSSS-88 - Change from baseline: Subscale 6 (Body movement; 21 items, 5 point scale) (MD >0 favours THC:CBD capsules)										
1 (Zajicek 2012)	Parallel RCT	277	MD 2.10 (0.26, 3.94)	-	-	Serious[1]	N/A[2]	Not serious	Not serious	Moderate
Spasticity: MSSS-88 - Change from baseline: Subscale 7 (Feelings; 26 items, 5 point scale) (MD >0 favours THC:CBD capsules)										
1 (Zajicek 2012)	Parallel RCT	277	MD 0.30 (-1.82, 2.42)	-	-	Serious[1]	N/A[2]	Not serious	Serious[3]	Low

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Spasticity: MSSS-88 - Change from baseline: Subscale 8 (Social functioning; 16 items, 5 point scale) (MD >0 favours THC:CBD capsules)										
1 (Zajicek 2012)	Parallel RCT	277	MD 0.20 (-1.19, 1.59)	-	-	Serious[1]	N/A[2]	Not serious	Serious[3]	Low
Total adverse events (RR<1 favours THC:CBD capsules)										
2	Parallel RCTs	848	RR 1.09 (0.91, 1.31)	69 per 100	76 per 100 (63, 91)	Serious[1]	Serious[4]	Not serious	Serious[3]	Very low
Treatment-related adverse events (RR<1 favours THC:CBD capsules)										
1 (Zajicek 2012)	Parallel RCT	277	RR 1.25 (1.12, 1.39)	75 per 100	93 per 100 (84, 104)	Serious[1]	N/A[2]	Not serious	Not serious	Moderate
Total serious adverse events (RR<1 favours THC capsules)										
2	Parallel RCTs	701	RR 1.30 (0.80, 2.12)	7 per 100	10 per 100 (6, 16)	Serious[5]	Not serious	Not serious	Serious[3]	Low
Withdrawals due to adverse events (RR<1 favours THC capsules)										
3	Parallel RCTs	1115	RR 2.96 (1.81, 4.83)	3 per 100	10 per 100 (6, 17)	Serious[5]	Not serious	Not serious	Not serious	Moderate

1. Single study at moderate risk of bias. Downgraded 1 level
2. Inconsistency N/A as only 1 study
3. 95% confidence interval crosses line of no effect. Downgraded 1 level

4. I^2 between 33.3% and 66.7%. Downgraded one level
5. > 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias. Downgraded 1 level

Motor neurone disease

THC:CBD spray

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Spasticity: Modified Ashworth scale (6 point scale) - Change from baseline: Total score (MD <0 favours THC:CBD spray)										
1 (Riva 2019)	Parallel RCT	59	MD -0.27 (-0.51, -0.03)	-	-	Not serious	N/A[1]	Not serious	Not serious	High
Spasticity: Numerical rating scale (11 point scale) - Change from baseline (MD <0 favours THC:CBD spray)										
1 (Riva 2019)	Parallel RCT	59	MD -0.20 (-1.13, 0.73)	-	-	Not serious	N/A[1]	Not serious	Serious[2]	Moderate
Total adverse events (RR <1 favours THC:CBD oromucosal spray)										
1 (Riva 2019)	Parallel RCT	59	RR 2.84 (1.52, 5.33)	27 per 100	76 per 100 (41, 100)	Not serious	N/A[1]	Not serious	Not serious	High
Treatment-related adverse events (RR <1 favours THC:CBD spray)										
1 (Riva 2019)	Parallel RCT	59	RR 5.43 (2.12, 13.90)	13 per 100	72 per 100 (28, 100)	Not serious	N/A[1]	Not serious	Not serious	High

1. Inconsistency N/A as only 1 study
2. 95% confidence interval crosses line of no effect. Downgraded 1 level

THC capsules (synthetic THC)

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Spasticity: Ashworth scale (5 point scale) - Change from baseline: Total score (MD <0 favours nabilone)										
1 (Wissel 2006)	Cross-over RCT	26	MD -0.35 (-1.14, 0.45)	-	-	Very serious[1]	N/A[2]	Not serious	Serious[3]	Very low

1. Single study at high risk of bias. Downgraded 2 levels
2. Inconsistency N/A as only 1 study
3. 95% confidence interval crosses line of no effect. Downgraded 1 level

Spinal cord injury

THC capsules (synthetic THC)

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Spasticity: Ashworth scale (5 point scale) - Change from baseline: Total score (MD <0 favours nabilone)										
1 (Pooyania 2010)	Cross-over RCT	22	MD -2.55 (-3.84, -1.26)	-	-	Serious[1]	N/A[2]	Not serious	Not serious	Moderate
Spasticity: Ashworth scale (5 point scale) - Change from baseline: Most involved muscle group (MD <0 favours nabilone)										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
1 (Pooyania 2010)	Cross-over RCT	22	MD -0.91 (-1.44, -0.38)	-	-	Serious[1]	N/A[2]	Not serious	Not serious	Moderate
Spasticity: Visual analogue scale (100 point scale) - Change from baseline (MD <0 favours nabilone)										
1 (Pooyania 2010)	Cross-over RCT	22	MD -9.09 (-18.61, 0.43)	-	-	Serious[1]	N/A[2]	Not serious	Serious[3]	Low

1. Single study at moderate risk of bias. Downgraded 1 level
2. Inconsistency N/A as only 1 study
3. 95% confidence interval crosses line of no effect. Downgraded 1 level

Appendix I Adverse events

Multiple sclerosis

THC:CBD oromucosal spray

Study	Adverse events reported
Dose higher than recommended	
Collin 2007	Treatment-related adverse events experienced by more than 4 participants THC: CBD spray: Dizziness 32%; Fatigue 11%; Urinary tract infection 11%; Dry mouth 9%; Balance impaired 7%; Nausea 7%; Headache 7%; Diarrhoea 6%; Oral pain 5%; Somnolence 5%; Confusion 5%; Depressed mood 5%; Constipation 4%; Disorientation 4%; Dysgeusia 4%; Disturbance in attention 3%; Euphoric mood 3%; Blurred vision 3%; Weakness 3%; Limb pain 3% Placebo: Dizziness 11%; Fatigue 6%; Urinary tract infection 9%; Dry mouth 6%; Balance impaired 2%; Nausea 6%; Headache 6%; Diarrhoea 3%; Oral pain 10%; Somnolence 2%; Confusion 3%; Constipation 2%; Disorientation 2%; Dysgeusia 2%; Euphoric mood 3%; Weakness 2%; Limb pain 2%
Collin 2010	Total adverse events experienced by ≥10% participants THC: CBD spray: Nervous system disorders 69% (Dizziness 32%; Somnolence 14%; Spasticity 10%); General disorders 46% (Fatigue 25%; Asthenia 16%); Gastrointestinal disorders 35% (Nausea 32%; Dry mouth 14%); Infections 22% (Urinary tract infection NOS 11%); Psychiatric disorders 17%; Musculoskeletal and connective tissue disorders 14%; Ear and labyrinth disorders 11% (Vertigo 11%) Placebo: Nervous system disorders 78% (Dizziness 34%; Somnolence 10%; Spasticity 4%); General disorders 28% (Fatigue 19%; Asthenia 6%); Gastrointestinal disorders 20% (Nausea 10%; Dry mouth 4%); Infections 22% (Urinary tract infection NOS 12%); Psychiatric disorders 11%; Musculoskeletal and connective tissue disorders 9%; Ear and labyrinth disorders 4% (Vertigo 4%) Most commonly reported treatment-related adverse events which showed a higher incidence in the active treatment group than placebo: THC: CBD spray: Dizziness 32%; Fatigue 23%; Somnolence 14%; Nausea 14%; Asthenia 13%; Vertigo 11% Placebo: Dizziness 10%; Fatigue 16%; Somnolence 4%; Nausea 5%; Asthenia 6%; Vertigo 4%

Study	Adverse events reported
Wade 2004	Treatment-related adverse events with >4% incidence THC: CBD spray: Dizziness 33%; Disturbance in attention 9%; Headache 9%; Fatigue 15%; Somnolence 9%; Disorientation 8%; Feeling drunk 5%; Vertigo 6%; Application site discomfort 26%; Nausea 9%; Diarrhoea 8%; Mouth ulceration 5% Placebo: Dizziness 13%; Headache 16%; Fatigue 4%; Somnolence 1%; Application site discomfort 23%; Nausea 6%; Diarrhoea 3%; Mouth ulceration 1%
Within recommended dose	
Langford 2013	Treatment-related adverse events experienced by ≥3% participants (Phase A) THC: CBD spray: Ear and labyrinth disorder 12% (Vertigo 9%); Eye disorder 4% (Blurred vision 2%); Gastrointestinal disorder 32% (Nausea 8%; Dry mouth 7%; Diarrhoea 4%; Vomiting 3%); General disorders 24% (Fatigue 10%; Feeling abnormal 3%); Infections and infestations (20%); Musculoskeletal and connective tissue disorders 10% (Muscular weakness 1%); Nervous system disorders 44% (Dizziness 20%; Somnolence 10%; Headache 4%; Disturbance in attention 4%; Dysgeusia 4%; Memory impairment 4%; Balance disorder 3%; Psychomotor skills impaired 3%; Neuralgia 1%); Psychiatric disorders 16% (Depression 1%); Respiratory, thoracic and mediastinal disorders 5% (Pharyngolaryngeal pain 1%) Placebo: Ear and labyrinth disorder 5% (Vertigo 3%); Eye disorder 3% (Blurred vision 1%); Gastrointestinal disorder 23% (Nausea 4%; Dry mouth 6%; Diarrhoea 3%; Vomiting 3%); General disorders 17% (Fatigue 5%; Feeling abnormal 1%; Pain 1%); Infections and infestations (16%); Musculoskeletal and connective tissue disorders 12% (Pain in extremity 1%; Muscular weakness 1%); Nervous system disorders 30% (Dizziness 4%; Somnolence 2%; Headache 3%; Disturbance in attention 1%; Dysgeusia 1%; Memory impairment 1%; Balance disorder 1%; Neuralgia 1%); Psychiatric disorders 7%; Respiratory, thoracic and mediastinal disorders 6% (Pharyngolaryngeal pain 1%)
Leocani 2015	THC: CBD spray: Dizziness 21%; Lower limb weakness 6%; Vertigo 3%; Hypotension 6%; Hypertension 3%; Pharyngodia 3% Placebo: Dizziness 6%; Lower limb weakness 3%; Vertigo 3%; Somnolence 3%; Fever 3%
Markova 2018	Most frequently reported treatment-related adverse events experienced in Phase A (enriched enrolment) THC: CBD spray: Vertigo 7%; Somnolence 2%; Dizziness 2%; Diarrhoea 2%; Nausea 2%

Study	Adverse events reported
	Total serious adverse events in Phase B (RCT) THC: CBD spray: haematuria Placebo: Tubulointerstitial nephristis
Novotna 2011	Total adverse events experienced by ≥3% participants Phase A (enriched enrolment) THC: CBD spray: Ear and labyrinth disorders 4% (Vertigo 4%); Gastrointestinal disorders 13% (Dry mouth 4%; Nausea 4%; Diarrhoea 1%; Upper abdominal pain 1%); General disorders 14% (Fatigue 6%); Infections and infestations 7% (Urinary tract infection 3%; Naso-pharyngitis 1%); Musculo-skeletal and connective tissue 5% (Muscle spasms 1%; Back pain 0.2%; Pain in extremity 0.2%); Nervous system disorders 26% (Dizziness 14%; Somnolence 5%; Headache 2%; Spasticity 2%; MS relapse 1%); Psychiatric disorders 8% (Euphoric mood 1%) Phase B (RCT) THC: CBD spray: Ear and labyrinth disorders 6% (Vertigo 6%); Gastrointestinal disorders 15% (Dry mouth 3%; Nausea 4%; Diarrhoea 2%; Upper abdominal pain 3%); General disorders 14% (Fatigue 5%); Infections and infestations 15% (Urinary tract infection 7%; Naso-pharyngitis 3%); Musculo-skeletal and connective tissue 15% (Muscle spasms 6%; Back pain 4%); Nervous system disorders 15% (Dizziness 3%; Somnolence 3%; Headache 2%; Spasticity 2%; MS relapse 3%); Psychiatric disorders 11% (Euphoric mood 3%) Phase B (RCT) Placebo: Ear and labyrinth disorders 1% (Vertigo 1%); Gastrointestinal disorders 10% (Dry mouth 1%; Nausea 2%; Diarrhoea 5%); General disorders 8% (Fatigue 1%); Infections and infestations 22% (Urinary tract infection 10%; Naso-pharyngitis 3%); Musculo-skeletal and connective tissue 15% (Muscle spasms 7%; Back pain 3%; Pain in extremity 4%); Nervous system disorders 13% (Somnolence 1%; Headache 4%; Spasticity 3%; MS relapse 1%); Psychiatric disorders 6% (Euphoric mood 1%)

THC capsules (synthetic THC)

Study	Adverse events reported
Ball 2015	Adverse events experienced by ≥10% participants THC: Falls and injuries 31%; Mobility, balance and co-ordination problems 33%; Infections (excluding urinary tract) 29%; Fatigue and tiredness 25%; Dizziness and light-headedness 32%; Muscle disorders (spasticity, stiffness, spasms or tremor) 24%; Muscle weakness 22%; Dissociative and thinking or perception disorders 30%; Depression 20%; Musculoskeletal pain and aches 15%; Constipation, diarrhoea, faecal incontinence 17%; Joint disorders 14%; Urinary tract infections 13%

Study	Adverse events reported
	Placebo: Falls and injuries 31%; Mobility, balance and co-ordination problems 26%; Infections (excluding urinary tract) 29%; Fatigue and tiredness 23%; Dizziness and light-headedness 7%; Muscle disorders (spasticity, stiffness, spasms or tremor) 23%; Muscle weakness 20%; Dissociative and thinking or perception disorders 4%; Depression 16%; Musculoskeletal pain and aches 25%; Constipation, diarrhoea, faecal incontinence 13%; Joint disorders 17%; Urinary tract infections 17% Serious adverse events THC: Death 2%; Hospital admission 32%; Life-threatening or important medical event 3% Placebo: Death 0.6%; Hospital admission 27%; Life-threatening or important medical event 2%
Zajicek 2003	Adverse events THC: Bladder 24%; Gastrointestinal 30%; Pain 26%; Depression or anxiety 10%; Vision 6%; Infection 15%; Dizzy or lightheadedness 59%; Dry mouth 26%; Weakness or reduced mobility 25%; Sleep 35%; Spasms or stiffness 34%; Tremor or lack of coordination 12%; Numbness of paraesthesia 9%; Miscellaneous 28%; Improvement in symptoms 1% Placebo: Bladder 23%; Gastrointestinal 20%; Pain 32%; Depression or anxiety 8%; Vision 2%; Infection 17%; Dizzy or lightheadedness 18%; Dry mouth 7%; Weakness or reduced mobility 20%; Sleep 33%; Spasms or stiffness 33%; Tremor or lack of coordination 8%; Numbness of paraesthesia 7%; Miscellaneous 22%; Improvement in symptoms 0.5% Serious adverse events THC: MS relapse or possible relapse 0.5%; Urinary tract infection 2%; Pneumonia 1%; Blocked/insertion of suprapubic catheter 0.5%; Other 6% Placebo: MS relapse or possible relapse 4%; Urinary tract infection 2%; Pneumonia 0.5%; Blocked/insertion of suprapubic catheter 1%; Constipation 2%; Grand mal seizures 0.5%; Other 1%
Zajicek 2005	Adverse events THC: Bladder 16%; Depression or anxiety 6%; Dizziness or lightheadedness 9%; Dry mouth 2%; Falls 5%; Fatigue or sleep disturbance 8%; Gastrointestinal 12%; Infection 11%; Memory or concentration 2%; Miscellaneous 9%; MS relapse or exacerbation 6%; Numbness or paraesthesia 5%; Other skin problem 1%; Pain 13%; Pressure sores 0.5%; Spasms or stiffness 17%; Tremor or lack of coordination 5%; Vision symptoms 2%; Weakness or reduced mobility 12%

Study	Adverse events reported
	Placebo: Bladder 24%; Depression or anxiety 5%; Dizziness or lightheadedness 3%; Dry mouth 1%; Falls 4%; Fatigue or sleep disturbance 11%; Gastrointestinal 9%; Infection 14%; Memory or concentration 1%; Miscellaneous 9%; MS relapse or exacerbation 6%; Numbness or paraesthesia 4%; Other skin problem 7%; Pain 13%; Pressure sores 3%; Spasms or stiffness 19%; Tremor or lack of coordination 2%; Vision symptoms 0.5%; Weakness or reduced mobility 18% Serious adverse events THC: Relapse/possible relapse 5%; Urinary tract infection 1%; Other 5% Placebo: Relapse/possible relapse 2%; Urinary tract infection 2%; Pneumonia/chest infection 1%; Seizure 1%; Limb fracture 0.5%; Other 4%

THC capsules (purified THC from cannabis extract)

Study	Adverse events reported
Van Amerongen 2018	Adverse events reported more than once THC: Nervous system (Dizziness 58%; Headache 50%; Somnolence 25%; Muscular weakness 33%; Spasticity 25%; Paresthesia 17%; Tremor 17%; Tinnitus 17%); Psychiatric/mood (Euphoric mood 33%; Insomnia 8%); General disorders (Fatigue 17%; Feeling abnormal 8%; Feeling hot 17%); Gastrointestinal (Dry mouth 17%; Increased appetite 8%) Placebo: Nervous system (Dizziness 8%; Headache 25%; Somnolence 17%; Muscular weakness 8%; Spasticity 25%); Psychiatric/mood (Euphoric mood 33%; Insomnia 8%); General disorders (Fatigue 25%; Feeling abnormal 17%; Feeling hot 17%); Gastrointestinal (Nausea 8%)

THC:CBD cannabis extract capsules

Study	Adverse events reported
Zajicek 2003	Adverse events Cannabis extract: Bladder 26%; Gastrointestinal 37%; Pain 24%; Depression or anxiety 9%; Vision 8%; Infection 16%; Dizzy or lightheadedness 50%; Dry mouth 20%; Weakness or reduced mobility 23%; Sleep 40%; Spasms or stiffness 33%; Tremor or lack of coordination 10%; Numbness of paraesthesia 7%; Miscellaneous 30%; Improvement in symptoms 1% Placebo: Bladder 23%; Gastrointestinal 20%; Pain 32%; Depression or anxiety 8%; Vision 2%; Infection 17%; Dizzy or lightheadedness 18%;

Study	Adverse events reported
	Dry mouth 7%; Weakness or reduced mobility 20%; Sleep 33%; Spasms or stiffness 33%; Tremor or lack of coordination 8%; Numbness of paraesthesia 7%; Miscellaneous 22%; Improvement in symptoms 0.5% Serious adverse events Cannabis extract: MS relapse or possible relapse 0.5%; Urinary tract infection 0.5%; Pneumonia 0.5%; Blocked/insertion of suprapubic catheter 0.5%; Constipation 0.5%; Grand mal seizures 0.5%; Other 3% Placebo: MS relapse or possible relapse 4%; Urinary tract infection 2%; Pneumonia 0.5%; Blocked/insertion of suprapubic catheter 1%; Constipation 2%; Grand mal seizures 0.5%; Other 1%
Zajicek 2005	Adverse events Cannabis extract: Bladder 18%; Depression or anxiety 6%; Dizziness or light-headedness 13%; Dry mouth 1%; Falls 7%; Fatigue or sleep disturbance 8%; Gastrointestinal 15%; Infection 15%; Memory or concentration 2%; Miscellaneous 11%; MS relapse or exacerbation 8%; Numbness or paraesthesia 5%; Other skin problem 5%; Pain 23%; Pressure sores 1%; Spasms or stiffness 21%; Tremor or lack of coordination 2%; Vision symptoms 2%; Weakness or reduced mobility 14% Placebo: Bladder 24%; Depression or anxiety 5%; Dizziness or light-headedness 3%; Dry mouth 1%; Falls 4%; Fatigue or sleep disturbance 11%; Gastrointestinal 9%; Infection 14%; Memory or concentration 1%; Miscellaneous 9%; MS relapse or exacerbation 6%; Numbness or paraesthesia 4%; Other skin problem 7%; Pain 13%; Pressure sores 3%; Spasms or stiffness 19%; Tremor or lack of coordination 2%; Vision symptoms 0.5%; Weakness or reduced mobility 18% Serious adverse events Cannabis extract: Relapse/possible relapse 4%; Urinary tract infection 1%; Pneumonia/chest infection 3%; Seizure 0.5%; Insertion of baclofen pump 1%; Limb fracture 0.5%; Other 2% Placebo: Relapse/possible relapse 2%; Urinary tract infection 2%; Pneumonia/chest infection 1%; Seizure 1%; Limb fracture 0.5%; Other 4%
Zajicek 2012	Adverse events experienced by ≥10% participants Cannabis extract: Dizziness 46%; Urinary tract infection 15%; Dry mouth 23%; Headache 11%; Asthenia 13%; Fatigue 14% Placebo: Dizziness 7%; Urinary tract infection 12%; Dry mouth 8%; Headache 12%; Asthenia 8%; Fatigue 6%

Motor neurone disease

THC:CBD oromucosal spray

Study	Adverse events reported
Riva 2019	Most common adverse events THC: CBD spray: General disorders (Asthenia 24%; Malaise 3%); Nervous system disorders (Dizziness 7%; Balance disorder 3%; Memory impairment 3%; Somnolence 17%; Syncope 7%; Tremors 3%; Spasticity 3%); Psychiatric disorders (Anxiety 3%; Agitation 3%); Vertigo 17%; Blurred vision 3%; Palpitations 3%; Gastrointestinal disorders (Dry mouth 3%; Nausea 10%; Oral pain 3%); Fall 3% Placebo: General disorders (Asthenia 3%); Nervous system disorders (Somnolence 3%); Gastrointestinal disorders (Dry mouth 3%; Oral mucosal disorder 3%); Skin and subcutaneous tissue disorders (Erythema 3%; Skin exfoliation 3%; Pruritus 3%)

THC capsules (synthetic THC)

Study	Adverse events reported
Wissel 2006	Adverse events THC: Drowsiness (15%); Slight weakness in lower limbs Placebo: Drowsiness (8%); Slight dysphagia (8%) Severe adverse events THC: MS relapse (8%); Lower limb weakness (8%) Placebo: No severe adverse events

Spinal cord injury

Nabilone

Study	Adverse events reported
Pooyania 2010	THC: Drowsiness 27%; Dry mouth and asthenia 18%; Mild vertigo 18%; Mild ataxia, headache and lack of motivation 9% Adverse events not reported for placebo

Appendix J Excluded studies

Clinical studies

Study	Reason for exclusion
Abo Youssef, Nadim, Schneider, Marc P., Mordasini, Livio et al. (2017) Cannabinoids for treating neurogenic lower urinary tract dysfunction in patients with multiple sclerosis: a systematic review and meta-analysis. BJU international 119(4): 515-521	The relevant symptoms are not included
Anonymous (2014) Delta-9-tetrahydrocannabinol + cannabidiol (New Drug). Prescrire International 23(150): 145-148	Not a relevant study design
Anonymous (2014) Delta-9-tetrahydrocannabinol + cannabidiol. A reasonable option for some patients with multiple sclerosis. Prescrire international 23(150): 145-8	Narrative review
Aragona, Massimiliano, Onesti, Emanuela, Tomassini, Valentina et al. (2009) Psychopathological and cognitive effects of therapeutic cannabinoids in multiple sclerosis: a double-blind, placebo controlled, crossover study. Clinical neuropharmacology 32(1): 41-7	The relevant symptoms are not included
Beard, S.; Hunn, A.; Wight, J. (2004) Treatments for spasticity and pain in multiple sclerosis: a systematic review. Health Technology Assessment: 24	No outcomes of interest
Behm, Kate and Morgan, Prue (2018) The effect of symptom-controlling medication on gait outcomes in people with multiple sclerosis: a systematic review. Disability and rehabilitation 40(15): 1733-1744	Review article. The bibliography was reviewed for possible includes
Bravo-Soto, Gonzalo A. and Juri, Carlos (2017) Are cannabinoids effective for Parkinson's disease?. Son efectivos los cannabinoides en la enfermedad de Parkinson? 17(suppl2): e6974	The relevant symptoms are not included
Conte, Antonella, Bettolo, Chiara Marini, Onesti, Emanuela et al. (2009) Cannabinoid-induced effects on the nociceptive system: a neurophysiological study in patients with	Experimental pain model and used electrophysiological outcomes

Study	Reason for exclusion
secondary progressive multiple sclerosis. European journal of pain (London, England) 13(5): 472-7	
da Rovare, Victoria P., Magalhaes, Gabriel P. A., Jardini, Guilherme D. A. et al. (2017) Cannabinoids for spasticity due to multiple sclerosis or paraplegia: A systematic review and meta-analysis of randomized clinical trials. Complementary therapies in medicine 34: 170-185	Review article. The bibliography was reviewed for possible includes
Devinsky, O., Nabbout, R., Miller, I. et al. (2017) Maintenance of long-term safety and efficacy of cannabidiol (CBD) treatment in dravet syndrome (DS): results of the open-label extension (OLE) trial (GWPCARE 5). Developmental medicine and child neurology. Conference: 44th annual conference of the british paediatric neurology association, BPNA 2018. United kingdom 59(supplement4): 126	Conference abstract
Farzaei, Mohammad Hosein, Shahpiri, Zahra, Bahramsoltani, Roodabeh et al. (2017) Efficacy and Tolerability of Phytomedicines in Multiple Sclerosis Patients: A Review. CNS drugs 31(10): 867-889	Review article. The bibliography was reviewed for possible includes
Flachenecker, Peter (2013) A new multiple sclerosis spasticity treatment option: effect in everyday clinical practice and cost-effectiveness in Germany. Expert review of neurotherapeutics 13(3suppl1): 15-9	Observational study. No control group
Flachenecker, Peter; Henze, Thomas; Zettl, Uwe K. (2014) Nabiximols (THC/CBD oromucosal spray, Sativex) in clinical practice--results of a multicenter, non-interventional study (MOVE 2) in patients with multiple sclerosis spasticity. European neurology 71(56): 271-9	Observational study. No control group
Fox, P. and Zajicek, J. (2001) A multicentre randomised controlled trial of cannabinoids in multiple sclerosis. JNS 187(suppl1)	This article is no longer available from any source
Fox, P., Bain, P. G., Glickman, S. et al. (2004) The effect of cannabis on tremor in patients with multiple sclerosis. Neurology 62(7): 1105-9	The relevant symptoms are not included
Freeman, R. M., Adekanmi, O., Waterfield, M. R. et al. (2006) The effect of cannabis on urge incontinence in patients with multiple sclerosis: a multicentre, randomised placebo-	The relevant symptoms are not included

Study	Reason for exclusion
controlled trial (CAMS-LUTS). International urogynecology journal and pelvic floor dysfunction 17(6): 636-41	
Fu, Xiying, Wang, Yanqiao, Wang, Can et al. (2018) A mixed treatment comparison on efficacy and safety of treatments for spasticity caused by multiple sclerosis: a systematic review and network meta-analysis. Clinical rehabilitation 32(6): 713-721	Review article. The bibliography was reviewed for possible includes
Gras, Adrien and Broughton, Julie (2016) A cost-effectiveness model for the use of a cannabis-derived oromucosal spray for the treatment of spasticity in multiple sclerosis. Expert review of pharmacoeconomics & outcomes research 16(6): 771-779	Cost-effectiveness model
Green, Anita J. and De-Vries, Kay (2010) Cannabis use in palliative care - an examination of the evidence and the implications for nurses. Journal of clinical nursing 19(1718): 2454-62	Review article. The bibliography was reviewed for possible includes
Grotenhermen, F. (2004) Cannabinoids do not reduce objective measurements in muscle spasticity, but people with multiple sclerosis perceive some benefit. Evidence-Based Healthcare 8(3): 159-161	Letter to the editor
Haupts, M., Jonas, A., Witte, K. et al. (2015) Influence of optimized anti-spastic pre-treatment on the efficacy and tolerability of THC: CBD oromucosal spray in multiple sclerosis spasticity patients. A post-hoc RCT data analyses. Multiple sclerosis (houndmills, basingstoke, england) 23(11suppl1): 708-709	Post-hoc data that does not provide any additional information on the outcomes of interest
Haupts, M., Vila, C., Jonas, A. et al. (2016) Influence of Previous Failed Antispasticity Therapy on the Efficacy and Tolerability of THC: CBD Oromucosal Spray for Multiple Sclerosis Spasticity. European neurology 75(56): 236-243	Conference abstract
Herzog, Samuel, Shanahan, Marian, Grimison, Peter et al. (2018) Systematic Review of the Costs and Benefits of Prescribed Cannabis-Based Medicines for the Management of Chronic Illness: Lessons from Multiple Sclerosis. PharmacoEconomics 36(1): 67-78	No outcomes of interest

Study	Reason for exclusion
Hobart, J. C. and Zajicek, J. P. (2012) Cannabis as a symptomatic treatment for MS: clinically meaningful MUSEC to the stiffness and walking problems of people with MS. Multiple sclerosis. 18(4suppl1): 247	Conference abstract
Izquierdo, Guillermo (2017) Multiple sclerosis symptoms and spasticity management: new data. Neurodegenerative disease management 7(6s): 7-11	Review article. The bibliography was reviewed for possible includes
Katona, S., Kaminski, E., Sanders, H. et al. (2005) Cannabinoid influence on cytokine profile in multiple sclerosis. Clinical and experimental immunology 140(3): 580-5	No outcomes of interest
Keating, Gillian M. (2017) Delta-9-Tetrahydrocannabinol/Cannabidiol Oromucosal Spray (Sativex): A Review in Multiple Sclerosis-Related Spasticity. Drugs 77(5): 563-574	Narrative review
Killestein, J., Hoogervorst, E. L. J., Reif, M. et al. (2002) Safety, tolerability, and efficacy of orally administered cannabinoids in MS. Neurology 58(9): 1404-7	Data not in an extractable format
Lakhan, Shaheen E. and Rowland, Marie (2009) Whole plant cannabis extracts in the treatment of spasticity in multiple sclerosis: a systematic review. BMC neurology 9: 59	Review article. The bibliography was reviewed for possible includes
Leocani, L., Nuara, A., Houdayer, E. et al. (2014) Effect of THC-CBD oromucosal spray (Sativex) on measures of spasticity in multiple sclerosis: a doubleblind, placebo-controlled, crossover study. Multiple sclerosis (houndmills, basingstoke, england) 20(1suppl1): 498	Conference abstract
Lus, G., Cantello, R., Danni, M. C. et al. (2017) "Taste", a pilot study: palatability and oral cavity tolerability of Sativex and possible improvement measures in multiple sclerosis patients with resistant spasticity. Multiple sclerosis journal. Conference: 7th joint ECTRIMS-ACTRIMS, MSPARIS2017. France 23(3supplement1): 996-997	Conference abstract
Lus, G., Cantello, R., Danni, M. C. et al. (2018) Palatability and oral cavity tolerability of THC: CBD oromucosal spray and possible improvement measures in multiple sclerosis patients with resistant spasticity: a pilot study. Neurodegenerative disease management 8(2): 105-113	The relevant symptoms are not included

Study	Reason for exclusion
Maccarrone, Mauro, Maldonado, Rafael, Casas, Miguel et al. (2017) Cannabinoids therapeutic use: what is our current understanding following the introduction of THC, THC:CBD oromucosal spray and others?. Expert review of clinical pharmacology 10(4): 443-455	Narrative review
Marinelli, L., Balestrino, M., Mori, L. et al. (2017) A randomized controlled cross-over double blind study protocol on THC/CBD oromucosal spray as an add-on therapy for post-stroke spasticity. Clinical neurophysiology. Conference: 62nd national congress of the italian society for clinical neurophysiology. Italy 128(12): e421	Conference abstract
Markova, J. (2017) Sativex as Add-on therapy Vs. further optimized first-line ANTispastics (SAVANT) in resistant multiple sclerosis spasticity double blind randomized clinical trial. Multiple sclerosis journal. Conference: 7th joint ECTRIMS-ACTRIMS, MSPARIS2017. France 23(3supplement1): 990	Conference abstract
Markova, Jolana (2019) Newest evidence for tetrahydrocannabinol:cannabidiol oromucosal spray from randomized clinical trials. Neurodegenerative disease management	Review article. The bibliography was reviewed for possible includes
Maurer, M., Henn, V., Dittrich, A. et al. (1990) Delta-9-tetrahydrocannabinol shows antispastic and analgesic effects in a single case double-blind trial. European archives of psychiatry and clinical neuroscience 240(1): 1-4	Case study with one patient
Meuth, Sven G.; Vila, Carlos; Dechant, Kerry L. (2015) Effect of Sativex on spasticity-associated symptoms in patients with multiple sclerosis. Expert review of neurotherapeutics 15(8): 909-18	Narrative review
Meza, Rodrigo, Pena, Javier, Garcia, Karen et al. (2017) Are cannabinoids effective in multiple sclerosis?. 17(suppl1): e6865	Non-English language article
Ng, Louisa, Khan, Fary, Young, Carolyn A. et al. (2017) Symptomatic treatments for amyotrophic lateral sclerosis/motor neuron disease. The Cochrane database of systematic reviews 1: cd011776	No outcomes of interest

Study	Reason for exclusion
Nielsen, Suzanne, Germanos, Rada, Weier, Megan et al. (2018) The Use of Cannabis and Cannabinoids in Treating Symptoms of Multiple Sclerosis: a Systematic Review of Reviews. Current neurology and neuroscience reports 18(2): 8	Review article. The bibliography was reviewed for possible includes
Notcutt, W., Langford, R., Davies, P. et al. (2012) 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). Multiple sclerosis (Houndmills, Basingstoke, England) 18(2): 219-28	Withdrawal study
Otero-Romero, Susana, Sastre-Garriga, Jaume, Comi, Giancarlo et al. (2016) Pharmacological management of spasticity in multiple sclerosis: Systematic review and consensus paper. Multiple sclerosis (Houndmills, Basingstoke, England) 22(11): 1386-1396	Review article. The bibliography was reviewed for possible includes
Paisley, S., Beard, S., Hunn, A. et al. (2002) Clinical effectiveness of oral treatments for spasticity in multiple sclerosis: a systematic review. Multiple Sclerosis 8(4): 319-329	No outcomes of interest
Paolicelli, D., Direnzo, V., Manni, A. et al. (2015) Long-Term Data of Efficacy, Safety, and Tolerability in a Real-Life Setting of THC/CBD Oromucosal Spray-Treated Multiple Sclerosis Patients. Journal of Clinical Pharmacology	Observational study. No control group
Petro, D. J. and Ellenberger, C., Jr. (1981) Treatment of human spasticity with delta 9-tetrahydrocannabinol. Journal of clinical pharmacology 21(s1): 413S-416S	Unclear what scale was used to assess spasticity
Rog, David J. (2010) Cannabis-based medicines in multiple sclerosis--a review of clinical studies. Immunobiology 215(8): 658-72	Review article. The bibliography was reviewed for possible includes
Sacca, F., Pane, C., Carotenuto, A. et al. (2016) The use of medical-grade Cannabis (Bedrocan) in patients non-responders to nabiximols (sativex). Multiple sclerosis (Houndmills, Basingstoke, England) conference32ndcongressoftheeuropeancommitteefortreatmentandresearchinmultiplesclerosisectrims2016unitedkingdomconferencestart20160914conferenceend2016091722: 686	Conference abstract

Study	Reason for exclusion
Serpell, Michael G.; Notcutt, William; Collin, Christine (2013) Sativex long-term use: an open-label trial in patients with spasticity due to multiple sclerosis. Journal of neurology 260(1): 285-95	Observational study. No control group
Shakespeare, D. T.; Boggild, M.; Young, C. (2003) Anti-spasticity agents for multiple sclerosis. The Cochrane database of systematic reviews: cd001332	Review article. The bibliography was reviewed for possible includes
Slof, J. and Gras, A. (2012) Sativex in multiple sclerosis spasticity: A cost-effectiveness model. Expert Review of Pharmacoeconomics and Outcomes Research 12(4): 525-538	Cost-effectiveness model
Syed, Yahiya Y.; McKeage, Kate; Scott, Lesley J. (2014) Delta-9-tetrahydrocannabinol/cannabidiol (Sativex): a review of its use in patients with moderate to severe spasticity due to multiple sclerosis. Drugs 74(5): 563-78	Review article. The bibliography was reviewed for possible includes
Thaera, Greg M., Wellik, Kay E., Carter, Jonathan L. et al. (2009) Do cannabinoids reduce multiple sclerosis-related spasticity?. The neurologist 15(6): 369-71	Review article. The bibliography was reviewed for possible includes
Turner, S.; Kumar, R.; Fairhurst, C. (2017) Safety, efficacy and tolerability of oro-mucosal tetrahydrocannabinol/cannabidiol therapy to reduce spasticity in children and adolescents. results of a multicentre, double blind placebo controlled trial. Developmental medicine and child neurology. Conference: 44th annual conference of the british paediatric neurology association, BPNA 2018. United kingdom 59(supplement4): 12-13	Conference abstract
Ungerleider, J. T., Andyrsiak, T., Fairbanks, L. et al. (1987) Delta-9-THC in the treatment of spasticity associated with multiple sclerosis. Advances in alcohol & substance abuse 7(1): 39-50	Unclear what scale was used to assess spasticity
Van Amerongen, G., Beumer, T., Killestein, J. et al. (2014) Individualized dosing of a novel oral DELTA9-THC formulation improves subjective spasticity and pain in patients with progressive multiple sclerosis. Multiple sclerosis (houndmills, basingstoke, england) 20(1suppl1): 478-479	Conference abstract

Study	Reason for exclusion
Vaney, C., Heinzel-Gutenbrunner, M., Jobin, P. et al. (2004) Efficacy, safety and tolerability of an orally administered cannabis extract in the treatment of spasticity in patients with multiple sclerosis: a randomized, double-blind, placebo-controlled, crossover study. Multiple sclerosis (Houndmills, Basingstoke, England) 10(4): 417-24	Cross-over trial with inadequate washout period (<1 week)
Vermersch, Patrick (2011) Sativex() (tetrahydrocannabinol + cannabidiol), an endocannabinoid system modulator: basic features and main clinical data. Expert review of neurotherapeutics 11(4suppl): 15-9	Narrative review
Wade, D. T., Makela, P. M., House, H. et al. (2006) Long-term use of a cannabis-based medicine in the treatment of spasticity and other symptoms in multiple sclerosis. Multiple sclerosis (Houndmills, Basingstoke, England) 12(5): 639-45	Single-arm follow-up study
Wade, Derick T., Collin, Christine, Stott, Colin et al. (2010) Meta-analysis of the efficacy and safety of Sativex (nabiximols), on spasticity in people with multiple sclerosis. Multiple sclerosis (Houndmills, Basingstoke, England) 16(6): 707-14	Secondary publication of existing studies without additional data
Wright, S.; Vachova, M. M.; Novakova, I. (2013) The effect of long-term treatment with a prescription cannabisbased THC: CBD oromucosal spray on cognitive function and mood: a 12 month double blind placebo-controlled study in people with spasticity due to multiple sclerosis. Multiple sclerosis. 19(11suppl1): 572-573	Conference abstract
Zajicek, J.; Ball, S.; Wright, D.; Vickery, J. et al. (2013) Effect of dronabinol on progression in progressive multiple sclerosis (CUPID): a randomised, placebo-controlled trial. The Lancet. 12(9): 857-865	The relevant symptoms are not included
Zettl, Uwe K., Rommer, Paulus, Hipp, Petra et al. (2016) Evidence for the efficacy and effectiveness of THC-CBD oromucosal spray in symptom management of patients with spasticity due to multiple sclerosis. Therapeutic advances in neurological disorders 9(1): 9-30	Narrative review

Economic studies

Study	Reason for exclusion
Bellnier, T., Brown, G. W., & Ortega, T. R. (2018). Preliminary evaluation of the efficacy, safety, and costs associated with the treatment of chronic pain with medical cannabis. The mental health clinician, 8(3): 110–115.	Not a cost-utility analysis
Flachenecker P. (2013). A new multiple sclerosis spasticity treatment option: effect in everyday clinical practice and cost-effectiveness in Germany. Expert Rev Neurother, 13(3 Suppl 1):15-19.	Non-UK evaluation
Herzog, S., Shanahan, M., Grimison, P., Tran, A., Wong, N., Lintzeris, N., Simes, J., Stockler, M., 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.	Systematic review
Slof, J., Gras, A. (2012). Sativex in multiple sclerosis spasticity: a cost-effectiveness model. Expert Rev Pharmacoecon Outcomes Res, 12(4):439-441.	Non-UK evaluation
Lu, L., Pearce, H., Roome, C., Shearer, J., Lang, I. A., Stein, K. (2015). Erratum to: cost effectiveness of Oromucosal cannabis-based medicine (Sativex(®)) for spasticity in multiple sclerosis. Pharmacoeconomics, 33(6):611.	Erratum
Slof, J., Ruiz, L., Vila, C. (2015). Cost-effectiveness of Sativex in multiple sclerosis spasticity: new data and application to Italy. Expert Rev Pharmacoecon Outcomes Res, 15(3):379-391.	Editorial
Ball, S., Vickery, J., Hobart, J., Wright, D., Green, C., Shearer, J., Nunn, A., Cano, M. G., MacManus, D., Miller, D., Mallik, S., Zajicek, J. (2015). The Cannabinoid Use in Progressive Inflammatory brain Disease (CUPID) trial: a randomised double-blind placebo-controlled parallel-group multicentre trial and economic evaluation of	Evaluation of cannabis to slow MS progression, rather than to treat spasticity

Study	Reason for exclusion
cannabinoids to slow progression in multiple sclerosis. Health technology assessment (Winchester, England), 19(12), vii–187.	
Bellnier, T., Brown, G. W., & Ortega, T. R. (2018). Preliminary evaluation of the efficacy, safety, and costs associated with the treatment of chronic pain with medical cannabis. The mental health clinician, 8(3): 110–115.	Not a cost-utility analysis

Appendix K Research recommendations

1. **What is the clinical and cost effectiveness of cannabis based medicinal products other than Sativex for people with spasticity? In particular, what is the impact of spasticity on improvements in quality of life?**

Sixteen studies were identified which examined the clinical effectiveness of cannabis-based medicinal products. These studies identified the effectiveness of interventions such as THC:CBD oromucosal spray for treating spasticity in people with multiple sclerosis. However, there was limited evidence for other cannabis-based medicinal products and for conditions other than multiple sclerosis. In particular, there was limited evidence on the effects of a change in spasticity on quality of life.

Further research is needed using a robust study design such as a parallel RCT to explore the clinical and cost effectiveness of cannabis-based medicinal products other than Sativex as an adjunct to optimal therapy in children and adults with spasticity. This should include the development of a quality of life questionnaire validated specifically for people with spasticity. Studies should be UK based. Research in this area is essential to inform future updates of key recommendations in this guidance which in turn can help improve patient outcomes.

PICO	**Population:** Adults and children with spasticity who haven't fully responded to optimal treatment Specific subgroups: • People with cerebral palsy **Interventions:** Cannabis based product defined as: 1. A cannabis-based product for medicinal use that is a preparation or other product, other than one to which paragraph 5 of part 1 of schedule 4 applies, which: • is or contains cannabis, cannabis resin, cannabinol or a cannabinol derivative (not being dronabinol or its stereoisomers) • is produced for medicinal use in humans; and • is a medicinal product, or • a substance or preparation for use as an ingredient of, or in the production of an ingredient of, a medicinal product (MDR 2018 regulations) 2. Synthetic compounds which are identical in structure to naturally occurring cannabinoids such as delta-9-tetrahydrocannabinol (THC) for example dronabinol 3. Licensed products nabilone 4. Plant-derived cannabinoids such as pure cannabidiol **Cannabis based product used as an adjunct to optimal therapy** **Comparator:** Placebo, Optimal therapy

	Outcomes: • 30% or greater improvement in spasticity • Change in spasticity measured using any validated scale which measures spasticity • Quality of life using any validated scale for spasticity • Serious adverse events • Adverse events including but not limited to: sleep problems, fatigue, road traffic accidents, psychological distress, dizziness, headache, confusion state, paranoia, psychosis, substance dependence, diarrhoea at the start of treatment • Withdrawals due to adverse events • Substance abuse due to the use of cannabis-based medicinal product. • Misuse/diversion • Hepatic or renal failure
Current evidence base	16 RCTS (13 parallel RCTS, 3 crossover RCTs)
Study design	Randomised controlled trial
Other comments	Study should be adequately powered.

Appendix L Health economics evidence tables

Study, population, country and quality	Data sources	Other comments	Cost	Effect		Conclusions	Uncertainty
Gras et al. (2016) Patients with moderate to severe MS spasticity (NRS score ≥ 4, measured using the spasticity 0–10 NRS) who had not responded adequately to other anti-spasticity medication. The study was conducted in the UK **Directly applicable**	**Treatment effects** Taken from the pivotal trial (Novotna et al. 2011), an enriched design randomised controlled trial. (n=572 at the enrichment phase, n=241 double-blind randomised). THC: CBD spray n=124. Placebo n=117. Mean age was 48.9 years (SD 9.63) overall and 48.6 years (SD 9.33) during the double-blind phase. **Costs and resource use** Resource use was based on a published clinical expert survey (Stevenson et al. 2015), including community-based visits, outpatient clinic visits, A&E visits, hospital admissions, home care visits, equipment costs	The analysis took a Welsh NHS and PSS perspective. 30-year time horizon. Both utilities and costs were discounted at a rate of 3.5% per year. Funded by the manufacturer.	THC: CBD spray + SoC			“Treatment with a cannabis-derived oromucosal spray to be cost-effective at the willingness-to-pay threshold of £30,000 in Wales for the treatment of spasticity in MS, and to be dominant, if home carer costs were included.”	“PSA using unit cost, resource utilization rates, resource quantities, utility values, and discount rate highlighted that under plausible parameter variation, treatment with THC: CBD spray remains a cost-effective use of NHS resources (100% probability at £30,000 per QALY gained)”
			102,337 £GBP	11.00 QALYs			
			SoC alone				
			98,501 £GBP	10.65 QALYs			
			Incremental cost (95% CI)	**Incremental effect (95% CI)**	**ICER**		
			THC: CBD spray + SoC vs. SoC alone				
			3,836 £GBP (464 to 6,248)	0.35 QALYs (0.30 to 0.40)	10,891 £GBP per QALY gained (1,324 to 18,167)		

Study, population, country and quality	Data sources	Other comments	Cost	Effect		Conclusions	Uncertainty
Very serious limitations [a, b, c, d, e, f, g]	(such as wheelchairs, walking aids). Costs were taken from the Department of Health (DoH) NHS reference costs 2012-2013 and Unit costs of health and social care (PSSRU 2013). **Utility** Measured using the EQ-5D, in line with the NICE reference case. EQ-5D data were based on the available data from the pivotal trial (Novotna et al. 2011).						

(a) The model simplified health states by grouping NRS into five health states, rather than modelling NRS as a continuous variable. Mean utilities assigned to more severe health states (health state 4 and 5) were very similar. The model was unlikely to show any substantial benefit from preventing patients moving to the most severe health state.
(b) It is not appropriate to extrapolate short-term RCT data (4+12 weeks, Novotna et al. 2011) to a 30-year model time horizon.
(c) The model did not include adverse events and might favour THC: CBD spray strategy.
(d) It is unclear how the transition probability was derived from the RCT (Novatna et al. 2011), as the RCT might not have many (or any) patients with very low NRS or very high NRS (inclusion criteria specified that patients had ≥4 in NRS at baseline).
(e) Resource use data were based on subjective estimates in a healthcare professional survey. The model also assumed all resource use was attributed to spasticity alone while some of the costs might overlap with the management costs of MS patients.
(f) The model did not explore the uncertainty of the transition probabilities or the discontinuations in the probabilistic sensitivity analysis.
(g) Potential conflict of interest as this study was funded by the manufacturer of THC: CBD spray.

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Study, population, country and quality	Data sources	Other comments	Cost (95% CI)	Effect (95% CI)		Conclusions	Uncertainty
Lu et al. (2012) Patients with spasticity due to MS and did not respond adequately to oral anti-spasticity medication. The study was conducted in the UK.	**Treatment effects** Treatment withdraw rates taken from the pivotal trial (Novotna et al. 2011), an enriched design randomised controlled trial. (n=572 at the enrichment phase, n=241 double-blind randomised). THC: CBD spray n=124. Placebo n=117. Mean age was 48.9 years (SD 9.63) overall and 48.6 years (SD 9.33) during the double-blind phase. **Costs and resource use** Resource use was based on expert opinions and only consisted of clinical visits. Costs were taken from the NHS reference costs 2009.	The analysis took a UK NHS perspective. 5-year time horizon. Both utilities and costs were discounted at a rate of 3.5% per year. Funded by the NIHR through PenCLAHRC.	THC: CBD spray + standard treatment			"Based on available evidence and using the NICE willingness-to-pay threshold of £20,000 – 30,000 per QALY, THC: CBD spray as an add-on to oral anti-spasticity medicines appears unlikely to be cost effective compared with standard treatment (oral medicines alone or combined with treatment with botulinum toxin injections or a baclofen intrathecal	"Using a willingness-to-pay threshold of £30,000 per QALY, it is unlikely THC: CBD spray is cost effective compared with oral medicines alone for patients at 50 years of age with spasticity due to MS (the probability of THC: CBD spray being cost effective is 10.2%)."
			8,925 £GBP	2.3716 QALYs			
			Standard treatment alone				
			1,298 £GBP	2.2167 QALYs			
			Incremental cost (95% CI)	**Incremental effect (95% CI)**	**ICER**		
			THC: CBD spray + standard treatment vs. Standard treatment alone				
			7,627 £GBP (-2246 to 394)	0.1548 QALYs (-0.0298 to 0.0418)	49,257 £GBP per QALY gained		
Directly applicable							
Potentially serious limitations [a, b, c]							

Study, population, country and quality	Data sources	Other comments	Cost (95% CI)	Effect (95% CI)		Conclusions	Uncertainty
	Utility Measured using the EQ-5D, in line with the NICE reference case. EQ-5D data were based on a conference presentation (Montalban et al. 2009 using data the RCT by Novotna et al. 2011).					pump) at the current acquisition costs for the agent."	

(a) The model examined the transition from treatment response to treatment withdrawal. However, as the response is defined as a relative effect (reduction of ≥20% on the NRS for spasticity), the definition did not match to our protocol for the response (reduction of ≥30%on the NRS for spasticity).Additionally, the model did not explore the absolute changes in NRS scores.
(b) The model did not include adverse events and might favour THC: CBD spray strategy.
(c) Resource use data were based on expert opinions and only consisted of clinical visits. The model underestimated the resource use associated management for spasticity.

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Appendix M Economic model

Background

Following the legislation changes and the Home Office announcement in October 2018, doctors on the Specialist Register of the General Medical Council will be able to prescribe cannabis-based medicinal products.

NICE has never produced an economic analysis to determine the cost-effectiveness of medicinal cannabis in spasticity, albeit THC: CBD spray (Sativex) has been licensed by the MHRA as a treatment for spasticity in multiple sclerosis (MS) under Schedule 4 of the 2001 Regulations.

NICE has previously considered a published cost-effectiveness analysis of THC: CBD spray in MS spasticity within the guideline of multiple sclerosis in adults (CG186) and the advisory committee did not recommend its use because they concluded it was not a cost-effective treatment.

Given the recent legislation changes and more recent data became available, the committee was interested in developing a de novo economic model to examine the cost-effectiveness of medicinal cannabis in patients with spasticity who had not responded adequately to any standard oral anti-spasticity medications.

Methods

Population, interventions/comparators and outcomes

The objective of this analysis is to develop a de novo economic model to estimate the cost-effectiveness of the cannabis-derived medicinal products as a treatment option for spasticity. The target population in the model are patients with spasticity who had not responded adequately to any standard spasticity treatment, before undergoing invasive interventions or surgery.

The model compared the costs and effectiveness of the standard of care (SoC) plus cannabis to the standard of care alone. The standard of care is defined as any interventions that would usually be used in this patient group, including licensed oral anti-spasticity medications if appropriate (although our group are, by definition, non-responders to these). It is assumed that all patients in the cannabis strategy received a cannabis-derived medicinal product as an add-on treatment to the standard of care. The committee agree that this is consistent with the existing clinical practice.

Outcomes were measured in quality-adjusted life years (QALYs). The incremental cost-effectiveness ratio (ICER) is expressed as a cost per QALY.

The analysis was conducted from the perspective of NHS and Personal Social Services (PSS) in the UK and considered only the costs and outcomes which were relevant to this guideline. Productivity loss and carer's QALYs were not considered.

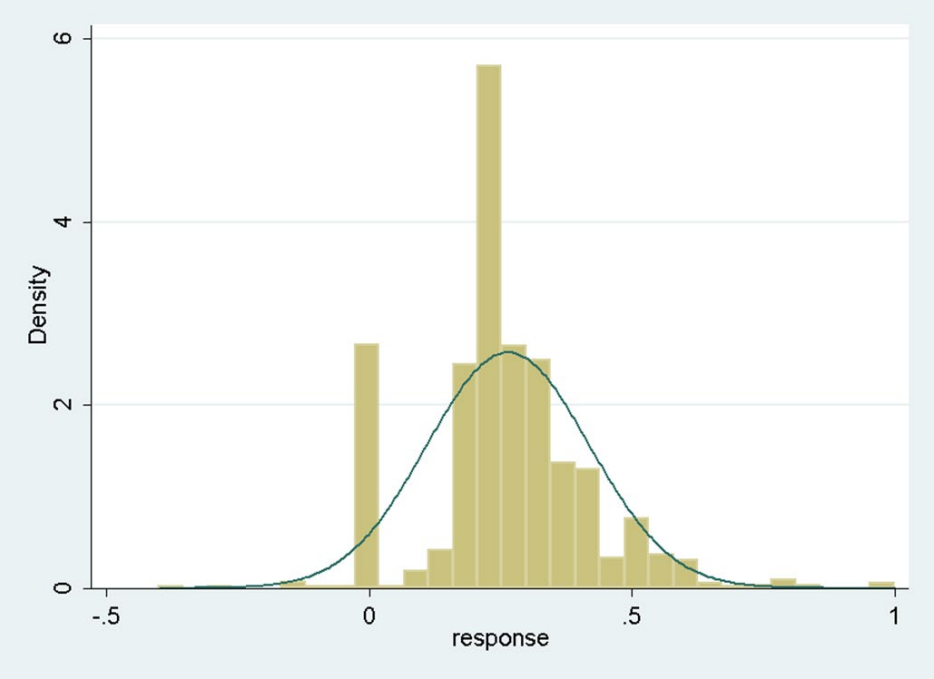
Model structure

This section is intended to give a structural overview of the model and its underpinning assumptions. Derivation of parameters is discussed in the Model Parameters section.

A Markov model was constructed in Excel. The model adopted a 4-week cycle length. All transition probabilities were adjusted accordingly using a standard methodology (Miller and Homan, 1994). The time horizon for the base case analysis was 5 years. The committee agreed that there is no evidence to suggest that medicinal cannabis would impact the mortality of patients with spasticity and that most of the available evidence is short term in nature. A short time horizon is therefore appropriate. A longer time horizons of 10, 20 and 30 years were considered in the sensitivity analysis.

We considered structuring our model in a similar way to the chronic pain model produced for this guideline, which tied NRS scores to costs and HRQoL but this structure would have required treatment effects to be assigned specific probability distributions. We tested the assumption that spasticity NRS treatment effects were normally distributed in two ways. Firstly we calculated change from baseline in a publicly available dataset that included >1,500 MS patients treated with CBD:THC oromucosal spray (Messina et al. 2017) and examined the histogram on percentage improvement (Figure 1).

Figure 1: Histogram of response in patients treated with CBD:THC



We also used the baseline and change from baseline NRS data from the RCTs to simulate 60,000 theoretical patients assuming bounded normal distributions, which enabled us to calculate the proportion who improved by >30% and >50% and compare the resulting relative risks with those observed in the RCTs. The results are in Table 2: Comparison of Relative Risks derived from Simulations and RCTs Table 2 and show reasonable agreement at the 30% level but poor agreement at the 50% level.

Table 2: Comparison of Relative Risks derived from Simulations and RCTs

Outcome	Sativex	Placebo	RR
Estimated using continuous outcomes			
Proportion achieving ≥30% reduction	35%	31%	**1.12**
Proportion achieving ≥50% reduction	17%	15%	**1.14**
Taken directly from Collin 2010			
Proportion achieving ≥30% reduction	31%	25%	**1.24**
Proportion achieving ≥50% reduction	-	-	**-**

Outcome	Sativex	Placebo	RR
Estimated using continuous outcomes			
Proportion achieving ≥30% reduction	41%	28%	**1.44**
Proportion achieving ≥50% reduction	23%	14%	**1.69**
Taken directly from Collin 2007			
Proportion achieving ≥30% reduction	40%	22%	**1.83**
Proportion achieving ≥50% reduction	18%	9%	**1.86**

Outcome	Sativex	Placebo	RR
Estimated using continuous outcomes			
Proportion achieving ≥30% reduction	77%	38%	**2.02**
Proportion achieving ≥50% reduction	55%	9%	**5.94**
Taken directly from Markova 2018			
Proportion achieving ≥30% reduction	77%	32%	**2.41**
Proportion achieving ≥50% reduction	-	-	**-**

Outcome	Sativex	Placebo	RR

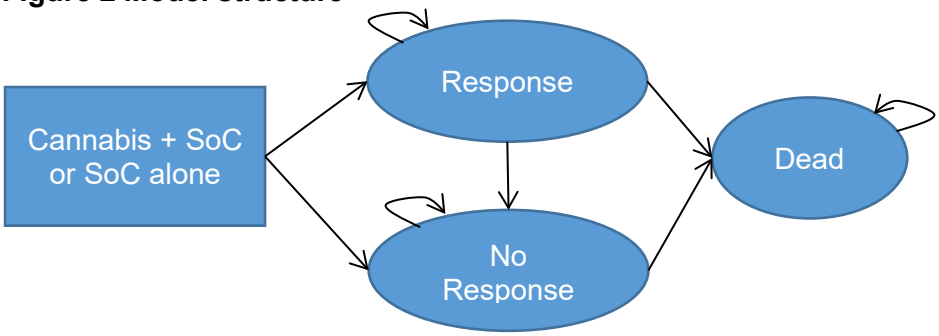
Estimated using continuous outcomes			
Proportion achieving ≥30% reduction	75%	53%	**1.41**
Proportion achieving ≥50% reduction	39%	20%	**1.95**
Taken directly from Novotna 2011			
Proportion achieving ≥30% reduction	74%	51%	**1.45**
Proportion achieving ≥50% reduction	45%	33%	**1.36**

Based on these data we concluded that the continuous data were not appropriate to use and we would adopt a categorical model structure.

The model structure (see Figure 2) is designed to reflect the clinical evidence from RCTs (Collin et al., 2007, 2010; Novotna et al., 2011; Markova et al., 2019). The model structure is similar to a published cost-effectiveness model funded by the National Institute for Health Research (NIHR) (Lu et al., 2012).

- The model focused on spasticity caused by MS as good clinical evidence was only available in this population.
- Cohorts of patients were followed from the initiation of the treatment. Patients received either cannabis plus SoC or SoC alone
- Treatment response was defined as a reduction of ≥30% on the numerical rating scale (NRS) for spasticity
- In the cannabis strategy, patients who did not achieve a response may discontinue cannabis and receive SoC alone
    - No patients who were not >30% responders continued treatment in the base case analysis. This is an important limitation as the committee felt that treatment might be offered on an ongoing basis to some >20% responders in clinical practice.
    - Responders remained on treatment but were subject to treatment discontinuation, after which they transitioned to the non-responder state
- In the SoC strategy, the model assumed that a proportion of responders would lose the treatment benefit and become non-responders. This was modelled as discontinuation of the treatment benefit.
    - The model assumed that all patients would always receive SoC in the background.
- The half-cycle correction was incorporated to take into account that the transitions happened continuously throughout each cycle, not just at the end of at the beginning of each cycle (Sonnenberg and Beck, 1993; Naimark, Kabboul and Krahn, 2013).
- Costs and outcomes were discounted at 3.5% in line with the latest NICE reference case (NICE, 2013).

Figure 2 Model structure



Model parameters

Baseline characteristics

Baseline characteristics of the model cohort are based on a large observational study (N=1,597) of THC: CBD spray (Sativex) in multiple sclerosis spasticity (Messina et al., 2017). The model assumed the mean age of the cohort at the start of the model was 51, and 47.3% are male. The model also assumed that patients had a spasticity NRS of 7.5 and MS expanding disability status scale (EDSS) of 6.4 at baseline. The mean NRS and EDSS were based on the average of the supplementary patient-level data from (Messina et al., 2017).

In the base case analysis, the model assumed a natural progression of NRS over time that NRS increased 0.227 per year, based on an increase of 1 unit in NRS took 1,609 days reported in an observational study (Arroyo et al. 2011, Gras et al. 2016).

Treatment effects

Treatment response was defined as a reduction of ≥30% on the spasticity NRS. The clinical review identified four relevant RCTs of THC: CBD spray in patients with MS spasticity. No evidence was available for other types of medicinal cannabis or for other indications.

Two of the 4 included RCTs allowed patients exceeding the maximum licenced daily dose (12 sprays) (Collin et al., 2007, 2010) and the mean THC: CBD spray doses were 9.4 and 8.5 sprays per day respectively. The other two RCTs only allowed patients receiving the within the licenced daily dose of THC: CBD spray (Novotna et al., 2011; Markova et al., 2019) and the mean THC: CBD spray dose were 8.3 and 7.3 sprays per day respectively. The two within-dose RCTs had an enrichment design that all patients received and responded to THC: CBD spray for 4 weeks prior to the placebo-controlled phase.

The treatment effects of THC: CBD spray, derived from the meta-analysis in the clinical review (see Appendix F for details), were presented as odds ratios (ORs) compared to the placebo from the RCTs. The OR results are summarised in Table 3. The committee agreed that the model applied ORs from all four RCTs in the base case as the mean daily dose from all these trials are less than the maximum licenced dose of 12 THC: CBD sprays per day. The OR for THC: CBD spray within dose was tested in a sensitivity analysis.

Table 3 Treatment effects in ORs

	ORs	
	Mean	**95% CI**
THC: CBD spray all doses	2.61	1.40 - 4.86
THC: CBD spray within the licensed dose	4.17	1.60 – 10.83
THC: CBD spray high dose	1.61	1.09 – 2.38

The OR results should be interpreted as follows:

- An OR of 1 indicates that there was no difference in the odds of an event between the active and placebo arms
- An OR <1 indicates that there are lower odds of an event in the treatment arm compared with the placebo (favours placebo)
- An OR >1 indicates that the odds of an event are higher in the treatment arm compared with the placebo (favours treatment)

We combined the reciprocal of these odds ratios with THC:CBD response data to obtain response in the SoC arm of the model.

We had a number of options with regard to THC:CBD response. In line with methods outlined in NICE DSU Technical Support Document 13 we preferred data from the Messina registry over data from the RCTs in the base case. We also performed random effect (because i2 >50%) meta-analyses of response in the Collin 2007 and 2010 RCTs and of all 4 RCTs combined. For this final analysis we had to account for the enrichment design and did this by multiplying the proportion of 30% responders in the cannabis arm of the second phase by the total number of 20% responders in the initial phase. The resulting number was divided by the total N to calculate the proportion of people who would have achieved a 30% response following treatment with THC:CBD. This produced data for Navotna 2011 and Markova 2018 of 33% and 43% respectively, which were similar to the 31% and 40% observed in the standard-design Collin RCTs. Standard errors for input into the meta-analyses were calculated using the standard error of a proportion approach.

Table 4: Response in Cannabis and SoC arms of the model

Data Source for Cannabis Response	Cannabis Response	SoC response (OR = 1/2.61)
Cannabis response from Messina 2017/ Patti 2016	28.3%	13.1%
Cannabis response (meta-analysis of 2 non-enriched studies, random effect)	35.2%	17.2%
Cannabis response (meta-analysis of 4 studies (enriched corrected), random effect)	36.4%	18.0%

The model allowed comparison of other types of medicinal cannabis plus SoC compared to SoC alone. However, due to lack of evidence, the model assumed all other medicinal cannabis has the same treatment effects as THC: CBD spray. This is highly uncertain as there is no good quality evidence on whether other types of medicinal cannabis influence MS spasticity.

Treatment discontinuation

Discontinuation following cannabis treatment initiation

As described in the model structure section, the model assumed that majority of patients who did not respond to THC: CBD spray would discontinue the treatment and switch to receive SoC only and no longer accrued costs associated with THC: CBD spray.

Discontinuation in patients achieving a treatment response

Following the initial treatment response, the model assumed that the treatment responders might discontinue THC: CBD spray, either due to loss of efficacy or adverse events. Patients who discontinued the treatment would lose the treatment benefit and become a non-responder. This was based on the observational study (Messina et al., 2017), which followed up the patients on THC: CBD spray for 2 years. These patients were treated for a period of 1 month with responders remaining on treatment and non-responders discontinuing. We selected only the responders, subtracted 28 days from the total time on treatment, converted the time on treatment from days to years and performed survival analysis on these patients where discontinuations were classed as events. The model contains multiple options for discontinuation. Option 1 was to fit a parametric curve to the data. Based on AIC/BIC statistics we selected a gompertz parametric curve to use within our economic model (Table 5).

Table 5: Model fit statistics for discontinuation survival curve

Parametric Survival Regression	AIC	BIC
Weibull	2641	2652
Exponential	3145	3150
Gompertz	**2412**	**2422**
Gamma	2497	2512
Lognormal	2588	2599
Loglogistic	2625	2635

The committee agreed that patients in the SoC alone strategy would also experience loss of treatment response over time. Option 1 assumed loss of response would be equal in the SoC arm and the CBMP arm. For Option 2 we fitted a competing risks model to the Messina data, coding adverse events alone as a separate, competing risk to other discontinuations. We followed the methodology in section 6.3 of the CRAN-R documentation on the flexsurv package[a] but used a gompertz model instead of the Weibull example given (because the original gompertz model provided the best fit to the data [Table 5]). The survival curve for the CBMP arm took account of both competing risks whereas the survival curve for the SoC arm included only non-adverse event related discontinuations. Option 3 was to fit an exponential curve and assume various levels of arbitrary discontinuation and hazard ratios to see how these might affect the results.

There were no deaths recorded in the dataset although there were a number of censoring events with no reason recorded and it is possible that some of these were in fact deaths. By

[a] https://cran.r-project.org/web/packages/flexsurv/vignettes/flexsurv.pdf

handling deaths separately from discontinuation it is possible that there is a small amount of double counting in the economic model. Given the relatively low average age in the dataset and therefore low mortality rate, and the fact that this issue would apply to both model arms, we assessed this limitation as minor.

Clearly there are limitations with all these approaches but in the absence of long-term data on changes in response in either the active treatment or standard of care arm the committee acknowledged that they were the best available, noted them as limitations and explored them in sensitivity analysis. Overall, Option 2 (the competing risks model with differential discontinuation) was preferred in the base case.

Figure 3: Cumulative Hazard Curves from Competing Risks Model

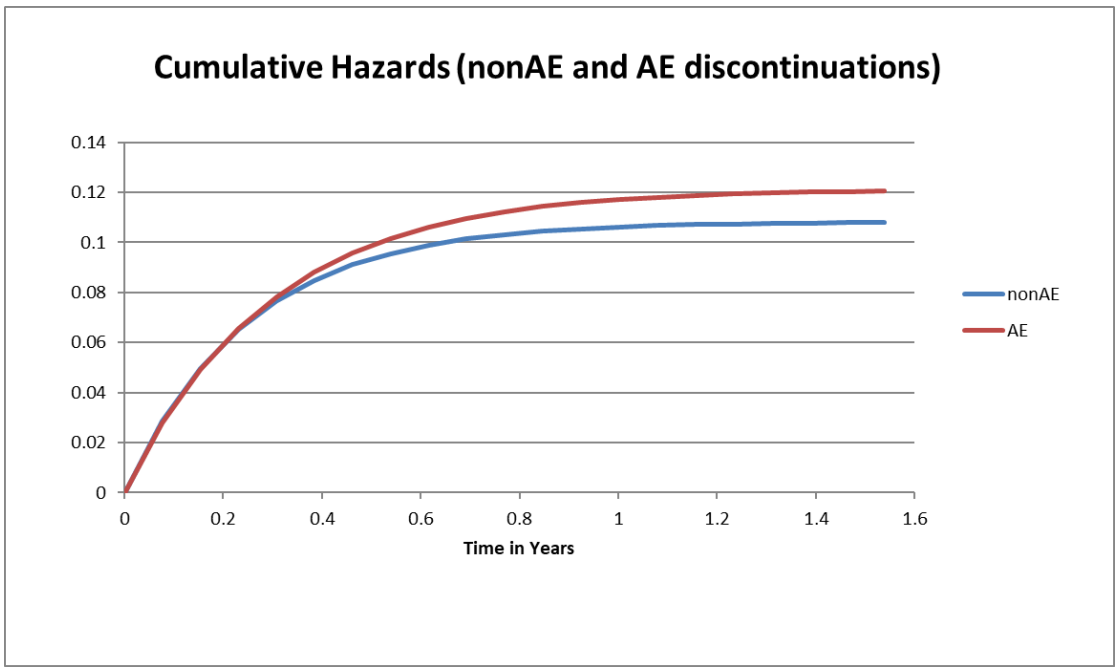
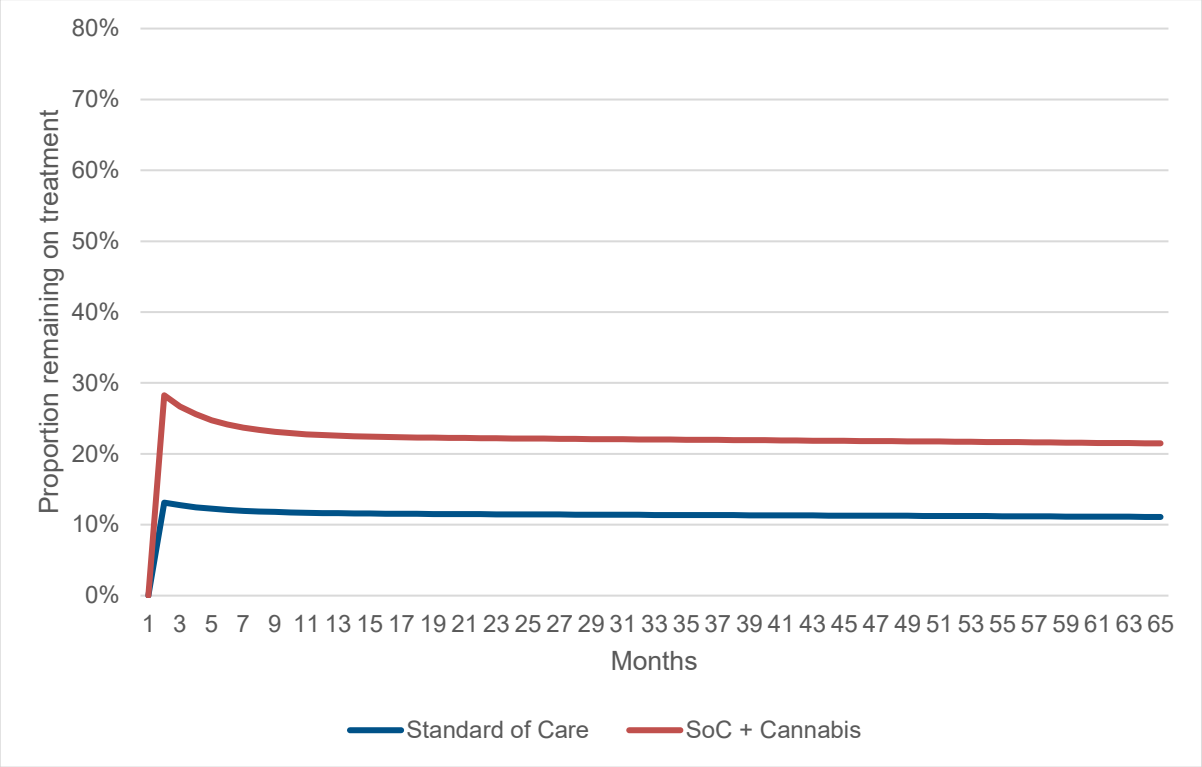


Figure 4 shows the estimated proportion of patients remaining as responders during the 5-year time horizon. The model assumed progression in NRS of 0.23 points per year (Gras et al 2016) in both groups in the base case so costs rise and QALYs decrease somewhat in both groups over time.

Figure 4 Proportion of patients remained as responders over time



Mortality

The model assumed that patients with MS have a higher mortality risk compared to the general population. Published standardised mortality ratios (SMRs) (Manouchehrinia et al., 2016) were applied to the UK life table (ONS, 2018) to estimate the mortality risk of patients with MS-related spasticity in the model.

The committee agreed that there is no evidence that medicinal cannabis has additional survival benefit compared to the SoC only strategy, so the model assumed the same mortality risk for both cannabis + SoC and SoC alone strategies.

Adverse events

A systematic review of adverse effects of medical cannabinoids (Wang et al., 2008) estimated the incidence rate of non-serious adverse events (AEs) for cannabinoid and control (placebo) were 10.37 and 6.87 events per person-year, respectively. For serious adverse events in cannabinoid and control were 0.37 and 0.25 events per person-year, respectively. The event rates per person-year were converted to per cycle event rate in the model.

For simplicity, we assumed non-serious adverse events were split between the important/ common AEs selected by the committee: dizziness, dry mouth, fatigue, headache, nausea. The frequency of non-serious AEs is based on data reported by Wang et al., 2008 and, because a very wide variety of events were reported, rescaled to include only those events listed above so the total added up to 100% (see Table 6 for details).

Table 6 Frequency of most important non-serious AEs (for determining proportions)

	Number of events	%
Dizziness	714	56.76%
Dry mouth	239	19.00%
Fatigue	109	8.66%
Headache	79	6.28%
Nausea	117	9.30%
Total	1,258	100%

The consequent event rates per cycle and per year in the model were summarised in Table **7**.

Table 7 Adverse event rates per cycle	Cannabis + SoC per cycle	SoC per cycle	Cannabis + SoC per year	SoC per year
Dizziness	0.45	0.30	5.89	3.90
Dry mouth	0.15	0.10	1.97	1.31
Fatigue	0.07	0.05	0.90	0.60
Headache	0.05	0.03	0.65	0.43
Nausea	0.07	0.05	0.96	0.64
Serious adverse event	0.03	0.02	0.37	0.25

Utility

Due to lack of relevant health utility data in the UK, health state utilities in the model were based on a published utility regression model of EQ-5D, spasticity NRS and EDSS of 98 patients in Sweden (Svensson, Borg and Nilsson, 2014). The R-squared for the regression model was 0.6545. The regression coefficients are summarised in Table 8.

Table 8 Utility regression model

	Coefficients
Constant	0.9229
NRS	-0.0505
EDSS 5	-0.0293
EDSS 5.5	-0.3417
EDSS 6	-0.1305
EDSS 6.5	-0.2521
EDSS 7	-0.3353
EDSS 7.5	-0.526
EDSS 8	-0.8124
EDSS 8.5	-0.9408
EDSS 9	-0.7648

We used simulations to produce a range of options for utility values associated with NRS scores 1-10.

We simulated 10,000 hypothetical patients with NRS and EDSS scores based on the baseline NRS (mean 7.5; SD 1.45) and mean EDSS (mean 6.4; SD 1.2) data from (Messina

et al., 2017) along with the correlation coefficient (=0.34) between these two variables, assuming a multivariate normal distribution For each option the average utility value for each NRS score would be the input used in the economic mode. The options we considered were:-

1. Full regression model for each theoretical patient
2. Full regression model but simulations use a weaker (0.17) correlation coefficient
3. Use the results of the full regression model to refit a coefficient for NRS alone
4. Use the reported NRS coefficient only
5. Use the reported NRS coefficient along with the coefficient for the mean level of EDSS of 6.5

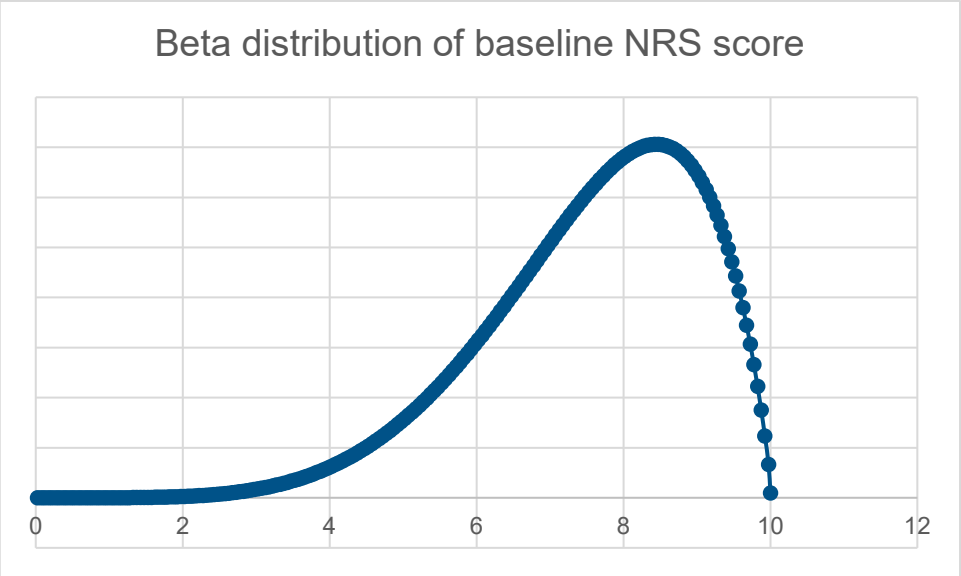
Table 9: Options for utility values at each spasticity NRS level

	Option 1	Option 2	Option 3	Option 4	Option 5
NRS 1	0.872	0.872	0.972	0.872	0.620
NRS 2	0.782	0.719	0.862	0.822	0.570
NRS 3	0.709	0.648	0.752	0.771	0.519
NRS 4	0.591	0.506	0.642	0.721	0.469
NRS 5	0.517	0.436	0.532	0.670	0.418
NRS 6	0.423	0.374	0.422	0.620	0.368
NRS 7	0.315	0.293	0.312	0.569	0.317
NRS 8	0.210	0.223	0.202	0.519	0.267
NRS 9	0.110	0.131	0.092	0.468	0.216
NRS 10	-0.025	0.056	-0.018	0.418	0.166

Based on their experience and there being reported difference in the EDSS outcome from the clinical review committee agreed that medicinal cannabis was unlikely to have an impact on EDSS scores but that mean EDSS should be reflected. They therefore agreed that option 5 was the most appropriate.

Next we needed to convert the utility estimates for NRS to dichotomous utility values for responders and non-responders. For non-responders we assumed they would have the baseline level NRS and so used the data from the Messina dataset to calculate an initial beta-distribution (chosen because NRS is bounded by 0 and 10) of NRS to calculate a weighted average. We used the method of moments method to convert mean and SD of NRS into the necessary alpha and beta parameters.

Figure 5: Beta distribution of baseline NRS score for calculating costs and utilities



For responders the method was somewhat more complex. Each of these patients must have improved by at least 30% but some would have improved a great deal more than that. To calculate the level of improvement at each 5% increment above 30% we used data on the patients who had improved by at least 29% (to account for rounding error) from the Messina dataset and fit a 'survival curve' to greater levels of response (see Figure 6). The 'survival' data that underpinned this were the proportional response data (change in NRS divided by baseline NRS) minus 0.29. Every observation was counted as an 'event' for the purposes of fitting the curve. Based on AIC/BIC statistics we selected a generalised gamma curve for use in our economic model (Table 10).

Table 10: Model fit data for >30% responders survival curve

Parametric Survival Regression	AIC	BIC
Weibull	1118	1126
Exponential	1139	1143
Gompertz	1136	1144
Gamma	**1106**	**1118**
Lognormal	1122	1130
Loglogistic	1122	1129

We included options in the model for this curve to be conditional on 25% and 28% response (using the same methodology as above but using data on patients who had improved by at least 25% or 28% instead of 29%) as there are some limitations with converting changes in a 1-10 categorical scale to percentage cut-offs but neither of these produced a significantly different survival curve (see Table 11).

Figure 6 % of patients had NRS improvement by at least 30%

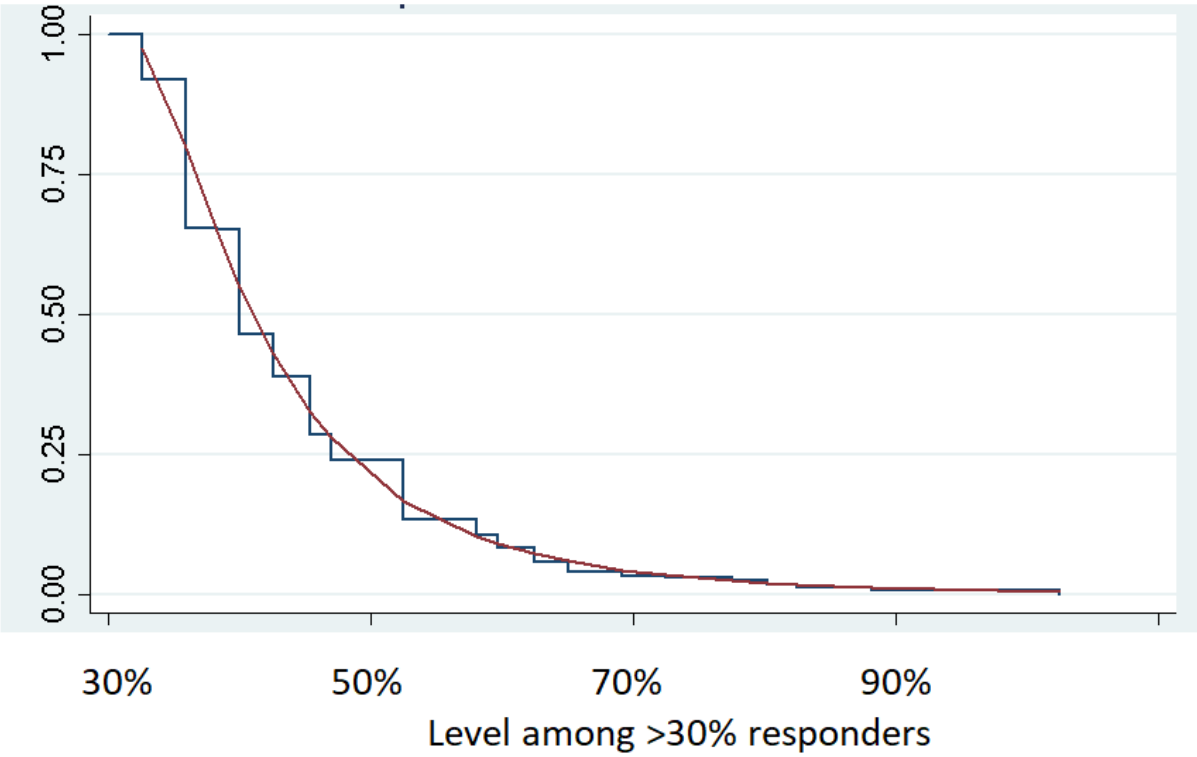


Table 11: Options for "response among responders" curve

Response among responders	30% cutoff	28% cutoff	25% cutoff
30-34%	26%	25%	29%
35-49%	27%	32%	30%
40-44%	18%	17%	16%
45-49%	11%	9%	9%
50-54%	7%	5%	5%
55-59%	4%	3%	3%
60-64%	3%	2%	2%
65-69%	2%	1%	1%
70-74%	1%	1%	1%
75-79%	1%	1%	1%
80-84%	0%	1%	1%
85-89%	0%	0%	0%
90-94%	0%	0%	0%
95-100%	0%	0%	0%

We multiplied this data on the proportion of patients achieving each level of 30%+improvement, calculated using 5% segments of the cumulative probability distribution from the fitted curve, along with the initial beta distribution of pain and the utility value at each NRS score to calculate a weighted average utility among the responder cohort.

The weighted average utility of response and no response were 0.44 and 0.288, respectively. Compared with the average QALY weight in the Swedish general population (50-59 years old) of 0.82 (Burström, Johannesson and Diderichsen, 2001; Svensson, Borg and Nilsson, 2014), patients with spasticity had substantially lower utility regardless of treatment response. These values were applied as the health states utilities in the model.

The magnitude of utility difference between responder's and nonresponses in our analysis was much greater than observations from published studies. Compared with the response and no response utilities in a published UK cost-effectiveness model (Lu et al., 2012), the authors assumed 0.57 utility for responders and 0.48 for non-responders.

EQ-5D data from the RCTs showed a limited difference in quality of life between THC: CBD spray and placebo arms (Novotna et al., 2011) but reported a significant difference between THC: CBD spray and placebo in spasticity treatment response. However, the study only observed mean EQ-5D difference of 0.02 between THC: CBD spray and placebo. Similar results were reported in another RCT (Collin et al., 2010) that the difference in EQ-5D was 0.02 between THC: CBD spray and placebo. Neither observation was statistically significant. These studies also reported very small differences between the arms on the 0-100 Visual Analogue Scale despite the large treatment effect on spasticity. Two studies (Langford et al., 2013; Markova et al., 2019) reported no significant difference in SF-36. Overall, there was limited evidence that reduction in spasticity would lead to meaningful improvements in HRQoL, as measured by conventional instruments. The contribution of the severity of the condition, the 'true' relationship between spasticity and HRQoL and the insensitivity of the measures are unknown. It is possible, given the other observed data, that our model overestimates the utility gain associated with response to treatment.

AE utility decrements were taken from the literature (Ara and Brazier, 2011; Hagiwara et al., 2018) as shown in Table 12. The model assumed that all adverse events lasted for a short duration (3-7 days).

Table 12 AE disutility and duration of the events

	Utility decrement	Duration (days)
Dizziness	0.02	3.00
Dry mouth	0.02	7.00
Fatigue	0.02	7.00
Headache	0.04	3.00
Nausea	0.06	3.00
Serious AE	0.10	3.00

The synthesis of utilities in the model follows a validated multiplicative approach (Ara and Wailoo, 2012):

Evidence shows that using the baseline utility of perfect health (utility=1) ignores the natural decline in mental/physical functions due to age and co-morbidities which also affect QoL. This also assumes the detriment on QoL associated with a health condition is constant irrespective of age (Ara and Brazier, 2010). To avoid these limitations, the baseline utility that

was applied in the economic model is based on age-adjusted EQ-5D data for UK general population (Kind, Hardman and Macran, 1999).

To derive the condition-specific utility values for the model health states and adverse events, a multiplier (M_A) is estimated based on the proportional difference between the health condition utility (U_A) and the utility of people without the condition (U_{nA}):

$M_A = U_A / U_{nA}$

Utility multipliers were calculated according to the health states (response and no response) and adverse events.

Multiplicative approach, as described by Ara and Wailoo, 2012, is applied to combine the health state utility multiplier (M_A) and AE utility multiplier (M_B):

$M_{A.B} = M_A \times M_B$

The combined multipliers were applied to the UK general population utility to estimate the utility of patients in the model. All utilities were adjusted by the cycle length (4 weeks).

Following the utility synthesis methods described above, the health state utility multipliers for response and no response were 0.537 and 0.352, respectively.

The AE disutility was estimated as a utility decrement and was applied using the additive approach (Ara and Wailoo, 2012). Each of the AE multipliers was summarised in Table 13:

Table 13 AE disutility per event

	QALY losses
Dizziness	0.00018
Dry mouth	0.00042
Fatigue	0.00042
Headache	0.00035
Nausea	0.00051
Serious AE	0.00078

To estimate the treatment specific AE utility decrement, the AE disutility were aggregated with the AE probabilities (dizziness for example):

The utility decrement for dizziness = dizziness disutility * % of patients with dizziness * number of days having dizziness

The weighted average AE utility decrement per year for cannabis + SoC and SoC alone strategies are 0.00329 and 0.00218, respectively.

As shown above, adverse events have almost no influence on utility. This is primarily because they only last for a few days each.

Costs

Treatment costs

Drug acquisition costs were estimated using pack/vial costs, the number of doses required per 4-week cycle. Pack/vial costs, and the associated dose strengths and pack sizes, were

sourced from NHS Drug Tariff or other publicly available sources, with the doses per cycle and packs per cycle sourced from the product monographs for each therapy or published literature. The summary of drug acquisition costs was summarised in Table 14. For medicinal cannabis, which is unavailable in the UK, such as Bedrocan products and dronabinol, the costs do not include any other costs (e.g. importation costs).

The model focused on THC: CBD spray (Sativex) as most of the evidence was on THC: CBD spray. THC: CBD spray costs £300 per 270 doses (note that the consultation version of this guideline was based on a previous list price of £375, but this was subsequently reduced by the manufacturer). The licensed dose of THC: CBD spray is a maximum of 12 sprays per day. The model applied the THC: CBD spray discount: NHS Pay for Responder scheme that first 3 x 10ml vial (90 doses per vial) for free and pay for responder only.

The model assumed a mean THC: CBD spray initial dose of 8.55 sprays per day based on the weighted average dose from the included RCTs (Collin et al., 2007, 2010; Novotna et al., 2011; Markova et al., 2019). The model assumed the mean dose decreased to 6.5 per day by 12 weeks and to 6.3 by 24 weeks and remained constant. This was tested in the sensitivity analysis.

Based on the clinical expert opinions, the committee believes that the initial dose would decrease over time and stabilise around 6 months. The committee also agreed that the mean initial dose from a dataset of Sativex use at a large UK tertiary centre (De Trane et al. 2016, 2017 and personal communications with author) is similar to the mean dose from RCTs. The doses among responders decreased over time, similar to the ones reported in the Italian registry by Messina et al. 2017. Therefore, the committee agreed that it is appropriate to use the mean dose data from Messina et al. 2017 and assume doses decrease over time. The committee decided that it is more appropriate to take the doses from the same reference (Messina et al. 2017) for other model parameters such as treatment response and discontinuation.

The committee reviewed the post-marketing study by Etges et al. 2016. They had concerns that reported mean dose is based on a combination of patients with MS spasticity and other indications from the UK, Germany and Switzerland. It does not report the mean dose for UK patients with spasticity. They also had concerns that this study does not report the efficacy data or reported doses decreasing over time, as observed in the Sativex patient registries. Therefore, they concluded that it is not appropriate to use the mean dose from Etges et al. 2016.

For dronabinol, the model applied an average acquisition cost of £1.63 per capsule (converted from US price) and assumed that patients received 6.3 capsules per day observed in an RCT (Zajicek et al., 2003).

As patients in both cannabis + SoC and SoC alone strategy received SoC, the model assumed £0 drug treatment cost for the SoC.

Table 14 Medicinal cannabis costs

Drug name	Ingredients	Pack size	Price (country)	Cost per day (£, min to max)	Licensed dosage
Sativex oromucosal spray a	Nabiximols: Cannabidiol (CBD) 2.5 mg & Dronabinol (THC) 2.7 mg per 1 dose	270 doses	£300(UK)	1.39 to 16.67	Starting from 1 spray a day, increased by 1 spray per day. Maximum 12 sprays per day (adults only)
Nabilone b	Nabilone (synthetic THC) 1 mg	20 capsules	£196 (UK)	19.60 to 58.80	1mg or 2mg twice a day, maximum daily dose of 6 mg (adults only). The first dose should be administered the night before initiation of chemotherapy, and the second dose should be given one to three hours before the first dose of the oncolytic agent is administered. It may be administered throughout each cycle of chemotherapy and, if necessary, for 48 hours after the last dose of each cycle.
EPIDIOLEX® c	Cannabidiol (CBD) 100 mg/ mL oral solution	100 mL	$1,235 (US)	10.84 to 43.38	Starting dose 2.5 mg/kg twice daily for one week then 5 mg/kg twice daily, can be increased up to maximum 10 mg/kg twice daily (patients 2+ years old)
Dronabinol d	Dronabinol (THC) 2.5 mg	60 capsules	$2.14 per capsule (US)	26.11 to 39.16	Anorexia associated with weight loss with AIDS - 2.5 mg twice daily (adults only) Nausea and vomiting associated with chemotherapy - 5 mg/m2 1-3 hours prior to chemotherapy then every 2-4 hours after chemotherapy for a total of 4 to 6 doses per day. (adults only)
	Dronabinol (THC) 5 mg	60 capsules	$3.97 per capsule (US)	24.27 to 36.40	
	Dronabinol (THC) 10 mg	60 capsules	$7.08 per capsule (US)	21.64 to 32.45	
Dronabinol (SYNDROS®) e	Dronabinol (THC) 5mg/ mL oral solution	30 mL	$1226.49 (US)	187.74 to 281.61	Anorexia associated with weight loss with AIDS - 2.1mg twice daily (adults only) Nausea and vomiting associated with chemotherapy - 4.2 mg/m2 1-3 hours prior to chemotherapy then every 2-4 hours after chemotherapy for a total of 4 to 6 doses per day. (adults only)

Drug name	Ingredients	Pack size	Price (country)	Cost per day (£, min to max)	Licensed dosage
Bedica® THC 2.0% oil f	14% THC and <1% CBD 0.05 ml = 1 mg THC	10 mL	€46.78 (Netherlands)	0.60	Epilepsy case study: 1 mg Bedica (THC) three times a day and 150 mg Bedrolite (CBD) twice a day
Bediol® CBD 2.0%/THC 1.3% oil f	6.3% THC and 8% CBD 0.05 ml = 1 mg CBD and 0.65 mg THC	10 mL	€46.78 (Netherlands)	-	
Bedrolite® CBD 2.0% oil f	<1% THC and 9% CBD 0.05 ml = 1 mg CBD	10 mL	€20.51 (Netherlands)	26.49	
Bedrolite® CBD 10% oil f	<1% THC and 9% CBD 0.05 ml = 5 mg CBD	10 mL	€77.12 (Netherlands)	19.92	
Tilray 2:100 (TIL-TC150) g	CBD: THC = 50:1; 2 mg/mL THC and 100 mg/mL CBD	40 mL	CAD $390 (Canada)	2.56 to 20.47	From open-label trial by McCoy et al. 2018: 2 mg/kg/day CBD (0.04 mg/kg/day THC) divided twice daily with weekly titration by 2 mg/kg/day every 7 days up to a maximum dose of 16 mg/kg/day CBD (0.32 mg/kg/day THC)
Avidekel™ oil h	>1% THC and 16-19% CBD (THC <2 mg/mL, CBD 20-25 mg/mL)	40 mL	CAD $120 (Canada)	3.15 to 78.74	From observational studies by Hausman-Kedem et al. 2018 (mix of Avidekel and Cheesepie [EP1]): 2–5 mg/kg/day, dosage increments were performed until maximum dose of 50 mg/kg per day of CBD
Sativex: Price: NHS Drug Tariff http://www.drugtariff.nhsbsa.nhs.uk/#/00710361-DA/DA00710133/Part%20VIIIA%20products%20D; Dosing: eMC https://www.medicines.org.uk/emc/product/602#INDICATIONS accessed on 6 March 2019; THC: CBD spray discount: Sativex NHS Pay for Responder scheme(3 x 10ml vial; 90 doses per vial; 270 doses per pack and pay for responder only): http://sativex.co.uk/static/documents/NHS_Pay-for-Responder_scheme_order_form.pdf Nabilone: Price: NHS Drug Tariff http://www.drugtariff.nhsbsa.nhs.uk/#/00710361-DA/DA00709784/Part%20VIIIA%20products%20N accessed on 6 March 2019; Dosing: eMC https://www.medicines.org.uk/emc/product/6176#INDICATIONS accessed on 6 March 2019 EPIDIOLEX: Price: GW Pharmaceuticals documents FORM 8-K for US Securities and Exchange Commission http://ir.gwpharm.com/static-files/fcc5c52a-910d-4db2-a0da-accaf9e5c35f accessed on 7 March 2019; Dosing: FDA label https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210365lbl.pdf accessed on 6 March 2019					

Drug name	Ingredients	Pack size	Price (country)	Cost per day (£, min to max)	Licensed dosage
Dronabinol: Price: US NADAC (National Average Drug Acquisition Cost) effective date 20 February 2019 https://healthdata.gov/dataset/nadac-national-average-drug-acquisition-cost CSV file, accessed on 7 March 2017; Dosing: FDA labels https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/018651s029lbl.pdf accessed on 6 March 2019 SYNDROS: Price: https://www.drugs.com/price-guide/syndros, accessed on 7 March 2017; Dosing: FDA labels https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/205525s007lbl.pdf accessed on 6 March 2019 Bedrocan products: Price: https://www.cannabiszorg.nl/en/#products accessed on 21 March 2019; Bedica THC 2% (assume it is Bedrocan's Indica) https://www.cannabiszorg.nl/en/product/thc-20-indica/; Bediol CBD 2.0%/THC 1.3% https://www.cannabiszorg.nl/en/product/cbd-20-thc-13-sativa/; Bedrolite CBD 2% and 10% https://www.cannabiszorg.nl/en/product/cbd-from-purified-cbd/; CBD and THC concentration strength: https://www.transvaalapotheek.nl/wp-content/uploads/2017/12/Patient-leaflet-Cannabis-oil-1.pdf; Dosing: Personal communication (Dr David Spraggett on 19 March 2019) Tilray 2:100: Price: https://www.livingwithpain.ca/unbranded/sneaky2100.html and Tilray Twitter https://twitter.com/tilray/status/997189798715711490 accessed on 8 March 2019; Dosing: McCoy et al. A prospective open-label trial of a CBD/THC cannabis oil in dravet syndrome. Ann Clin Transl Neurol. 2018 Aug 1;5(9):1077-1088. Avidekel: Price: http://www.gardenofcannabis.ca/product/avidekel-oil/ and https://hmed.ca/wp-content/uploads/2018/07/MedReleaf-Titration-Guide-July-2018.pdf accessed on 8 March 2019; Dosing: Hausman-Kedem et al. Efficacy of CBD-enriched medical cannabis for the treatment of refractory epilepsy in children and adolescents - An observational, longitudinal study. Brain Dev. 2018 Aug;40(7):544-551.					

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Background management costs

The background resource uses associated with various levels of spasticity were taken from a published UK study (Stevenson et al. 2015), which reported spasticity management costs by NRS categories: NRS 0-2, 2-4, 4-6, 6-8 and 8-10. The costs associated with each type of resource use were inflated from 2013 price to 2017/18 price using PSSRU 2018 HCHS inflation index (PSSRU 2018). The estimations were based on a survey of health care professionals. Advanced spasticity is highly associated with advanced disease more generally and as such, moving an average patient who is experiencing NRS 8-10 to NRS 6-8 would be unlikely to reduce resource use by the total difference between the two categories. This is because some of the reported resource use might not be spasticity specific, such as wheelchair use. The resource use costs were summarised in Table 15:

Table 15 spasticity management costs by NRS (based on Stevenson et al. 2015)

	NRS 0-2	NRS 2-4	NRS 4-6	NRS 6-8	NRS 8-10
Community-based visits (annual)	£42.62	£59.26	£120.59	£457.41	£903.38
Outpatient clinic visits (annual)	£149.70	£640.37	£1,588.45	£2,155.01	£2,756.92
A&E visits (annual)	£4.16	£10.40	£29.11	£38.46	£61.33
Hospital admissions (annual)	£7.28	£45.74	£152.82	£485.48	£920.01
Home care visits (annual)	£1.04	£1,692.41	£6,720.77	£17,261.92	£29,521.47

Based on the committee consensus and topic expert opinion, the committee does not think that the resource use reported in Stevenson et al. 2015 is 100% attributable to spasticity alone. The committee felt that the vignette from the health care professional survey could be misleading as it implied the disability described in the health states were caused by spasticity only. They felt that some of the physical disability specified in the vignette, particularly in the most severe health state, were most likely related to the underlying MS. Based on published evidence and the committee clinical opinions, they do not think treating spasticity would improve the underlying disability associated with MS (measured by EDSS). Therefore, the committee believes that Stevenson et al. 2015 overestimated spasticity-related resource use.

The committee estimated that 50% of the resource use costs from Stevenson et al. (2015) could be attributed to spasticity alone and therefore could be influenced by the treatment effect. However, this estimation was highly uncertain, and it was tested in the sensitivity analysis.

Not all the costs of social care come under the NHS/PSS perspective. The model assumed that the home care visits were funded by various bodies, as shown in Table 16, based on data from Parkinson's disease guideline (NG71). The model also assumed that 50% of part self-part NHS/PSS-funded home care visits were paid by the patients. The model did not include the costs of self-funded home care visits.

Table 16 Proportion of funding bodies for home care visits

	Proportion
Self-funded	0.4340
Part self- part NHS/PSS-funded	0.1390

	Proportion
PSS funded	0.3550
NHS continuing care funded	0.0720

The weighted average spasticity management costs for responders and non-responders were derived in the same way as the estimates for utility. The average spasticity management costs of response and no response of the 10,000 simulations were £207.18 and £473.09 per cycle, respectively.

Adverse event costs

For non-serious AEs, we assumed that 50% of patients would visit their GP and accrued a GP visit cost.

For the serious adverse events, the model assumed these events required an A&E visit and a proportion of patients required an ambulance (25%) or an inpatient stay (25%).

The unit costs of the resource use were summarised in Table 17.

Table 17 resource use of AE management

	Unit cost	Source
GP visit	£37.00	PSSRU (Curtis and Burns, 2018)
A&E visit	£225.82	NHS Reference costs - Weighted average of emergency medicine costs (excluding dental care, no investigation with no significant treatment, and dead on arrival)
Ambulance	£251.93	NHS Reference costs - see and treat and convey
Inpatient stay	£1,590.00	NHS Reference Costs 2016/2017

The costs per event applied in the model were summarised in Table 18:

Table 18 Resource use costs per AE

	Cost
Dizziness	£18.50
Dry mouth	£18.50
Fatigue	£18.50
Headache	£18.50
Nausea	£18.50
Serious adverse event	£686.31

Scenario analysis: 20% response cut-off

We undertook a special scenario analysis where we tried to approximate the use of THC:CBD in clinical practice, where patients are likely to continue with treatment if they achieve at least a 20% response. In order to do this we had to calculate several new parameters; the probability of response on cannabis, the odds ratio of response and the distribution of response among responders. All other parameters within the model remained the same except those that depend on the values taken by the above (such as utility among responders).

The baseline probability of achieving a 20% response was taken from the Messina 2017 data, where 1009 out of 1432 patients with complete response data achieved this level of response.

The odds ratio of treatment response was taken from studies that reported these data and pooled in fixed effects (i2=0%) meta-analysis.

Table 19: OR of response at 20% cut-off

	THC:CBD Spray		Placebo			OR from RevMan	
Study	R	N	R	N	Time (weeks)	Mean	95% CI
Markova 2018	43	53	24	53	4	5.20	2.17-12.47
Haupts 2016 post hoc of Novotna 2011	107	124	77	117	12	3.27	1.73-6.19
Fixed Effects Meta-analysis						3.84	2.29-6.42

As with the primary analysis, levels of response beyond 20% were dictated by fitting a survival curve to the percentage response data, this time subtracting 0.19 from each value. AIC/BIC statistic again showed a gamma curve provided the best fit to these data. The resulting data are in

Table 20.

Table 20: Proportion of responders in each response category (>=20%)

NRS response category among responders (>=20%)	Percentage of responders in category
0.2 - 0.26	27%
0.26 - 0.31	30%
0.31 - 0.37	18%
0.37 - 0.43	10%
0.43 - 0.49	6%
0.49 - 0.54	3%
0.54 - 0.6	2%
0.6 - 0.66	1%
0.66 - 0.71	1%
0.71 - 0.77	1%
0.77 - 0.83	0%
0.83 - 0.89	0%
0.89 - 0.94	0%
0.94 - 1	0%

The response proportions are used to dictate the utility and resource use among responders. In this scenario analysis the overall NRS among responders is slightly higher because

patients do not need to have improved by as much to continue treatment. The model calculates a utility among >=20% responders as 0.4 (down from 0.44) and a mean resource use per cycle of £104 (up from £69). The utility and resource use among non-responders remains the same as these patients were assumed to drop back to baseline in the model.

In this analysis substantially more patients respond to both Cannabis (70% vs 29%) and the SoC (38% vs 13%). These data are both somewhat lower than those reported in the clinical trials because they are anchored to the real-world response observed in Messina, which was lower than in the RCTs.

In this scenario analysis we removed the assumption that 10% of non-responders continue treatment.

Parametrisation in the probabilistic sensitivity analysis

Table 21 summarised all the parameters included in the probabilistic sensitivity analysis (PSA).

Table 21 parameters in the probabilistic sensitivity analysis

Parameter	mean	SE	Lo/Min	Hi/Max	Source	Dist	Param1	Param2
Baseline population: starting age	51.00	1.17	21.00	84.00	Messina 2017	Gamma	α=1904.473	β=0.027
Baseline population: sex (% male)	0.47	0.01	0.45	0.50	Messina 2017	Beta	α=756	β=841
Spasticity NRS at baseline	7.50	0.04			Messina 2017	Multivariate normal		
EDSS at baseline	6.40	0.03			Calculated from Messina 2017	Multivariate normal		
Cannabis response from Messina 2017/ Patti 2016	0.283	0.012	0.25979	0.30643	Messina 2017; Patti 2016	Beta	α=404.717	β=1026.283
Cannabis response (meta-analysis of 2 non-enriched studies, random effect)	0.3516	0.0441	0.26777	0.44027	Meta-analysis	Beta	α=40.864	β=75.359
THC: CBD spray Response (meta-analysis of 4 studies, random effect)	0.36	0.0281	0.31	0.42	Meta-analysis	Beta	α=106.273	β=185.846
Placebo response (Wade 2010)	0.26	0.03	0.21	0.31	Wade 2010	Beta	α=77	β=219
Odds ratio vs. placebo - response: THC: CBD spray - Within Dose	4.17	0.49	1.60	10.83	Clinical review: meta-analysis random effect	Lognormal	μ=1.428	σ=0.488
Odds ratio vs. placebo - response: THC: CBD spray - Higher Dose	1.61	0.20	1.09	2.38	Clinical review: meta-analysis fixed effect	Lognormal	μ=0.476	σ=0.199

Parameter	mean	SE	Lo/Min	Hi/Max	Source	Dist	Param1	Param2
Odds ratio vs. placebo - response: THC: CBD spray - All Doses	2.61	0.32	1.40	4.86	Clinical review: meta-analysis random effect	Lognormal	μ=0.959	σ=0.317
SMR of MS versus general population	2.80	0.01	2.74	2.87	Manouchehrinia 2016	Lognormal	μ=1.030	σ=0.012
Competing Risks Model (Messina)								
shape	-4.609				Calculated from Messina 2017	Multivariate normal		
rate	-0.786				Calculated from Messina 2017	Multivariate normal		
trans	-0.053				Calculated from Messina 2017	Multivariate normal		
shape(trans)	0.615				Calculated from Messina 2017	Multivariate normal		
HR for discontinuation: placebo vs. cannabis	0.48	0.06	0.38	0.62	Assumption	Lognormal	μ=-0.730	σ=0.061
Non-serious adverse event rate (Cannabis) per year	10.370	0.311	4.79539	18.39036	Wang 2008	Beta	α=2.339	β=0.311
Non-serious adverse event rate (Placebo) per year	6.870	0.382	2.50438	13.74420	Wang 2008	Beta	α=1.927	β=0.382
Serious adverse event rate (Cannabis) per year	0.370	0.038	0.34365	0.39838	Wang 2008	Beta	-α=0.994	β=0.038
Serious adverse event rate (Placebo) per year	0.250	0.056	0.22406	0.27895	Wang 2008	Beta	-α=1.386	β=0.056

Parameter	mean	SE	Lo/Min	Hi/Max	Source	Dist	Param1	Param2
% of AE which are dizziness	0.57	0.01	0.54	0.59	Wang 2008	Beta	α=714	β=544
% of AE which are dry mouth	0.19	0.01	0.17	0.21	Wang 2008	Beta	α=239	β=1019
% of AE which are fatigue	0.09	0.01	0.07	0.10	Wang 2008	Beta	α=109	β=1149
% of AE which are headache	0.06	0.01	0.05	0.08	Wang 2008	Beta	α=79	β=1179
% of AE which are nausea	0.09	0.01	0.08	0.11	Wang 2008	Beta	α=117	β=1141
THC: CBD spray: initial dose per day: pooled from RCTs	8.55	0.72	8.48	8.61	Pooled from RCTs (Collin 2007, Collin 2010, Novotna 2011 phase B, Markova 2018 phase B)	Gamma	α=66496.133	β=0.000
THC: CBD spray: initial doses per day: Messina 2017	6.80	0.07	6.67	6.93	Messina 2017 T1	Gamma	α=10923.858	β=0.001
THC: CBD spray: subsequent dose per day: up to 12 weeks	6.5	0.07	6.37	6.63	Messina 2017 T2 (12 weeks)	Gamma	α=9981.250	β=0.001
THC: CBD spray: subsequent dose per day: >12 weeks	6.3	0.07	6.16	6.44	Messina 2017 T3 (24 weeks)	Gamma	α=8084.813	β=0.001
Oral dronabinol: doses per day	6.30	0.23	5.85	6.75	Zajicek 2003	Gamma	α=756.000	β=0.008
% of non-responders continuing cannabis treatment	0.10	0.05102	0	0.2	Assumption	Beta	α=3.357	β=30.216
Resource use: State 1 (NRS 0-2):								

Parameter	mean	SE	Lo/Min	Hi/Max	Source	Dist	Param1	Param2
Community-based visits (annual)	42.62	8.52	25.91	59.33	Stevenson 2015: 2013 price inflated to 2017/18 price using PSSRU 2018 HCHS inflation index	Gamma	α=25.000	β=1.705
Outpatient clinic visits (annual)	149.70	29.94	91.02	208.38	Stevenson 2015: 2013 price inflated to 2017/18 price using PSSRU 2018 HCHS inflation index	Gamma	α=25.000	β=5.988
A&E visits (annual)	4.16	0.83	2.53	5.79	Stevenson 2015: 2013 price inflated to 2017/18 price using PSSRU 2018 HCHS inflation index	Gamma	α=25.000	β=0.166
Hospital admissions (annual)	7.28	1.46	4.42	10.13	Stevenson 2015: 2013 price inflated to 2017/18 price using PSSRU 2018 HCHS inflation index	Gamma	α=25.000	β=0.291
Home care visits (annual)	1.04	0.21	0.63	1.45	Stevenson 2015: 2013 price inflated to 2017/18 price using PSSRU 2018 HCHS inflation index	Gamma	α=25.000	β=0.042
Resource use: State 2 (NRS 2-4):								
Community-based visits (annual)	59.26	11.85	36.03	82.48	Stevenson 2015: 2013 price inflated to 2017/18 price using PSSRU 2018 HCHS inflation index	Gamma	α=25.000	β=2.370

Parameter	mean	SE	Lo/Min	Hi/Max	Source	Dist	Param1	Param2
Outpatient clinic visits (annual)	640.37	128.07	389.35	891.39	Stevenson 2015: 2013 price inflated to 2017/18 price using PSSRU 2018 HCHS inflation index	Gamma	α=25.000	β=25.615
A&E visits (annual)	10.40	2.08	6.32	14.47	Stevenson 2015: 2013 price inflated to 2017/18 price using PSSRU 2018 HCHS inflation index	Gamma	α=25.000	β=0.416
Hospital admissions (annual)	45.74	9.15	27.81	63.67	Stevenson 2015: 2013 price inflated to 2017/18 price using PSSRU 2018 HCHS inflation index	Gamma	α=25.000	β=1.830
Home care visits (annual)	1692.41	338.48	1029.00	2355.82	Stevenson 2015: 2013 price inflated to 2017/18 price using PSSRU 2018 HCHS inflation index	Gamma	α=25.000	β=67.696
Resource use: State 3 (NRS 4-6):								
Community-based visits (annual)	120.59	24.12	73.32	167.86	Stevenson 2015: 2013 price inflated to 2017/18 price using PSSRU 2018 HCHS inflation index	Gamma	α=25.000	β=4.824
Outpatient clinic visits (annual)	1588.45	317.69	965.79	2211.11	Stevenson 2015: 2013 price inflated to 2017/18 price using PSSRU 2018 HCHS inflation index	Gamma	α=25.000	β=63.538

Parameter	mean	SE	Lo/Min	Hi/Max	Source	Dist	Param1	Param2
A&E visits (annual)	29.11	5.82	17.70	40.52	Stevenson 2015: 2013 price inflated to 2017/18 price using PSSRU 2018 HCHS inflation index	Gamma	α=25.000	β=1.164
Hospital admissions (annual)	152.82	30.56	92.91	212.72	Stevenson 2015: 2013 price inflated to 2017/18 price using PSSRU 2018 HCHS inflation index	Gamma	α=25.000	β=6.113
Home care visits (annual)	6720.77	1344.15	4086.27	9355.26	Stevenson 2015: 2013 price inflated to 2017/18 price using PSSRU 2018 HCHS inflation index	Gamma	α=25.000	β=268.831
Resource use: State 4 (NRS 6-8):								
Community-based visits (annual)	457.41	91.48	278.11	636.71	Stevenson 2015: 2013 price inflated to 2017/18 price using PSSRU 2018 HCHS inflation index	Gamma	α=25.000	β=18.296
Outpatient clinic visits (annual)	2155.01	431.00	1310.26	2999.76	Stevenson 2015: 2013 price inflated to 2017/18 price using PSSRU 2018 HCHS inflation index	Gamma	α=25.000	β=86.200
A&E visits (annual)	38.46	7.69	23.39	53.54	Stevenson 2015: 2013 price inflated to 2017/18 price using PSSRU 2018 HCHS inflation index	Gamma	α=25.000	β=1.539

Parameter	mean	SE	Lo/Min	Hi/Max	Source	Dist	Param1	Param2
Hospital admissions (annual)	485.48	97.10	295.17	675.78	Stevenson 2015: 2013 price inflated to 2017/18 price using PSSRU 2018 HCHS inflation index	Gamma	α=25.000	β=19.419
Home care visits (annual)	17261.92	3452.38	10495.37	24028.47	Stevenson 2015: 2013 price inflated to 2017/18 price using PSSRU 2018 HCHS inflation index	Gamma	α=25.000	β=690.477
Resource use: State 5 (NRS 8-10):								
Community-based visits (annual)	903.38	180.68	549.26	1257.50	Stevenson 2015: 2013 price inflated to 2017/18 price using PSSRU 2018 HCHS inflation index	Gamma	α=25.000	β=36.135
Outpatient clinic visits (annual)	2756.92	551.38	1676.23	3837.61	Stevenson 2015: 2013 price inflated to 2017/18 price using PSSRU 2018 HCHS inflation index	Gamma	α=25.000	β=110.277
A&E visits (annual)	61.33	12.27	37.29	85.38	Stevenson 2015: 2013 price inflated to 2017/18 price using PSSRU 2018 HCHS inflation index	Gamma	α=25.000	β=2.453
Hospital admissions (annual)	920.01	184.00	559.37	1280.65	Stevenson 2015: 2013 price inflated to 2017/18 price using PSSRU 2018 HCHS inflation index	Gamma	α=25.000	β=36.800

Parameter	mean	SE	Lo/Min	Hi/Max	Source	Dist	Param1	Param2
Home care visits (annual)	29521.47	5904.29	17949.27	41093.67	Stevenson 2015: 2013 price inflated to 2017/18 price using PSSRU 2018 HCHS inflation index	Gamma	α=25.000	β=1180.859
Distribution of home care funding categories								
Self-funded	0.43	0.04	0.35	0.52	Parkinson's guideline	Dirichlet	α=0.367	
Part self- part NHS/PSS-funded	0.14	0.01	0.11	0.17	Parkinson's guideline		α=0.159	
PSS funded	0.36	0.04	0.29	0.42	Parkinson's guideline		α=0.322	
NHS continuing care funded	0.07	0.01	0.06	0.09	Parkinson's guideline		α=0.084	
Proportion of costs that are spasticity related	0.5	0.1	0.31	0.69	Assumption	Beta	α=12.000	β=12.000
Dizziness - proportion of patients who visit GP	0.50	0.05	0.40	0.60	Assumption	Beta	α=50	β=50
Dry mouth - proportion of patients who visit GP	0.50	0.05	0.40	0.60	Assumption	Beta	α=50	β=50
Fatigue - proportion of patients who visit GP	0.50	0.05	0.40	0.60	Assumption	Beta	α=50	β=50
Headache - proportion of patients who visit GP	0.50	0.05	0.40	0.60	Assumption	Beta	α=50	β=50
Nausea - proportion of patients who visit GP	0.50	0.05	0.40	0.60	Assumption	Beta	α=50	β=50
Serious adverse event - proportion of patients who require ambulance journey to A&E	0.25	0.03	0.20	0.30	Assumption	Beta	α=75	β=224

Parameter	mean	SE	Lo/Min	Hi/Max	Source	Dist	Param1	Param2
Serious adverse event - proportion of patients who require an inpatient stay	0.25	0.03	0.20	0.30	Assumption	Beta	α=75	β=224
Population utility (aged 50-59) from study country (Sweden)	0.82	0.01	0.81	0.83	Svensson 2013, Burstrom 2001	Beta	α=2469	β=542
QoL decrements: Dizziness	0.02	0.02	-0.01	0.05	Hagiwara 2018 - assumed to be equivalent to disutility of fatigue	Gamma	α=1.874	β=0.012
QoL decrements:Dry mouth	0.02	0.02	-0.01	0.05	Hagiwara 2018 - assumed to be equivalent to disutility of fatigue	Gamma	α=1.874	β=0.012
QoL decrements: Fatigue	0.02	0.02	-0.01	0.05	Hagiwara 2018	Gamma	α=1.874	β=0.012
QoL decrements: Headache	0.04	0.02	0.01	0.08	Ara and Brazier 2011	Gamma	α=6.377	β=0.007
QoL decrements: Nausea	0.06	0.02	0.03	0.10	Hagiwara 2018	Gamma	α=9.708	β=0.006
QoL decrements: Serious adverse event	0.10	0.07	-0.05	0.24	Hagiwara 2018 - grade 2 vomiting	Gamma	α=1.638	β=0.058
Adverse event durations (days): Dizziness	3.00	0.60	1.82	4.18	Assumption	Gamma	α=25.000	β=0.120
Adverse event durations (days): Dry mouth	7.00	1.40	4.26	9.74	Assumption	Gamma	α=25.000	β=0.280
Adverse event durations (days): Fatigue	7.00	1.40	4.26	9.74	Assumption	Gamma	α=25.000	β=0.280
Adverse event durations (days): Headache	3.00	0.60	1.82	4.18	Assumption	Gamma	α=25.000	β=0.120
Adverse event durations (days): Nausea	3.00	0.60	1.82	4.18	Assumption	Gamma	α=25.000	β=0.120

Parameter	mean	SE	Lo/Min	Hi/Max	Source	Dist	Param1	Param2
Adverse event durations (days): Serious adverse event	3.00	0.60	1.82	4.18	Assumption	Gamma	α=25.000	β=0.120
EQ-5D in men								
age < 25	0.94	0.01	0.92	0.96	Kind et al. 1999	Beta	α=470.313	β=30.020
24 < age < 35	0.93	0.01	0.91	0.95	Kind et al. 1999	Beta	α=779.507	β=58.673
34 < age < 45	0.91	0.01	0.89	0.93	Kind et al. 1999	Beta	α=659.278	β=65.203
44 < age < 55	0.84	0.02	0.80	0.87	Kind et al. 1999	Beta	α=341.410	β=65.030
54 < age < 65	0.78	0.02	0.74	0.82	Kind et al. 1999	Beta	α=333.840	β=94.160
64 < age < 75	0.78	0.02	0.74	0.82	Kind et al. 1999	Beta	α=388.472	β=109.569
74 < age	0.75	0.03	0.70	0.80	Kind et al. 1999	Beta	α=192.968	β=64.323
EQ-5D in women								
age < 25	0.94	0.01	0.92	0.96	Kind et al. 1999	Beta	α=647.033	β=41.300
24 < age < 35	0.93	0.01	0.92	0.94	Kind et al. 1999	Beta	α=1137.278	β=85.602
34 < age < 45	0.91	0.01	0.89	0.93	Kind et al. 1999	Beta	α=1009.372	β=99.828
44 < age < 55	0.85	0.01	0.82	0.88	Kind et al. 1999	Beta	α=546.147	β=96.379
54 < age < 65	0.81	0.02	0.78	0.84	Kind et al. 1999	Beta	α=530.282	β=124.387
64 < age < 75	0.78	0.02	0.75	0.81	Kind et al. 1999	Beta	α=556.028	β=156.828
74 < age	0.71	0.02	0.67	0.75	Kind et al. 1999	Beta	α=412.389	β=168.441

Results

In the base case, THC: CBD spray + SoC was compared to SoC alone strategy. The total QALYs gained, and total costs, as well as the breakdown of the total costs, are outlined in Table 22. Over the 5-year time horizon, THC: CBD spray + SoC strategy accrued higher treatment costs and AE costs but had a cost saving of £2,460 from reducing the resource use of the spasticity management. Compared to SoC alone, THC: CBD spray + SoC accrued £1,580 more costs and generated 0.081 more QALYs. The ICER was £19,512 per QALY gained.

Table 22 Base case results

	SoC	THC: CBD spray + SoC	Incremental
LYs	4.506	4.506	0.000
QALYs	1.286	1.367	0.081
Total costs	£30,630	£32,210	£1,580
Treatment cost	£0	£3,377	£3,377
AE cost	£1,345	£2,008	£663
Management cost	£29,284	£26,825	-£2,460
ICER			£19,512
Net monetary benefit @ £20k/QALY)	-£4,907	-£4,868	

The PSA results were based on the mean of 5,000 iterations and the graphical presentation all PSA iterations was shown in Figure 7. The mean ICER from PSA was £21,167 per QALY, and THC: CBD spray + SoC generated £1,654 more costs and 0.078 more QALYs, similar to the ICER in the base case. At the £20,000/QALY threshold, there is a 47.7% probability that THC: CBD spray + SoC will be cost-effective, compared with a 66.0% probability of being cost-effective at the £30,000/QALY threshold(Figure 8).

Figure 7 PSA scatterplot

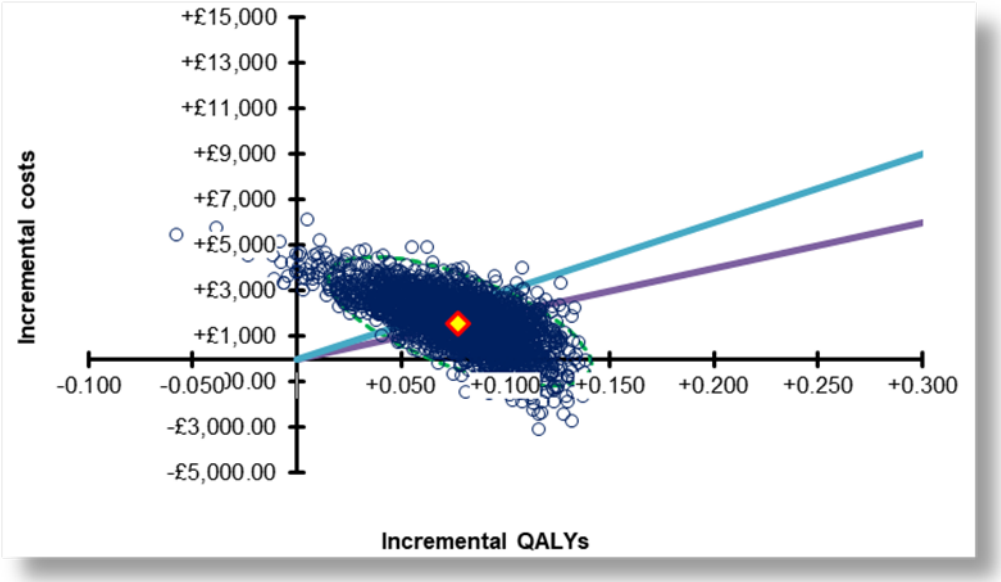


Figure 8 Cost-effectiveness acceptability curve

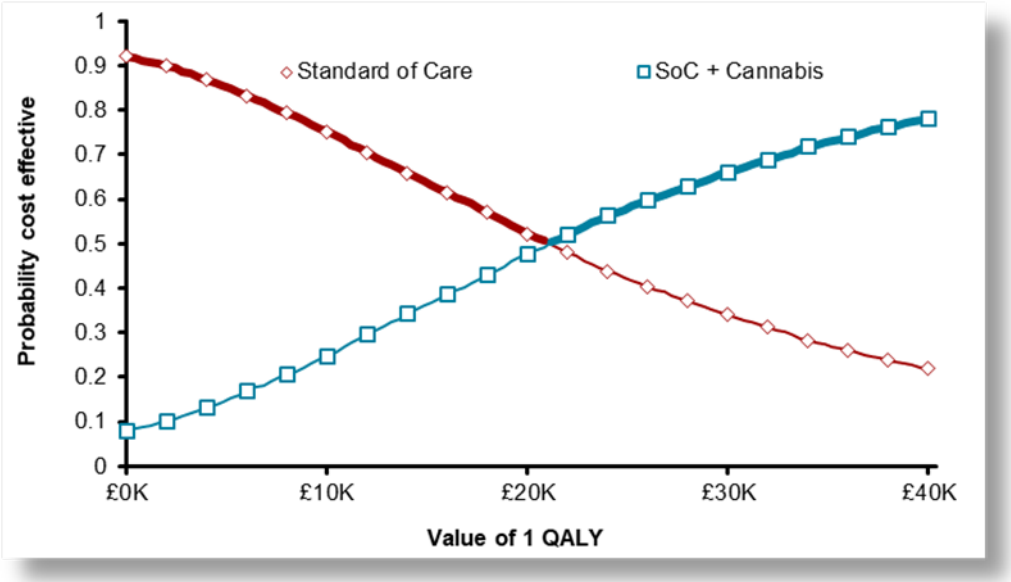


Table 23 showed the scenario analyses using different model assumptions. The model was sensitive to the assumptions related to treatment effects (odds ratios), the dosing of THC: CBD spray and the QoL assumptions.

Table 23 scenario analyses

Scenario	Incremental cost	Incremental QALYs	ICER
Base case	£1,580	0.081	£19,512
Odds ratio from enriched design RCTs only, within licensed dose (Novotna 2011; Markova 2018)	£693	0.111	£6,260
Odds ratio from Collin 2007, 2010 (unrestricted dose) only	£2,876	0.038	£76,300
Discontinuation rates (loss of response) the same in both arms	£1,330	0.089	£14,890
Discontinuation rates (loss of response the same in both arms and set at 10% rate per year)	£1,329	0.089	£14,958
No discontinuation in treatment response in SoC	£1,891	0.071	£26,762
No natural progression in NRS	£1,879	0.075	£25,013
Lower initial THC: CBD spray dose (6.8 sprays/ day from Messina 2017 T1)	£1,570	0.081	£19,383
Allow decreasing Sativex dose after 24 weeks	£1,134	0.081	£14,001
Maximum constant THC: CBD spray dose (12 sprays/ day)	£4,722	0.081	£58,302
Constant THC: CBD spray dose (6.8 sprays/ day from Messina 2017 T1)	£1,840	0.081	£22,715
Lower constant THC: CBD spray dose (5.4 sprays/ day from Etges 2016)	£1,064	0.081	£13,134
QoL: assume correlation (0.34) between NRS and EDSS	£1,580	0.164	£9,612
QoL: assume correlation (0.17) between NRS and EDSS	£1,580	0.125	£12,670
QoL: assume 5% decrement by NRS alone	£1,580	0.081	£19,615
QoL: Assume 10% decrement by NRS	£1,580	0.179	£8,851
Utility data from Lu 2012 and no NRS progression (response utility = 0.57, no response utility = 0.48)	£1,879	0.044	£42,344
10 years time horizon	£2,728	0.149	£18,325
20 years time horizon	£4,301	0.239	£17,999
30 years time horizon	£4,994	0.277	£18,026
Dronabinol costs + SoC vs SoC	£3,565	0.081	£44,017
Nabilone costs + SoC vs SoC	£8,426	0.081	£104,028
Background management costs doubled	-£879	0.081	dominant
Background management costs halved	£2,810	0.081	£34,695
Cannabis response = meta-analysis of 2 non-enriched RCTs	£914	0.122	£7,500
Cannabis response = meta-analysis of 2 non-enriched RCTs + 2 enriched RCTs (corrected for run-in phase)	£796	0.129	£6,163
THC:CBD is not free for patients in first cycle or with sub-threshold response	£1,929	0.081	£23,810
Assume 20% of non-responders continuing receiving cannabis treatment	£2,451	0.081	£30,265
Assume 0% of non-responders continuing receiving cannabis treatment	£709	0.081	£8,759

Scenario	Incremental cost	Incremental QALYs	ICER
Assume 20% improvement as response criteria for continuing treatment	£3,083	0.123	£24,992

Figure 9 and Figure 10 showed results of ten of the most sensitive parameters in a tornado diagram.

Figure 9 Tornado diagram of one-way sensitivity analysis at the £20,000/QALY threshold

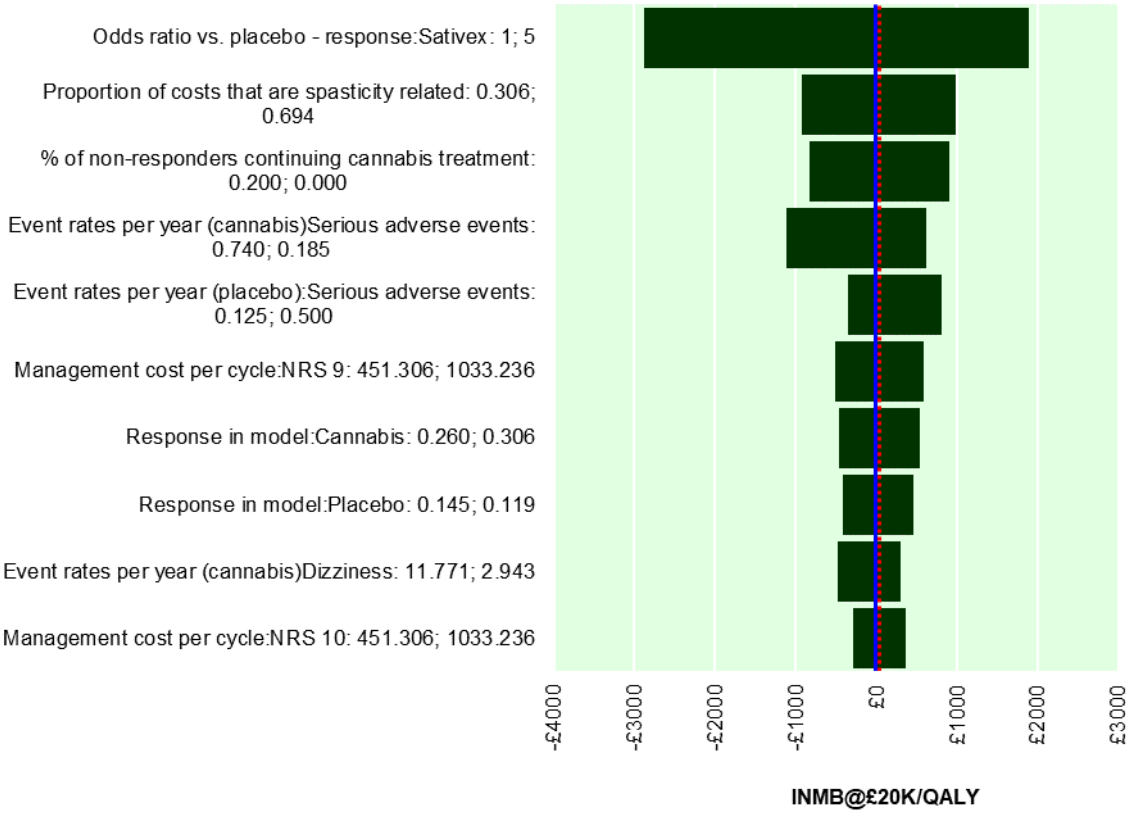
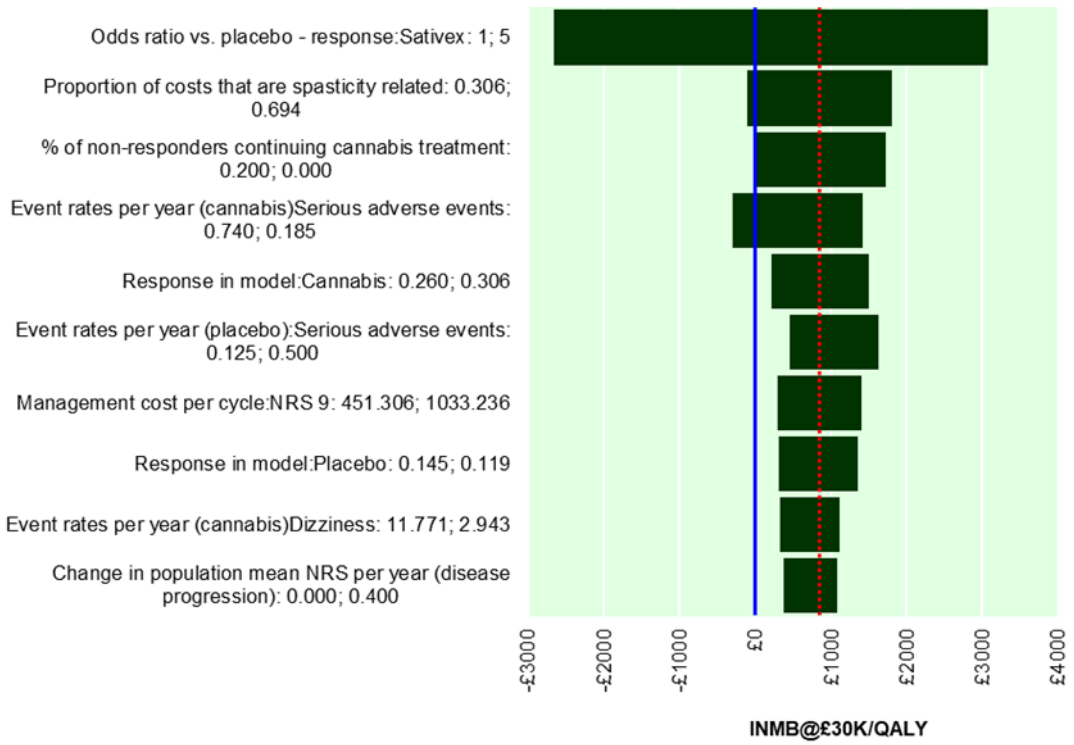


Figure 10 Tornado diagram of one-way sensitivity analysis at the £30,000/QALY threshold



Two-way sensitivity analyses were conducted some of the most important parameters; probability of response and utility values associated with the two health states. The green areas in Figure 11 show the combinations of values that lead to THC:CBD spray being cost-effective when QALYs are valued at either £20,000 or £30,000 each and the default values are indicated by orange highlights. The values within each cell represent incremental net monetary benefit.

Figure 11: Results of Two-way sensitivity analyses

Treatment response of cannabis vs. standard of care at £20,000 threshold

£20k threshold	Cannabis response																	
Standard Care response	0.1	0.15	0.2	0.25	0.28	0.35	0.4	0.45	0.5	0.55	0.6	0.65	0.7	0.75	0.8	0.85	0.9	0.95
0.1	-2872	-1793	-715	364	1071	2520	3599	4677	5756	6834	7913	8991	10070	11148	12227	13305	14384	15462
0.13	-3904	-2825	-1747	-668	40	1489	2567	3645	4724	5802	6881	7959	9038	10116	11195	12273	13352	14430
0.2	-6173	-5095	-4016	-2938	-2230	-781	298	1376	2455	3533	4612	5690	6769	7847	8925	10004	11082	12161
0.25	-7824	-6745	-5667	-4588	-3880	-2431	-1353	-274	804	1883	2961	4040	5118	6196	7275	8353	9432	10510
0.3	-9474	-8396	-7317	-6239	-5531	-4082	-3003	-1925	-846	232	1310	2389	3467	4546	5624	6703	7781	8860
0.35	-11125	-10046	-8968	-7889	-7181	-5732	-4654	-3575	-2497	-1419	-340	738	1817	2895	3974	5052	6131	7209
0.4	-12775	-11697	-10618	-9540	-8832	-7383	-6304	-5226	-4148	-3069	-1991	-912	166	1245	2323	3402	4480	5559
0.45	-14426	-13347	-12269	-11190	-10483	-9034	-7955	-6877	-5798	-4720	-3641	-2563	-1484	-406	673	1751	2830	3908
0.5	-16076	-14998	-13919	-12841	-12133	-10684	-9606	-8527	-7449	-6370	-5292	-4213	-3135	-2056	-978	101	1179	2257
0.55	-17727	-16648	-15570	-14492	-13784	-12335	-11256	-10178	-9099	-8021	-6942	-5864	-4785	-3707	-2629	-1550	-472	607
0.6	-19378	-18299	-17221	-16142	-15434	-13985	-12907	-11828	-10750	-9671	-8593	-7514	-6436	-5358	-4279	-3201	-2122	-1044
0.65	-21028	-19950	-18871	-17793	-17085	-15636	-14557	-13479	-12400	-11322	-10243	-9165	-8087	-7008	-5930	-4851	-3773	-2694
0.7	-22679	-21600	-20522	-19443	-18735	-17286	-16208	-15129	-14051	-12973	-11894	-10816	-9737	-8659	-7580	-6502	-5423	-4345
0.75	-24329	-23251	-22172	-21094	-20386	-18937	-17858	-16780	-15702	-14623	-13545	-12466	-11388	-10309	-9231	-8152	-7074	-5995
0.8	-25980	-24901	-23823	-22744	-22036	-20587	-19509	-18431	-17352	-16274	-15195	-14117	-13038	-11960	-10881	-9803	-8724	-7646
0.85	-27630	-26552	-25473	-24395	-23687	-22238	-21160	-20081	-19003	-17924	-16846	-15767	-14689	-13610	-12532	-11453	-10375	-9297
0.9	-29281	-28202	-27124	-26046	-25338	-23889	-22810	-21732	-20653	-19575	-18496	-17418	-16339	-15261	-14182	-13104	-12026	-10947
0.95	-30932	-29853	-28775	-27696	-26988	-25539	-24461	-23382	-22304	-21225	-20147	-19068	-17990	-16912	-15833	-14755	-13676	-12598

Treatment response of cannabis vs. standard of care at £30,000 threshold

£30k threshold	Cannabis response																	
Standard Care response	0.1	0.15	0.2	0.25	0.28	0.35	0.4	0.45	0.5	0.55	0.6	0.65	0.7	0.75	0.8	0.85	0.9	0.95
0.1	-2941	-1565	-190	1185	2088	3936	5311	6687	8062	9438	10813	12188	13564	14939	16315	17690	19065	20441
0.13	-4180	-2804	-1429	-53	850	2697	4073	5448	6824	8199	9574	10950	12325	13701	15076	16451	17827	19202
0.2	-6903	-5528	-4152	-2777	-1874	-26	1349	2725	4100	5475	6851	8226	9602	10977	12352	13728	15103	16479
0.25	-8884	-7509	-6134	-4758	-3855	-2007	-632	743	2119	3494	4870	6245	7620	8996	10371	11747	13122	14497
0.3	-10866	-9490	-8115	-6739	-5837	-3989	-2613	-1238	138	1513	2888	4264	5639	7015	8390	9765	11141	12516
0.35	-12847	-11471	-10096	-8721	-7818	-5970	-4594	-3219	-1844	-468	907	2283	3658	5033	6409	7784	9160	10535
0.4	-14828	-13453	-12077	-10702	-9799	-7951	-6576	-5200	-3825	-2449	-1074	301	1677	3052	4428	5803	7178	8554
0.45	-16809	-15434	-14058	-12683	-11780	-9932	-8557	-7181	-5806	-4431	-3055	-1680	-304	1071	2446	3822	5197	6573
0.5	-18790	-17415	-16040	-14664	-13761	-11913	-10538	-9163	-7787	-6412	-5036	-3661	-2286	-910	465	1841	3216	4591
0.55	-20771	-19396	-18021	-16645	-15742	-13895	-12519	-11144	-9768	-8393	-7018	-5642	-4267	-2891	-1516	-141	1235	2610
0.6	-22753	-21377	-20002	-18626	-17724	-15876	-14500	-13125	-11749	-10374	-8999	-7623	-6248	-4873	-3497	-2122	-746	629
0.65	-24734	-23358	-21983	-20608	-19705	-17857	-16481	-15106	-13731	-12355	-10980	-9604	-8229	-6854	-5478	-4103	-2727	-1352
0.7	-26715	-25340	-23964	-22589	-21686	-19838	-18463	-17087	-15712	-14336	-12961	-11586	-10210	-8835	-7459	-6084	-4709	-3333
0.75	-28696	-27321	-25945	-24570	-23667	-21819	-20444	-19068	-17693	-16318	-14942	-13567	-12191	-10816	-9441	-8065	-6690	-5314
0.8	-30677	-29302	-27927	-26551	-25648	-23800	-22425	-21050	-19674	-18299	-16923	-15548	-14173	-12797	-11422	-10046	-8671	-7296
0.85	-32659	-31283	-29908	-28532	-27630	-25782	-24406	-23031	-21655	-20280	-18905	-17529	-16154	-14778	-13403	-12028	-10652	-9277
0.9	-34640	-33264	-31889	-30514	-29611	-27763	-26387	-25012	-23637	-22261	-20886	-19510	-18135	-16760	-15384	-14009	-12633	-11258
0.95	-36621	-35246	-33870	-32495	-31592	-29744	-28369	-26993	-25618	-24242	-22867	-21492	-20116	-18741	-17365	-15990	-14615	-13239

Utility of responder vs. non-responder at £20,000 threshold

£20k threshold	Responder utility																	
Non-responder utility	0.1	0.15	0.2	0.25	0.3	0.35	0.4	0.44	0.5	0.55	0.6	0.65	0.7	0.75	0.8	0.85	0.9	0.95
0.1	-1547	-1058	-568	-79	410	899	1389	1793	2367	2856	3346	3835	4324	4813	5303	5792	6281	6770
0.15	-2007	-1517	-1028	-539	-50	440	929	1334	1907	2397	2886	3375	3864	4354	4843	5332	5821	6311
0.2	-2466	-1977	-1488	-999	-509	-20	469	874	1448	1937	2426	2915	3405	3894	4383	4872	5362	5851
0.25	-2926	-2437	-1948	-1458	-969	-480	9	414	988	1477	1966	2456	2945	3434	3923	4413	4902	5391
0.29	-3301	-2811	-2322	-1833	-1344	-854	-365	40	613	1102	1592	2081	2570	3059	3549	4038	4527	5016
0.35	-3846	-3356	-2867	-2378	-1889	-1399	-910	-505	68	558	1047	1536	2025	2514	3004	3493	3982	4471
0.4	-4305	-3816	-3327	-2838	-2348	-1859	-1370	-965	-392	98	587	1076	1565	2055	2544	3033	3522	4012
0.45	-4765	-4276	-3787	-3298	-2808	-2319	-1830	-1425	-851	-362	127	616	1106	1595	2084	2573	3063	3552
0.5	-5225	-4736	-4247	-3757	-3268	-2779	-2290	-1885	-1311	-822	-333	157	646	1135	1624	2114	2603	3092
0.55	-5685	-5196	-4706	-4217	-3728	-3239	-2749	-2345	-1771	-1282	-792	-303	186	675	1165	1654	2143	2632
0.6	-6145	-5655	-5166	-4677	-4188	-3698	-3209	-2804	-2231	-1741	-1252	-763	-274	216	705	1194	1683	2173
0.65	-6604	-6115	-5626	-5137	-4647	-4158	-3669	-3264	-2690	-2201	-1712	-1223	-733	-244	245	734	1224	1713
0.7	-7064	-6575	-6086	-5596	-5107	-4618	-4129	-3724	-3150	-2661	-2172	-1682	-1193	-704	-215	275	764	1253
0.75	-7524	-7035	-6545	-6056	-5567	-5078	-4588	-4184	-3610	-3121	-2631	-2142	-1653	-1164	-675	-185	304	793
0.8	-7984	-7494	-7005	-6516	-6027	-5537	-5048	-4643	-4070	-3580	-3091	-2602	-2113	-1624	-1134	-645	-156	333
0.85	-8443	-7954	-7465	-6976	-6486	-5997	-5508	-5103	-4530	-4040	-3551	-3062	-2573	-2083	-1594	-1105	-616	-126
0.9	-8903	-8414	-7925	-7436	-6946	-6457	-5968	-5563	-4989	-4500	-4011	-3522	-3032	-2543	-2054	-1565	-1075	-586
0.95	-9363	-8874	-8385	-7895	-7406	-6917	-6428	-6023	-5449	-4960	-4471	-3981	-3492	-3003	-2514	-2024	-1535	-1046

Utility of responder vs. non-responder at £30,000 threshold

£30k threshold	Responder utility																	
Non-responder utility	0.1	0.15	0.2	0.25	0.3	0.35	0.4	0.44	0.5	0.55	0.6	0.65	0.7	0.75	0.8	0.85	0.9	0.95
0.1	-1530	-796	-62	672	1406	2139	2873	3480	4341	5075	5809	6543	7276	8010	8744	9478	10212	10946
0.15	-2220	-1486	-752	-18	716	1450	2184	2791	3651	4385	5119	5853	6587	7321	8054	8788	9522	10256
0.2	-2909	-2175	-1442	-708	26	760	1494	2101	2962	3695	4429	5163	5897	6631	7365	8099	8833	9566
0.25	-3599	-2865	-2131	-1397	-663	70	804	1411	2272	3006	3740	4474	5207	5941	6675	7409	8143	8877
0.29	-4161	-3427	-2693	-1959	-1225	-492	242	850	1710	2444	3178	3912	4646	5379	6113	6847	7581	8315
0.35	-4978	-4244	-3511	-2777	-2043	-1309	-575	32	893	1626	2360	3094	3828	4562	5296	6030	6764	7497
0.4	-5668	-4934	-4200	-3466	-2732	-1999	-1265	-658	203	937	1671	2405	3138	3872	4606	5340	6074	6808
0.45	-6358	-5624	-4890	-4156	-3422	-2688	-1954	-1347	-487	247	981	1715	2449	3183	3916	4650	5384	6118
0.5	-7047	-6313	-5580	-4846	-4112	-3378	-2644	-2037	-1176	-443	291	1025	1759	2493	3227	3961	4695	5428
0.55	-7737	-7003	-6269	-5535	-4801	-4068	-3334	-2727	-1866	-1132	-398	336	1069	1803	2537	3271	4005	4739
0.6	-8427	-7693	-6959	-6225	-5491	-4757	-4023	-3416	-2556	-1822	-1088	-354	380	1114	1847	2581	3315	4049
0.65	-9116	-8382	-7649	-6915	-6181	-5447	-4713	-4106	-3245	-2512	-1778	-1044	-310	424	1158	1892	2626	3359
0.7	-9806	-9072	-8338	-7604	-6871	-6137	-5403	-4796	-3935	-3201	-2467	-1733	-1000	-266	468	1202	1936	2670
0.75	-10496	-9762	-9028	-8294	-7560	-6826	-6092	-5485	-4625	-3891	-3157	-2423	-1689	-955	-222	512	1246	1980
0.8	-11185	-10451	-9718	-8984	-8250	-7516	-6782	-6175	-5314	-4581	-3847	-3113	-2379	-1645	-911	-177	557	1290
0.85	-11875	-11141	-10407	-9673	-8940	-8206	-7472	-6865	-6004	-5270	-4536	-3802	-3069	-2335	-1601	-867	-133	601
0.9	-12565	-11831	-11097	-10363	-9629	-8895	-8161	-7554	-6694	-5960	-5226	-4492	-3758	-3024	-2291	-1557	-823	-89
0.95	-13254	-12520	-11787	-11053	-10319	-9585	-8851	-8244	-7383	-6650	-5916	-5182	-4448	-3714	-2980	-2246	-1512	-779

THC:CBD spray (Sativex) dose per day vs. % of resource use attributable to spasticity at £20,000 threshold

£20k threshold		Sativex dose per day																	
Initial dose per day		5.4	5.7	6	6.3	6.5	6.8	7.1	7.4	7.7	8	8.3	8.55	8.9	9.2	9.5	9.8	10.1	10.4
Dose per day (up to 12 weeks)		3.2	3.5	3.8	4.1	4.4	4.7	5	5.3	5.6	5.9	6.2	6.5	6.8	7.1	7.4	7.7	8	8.3
Dose per day (>12 weeks)		3	3.3	3.6	3.9	4.2	4.5	4.8	5.1	5.4	5.7	6	6.3	6.6	6.9	7.2	7.5	7.8	8.1
% of resource use attributable to spasticity	0%	-592	-758	-924	-1091	-1256	-1423	-1589	-1755	-1921	-2088	-2254	-2420	-2587	-2753	-2919	-3086	-3252	-3418
	5%	-346	-512	-678	-845	-1010	-1177	-1343	-1509	-1676	-1842	-2008	-2174	-2341	-2507	-2673	-2840	-3006	-3172
	10%	-100	-266	-432	-599	-764	-931	-1097	-1263	-1430	-1596	-1762	-1928	-2095	-2261	-2427	-2594	-2760	-2926
	15%	146	-20	-186	-353	-518	-685	-851	-1017	-1184	-1350	-1516	-1682	-1849	-2015	-2181	-2348	-2514	-2680
	20%	392	226	60	-107	-272	-439	-605	-771	-938	-1104	-1270	-1436	-1603	-1769	-1935	-2102	-2268	-2434
	25%	638	472	306	139	-26	-193	-359	-525	-692	-858	-1024	-1190	-1357	-1523	-1689	-1856	-2022	-2188
	30%	884	718	551	385	219	53	-113	-279	-446	-612	-778	-944	-1111	-1277	-1444	-1610	-1776	-1942
	35%	1130	964	797	631	465	299	133	-33	-200	-366	-532	-698	-865	-1031	-1198	-1364	-1530	-1696
	40%	1376	1210	1043	877	711	545	379	212	46	-120	-286	-452	-619	-785	-952	-1118	-1284	-1450
	45%	1622	1456	1289	1123	957	791	625	458	292	126	-40	-206	-373	-539	-706	-872	-1038	-1205
	50%	1868	1702	1535	1369	1203	1037	871	704	538	372	206	40	-127	-293	-460	-626	-792	-959
	60%	2360	2194	2027	1861	1695	1529	1363	1196	1030	864	697	531	365	199	32	-134	-300	-467
	70%	2852	2685	2519	2353	2187	2021	1855	1688	1522	1356	1189	1023	857	690	524	358	192	25
	80%	3344	3177	3011	2845	2679	2513	2346	2180	2014	1848	1681	1515	1349	1182	1016	850	683	517
	90%	3836	3669	3503	3337	3171	3005	2838	2672	2506	2339	2173	2007	1841	1674	1508	1342	1175	1009
	100%	4327	4161	3995	3829	3663	3497	3330	3164	2998	2831	2665	2499	2332	2166	2000	1834	1667	1501

THC:CBD spray (Sativex) dose per day vs. % of resource use attributable to spasticity at £30,000 threshold

£30k threshold		Sativex dose per day																	
Initial dose per day		5.4	5.7	6	6.3	6.5	6.8	7.1	7.4	7.7	8	8.3	8.55	8.9	9.2	9.5	9.8	10.1	10.4
Dose per day (up to 12 weeks)		3.2	3.5	3.8	4.1	4.4	4.7	5	5.3	5.6	5.9	6.2	6.5	6.8	7.1	7.4	7.7	8	8.3
Dose per day (>12 weeks)		3	3.3	3.6	3.9	4.2	4.5	4.8	5.1	5.4	5.7	6	6.3	6.6	6.9	7.2	7.5	7.8	8.1
% of resource use attributable to spasticity	0%	218	52	-114	-281	-446	-613	-779	-945	-1111	-1278	-1444	-1610	-1777	-1943	-2109	-2276	-2442	-2608
	5%	464	298	132	-35	-200	-367	-533	-699	-866	-1032	-1198	-1364	-1531	-1697	-1863	-2030	-2196	-2362
	10%	710	544	378	211	46	-121	-287	-453	-620	-786	-952	-1118	-1285	-1451	-1617	-1784	-1950	-2116
	15%	956	790	624	457	292	125	-41	-207	-374	-540	-706	-872	-1039	-1205	-1371	-1538	-1704	-1870
	20%	1202	1036	870	703	538	371	205	39	-128	-294	-460	-626	-793	-959	-1125	-1292	-1458	-1624
	25%	1448	1282	1115	949	783	617	451	285	118	-48	-214	-380	-547	-713	-879	-1046	-1212	-1378
	30%	1694	1528	1361	1195	1029	863	697	531	364	198	32	-134	-301	-467	-634	-800	-966	-1132
	35%	1940	1774	1607	1441	1275	1109	943	777	610	444	278	112	-55	-221	-388	-554	-720	-886
	40%	2186	2020	1853	1687	1521	1355	1189	1022	856	690	524	358	191	25	-142	-308	-474	-640
	45%	2432	2266	2099	1933	1767	1601	1435	1268	1102	936	770	604	437	271	104	-62	-228	-395
	50%	2678	2512	2345	2179	2013	1847	1681	1514	1348	1182	1015	850	683	517	350	184	18	-149
	60%	3170	3003	2837	2671	2505	2339	2173	2006	1840	1674	1507	1341	1175	1009	842	676	510	343
	70%	3662	3495	3329	3163	2997	2831	2665	2498	2332	2166	1999	1833	1667	1500	1334	1168	1002	835
	80%	4154	3987	3821	3655	3489	3323	3156	2990	2824	2658	2491	2325	2159	1992	1826	1660	1493	1327
	90%	4646	4479	4313	4147	3981	3815	3648	3482	3316	3149	2983	2817	2651	2484	2318	2152	1985	1819
	100%	5137	4971	4805	4639	4473	4307	4140	3974	3808	3641	3475	3309	3142	2976	2810	2644	2477	2311

A number of threshold analyses were conducted on the response, ORs of THC: CBD spray + SoC vs SoC, cost per pack for THC: CBD spray, proportion of management costs that are spasticity related, as shown in Figure 12 to Figure 16.

Figure 12 Threshold analysis on placebo response (fixed value for cannabis response)

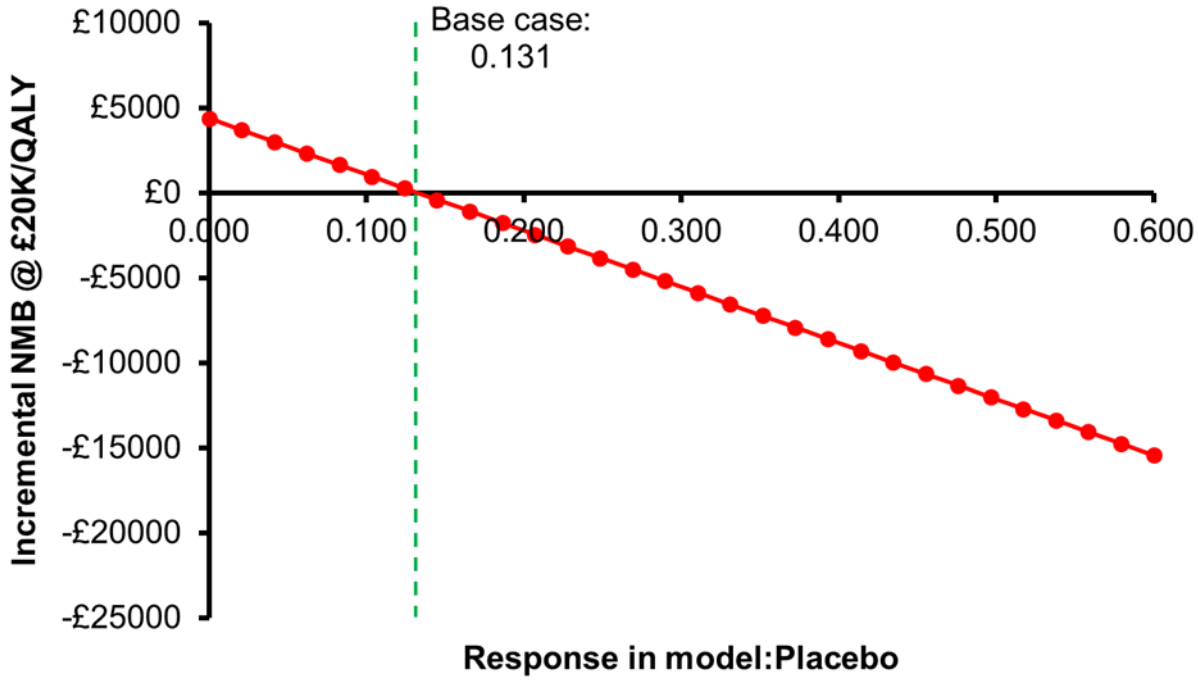


Figure 13 Threshold analysis on cannabis response (fixed value for placebo response)

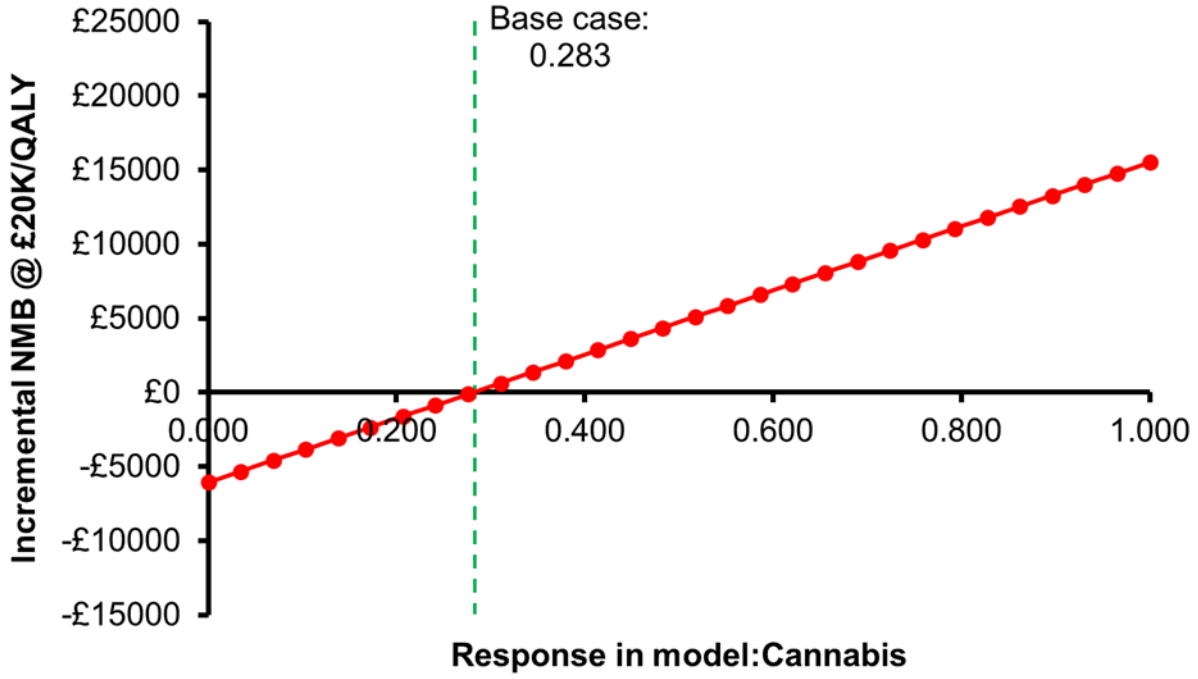


Figure 14 Threshold analysis on OR vs placebo

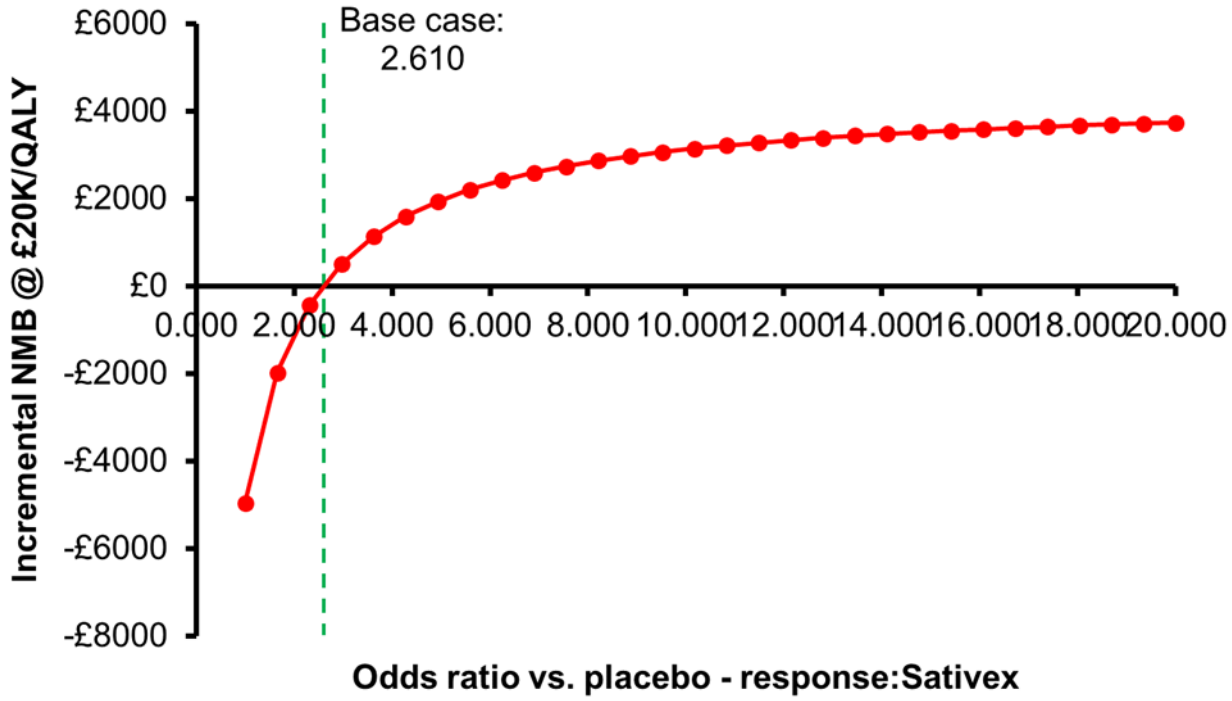
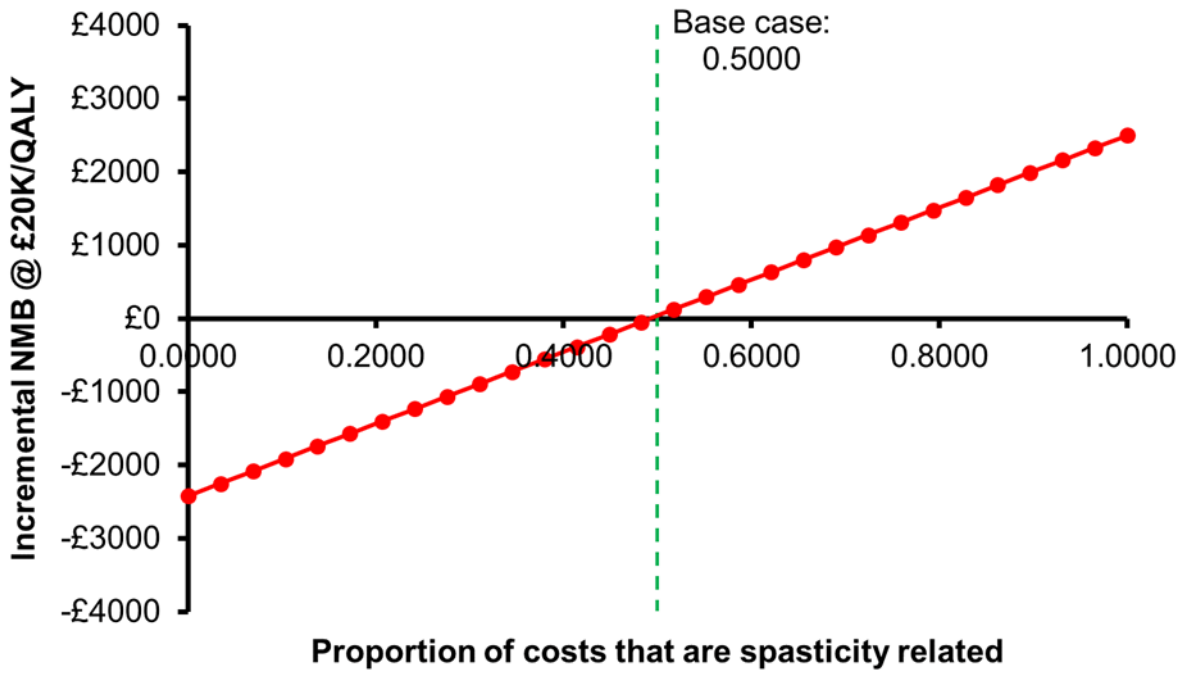


Figure 15 Threshold analysis on THC: CBD spray pack cost

Figure 16 Threshold analysis on proportion of management costs that are spasticity related



Discussion

The base-case analysis showed that compared to SoC alone, at the new list price of £300 per pack, THC: CBD spray + SoC was associated with an ICER of £19,512 per QALY gained over a 5-year time horizon. The ICER results were lower than another UK cost-effectiveness model by Lu et al., 2012, which reported an ICER of £49,257, which is probably due to the more favourable utility estimates we used in our model. Using the Lu et al utility estimates, the model produces an ICER of £42,344/QALY. This difference may be due to a number of input parameters, particularly the use of all 4 RCTs and a patient registry within our model rather than the results of a single RCT.

The clinical evidence showed THC: CBD spray + SoC improved the spasticity NRS compared to SoC alone and accrued cost saving in the resource use related to spasticity management. The clinical evidence also showed that THC: CBD spray had little impact on the disability scale (EDSS) (Ball et al. 2015, Kilestein et al. 2012, Markova et al. 2019, van Amerongen et al. 2018, Zajicek et al. 2012) which importantly influences patients' quality of life. This was reflected in the minimal EQ-5D difference observed in the THC: CBD spray trials (Novotna et al., 2011, Collin et al., 2010). Nevertheless, using a published regression analysis, our model estimated utility values of 0.29 and 0.44 for responders and non-responders. This 50% gain in HRQoL for treatment response may be an overestimate, given the lack of empirical data in support of this finding. In the committee's experience, observable differences in quality of life are common in patients who achieve a spasticity response following treatment with THC: CBD spray, however.

The model was most sensitive to the cost of treatment, number of sprays per day, the treatment effects and treatment response parameters, which was expected. However, the THC: CBD spray strategy had much lower ICERs in the scenarios where we assumed medicinal cannabis had a strong impact on patients' disability scale (EDSS), which the committee decided were not credible.

It is worth noting that the model was highly sensitive to the assumptions related to resource use. Doubling background management cost, effectively assuming that 100% of MS management was related specifically to spasticity, the cannabis strategy became dominant. A published study estimated that worse spasticity NRS was associated with higher resource use for spasticity management in MS (Stevenson et al. 2015). It was unclear how much of the reported resource use from Stevenson et al. (2015) attributed to spasticity only as there appeared to be large overlaps between the resource used managing spasticity and that used managing patients' underlying disease. The manufacturer's published model assumed that all reported resource use from Stevenson et al. (2015) were attributed to spasticity (Gras et al. 2016), which may have led to an overestimate of cost-saving from THC: CBD spray and therefore a very low ICER of £10,891 per QALY.

The model produces somewhat different total costs and QALYs to the published cost-effectiveness analyses. On the cost side, this is principally due to the omission of social care costs in Lu and the inclusion of probable non-spasticity social care costs in Gras as well as the much longer time horizon in the case of the latter. Our model produced the lowest overall QALYs because its baseline utility values were the lowest but it also included the most optimistic QoL differential for treatment effect. The manufacturer funded Gras study only produced 0.35 incremental QALYs over a 30 year time horizon.

In the base case, the model assumed patients in the SoC alone strategy would have a response similar to the placebo response observed in the RCTs. Due to lack of long-term data, the model assumed that the treatment effect (the relative difference between THC: CBD spray + SOC and SoC alone) remain constant throughout the 5-year time horizon. As the long-term observational study of THC: CBD spray indicated that the treatment response was sustained over at least 2 years, the model assumed the response in the SoC alone strategy sustained as well. This preserved the regression to the mean and placebo effect components of the changes from baseline observed in the trials, which should be the same in both arms. To discontinue more patients from response in the SoC arm than in the cannabis arm would either imply a differential placebo effect or a strengthening treatment effect and we did not have any evidence of either. This might be a limitation as the committee thought that the placebo response from the RCTs would diminish after 6 months or so, however. We experimented with different shaped discontinuation curves: assuming that there is a 10% year-on-year discontinuation in both arms, for example, resulted in a lower ICER of £14,958/QALY.

The model included the current publicly available discount scheme offered by the only manufacturer of THC: CBD to the NHS, in which that treatment is provided for free during the first cycle but that the NHS pays for responders thereafter. Because the indication for responders is 20% improvement rather than the 30% cutoff used in the clinical trials it is likely that THC: CBD, as it is used in practice, will be offered to patients who have seen between a 20% and 30% improvement. The primary analysis attempts to adjust for this by assuming that 10% of people in the treatment arm would continue treatment even if they didn't achieve a 30% response. Without this adjustment, the model produces an ICER of £8,759/QALY, which would be an overestimate of the cost-effectiveness of THC:CBD spray as if people with less than a 30% response would continue treatment as they would gain

fewer QALYs and management savings and incur the same treatment costs as their full-responder counterparts. It is unclear whether the 10% adjustment produces an under or over-estimate of the true cost-effectiveness of this intervention. We then conducted a specific scenario analysis adjusting multiple parameters to model 20% responders receiving ongoing treatment and the model produced an ICER of £24,992/QALY. This was principally because there was an expected lower utility differential between responders and non-responders, fewer resource savings between the two groups and greater response in the SoC arm. Overall, this is an important limitation of the analysis but the explorations we have conducted on the model do not indicate that plausible adjustments lead to ICERs that are qualitatively different from those produced by the primary analysis.

When varied over their plausible ranges, a large number of the examined parameters had the potential to change model outputs to one side or the other of a £20,000 / QALY threshold. However, the model was relatively robust if QALYs are valued at £30,000 each: only the main effectiveness parameter (relative likelihood of response to THC:CBD spray), the probability of adverse events, and the proportion of costs that are attributable to spasticity had sufficient impact that the ICER could exceed £30,000/QALY.

The model did not compare different medicinal cannabis products against each other. Due to a lack of clinical evidence, the model could not accurately determine the cost-effectiveness of any other medicinal cannabis except THC: CBD spray. It is worth noting that THC: CBD spray had one of the lowest daily costs compared to most of the other medicinal cannabis products. Hence, if assuming all medicinal cannabis had the same treatment effects, THC: CBD spray would potentially dominate all the other cannabis products for treating patients with spasticity.

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Appendix N Included studies

Study
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