Cannabis-based medicinal products

Consultation on draft guideline - Stakeholder comments table
08/08/19 to 05/09/19

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Alder Hey Children's NHS Foundation Trust	Guideline	General	General	Overall this is a sensible, measured document. It seems to fit well with the Health select committee report released last month (https://irp-cdn.multiscreensite.com/51b75a3b/files/uploaded/Report%20%7C%20CBD%20in%20the%20UK%20-%20Exec%20Summary.pdf) and the guideline may benefit from including a reference to this report I only feel able to comment on the section related to Childhood Epilepsy, as this is the most relevant section to us There are as yet, no Cannabis based medicinal products which are licensed in the UK for the management of childhood epilepsy and therefore this report does not name any of the products. However one product is available via a company managed access scheme, Epidiolex and a licensing application has been submitted by the company. I wonder if this will be available when the final guideline is published and whether reference will need to be made to it in this guideline to prevent the guideline very quickly becoming out of date. The guideline correctly references the BPNA guidance in relation to cannabis based medicinal products in childhood epilepsy.	Thank you for your comment. Cannabidiol for the treatment of seizures associated with Lennox-Gastaut and Dravet syndrome will be covered in NICE technology appraisals which are expected to publish in December 2019.
All-Party Parliamentary Group	General	General	General	RESPONSE TO NICE GUIDELINES from the ALL PARTY PARLIAMENTARY GROUP (APPG) on MEDICAL CANNABIS UNDER PRESCRIPTION The APPG on Medical Cannabis under Prescription was established to help secure legislation for access to natural cannabis for medical purposes in the UK under prescription from a medical professional. This is to include the prescription of full extract cannabis or in formulations produced to a consistent, high quality, pharmaceutical grade and manufactured to GMP standard. Despite the law change on November 1st 2018 natural cannabis for medical purposes in the UK is not available for patients who wish to access it. Instead, what has emerged is a two-tier system that has meant that if you have the money to obtain a private prescription, then you can access medical cannabis. Furthermore, if you are willing to travel abroad and face criminalising yourself then you are able to access the medication. This is an unsustainable and dangerous state of affairs. The NICE guidelines must reflect the urgent need within the population for safe access to wholeplant medical cannabis products.	Thank you for your comment. The committee were unable to recommend the use of any whole plant products due to a lack of robust evidence.
All-Party Parliamentary Group	General	General	General	INTRODUCTION A very significant part of the campaigning and political effort that led to the 1st November law change focused on a small number of high-profile cases of childhood epilepsy. As Nick Hurd MP, the then Home Office Minister responsible for this portfolio pointed out, these cases demonstrated the Government's existing position was not the right one. And, subsequent to the law change and the almost total block on NHS prescriptions since, a great deal of the ongoing campaigning work has also focussed on similar cases. For that reason, the main body of our consultation response is in three main parts. The first part addresses those parts of the draft guidelines relating to intractable paediatric epilepsy, the second relates to other conditions, and the third relates to some general points relating to what evidence has been reviewed and how it appears to have been factored into the draft guidelines.	Thank you for your comments.
All-Party Parliamentary Group	General	General	General	The Political Context The draft guidelines repeatedly question whether there is sufficient evidence for the efficacy of medical cannabis. But this seems to ignore the fact that the various bodies that advise the Government such as the Chief Scientific Officer, Dame Sally Davies who, in her review of the evidence (commissioned on the 19th June 2018) who reviewed evidence of the therapeutic benefit of cannabis-based medicinal products for certain medical conditions. She concluded There is now however, conclusive evidence of the therapeutic benefit of cannabis based medicinal products for certain medical conditions and reasonable evidence of therapeutic benefit in several other medical conditions' and continued 'Moving these drugs out of	Thank you for your comment. NICE makes an independent consideration of both the clinical and cost effectiveness of cannabis-based medicinal products and recommendations were made on a whole population basis. We recognise that the CMO identified sufficient evidence to reschedule CBMPs. NICE considers cost-effectiveness evidence as well as clinical effectiveness when determining which treatments to recommend on a population-wide basis. For the chronic pain population, the evidence showed that CBMPs were not clinically and cost effective. For the epilepsy population, the committee did not feel that there was sufficient evidence available to make a

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				Schedule 1 would allow them to be prescribed under controlled conditions by registered practitioners for medical benefit'. Dame Sally Davies, the Chief Medical Officer position is totally undermined in the NICE Guidelines which refer to a lack of good quality evidence that meant the committee was unable to make a recommendation on the use of CBMPs. Meaning that they instead made research recommendations to promote further research and inform future practice. If good quality evidence for the efficacy of medical cannabis led to a change in the law, it is somewhat paradoxical that the guidelines in their current form will not recommend its prescription citing a lack of good quality evidence. Indeed, it was the advice from those bodies that was key in persuading the Home Secretary and the Government to change the law. Put simply, if there wasn't sufficient evidence of efficacy, why did the Government change the law?	positive or negative recommendation. Clinicians can still make their own individual prescribing decisions in the best interest of their patients.
All-Party Parliamentary Group	General	General	General	PAEDEATRIC EPILEPSY The Impact and Role of the Guidelines Lines 1 to 10 of Page 17 makes a number of statements that we believe need to be changed. We can report without any shadow of doubt that medical professionals caring for some of the most severe cases of intractable paediatric epilepsy routinely cite 'the guidelines' as a reason for not prescribing cannabis-based products containing THC. If the intention of lines 1 to 10 of page 17 was to give clinicians the confidence, that in some limited situations involving the most severe paediatric epilepsy cases, the confidence to prescribe we feel the language used falls far short. Additionally, we take issue with the expression 'there is no clear evidence' in line 9 of page 17 in relation to efficacy. Our contention is that there is indeed 'clear' evidence of efficacy. This is in three main forms: a. There is a significant number of well documented individual cases in which parents have privately sourced THC bearing medical cannabis and have demonstrated efficacy. Indeed, we understand that some of the families involved with those cases have made personal submissions to NICE. So at the very least, we believe that this form of words should be amended to say something along the lines of ' '…. Whilst there is limited RCT evidence of efficacy in intractable paediatric epilepsy, there is a growing body of individual case evidence based over a significant number of months that for some paediatric epilepsy cases the use of THC bearing medical cannabis products has brought about sustained and dramatic reductions in seizure frequency and severity together with dramatic improvements in quality of life. Additionally, any concerns about the possibility of longterm harm from low concentrations of THC should be set in context against the reality that in many of these cases there is already significantly reduced cognitive and development capability ……' It is our firm understanding that the families would not be obtaining private prescriptions at a huge personal cost, and some actually criminalising themselves, unless their child was receiving a significant benefit from accessing the medicine.	Thank you for your comments. The committee were aware that there are reports of individual patients having fewer seizures with these medicines when other treatments have not fully controlled the seizures. But current research is limited and of low quality, making it difficult to assess just how effective these medicines are for people with epilepsy. The committee discussed the limited evidence and agreed that it did not warrant a practice recommendation. However, they also agreed that they should not make a recommendation against the use of cannabis-based medicinal products as this would restrict further research in this area and would prevent people who are currently apparently benefiting from continuing with their treatment. Until there is clear evidence, specialists, people with epilepsy and their carers should continue to make treatment decisions in the best interests of each person with epilepsy. However, people seeking treatment for severe epilepsy should be made aware that currently there is no clear evidence of the safety and effectiveness of cannabis-based medicinal products.
All-Party Parliamentary Group	General	General	General	The Balance of Quality of Life and Risk of Harm Additionally, the guidelines make repeated mentions of the lack of evidence relating to possible long-term harm from the administration of CBMPs. However, what the guidelines do not reflect is the fact that in many cases of extreme intractable paediatric epilepsy there are already significant degrees of brain, developmental and cognitive damage. In lay person's terms, it seems perverse to have such a focus around the concerns of possible long term harm in a child's developing brain when the child's brain is already severely affected by one,	Thank you for your comment. Whilst the committee were mindful about the harms of not treating the underlying condition optimally, they agreed that from a patient safety perspective, it is in the child's best interest to highlight to their family or carer the unknown effects on brain and cognitive development and the effect of sedation in the absence of data. NICE makes an independent consideration of both the clinical and cost effectiveness of cannabis-based medicinal products and recommendations were made on a whole population

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				or a combination of, the condition itself or the repeated use of powerful AEDs all with acknowledged adverse side effects. Further, some of the conditions are so severe that life expectancy is limited. It is our contention that these factors are not adequately reflected in the draft guidance. For this reason, special dispensation must be given to these most severe cases. We understand that NICE write guidelines across whole populations, but the sweeping guidelines do not account for the very small population whom have severe drug-resistant intractable epilepsy and do not respond to any other treatments.	basis. Clinicians can still make their own individual prescribing decisions in the best interest of their patients.
All-Party Parliamentary Group	General	General	General	OTHER CONDITIONS Much of the work of the APPG has focussed on the distressing cases of paediatric epilepsy. However, the APPG is aware of a number of situations in which there appears to be a compelling case for the prescription on the NHS of medical cannabis containing THC. We note that the draft guidelines indicate that there is some benefit for medical cannabis in the treatment of pain. However, the guidelines then indicate against prescribing on the basis of this not being cost effective. However, in the same vein as our comments relating to the paediatric neurology cases above, we feel that the draft guidelines fail to address that there are some 'in extremis' cases of pain in which the patient has exhausted all other treatments and for which medical cannabis has should benefit. In the case of one patient, [redacted] (who has given her express permission to be identified in this submission), the use of medical cannabis means that she is now not consuming the panoply of other medications such as Tramadol, Oxycodone, Buphrenophine and Fentynl. We contend that the guidelines need to make allowance for these extreme cases in which cost effectiveness is almost guaranteed on the basis of the patient subsequently being free from opioid use. [redacted] has arthritis and had two discs replaced in her neck. She has been left with nerve damage that affects her spinal cord. Bedrocan is the only medication that has ever alleviated the Lhermitte's sign (electric shocks) that she gets into her limbs upon neck extension/ flexion. The opioid medication gave her heart palpitations, vomiting and extreme drowsiness. [redacted] cannot tolerate Nabilone, as it lowers her heart rate to less than 50bpm and causes her blood pressure to drop, to the point that she faints. [redacted] has found a private pain specialist who is prepared to write prescriptions for her. However, she now has to raise thousands of pounds a year to pay for her medical cannabis and undertake stressful and costly journeys abroad to secure it.	Thank you for your comment. The chronic pain evidence review catered for 'in extremis' pain because medicinal cannabis was to be the final treatment considered after usual medical care options had been tried or contemplated. You are correct that the data favours some types of medicinal cannabis for managing chronic pain compared to placebo. However, although this reaches statistical significance, the effect size is so small that individual people are unlikely to notice any difference. For example, pain intensity is measured on a scale of 0 to 10, 0 being no pain and 10 being maximum pain. In order for a person to notice any difference, analgesia should reduce pain intensity by at least 2 or even 3 points. Most pain intensity effect sizes were either statistically insignificant (oral delta-9-THC, oromucosal THC, vaporised THC (minimal CBD), vaporised THC:CBD, vaporised CBD (minimal THC)), or they caused less than a 2 point pain intensity drop (oromucosal CBD:THC) or the 95% confidence interval crossed the 2 point pain intensity drop threshold (oral nabilone). Even in cases where people with chronic pain are able to notice the benefit from CBMPs, the cost of medicinal cannabis is around 6 times greater than the NHS would normally deem an efficient use of resources.
All-Party Parliamentary Group	General	General	General	GENERAL OBSERVATIONS In addition to the detailed points above, we have the following general points: We contend that the rationale for the recommendations (draft guideline, pp.16-17), and the discussion of evidence in Evidence Review D under "Benefits and harms" (Evidence Review D, p.20) do not appear to represent a fair summary of the evidence reviewed. In particular: a) They underplay the extent of the evidence as to the reduction in seizures with CBMPs. Both the Guideline and the Evidence Review acknowledge only that there are "some reports" of individual patients having fewer seizures with these products. We firmly believe that the evidence of the patients currently receiving private prescriptions in the UK should be taken into account when writing the guidelines. b) They place an over-emphasis on adverse events, particularly on the single observational study with 40 participants recording 98% adverse events. although the committee acknowledge that it was not possible to determine how many of these were due to the	Thank you for your comments. During the development of the review protocol, the committee agreed that randomised controlled trials (RCTs) and systematic reviews of RCTs should be included. If sufficient RCT data was not available, then observational studies were also included. However, evidence for individual patients did not meet the inclusion criteria for evidence. The committee discussed the adverse events as they considered this to be one of the key concerns when considering prescribing CBMPs. The committee were also aware of the side-effects of seizures, however the low-quality evidence that is currently available made it difficult to compare both the benefits and harms of CBMPs. This is what led to the development of the research recommendations. The evidence for the observational studies was considered low quality. Although there was RCT evidence, this was for Lennox-Gastaut and Dravet syndromes, this will be covered by the technology appraisal guidance. Furthermore, the committee considered whether it would be possible to extrapolate the findings from the Lennox-Gastaut and Dravet populations but felt that this wouldn't be appropriate given the differences between different types of epilepsy.

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				CBMPs. This is highly contentious, the parents constantly tell the APPG what the horrendous side-effects are of the seizures, the licensed and unlicensed drugs they are taking without significant seizure control and also the adverse effects of brain surgery. We cannot understand the logic of emphasising adverse events in using CBMPs if the adverse events associated with using other AEDs are not taken into consideration. c) There is also a heavy emphasis on what is prescribed as the "low quality" of the evidence without reference to the fact that two of the four RCTs that were reviewed were assessed as being of "moderate" quality. Again, if the Chief Medical Officer reviewed 'good quality evidence' and concluded that this was sufficient to reschedule medical cannabis, why does it not constitute good evidence in this instance.	For this reason, they could not form a major part of the committee's decisions on recommendations. We recognise that the CMO identified sufficient evidence to reschedule CBMPs. NICE considers cost-effectiveness evidence as well as clinical effectiveness when determining which treatments to recommend on a population-wide basis. For the chronic pain population, the evidence showed that CBMPs were not clinically and cost effective. For the epilepsy population, the committee did not feel that there was sufficient evidence available to make a positive or negative recommendation. Clinicians can still make their own individual prescribing decisions in the best interest of their patients.
All-Party Parliamentary Group	General	General	General	CONCLUSION As currently drafted, the guidelines do not make adequate provision for the small populations of extreme cases in which efficacy has already been demonstrated in a number of cases. Our experience with the interim guidelines leaves us in no doubt that as drafted these guidelines will perpetuate the suffering of some of the most vulnerable families in the UK. The need for the guidelines to address issues relating to the large population of sufferers in certain conditions is understood. However, we do not believe this should preclude them from addressing the needs of smaller patient populations suffering extreme symptoms where efficacy has been demonstrated.	Thank you for your comments. The reason that no population level recommendations were made was because of a lack of high-quality evidence. The research recommendations were therefore made with the aim of improving the evidence base to help inform recommendations in future updates. NICE makes an independent consideration of both the clinical and cost effectiveness of cannabis-based medicinal products and recommendations were made on a whole population basis. Clinicians can still make their own individual prescribing decisions in the best interest of their patients.
Almirall Ltd	Guideline	15	12	Almirall understand that NICE have conducted a NMA of 4 separate trials of Sativex and synthesised the results to arrive at an effect size. The studies appear to be highly heterogeneous and there is an associated risk of bias. It is our understanding that 2 of the trials used had a 4 week trial period before randomisation and 2 of the trials did not. The different trial designs would normally be considered a barrier to evidence synthesis in a NMA. A better approach would have been to use the most recent / robust RCT as a base case and explore other RCT effect size inputs as scenario analyses. As described above in the comment regarding the NMA and trial design, the SMPC for Sativex includes a 4 week run in period to check for response with only responding patients continuing treatment. It is not clear from the guidance document nor from the Evidence Review Document C whether this requirement was modelled, and how this was accounted for in the placebo arm analysis. The model also seems to include patients who do not respond but who continue on treatment (10%) – this is outside the SMPC recommendation.	Thanks for your comments. No network meta-analysis (NMA) was conducted for this question; rather, RCTs comparing THC:CBD spray were combined in pairwise meta-analyses. The enriched enrolment trials were highlighted in the forest plots (see spasticity evidence review) and brought to the attention of the committee. This was not to dismiss the evidence but to generate discussion over the methods which are different to a traditional RCT. While there was discussion over the potential for these studies to overestimate the treatment effect, it was also argued, as you suggest, that this trial design better reflects clinical practice. As a result, these findings were still considered as a part of the evidence base and helped to form the committee's opinion that THC:CBD spray appears to have benefits for people with spasticity. It is notable that, despite some a priori grounds for suspecting heterogeneity of effect between trials of different design, there was no evidence that results were statistically different between enriched-enrolment and conventional RCTs for any outcome (see 'test for subgroup differences' in each forest plot – appendix F). The decision not to recommend THC:CBD spray was therefore made based on lack of cost-effectiveness rather than questions over clinical effectiveness or trial design. We acknowledged the limitations of the heterogeneity of the 4 RCTs. Hence, the economic analysis reported sensitivity analysis which tested different treatment effects (ORs), such as pooled OR from two enriched trials only and pooled OR from two non-enriched trials only. As explained in the 'model structure' section of appendix M, the initial cycle of the economic model simulates the 4-week run-in phase that is used in clinical practice. Patients enter the model before trying THC: CBD spray and then receive treatment for 4 weeks. Most non-responders are assumed to discontinue treatment; however, the model allows a small proportion of patients to continue treatment as the trials on which its estimate of response is based had more restrictive response criteria (30% improvement) than the 20% improvement criteria specified within SPC. The model included the publicly available discount scheme offered by the manufacturer of THC: CBD spray (Sativex) to the NHS. The treatment is free for the first three vials, but the NHS pays for responders after that. The indication for responders is 20% improvement in NRS spasticity rather than the 30% improvement criteria used in the clinical trials. The committee advised that, in practice, THC: CBD spray 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. It is unclear whether the 10% adjustment produces an under

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					or over-estimate of the true cost-effectiveness of THC: CBD spray. We have tested this parameter in the sensitivity analysis and reported in Appendix M of the spasticity evidence review.
Almirall Ltd	Guideline	15	13 to 17	Almirall understand that resource use which informed the model and ICER was estimated from a single study. From this they assume that 25% of the resource use cost is spasticity-specific. Almirall are concerned that this is an over-simplified approach which might significantly underestimate the associated cost of spasticity in MS and change the ICER. We would have expected an approach which explored risk ratios of moving between health states for MS spasticity and the true costs of each health state being carefully determined.	Thank you for your comments. Based on committee consensus, the committee agreed that the resource use estimated in Stevenson et al. 2015 cannot be said to be 100% attributable to spasticity alone. The committee felt that the vignette from the health care professional survey could be misleading as it explicitly stated that the disability described in the health states was caused by spasticity only. The committee agreed that some of the physical disability specified in the vignette, particularly in the most severe health states, would have involved multiple other features of the underlying MS. Based on published evidence and the committee's experience, the committee does not think treating spasticity would have a major impact on underlying disability associated with MS (measured by EDSS). Therefore, the committee concluded that Stevenson et al. 2015 overestimated the amount of resource use that is solely attributable to medically modifiable spasticity. However, the committee was sensitive to comments such as this, and did not want to underestimate the possible benefits of THC:CBD spray. Therefore, the committee made a consensus to change this parameter to 50%. The committee agreed that this parameter is highly uncertain, and it should be tested in the sensitivity analysis. This parameter has been modified in the model, tested extensively and reported in the spasticity evidence review chapter (Table 23). When doubling the background management costs (assuming 100% of costs from Stevenson et al. 2015 are attributable to spasticity alone), the cannabis strategy became dominant. When halving the background management costs (assuming 25% of costs are related to spasticity), the ICER is around £35,000. The modelling approach you propose would be attractive if any data were available for either the effectiveness of THC:CBD spray in influencing transit between spasticity health states or for the resource use independently associated with any such health states. As no such data are available, the model structure adopted made use of best-available evidence regarding the effectiveness of THC:CBD spray and the resource use associated with spasticity.
Almirall Ltd	Guideline	5	4	Almirall is concerned that the recommendation regarding THC:CBD spray (Sativex) is based on the outputs of a HE analysis which is less robust that we would have expected – see comments below	Thank you for your comment. We have responded to your comments separately.
Association of British Neurologists	Evidence Review D	21	31 +	We agree with the evaluation outcome, in particular the observation that data are sparse and that there is a need for more research in severe treatment-resistant epilepsy. Importantly, the recommendation leaves open the door for more research. The thorough review of the area from NICE should be of value to companies who wish to have their products properly evaluated.	Thank you for your comments and support for this guideline.
Association of British Neurologists	Evidence Review D	7	Table 1	Under 'Outcomes' "Proportion of patients achieving seizure freedom (50% or greater seizure reduction)" is misinterpretation or misinterpretable: seizure freedom is not the same as 50% or greater reduction – it is only seizure freedom	Thank you for your comment. The committee defined seizure freedom as 50% or greater reduction in seizures. The PICO table and review protocol have been amended to provide further clarification of the outcomes.
Association of British Neurologists	General	General	General	We completely agree with the guideline recommendation for chronic pain, as well as the specific points raised regarding future research needed regarding the use of cannabis based medicinal products in fibromyalgia and treatment resistant neuropathic pain. In summary this document aligns with our understanding of the evidence base and I think is a helpful guideline in relation to chronic pain.	Thank you for your comment.
Aurora Cannabis Inc	Guideline	13	17	**Harm Reduction:** The draft guidelines state that evidence does not show a reduction in opioid use in people prescribed CBMPs. However, there is a growing body of evidence showing that CBMPs could be used as a replacement for opioids prescribed for pain management. Note the use of 'medical cannabis' or 'medical marijuana' in this section is reflective of the studies referenced. One study examined opioid prescriptions and daily dosage in chronic pain patients on opioids who also began medical cannabis (n=37) versus chronic pain patients only on opioids (n=29)	Thank you for your comment. Our systematic review of RCTs found that the outcomes for opioid usage were not statistically significant.

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				and found cannabis use resulted in 40.5% of patients stopping opioid use, 83.5% reducing their daily opioid dosage and an overall reduction in mean prescribed daily opioid dosage. Please see: Vigil JM, Stith SS, Adams IM, et al. Associations Between Medical Cannabis and Prescription Opioid Use in Chronic Pain Patients: A Preliminary Cohort Study. Vrana KE, ed. PLoS One. 2017;12(11):e0187795. A retrospective study of 244 patients who used a medical cannabis dispensary found cannabis use resulted in a 64% reduction in opioid use, a decrease in the side effects from other prescribed medications and an overall improvement of their quality of life. Please see: -Boehnke KF, Litinas E, Clauw DJ. Medical Cannabis Use Is Associated with Decreased Opiate Medication Use in a Retrospective Cross-Sectional Survey of Patients with Chronic Pain. J Pain. 2016;17(6):739-744. Data collected from the USA show opioid related mortality and addiction rates are reduced in states with medical cannabis policies in comparison to states who do not have medical cannabis policies. For instance, drivers fatally injured between the ages of 21 and 40 years old in states prior to their operational medical marijuana laws had greater odds of opioid positivity than drivers of the same age in states with active medical marijuana laws. Additionally, the presence of medical marijuana policies reduced hospitalizations due to opioid dependence or abuse by 13% and opioid related overdoses by 11% while there was no significant associations with hospitalizations due to marijuana dependence or abuse. Please see: -Bachhuber MA, Saloner B, Cunningham CO, et al. Medical Cannabis Laws and Opioid Analgesic Overdose Mortality in the United States. JAMA intern med. 2014;174(10):1668-1673. -Shi Y. Medical Marijuana Policies and Hospitalizations Related to Marijuana and Opioid Pain Reliever. Drug Alcohol Depend. 2017;173:144-150. -Kim JH, Santaella-Tenorio J, Mauro C, et al. State Medical Marijuana Laws and the Prevalence of Opioids Detected Among Fatally Injured Drivers. Am J Public Health. 2016;106(11):2032-2037. While the studies above show evidence that CBMPs may have a role in opioid sparing, a prospective study found that this was not the case. In a study of individuals with chronic, non-cancer pain who were prescribed opioids and also using CBMPs there was no evidence that CBMPs improved patient outcomes. CBMP use did not lead to opioid sparing or pain reduction, with patients using CBMPs reporting greater pain and lower self-efficacy in managing their pain versus patients who did not use it. However, this study was conducted in Australia where cannabis was still illegal and may have introduced a bias. As the authors suggested, perhaps patients with the highest pain severity were the individuals seeking out an illegal substance and their pain would have been worse without CBMPs. Please see: -Campbell G, Hall WD, Peacock A, et al. Effect of Cannabis Use in People with Chronic Non-cancer Pain Prescribed Opioids: Findings from a 4-year Prospective Cohort Study. Lancet Public Heal. 2018;3(7):e341-e350. Future work is required to examine the potential of prescribing CBMPs as a means to reduce the use of other pharmaceuticals, such as opioids.	Thank you for this reference. We have checked this paper against our inclusion criteria and this paper has been excluded as it is not an RCT. Thank you for this reference. We have checked this paper against our inclusion criteria and this paper has been excluded as it is not an RCT. Thank you for providing these references. We have checked these references and they have been excluded as they are outside the scope of this guideline.

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					Thank you for this reference. We have checked this paper against our inclusion criteria and this paper has been excluded as it is not an RCT.
Aurora Cannabis Inc	Guideline	4	3	**Nausea** We believe that future research will be needed in reference to CBMPs and the treatment of Nausea. While the evidence for CBMPs derived from cannabis plants in treating nausea is currently limited, it is an area of active research with some emerging positive findings. One systematic review (n=>10,000 abstracts) found conclusive or substantial evidence of efficacy for cannabis-based therapies in treating chemotherapy-induced nausea and vomiting. Furthermore, Sativex® as an adjunct therapy, has been shown to provide symptomatic relief of chemotherapy-induced nausea and vomiting in 71% of patients in comparison to 22% of patients receiving the placebo. However, a different systematic review (n=79 randomly controlled trials) found low-quality evidence of benefit for cannabinoid therapies in treating nausea and vomiting due to chemotherapy. Thus, further investigation is required, and we ask that NICE consider these additional publications in their review as well as any new scientific publications as ongoing studies conclude and report their findings on the efficacy of CBMPs derived from cannabis plants in treating nausea. The results of these studies can be found here: -Duran M, Pérez E, Abanades S, et al. Preliminary Efficacy and Safety of an Oromucosal Standardized Cannabis Extract in Chemotherapy-Induced Nausea and Vomiting. Br J Clin Pharmacol. 2010;70(5):656-663. -United States of America's National Academies of Sciences E and M. The Health Effects of Cannabis and Cannabinoids : The Current State of Evidence and Recommendations for Research.; 2017. -Whiting PFP, Wolff RRFR, Deshpande S, et al. Cannabinoids for Medical Use A Systematic Review and Meta-analysis. JAMA - J Am Med Assoc. 2015;313(24):2456-2473.	Thank you for your comment. This guidance considered the highest quality research available on CBMPs for intractable nausea and vomiting. The committee recommended the use of nabilone as an add-on treatment for adults with chemotherapy-induced nausea and vomiting which persists with optimised conventional antiemetics. The committee also made research recommendations to improve the evidence base. Duran 2010 was reviewed in full and excluded as participants in the trial received different standard antiemetic therapies. Relevant articles from systematic reviews were assessed for inclusion. Consensus based guidance were not included in this review.
Aurora Cannabis Inc	Guideline	4	11	**Chronic Pain** The draft guidelines recommend to not offer nabilone, dronabinol, THC, CBD, or a combination of THC and CBD to treat chronic pain. However, we would like to draw attention to some of the current scientific evidence that shows CBMPs have been effective in treating and managing chronic pain. There is evidence from clinical studies that CBD and THC alone as well as in combination may be effective in treating neuropathic and chronic pain. A systematic review (n=79) encompassing randomized controlled trials found moderate-quality evidence of benefit for CBMPs in treating chronic neuropathic pain and cancer pain, while a second systematic review (n=>10,000 abstracts) found conclusive or substantial evidence of efficacy for CBMPs in treating chronic pain. Furthermore, the most common medical condition for which patients in the United States of America report using medical cannabis is chronic pain. Please see: -United States of America's National Academies of Sciences E and M. The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research.; 2017. -Whiting PFP, Wolff RRFR, Deshpande S, et al. Cannabinoids for Medical Use A Systematic Review and Meta-analysis. JAMA - J Am Med Assoc. 2015;313(24):2456-2473. -Boehnke KF, Gangopadhyay S, Clauw DJ, et al. Qualifying Conditions of Medical Cannabis License Holders in The United States. Health Aff (Millwood). 2019;38(2):295-302.	Thank you for your comment. You are correct that the data favours some types of medicinal cannabis for managing chronic pain compared to placebo. However, although this reaches statistical significance, the effect size is so small that individual people are unlikely to notice any difference. For example, pain intensity is measured on a scale of 0 to 10, 0 being no pain and 10 being maximum pain. In order for a person to notice any difference, analgesia should reduce pain intensity by 2 or even 3 points. Most pain intensity effect sizes were either statistically insignificant (oral delta-9-THC, oromucosal THC, vaporised THC (minimal CBD), vaporised THC:CBD, vaporised CBD (minimal THC)), or they caused less than a 2 point pain intensity drop (oromucosal CBD:THC) or the 95% confidence interval crossed the 2 point pain intensity drop threshold (oral nabilone). The cost of medicinal cannabis is around 6 times greater than the NHS would normally deem an efficient use of resources. Thank you for providing these references which we have checked against our review protocols. These papers did not meet the inclusion criteria (as they are non-intervention studies) and therefore have not been considered.

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				Additionally, a recent analysis of patient intake data collected from 33 cannabis clinics in Canada between April 2014 and June 2016 found that 66% of new patients were prescribed medical cannabis products to treat chronic general pain or musculoskeletal pain. Please see: Eurich DT, Hanlon JG, Boisvenue JJ, et al. A Description of the Medical Cannabis Use in Ontario, Canada. Cannabis Cannabinoid Res. 2019;x(X):1-5. Furthermore, as evidence begins to show efficacy for CBMPs in treating pain, it has been suggested that CBMPs could be used as a replacement for opioids prescribed for pain management, with preliminary evidence supporting this hypothesis. While this is quite early in the assessment of CBMP's role in opioid sparing, it is a promising area of research that is currently being explored. Please see our response for comment #6 (harm reduction) for the current scientific evidence surrounding CBMPs' potential in opioid sparing. Clinical trials (both interventional and observational) examining CBMPs as a therapy for treating pain report mostly positive effects on pain symptoms. These studies have utilized different CBMPs and routes of administration and have examined the efficacy of CBMPs in different pain conditions. Inhaled cannabis (1-8% THC) significantly reduced neuropathic pain in HIV patients, where a significantly greater number of patients achieved clinically meaningful pain relief. Furthermore, pain patients using a Syge® Inhaler with 3.08 ± 0.02 mg THC in a 15.1 ± 0.1 mg cannabis dose found a significant improvement in pain symptoms 20 minutes after inhalation with pain returning around 90 minutes post-inhalation. Please see: -Ellis RJ, Toperoff W, Vaida F, et al. Smoked Medicinal Cannabis for Neuropathic pain in HIV: A Randomized, Crossover Clinical Trial. Neuropsychopharmacology. 2009;34(3):672-680. -Abrams DI, Jay CA, Shade SB, et al. Cannabis in Painful HIV-associated Sensory Neuropathy: A Randomized Placebo-controlled Trial. Neurology. 2007;68(7):515-521. -Eisenberg E, Ogintz M, Almog S. The Pharmacokinetics, Efficacy, Safety, and Ease of Use of a Novel Portable Metered-Dose Cannabis Inhaler in Patients With Chronic Neuropathic Pain: A Phase 1a Study. J Pain Palliat Care Pharmacother. 2014;28(3):216-225. CanniMed by Aurora® has also provided cannabis for two pain-related clinical trials: a chronic non-cancer pain trial (median daily dose of 2.5 g/day of 12.5% THC; administered orally and/or inhaled based on patient preference) and a chronic neuropathic pain trial (25 mg of 9.4% THC; inhaled). Both of these trials have shown that cannabis use significantly improves pain symptoms, sleep, and overall quality of life in patients suffering from chronic pain. In the chronic, non-cancer pain trial, cannabis treatment also significantly reduced the sensory components of pain (tension-anxiety and depression-dejection). Please see: -Ware MA, Wang T, Shapiro S, et al. Cannabis for the Management of Pain: Assessment of Safety Study (COMPASS). J Pain. 2015;16(12):1233-1242. -Ware MA, Wang T, Shapiro S, et al. Smoked Cannabis for Chronic Neuropathic Pain: A Randomized Controlled Trial. CMAJ. 2010;182(14):E694-701. Real world data from chronic pain patients (n=800) who used Sativex® for 12 weeks found that Sativex® (7.1 ± 1.4 sprays per day by week 9) provided significant pain intensity relief for patients suffering from neuropathic chronic pain and mixed pain. However, it was not effective and/or worsened pain symptoms in patients with nociceptive pain. Additionally, 76.1% of neuropathic pain patients, 24.1% of mixed pain and 1.9% of nociceptive pain patients reported their lives were much better or very much better. Interestingly, no statistically important correlation was determined between the number of sprays and treatment response. Thus, Sativex® appears to be significantly less effective at relieving the symptoms of nociceptive pain than neuropathic and/or mixed pain. This data indicates Sativex® can be	Thank you for providing these references. These studies investigated smoked medicinal cannabis and HIV which are outside of the scope for this guideline. Thank you for providing these references which we have checked against our review protocols. These papers did not meet the inclusion criteria (as they were smoked cannabis trials) and therefore are beyond the scope of the guideline.

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				efficacious in treating certain types of chronic pain, specifically, chronic neuropathic pain. As scientific evidence was collected up until December 2018 for the drafting of the guidelines, Ueberall et al would not haven initially been included in the review of the literature. Furthermore, Health Canada has approved Sativex® as an adjunct therapy to treat pain in adult patients with advanced cancer who experience moderate to severe pain during the highest tolerated dose of strong opioids, as well as an adjunct therapy to treat spasticity and neuropathic pain in adult patients suffering from multiple sclerosis. Thus, we recommend that NICE further explore the scientific evidence surrounding CBMPs in treating pain and consider changing their recommendations before publishing these guidelines. It is worth noting that there are different types of chronic pain, and CBMPs have been shown to be more effective for neuropathic pain than nociceptive pain (as noted above). Because neuropathic pain has limited effective treatment options, CBMPs may be efficacious in the management of this type of chronic pain. Please see: -Ueberall MA, Essner U, Mueller-Schwefe GH. Effectiveness and Tolerability of THC:CBD Oromucosal Spray as add-on Measure in Patients with Severe Chronic Pain: Analysis of 12-week Open-label Real-world Data Provided by the German Pain e-Registry. J Pain Res. 2019;12:1577-1604. - Rog D, Nurmikko T, Young C. Oromucosal Δ9-tetrahydrocannabinol/Cannabidiol for Neuropathic Pain Associated with Multiple Sclerosis: An Uncontrolled, Open-label, 2-year Extension Trial. Clin Ther. 2007;29(9):2068-2079. - Fact sheet - Sativex (Tetranabinex and Nabidiolex) - Canada.ca. Found here: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/notice-compliance/conditions/fact-sheet-sativex.html	Thank you for providing these references. We have considered these: Ueberall et al (2019) doesn't meet our protocol inclusion criteria as it is not an RCT but a retrospective cohort study of patients. The study also does not include a comparison with a placebo. Rog et al 2005 was included and considered in evidence review B however Rog et al 2007 was excluded as placebo was not the comparator.
Aurora Cannabis Inc	Guideline	5	3	**Spasticity** The draft guidelines recommend not offering THC:CBD spray (Sativex®) to treat spasticity in individuals with multiple sclerosis (MS), as it is not effective at its list price. Furthermore, the only time that any CBMPs are recommended are if they are part of a clinical trial. We believe there is a moderate amount of strong evidence related to CBMPs' positive effect on spasticity that is in contrast to these recommendations. **Sativex® and Multiple Sclerosis** MS is a central nervous system autoimmune disease that leads to symptoms such as spasticity, weakness, pain, fatigue, lack of coordination, cognitive impairment and altered mood. There is currently no cure for MS, although there are treatment options to mitigate disease symptoms. There is evidence Sativex® may be efficacious in treating several MS-related symptoms.	After publication of the consultation draft of the guideline, the manufacturer reduced the list price of THC:CBD spray, and this had an important impact on our assessment of its cost effectiveness. In light of stakeholder comments, the committee also reviewed their estimates of likely resource use associated with spasticity symptoms. The committee are now able to make a more positive recommendation.

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				Sativex® has shown efficacy in reducing spasticity, pain, and sleep disturbances in patients with MS. In a systematic review of >10,000 abstracts it was reported that there was found to be conclusive or substantial evidence of efficacy for CBMPs in relieving patient-reported MS spasticity symptoms, though only limited evidence for reducing clinician-measured MS spasticity symptoms. Additionally, a systematic review encompassing 79 randomized controlled trials found moderate-quality evidence of benefit for CBMPs in treating MS spasticity symptoms. Please see: -Rog D, Nurmikko T, Young C. Oromucosal Δ9-tetrahydrocannabinol/Cannabidiol for Neuropathic Pain Associated with Multiple Sclerosis: An Uncontrolled, Open-label, 2-year Extension Trial. Clin Ther. 2007;29(9):2068-2079. - Wade DT, Collin C, Stott C, et al. Meta-analysis of the Efficacy and Safety of Sativex (nabiximols), on Spasticity in People with Multiple Sclerosis. Mult Scler. 2010;16(6):707-714. - Markovà J, Essner U, Akmaz B, et al. Sativex® as Add-on Therapy Vs. Further Optimized First-line Antispastics (SAVANT) in Resistant Multiple Sclerosis Spasticity: A Double-blind, Placebo-controlled Randomised Clinical Trial. Int J Neurosci. May 2018:1-28. -Rog DJ, Nurmikko TJ, Friede T, et al. Randomized, Controlled Trial of Cannabis-based Medicine in Central Pain in Multiple Sclerosis. Neurology. 2005;65(6):812-819. -Wade DT, Makela P, Robson P, et al. Do Cannabis-based Medicinal Extracts have General or Specific Effects on Symptoms in Multiple Sclerosis? A Double-blind, Randomized, Placebo-controlled Study on 160 Patients. Mult Scler J. 2004;10(4):434-441. -United States of America's National Academies of Sciences E and M. The Health Effects of Cannabis and Cannabinoids : The Current State of Evidence and Recommendations for Research.; 2017. - Whiting PFP, Wolff RRFR, Deshpande S, et al. Cannabinoids for Medical Use A Systematic Review and Meta-analysis. JAMA - J Am Med Assoc. 2015;313(24):2456-2473. Sativex® is currently available in 25 countries around the world (including Canada, New Zealand, Australia, many EU countries and the UK) as an adjunct therapy to treat spasticity and neuropathic pain in adult patients with MS and/or chronic pain. The draft NICE guidelines would conflict with the current approval of Sativex® in the UK for use in treating severe spasticity unresponsive to other anti-spasticity medications in patients with MS. We recommend NICE alter their recommended guidelines prior to publishing to allow for the use of CBMPs, such as Sativex®, as adjunct therapies in patients with MS who have failed to respond to other anti-spasticity medications. If the guidelines are not willing to recommend Sativex® based solely on its cost effectiveness at list price, other CBMPs should be considered, as their costs vary from Sativex®. Further exploration is also needed to determine how patients receive fair access to CBMPs for reasonable prices (or subsidized prices) for medical conditions where there is sufficient evidence.	
Aurora Cannabis Inc	Guideline	5	10	**CBMPs and Epilepsy** Epilepsy is one of the most common neurological conditions worldwide and can affect all ages. It is a chronic condition that is characterized by recurrent seizures involving involuntary movement of either parts or the entire body and possibly induces loss of consciousness and control of bowel or bladder function. People with epilepsy are 3-fold more likely to die prematurely than the general population. Paediatric patients suffering from prolonged seizures are at risk for lifelong developmental and intellectual delays. Please see: Lattanzi S, Brigo F, Trinka E, et al. Efficacy and Safety of Cannabidiol in Epilepsy: A Systematic Review and Meta-Analysis. Drugs. 2018;78(17):1791-1804. In particular, there have been approximately 20 publications from interventional and observational clinical studies, as well as post-trial open label expanded access programs in patients with severe, treatment-resistant epilepsy (eg, Dravet Syndrome and Lennox-Gastaut	Thank you for your comments. In relation to the studies on Lennox-Gastaut and Dravet syndrome, we were unable to make recommendations on the use of epidiolex for these conditions because they were under review by our technology appraisals committee and as such were out of scope of this guideline. Publication of the technology appraisal guidance is expected in December 2019. The only evidence found for the use of CBMP in the treatment of these conditions was on epidiolex. We included evidence from a number of observational studies within our review but the committee were concerned that these were low quality studies which did not include any control groups. The committee appreciated that some people have shown benefits from the use of cannabis-based medicinal products and so they did not make a recommendation against their use. However, they did not feel that current evidence was sufficient to confidently recommend their use either. Although the committee did not make a recommendation for the use of cannabis-based medicinal products they did make research recommendations to investigate the effectiveness of CBD and of CBD:THC for the treatment

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				Syndrome), investigating the effect of CBD in reducing seizure frequency and severity. In all, these clinical trials have shown CBD to have potential therapeutic benefits for the treatment of severe epilepsy with tolerable side effect profiles (most commonly, adverse events were rated as mild-moderate). These studies and their results are in direct opposition to the guidelines excluding CBD for the treatment of severe treatment-resistant epilepsy. We believe NICE should not limit the evidence reviewed strictly to the population of the UK, as the evidence found in other populations can help inform NICE's decisions related to these guidelines. Please see: - Devinsky O, Marsh E, Friedman D, et al. Cannabidiol in Patients with Treatment-resistant Epilepsy: An Open-label Interventional Trial. Lancet Neurol. 2016;15(3):270-278. -Geffrey AL, Pollack SF, Bruno PL, et al. Drug-drug Interaction Between Clobazam and Cannabidiol in Children with Refractory Epilepsy. Epilepsia. 2015;56(8):1246-1251. -Sands TTT, Rahdari S, Oldham MSS, et al. Long-Term Safety, Tolerability, and Efficacy of Cannabidiol in Children with Refractory Epilepsy: Results from an Expanded Access Program in the US. CNS Drugs. 2019;33(1):47-60. -Lattanzi S, Brigo F, Trinka E, et al. Efficacy and Safety of Cannabidiol in Epilepsy: A Systematic Review and Meta-Analysis. Drugs. 2018;78(17):1791-1804. -Szaflarski JP, Bebin EM, Comi AM, et al. Long-term Safety and Treatment Effects of Cannabidiol in Children and Adults with Treatment-Resistant Epilepsies: Expanded Access Program Results. Epilepsia. 2018;59(8):1540-1548. -Szaflarski JP, Bebin EM, Cutter G, et al. Cannabidiol Improves Frequency and Severity of Seizures and Reduces Adverse Events in an Open-label Add-on Prospective Study. Epilepsy Behav. 2018;87:131-136. -Laux LC, Bebin EM, Checketts D, et al. Long-term Safety and Efficacy of Cannabidiol in Children and Adults with Treatment-resistant Lennox-Gastaut Syndrome or Dravet Syndrome: Expanded Access Program Results. Epilepsy Res. 2019;154:13-20. -Szaflarski JP, Hernando K, Bebin EM, et al. Higher Cannabidiol Plasma Levels are Associated with Better Seizure Response Following Treatment with a Pharmaceutical Grade Cannabidiol. Epilepsy Behav. 2019;95:131-136. -Huntsman RJ, Tang-Wai R, Alcorn J, et al. Dosage Related Efficacy and Tolerability of Cannabidiol in Children with Treatment-Resistant Epileptic Encephalopathy: Preliminary Results of the CARE-E Study. Front Neurol. 2019;10:716. - Pietrafusa N, Ferretti A, Trivisano M, et al. Purified Cannabidiol for Treatment of Refractory Epilepsies in Pediatric Patients with Developmental and Epileptic Encephalopathy. Pediatr Drugs. 2019;(0123456789). - Devinsky O, Patel AD, Cross JH, et al. Effect of Cannabidiol on Drop Seizures in the Lennox–Gastaut Syndrome. N Engl J Med. 2018;378(20):1888-1897. -McCoy B, Wang L, Zak M, et al. A Prospective Open-label Trial of a CBD/THC Cannabis Oil in Dravet Syndrome. Ann Clin Transl Neurol. 2018;5(9):1077-1088. -Devinsky O, Nabbout R, Miller I, et al. Long-term Cannabidiol Treatment in Patients with Dravet Syndrome: An Open-label Extension Trial. Epilepsia. 2019;60(2):294-302. -Thiele E, Marsh E, Beldzinska-Mazurkiewicz M, et al. Cannabidiol in Patients with Lennox-Gastaut Syndrome: Interim Analysis of an Open-Label Extension Study. Epilepsia. 2019;60(3):419-428. -Gaston TE, Szaflarski M, Hansen B, et al. Quality of Life in Adults Enrolled in an Open-label Study of Cannabidiol (CBD) for Treatment-resistant Epilepsy. Epilepsy Behav. 2019;95:10-17. -Gaston TE, Bebin EM, Cutter GR, et al. Interactions Between Cannabidiol and Commonly Used Antiepileptic Drugs. Epilepsia. 2017;58(9):1586-1592. -Martin RC, Gaston TE, Thompson M, et al. Cognitive Functioning Following Long-term Cannabidiol Use in Adults with Treatment-resistant Epilepsy. Epilepsy Behav. 2019;97:105-110.	of epilepsy. These research recommendations are aimed at improving the quality of evidence so that future committees will be able to make more evidence-based decisions on the use of cannabis-based medicinal products. Thank you for providing these references. We have checked these against our protocol inclusion criteria: Devinsky et al 2016 – was included in the review in appendix K, single arm observational studies Geffrey et al 2015 – was excluded as the trial studies drug-druginteractions Sands et al 2019 - was included in the review in appendix K, single arm observational studies Lattanzi et al (2018 – was a review article and therefore was not included. The bibliography was reviewed for possible includes Szaflarski et al 2018 - was included in the review in appendix K, single arm observational studies Laux et al 2019 - was published in March 2019 and our evidence review literature searches were carried out in December 2018 – January 2019. This paper will be considered in any future update of this guideline. Szaflarski et al 2019 - was published in June 2019 and our evidence review literature searches were carried out in December 2018 – January 2019. This paper will be considered in any future update of this guideline Huntsman et al 2019 - was published in July 2019 and our evidence review literature searches were carried out in December 2018 – January 2019. This paper will be considered in any future update of this guideline Pietrafusa et al - was published in August 2019 and our evidence review literature searches were carried out in December 2018 – January 2019. This paper will be considered in any future update of this guideline Devinsky et al 2018 – was included in the evidence review McCoy et al 2018 - was included in the review in appendix K, single arm observational studies Devinsky et al 2019 – was published in February 2019 and our evidence review literature searches were carried out in December 2018 – January 2019. This paper will be considered in any future update of this guideline Thiele et al 2019 - was published in March 2019 and our evidence review literature searches were carried out in December 2018 – January 2019. This paper will be considered in any future update of this guideline Gaston et al 2019 - was published in June 2019 and our evidence review literature searches were carried out in December 2018 – January 2019. This paper will be considered in any future update of this guideline Gaston et al 2017 – was excluded as the paper examined drug interactions

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				Anti-epileptic Effects of CBD CBD has been shown to have potent anti-epileptic effects in clinical trials in patients with severe, treatment resistant epilepsy, such as Dravet and Lennox-Gastaut syndromes. Furthermore, CBD has been shown to have a tolerable side effect profile in these clinical trials, with the most common adverse events rated as mild-moderate in severity. In a clinical trial in participants suffering from various epileptic syndromes, an average CBD dose of 11.4 mg/kg a day from a cannabis oil (20:1 CBD:THC) for three months found that 4% of participants became seizure free, 22% of participants experienced a reduction in seizure frequency by 50-75%, and 30% of participants experienced a reduction in seizure frequency by 85-99%, while 43.5% of participants experienced a reduced seizure frequency of <50%. No difference in efficacy of CBD between the different epileptic etiologies was reported, indicating CBD could be an add on anti-epileptic therapy for all types of treatment resistant epilepsies. Supporting this conclusion, in a longer clinical trial of treatment resistant epileptic patients, a median dose of 25 mg/kg CBD a day led to a median monthly convulsive seizure reduction of 51% and a total seizure reduction of 48% by week 12, with this reduction holding steady for up to 96 weeks (median treatment period was 48 weeks). 25 or 50 mg/kg CBD for 12 weeks was also found to reduce 1/3 of motor and overall seizures in treatment resistant epilepsy patients. In an open label expanded access program utilizing Epidiolex® (maximum dose was 50 mg/kg/day) in treatment resistant epilepsy patients, seizure frequency and severity was significantly decreased independently of other anti-epileptics, such as clobazam, rufinamide, topiramate, zonisamide and eslicarbazepine, which the authors concluded indicated no drug-CBD interactions altered the treatment effects in this cohort. However, blood plasma levels of drugs were not collected, and it was noted that clobazam doses were decreased throughout the study period. Importantly, this reduction in seizure frequency and severity remained consistent for 48 weeks. Cognitive function was also examined in a portion of the patients enrolled in this open label expanded access program via assessing cognitive function at baseline and at a 1-year mark. Martin et al found no significant changes in cognitive function nor any correlation between cognitive function and CBD dosage or between cognitive function and seizure severity after 1 year of Epidiolex® use. Please see: -Hausman-Kedem M, Menascu S, Kramer U. Efficacy of CBD-enriched Medical Cannabis for Treatment of Refractory Epilepsy in Children and Adolescents - An Observational, Longitudinal Study. Brain Dev. 2018;40(7):544-551. - Szaflarski JP, Bebin EM, Comi AM, et al. Long-term Safety and Treatment Effects of Cannabidiol in Children and Adults with Treatment-Resistant Epilepsies: Expanded Access Program Results. Epilepsia. 2018;59(8):1540-1548. - Devinsky O, Marsh E, Friedman D, et al. Cannabidiol in Patients with Treatment-resistant Epilepsy: an Open-label Interventional Trial. Lancet Neurol. 2016;15(3):270-278. - Gaston TE, Bebin EM, Cutter GR, et al. Drug–drug Interactions with Cannabidiol (CBD) Appear to Have no Effect on Treatment Response in an Open-label Expanded Access Program. Epilepsy Behav. 2019;98(Pt A):201-206. - Martin RC, Gaston TE, Thompson M, et al. Cognitive Functioning Following Long-term Cannabidiol Use in Adults with Treatment-resistant Epilepsy. Epilepsy Behav. 2019;97:105-110. In Lennox-Gastaut Syndrome patients over 12-14-week trials, 10 and 20 mg/kg CBD has been found efficacious in reducing drop seizures by about 40%, and overall seizures by 35-50%. Please see: - Devinsky O, Marsh E, Friedman D, et al. Cannabidiol in Patients with Treatment-resistant Epilepsy: An Open-label Interventional Trial. Lancet Neurol. 2016;15(3):270-278.	Martin et al 2019 - was published in August 2019 and our evidence review literature searches were carried out in December 2018 – January 2019. This paper will be considered in any future update of this guideline Hausman-Kedem et al 2018 - was included in the review in appendix K, single arm observational studies

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				- Devinsky O, Patel AD, Cross JH, et al. Effect of Cannabidiol on Drop Seizures in the Lennox–Gastaut Syndrome. N Engl J Med. 2018;378(20):1888-1897 - Thiele EA, Marsh ED, French JA, et al. Cannabidiol in Patients with Seizures Associated with Lennox-Gastaut Syndrome (GWPCARE4): A Randomised, Double-blind, Placebo-controlled Phase 3 Trial. Lancet (London, England). 2018;391(10125):1085-1096. In refractory epileptic patients, CBD as an add on treatment with clobazam reduced seizures more than 50% in 9/13 patients. Interestingly, 10/13 patients were able to reduce their dose of clobazam while still experiencing a 50% reduction in seizures. In another trial examining CBD in refractory epileptic patients, patients who achieved greater than 50% reduction in seizures ranged between 9-15/26 patients over the first 2 years (mean duration of CBD use was 21 months, ranging from 4-53 months) and stabilized at 7/26 patients at 36 months until the end of the trial. Please see: -Geffrey AL, Pollack SF, Bruno PL, et al. Drug-drug Interaction Between Clobazam and Cannabidiol in Children with Refractory Epilepsy. Epilepsia. 2015;56(8):1246-1251. - Sands TT, Rahdari S, Oldham MS, et al. Long-Term Safety, Tolerability, and Efficacy of Cannabidiol in Children with Refractory Epilepsy: Results from an Expanded Access Program in the US. CNS Drugs. 2019;33(1):47-60. In 7 pediatric patients with either Lennox-Gastaut or Dravet Syndrome, CanniMed 1:20 (a product produced at an Aurora Cannabis facility) at a 5-6 mg/kg/day CBD equivalent dose reduced daily seizure frequency >25% in 6 patients, with 4 of these patients experiencing a >50% reduction. At a 10-12 mg/kg/day CBD equivalent dose, CanniMed 1:20 caused a 74% reduction in mean seizure frequency with 3 patients becoming seizure free. Furthermore, 1 patient was seizure free at the 8-9 mg/kg/day CBD equivalent dose. All patients showed improvements in their QOLCE-55 scores, especially in the cognitive, social and emotional function subscales. EEG encephalopathy rating scales increased by 1 point for 5/7 patients, with 1 patient having an increase by 2 points and the final 7th patient showing no improvement as they had had normal ratings at baseline. Patients were weaned off CanniMed 1:20 in the last month of the trial and their reduction in seizure frequency remained consistent, with 3 having continuous improvement, though no other changes to their medications occurred. QOLCE-55 scores did decrease during the weaning period however, they remained greater than baseline. Please see: - Huntsman RJ, Tang-Wai R, Alcorn J, et al. Dosage Related Efficacy and Tolerability of Cannabidiol in Children with Treatment-Resistant Epileptic Encephalopathy: Preliminary Results of the CARE-E Study. Front Neurol. 2019;10:716. Two recently published interim reports from extension-open label trials of Epidiolex in Dravet and Lennox-Gastaut syndrome patients show consistent dosage, efficacy and adverse event profiles when compared to their parent studies over the first 48 weeks of these trials. Dosages between the two extension trials were also comparable, with mean dosages of approximately 22 mg/kg. For the extension trial in Dravet syndrome patients, the reduction in convulsive seizure frequency ranged from 38-44% while total seizure frequency decrease ranged from 39-51%. These values were similar to the ones reported from the ongoing extension trial in Lennox-Gastaut syndrome patients with total drop seizure frequency decrease ranging from 48-60% and total seizure frequency reduction ranging from 48-57%. Please see: -Devinsky O, Nabbout R, Miller I, et al. Long-term Cannabidiol Treatment in Patients with Dravet Syndrome: An Open-label Extension Trial. Epilepsia. 2019;60(2):294-302. -Thiele E, Marsh E, Beldzinska-Mazurkiewicz M, et al. Cannabidiol in Patients with Lennox-Gastaut Syndrome: Interim Analysis of an Open-Label Extension Study. Epilepsia. 2019;60(3):419-428.	

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				In June 2018, Epidiolex (CBD) was approved by the FDA for use in Lennox-Gastaut and Dravet Syndrome patients greater than 2 years old. On 25 July 2019, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product Epidyolex (CBD), intended for the treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome. These developments further show that a growing number of regulatory agencies are comfortable approving CBD for use in treatment-resistant epilepsy. By failing to acknowledge evidence deemed credible by a growing number of international governing bodies, the evidence base contained in the NICE guidelines is insufficient to provide a recommendation on treatment-resistant epilepsy based on the most up to date scientific knowledge. It is recommended that NICE acknowledges the evidence provided in these comments, and revisits evidence outside of that collected for this draft (ie, evidence reported in peer-reviewed literature between December 2018 to present, along with CBMP status granted by other regulatory agencies), before publishing these guidelines. Please see: -Commissioner O of the. Press Announcements - FDA Approves First Drug Comprised of an Active Ingredient Derived from Marijuana to Treat Rare, Severe Forms of Epilepsy.	
Aurora Cannabis Inc	Guideline	6	2	**Prescribing Medical Cannabis** The proposed model asserts that only specialists in those conditions for which CBMPs may have efficacy would have the ability to prescribe CBMPs. This may create problems for those patients who may benefit from CBMPs by impeding their access due to the limited number of proposed prescribers. These problems will only become more prevalent as patients' and physicians' demand for these products increase.	Thank you for your comment. The recommendation about who should prescribe is set out in UK legislation, The Misuse of Drugs (Amendments) (Cannabis and Licence Fees) (England, Wales and Scotland) Regulations 2018, regulation 16A.
Aurora Cannabis Inc	Guideline	6	3	**Who Should Prescribe Medical Cannabis?** Whether a general practitioner/family doctor or a specialist is responsible for determining a patient's suitability for a trial on CBMPs, that doctor must be familiar with the emerging medical cannabis scientific evidence and understand the nuances of utilizing CBMPs as medical therapies. General practitioners/family doctors and specialists may be responsible for the healthcare of a patient using CBMPs, ensuring access to a qualified physician is not a barrier for a patient who could benefit from CBMPs. For instance, in Canada, medical cannabis clinics with general practitioners/family doctors who have expertise in prescribing medical cannabis/CBMPs provide the wider physician community with a place to refer their patients who are interested in using medical cannabis/CBMPs. After the referred patient is assessed in the medical cannabis clinic, the clinic doctor sends a consultation report back to the referring doctor detailing the following: i) if CBPMs were prescribed, ii) the format, iii) the dose, and iv) the patient follow-up plan. The system utilized in Canada has allowed Canadian patients reasonable access to CBMPs, with over 3500 doctors prescribing CBMPs between April 2018 and March 2019 (per Health Canada's latest annual report). With a significant amount of evidence showing the safety of CBMPs and their efficacy in specific medical conditions, Canadian physicians work within a medical regime that allows Canadian citizens the ability to safely use CBMPs. **It is recommended that NICE evaluate the work done by Health Canada when reviewing these guidelines.** Please see: -Government of Canada - Market Data Under the Access to Cannabis for Medical Purposes Regulations. Found here: https://www.canada.ca/en/health-canada/services/drugs-medication/cannabis/licensed-producers/market-data.html -Health Canada - Information for Health Care Professionals: Cannabis (marihuana, marijuana) and the Cannabinoids. Found here: https://www.canada.ca/en/health-	Thank you for your comment. The NICE guideline considered and included international guidelines as part of the evidence review. This included the Canadian guideline. However, the recommendation about who should prescribe is set out in UK legislation, The Misuse of Drugs (Amendments) (Cannabis and Licence Fees) (England, Wales and Scotland) Regulations 2018, regulation 16A which differs from that in Canada.

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				canada/services/drugs-medication/cannabis/information-medical-practitioners/information-health-care-professionals-cannabis-cannabinoids.html	
Aurora Cannabis Inc	Guideline	General	General	Aurora Cannabis Enterprises Inc. has welcomed the opportunity to be part of the NICE consultation on cannabis-based medicinal products (CBMPs), which we hope will be an important step towards the integration of medical cannabis to routine healthcare practice in the UK. Aurora currently manufactures cannabis products that are sold to medical patients both in Canada as well as other countries where there are medical cannabis regulations in place, such as in Europe and Australia. Aurora also has several ongoing clinical trials where our cannabis products are being investigated for the treatment of medical conditions such as epilepsy and pain management in cancer. For Aurora's clinical trials conducted in Canada, the applications are reviewed and approved by Health Canada. We have observed first-hand how our cannabis products have made a positive impact on medical patients in Canada and worldwide. The draft guidance published on 8 August 2019 omits certain aspects from consideration, (in particular, a significant portion of the 2019 scientific literature has not been included) that could have a bearing on the final shape of NICE's guidance. Most importantly, we feel strongly that significant scientific evidence is already in place for NICE to make a positive recommendation for the use of CBMPs for some medical conditions, such as epilepsy. A suspended recommendation will only delay the provision of beneficial and, in some cases lifesaving, medical care for UK patients.	Thank you for your comments. Specific comments have been addressed separately.
Aurora Cannabis Inc	Guideline	General	General	**Cannabis Related Research** There are ongoing discussions amongst researchers, healthcare practitioners, patients, policy makers and regulatory bodies, etc. about the types and amount of scientific data that are required in the CBMP space. As such, research related to CBMPs (especially unlicensed cannabis products) may not be approached the same as research related to traditional single active ingredient pharmaceuticals, particularly around cohort size, patient-reported outcomes and real-world evidence. We advise that further guidelines are drafted with this in mind, and that evidence requirements for certain CBMPs are defined.	Thank you for your comment. The committee considered the clinical and cost effectiveness of licensed and unlicensed CBMPs, however recommendations were not made for unlicensed CBMPs due to a lack of evidence for these products. The review protocols did allow for consideration of observational studies when there were insufficient RCTs Recommendations for further research outline the use of RCTs as they remain the gold standard study design for evaluating clinical effectiveness.
Aurora Cannabis Inc	Guideline	General	General	**Synthetic Cannabinoids versus Phytocannabinoids** Throughout the draft guidelines synthetic cannabinoids (dronabinol and nabilone) and phytocannabinoids (cannabis plant-derived products) are placed in the same category of CBMPs. Both nabilone and dronabinol are laboratory synthesized chemicals, created to have similar actions to THC derived from the cannabis plant. Phytocannabinoid extracts likely have different characteristics when compared to synthetic cannabinoids. As such, the potential differences in efficacy, potency and adverse events of synthetic cannabinoids in comparison to phytocannabinoids should be addressed in the final guidelines. In addition, further definitions of other United States Food and Drug Adminstration (FDA)-approved CBMPs, such as Sativex® [a GW Pharmaceutical product that contains equal concentrations of tetranabinex® (27 mg/mL THC extract) and nabidiolex® (25 mg/mL CBD extract], residual cannabinoids (5%) and other extracted compounds, such as terpenes and flavonoids) and Epidiolex® (GW Pharmaceutical's 100 mg/ml CBD oral solution), should also be included. To date, and to our knowledge, direct comparison of the efficacy and safety of synthetic cannabinoids to phytocannabinoids extracted from cannabis has yet to be scientifically investigated. In November 2018, the WHO Expert Committee on Drug Dependence (ECDD) reviewed its position on cannabis and cannabis-related substances and recommended that cannabis and cannabis resins (i.e. phytocannabinoids) be deleted from Schedule IV while	Thank you for providing this information. This guideline is underpinned by legislation in terms of which cannabis based medicinal products can be considered. Therefore we only considered the following: • cannabis-based medicinal products as defined by the UK Government in November 2018 • the licensed products nabiximols (Sativex) and nabilone. • plant-derived cannabinoids such as pure cannabidiol. • synthetic compounds which are identical in structure to naturally occurring cannabinoids such as delta-9-tetrahydrocannabinol (THC), for example dronabinol. Regarding the comparison of synthetics vs. phytocannabinoids, we could not find any evidence where these were compared. The guideline considered all types of CBMPs. If comparative data was available then the committee would have considered this.

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				continuing to be included as a Schedule I of the 1961 Single Convention on Narcotic Drugs. The committee did not feel cannabis and cannabis resin were associated with the same level of danger (such as a risk of death) as heroin, fentanyl and other opioids and as such recommended removing cannabis and cannabis resin from Schedule IV. While cannabis and cannabis resins were descheduled, the expert committee also recommended that the classification of dronabinol, a synthetic molecule mimicking the phytocannabinoid Δ^9-THC, as well as its stereoisomers, be moved from a Schedule II under the 1971 Convention on Psychotropic Substances to a Schedule I designation under the 1961 Single Convention on Narcotic Drugs. This recommendation moves dronabinol and its stereoisomers from the second most severe scheduling for a psychotropic substance to the least severe scheduling for a narcotic drug. From the Critical Review report compiled by the WHO on CBD, the following conclusions were made: • There are no known case reports of abuse or dependence relating to the use of pure CBD at this time • There are no published statistics on non-medical use of pure CBD at this time • There are reports of unsanctioned medical use of CBD-based products to treat disease conditions and/or symptoms such as epilepsy, cancer, AIDS/HIV, anxiety, arthritis, pain, post-traumatic stress disorder (PTSD) • CBD is currently being used in skin and beauty products like shampoos and cream • There are no public health problems that have been associated with the use of pure CBD at this time • CBD is generally well tolerated with a good safety profile • The CBD reported adverse events may be a result of drug-drug interactions between CBD and other medications In general, the changes in scheduling indicate a shift in understanding of the effects and safety risk of cannabis and CBMPs as more scientific evidence is generated showing tolerable safety profiles and efficacy in different medical conditions. It also highlights the importance in differentiating between the phytocannabinoids (i.e. CBD versus Δ^9-THC) in terms of physiological effects and safety profiles. It is recommended that NICE take into consideration these changes to cannabis and CBMP scheduling by the WHO and further explore and clarify the differences between synthetic cannabinoids and phytocannabinoids, as well as between different phytocannabinoids before publishing final guidelines. In general, clinical trials investigating CBMPs derived from cannabis plants have reported tolerable safety profiles with primarily mild to moderate severity of adverse events. For instance, the most common adverse events reported for CBD extract therapies have been somnolence, diarrhoea and vomiting, and dizziness. Please see the representative studies below: -Sands TTT, Rahdari S, Oldham MSS, et al. Long-Term Safety, Tolerability, and Efficacy of Cannabidiol in Children with Refractory Epilepsy: Results from an Expanded Access Program in the US. CNS Drugs. 2019;33(1):47-60. - Lattanzi S, Brigo F, Trinka E, et al. Efficacy and Safety of Cannabidiol in Epilepsy: A Systematic Review and Meta-Analysis. Drugs. 2018;78(17):1791-1804. - Szaflarski JP, Bebin EM, Comi AM, et al. Long-term Safety and Treatment Effects of Cannabidiol in Children and Adults With Treatment-Resistant Epilepsies: Expanded Access Program Results. Epilepsia. 2018;59(8):1540-1548. -World Health Organization: Expert Committee on Drug Dependence. CANNABIDIOL (CBD) Critical Review Report Expert Committee on Drug Dependence Fortieth Meeting. Cannabidiol Crit Rev Rep. 2018;(June):4-7. WHO. *Annex 1-Extract from the Report of the 41 St Expert Committee on Drug Dependence: Cannabis and Cannabis-Related Substances*.	Thank you for providing these references which we have checked against our review protocols. Sands et al (2019), Szaflarski et al (2018), and Devinsky et al (2016) are included in evidence review D. Lattanzi et al (2018) was considered but excluded from evidence review D as it was a review article, however the bibliography was reviewed for possible includes. The WHO report, Geffrey et al (2015), Laux et al (2019), Schleider et al (2019) and Hoggart et al (2015) were also considered but did not meet our protocol inclusion criteria and were therefore excluded. The reasons for exclusion are outlined as an appendix in the evidence reviews.

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				- Devinsky O, Marsh E, Friedman D, et al. Cannabidiol In Patients With Treatment-resistant Epilepsy: An Open-label Interventional Trial. Lancet Neurol. 2016;15(3):270-278. - Geffrey AL, Pollack SF, Bruno PL, et al. Drug-drug Interaction Between Clobazam and Cannabidiol in Children with Refractory Epilepsy. Epilepsia. 2015;56(8):1246-1251. - Szaflarski JP, Bebin EM, Cutter G, et al. Cannabidiol Improves Frequency and Severity of Seizures and Reduces Adverse Events in an Open-label Add-on Prospective Study. Epilepsy Behav. 2018;87:131-136. -Laux LC, Bebin EM, Checketts D, et al. Long-term safety and efficacy of cannabidiol in children and adults with treatment resistant Lennox-Gastaut syndrome or Dravet syndrome: Expanded Access Program Results. Epilepsy Res. 2019;154:13-20. - Schleider LB-L, Mechoulam R, Saban N, et al. Real Life Experience of Medical Cannabis Treatment in Autism: Analysis of Safety and Efficacy. Sci Reports 2019 91. 2019;9(1):200. - Hoggart B, Ratcliffe S, Ehler E, et al. A Multicentre, Open-label, Follow-on Study to Assess the Long-term Maintenance of Effect, Tolerance and Safety of THC/CBD Oromucosal Spray in the Management of Neuropathic Pain. J Neurol. 2015;262(1):27-40.	
Bayer plc	Evidence Review C	12		THC:CBD Oromucosal Spray is indicated as treatment for symptom improvement in adult patients with moderate to severe spasticity due to multiple sclerosis (MS) who have not responded adequately to other anti-spasticity medication and who demonstrate clinically significant improvement in spasticity related symptoms during an initial trial of therapy.[1] It should be made clear that THC:CBD Oromucosal Spray does not have a marketing authorisation for central neuropathic pain using the wording as outlined in the NICE guidelines manual.[2] 1. GW Pharma Ltd. Summary of Product Characteristics - Sativex Oromucosal Spray. Last updated: 24/08/2018. Last accessed: 22/08/2019. Available from: https://www.medicines.org.uk/emc/product/602. 2. National Institute for Health and Care Excellence. Developing NICE guidelines: the manual. Last updated: 10/2018. Last accessed: 02/09/2019. Available from: https://www.nice.org.uk/process/pmg20.	Thank you for your comments. An explanation that Sativex does not currently have marketing authorisation for motor neurone disease or spinal cord injury has now been added to the introduction of the evidence review (in the Interventions section).
Bayer plc	Evidence Review C	153		THC:CBD Oromucosal Spray is indicated as treatment for symptom improvement in adult patients with moderate to severe spasticity due to multiple sclerosis (MS) who have not responded adequately to other anti-spasticity medication and who demonstrate clinically significant improvement in spasticity related symptoms during an initial trial of therapy.[1] It should be made clear that THC:CBD Oromucosal Spray does not have a marketing authorisation for motor neurone disease using the wording as outlined in the NICE guidelines manual.[2] 1. GW Pharma Ltd. Summary of Product Characteristics - Sativex Oromucosal Spray. Last updated: 24/08/2018. Last accessed: 22/08/2019. Available from: https://www.medicines.org.uk/emc/product/602. 2. National Institute for Health and Care Excellence. Developing NICE guidelines: the manual. Last updated: 10/2018. Last accessed: 02/09/2019. Available from: https://www.nice.org.uk/process/pmg20.	Thank you for your comments. An explanation that Sativex does not currently have marketing authorisation for motor neurone disease or spinal cord injury has now been added to the introduction of the evidence review (in the Interventions section).
Bayer plc	Evidence Review C	185	10-12	The mean dose of Sativex used in the model was based on Italian registry data, which reported a mean 6.8 sprays per day.[1] However, an observational post-marketing safety registry[2] that contains data on 941 patients of which 761 (80.9%) are from the UK has been published which provides the daily dose information for 798 patients (85%). This gives a mean figure of 5.4 (SD 4.9). We suggest that this would be a more representative data source of UK clinical practice than the Italian observational study and should form the base case for this model input. It is also more appropriate as it represents the actual cost incurred by the NHS in the UK. 1. S. Messina, et al. Sativex in resistant multiple sclerosis spasticity: Discontinuation study in a large population of Italian patients (SA.FE. study). 2017;12(8):e0180651.	Thank you for your comments. The committee reviewed different published doses of THC: CBD spray (Sativex). The mean THC:CBD spray dose from RCTs is around 7–9 sprays per day. The committee agreed that the initial dose would decrease over time and stabilise around 6 months. The committee also noted that the mean initial dose from a dataset of THC:CBD spray 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

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				2. T. Etges, et al. An observational postmarketing safety registry of patients in the UK, Germany, and Switzerland who have been prescribed Sativex® (THC:CBD, nabiximols) oromucosal spray. Therapeutics and clinical risk management. 2016;12:1667-75.	responders decreased over time, similar to the ones reported in the Italian registry by Messina et al. 2017. The committee reviewed the post-marketing study by Etges et al. 2016. While the committee agreed that, all other things being equal, it would prefer to use UK-specific data, it chose to retain its reliance on Messina et al. (2017), for the following reasons: • Etges et al. (2016) reports spasticity of various types, whereas Messina et al. (2017) is solely concerned with confirmed MS-related spasticity. • Etges et al. (2016) relied on voluntary submission of data, whereas Messina et al. (2017) is based on a mandatory regulatory registry, meaning it reflects the whole population of interest, rather than a subset selected according to unknown criteria. • Messina et al. (2017) provide patient-level data on response and continuation rates that are used in the model, whereas Etges et al. (2016) provide no such data. Therefore, using Messina et al. (2017) gives the model the important strength that dosage data and effect data are kept together. • The dosage data reported by Messina et al. (2017) are closer to committee-members' own experience (including their knowledge of unpublished audit data from UK practice). On a balance of these considerations, the committee concluded that, despite comprising mostly UK participants, Etges et al. (2016) provides a less reliable estimate of dosage than Messina et al. (2017). However, the committee noted that the value from Messina et al. (2017) used in the consultation draft (6.8 sprays/day) had been taken from the first period of that study and, in common with other evidence, average dosage had reduced over time. Therefore, it agreed that it was inappropriate to use 6.8 sprays/day throughout the treatment phase of the model, and revised its base case so that the dosage reduced to 6.3 sprays/day from 12 weeks onwards, in reflection of Messina et al.'s findings. The revised model assumes: • For the first 4 weeks, a mean THC: CBD spray dose of 8.55 sprays per day, based on a weighted average of doses observed in the 4 included RCTs. • The mean dose decreases to 6.5 per day by 12 weeks and to 6.3 by 24 weeks (Messina et al., 2017) • Beyond this point, a constant dose of 6.3 sprays/day is assumed. This was tested in the sensitivity analysis. With the new daily THC: CBD spray assumption (decrease over time), the ICER is lower than the scenario assuming a constant daily dose of 6.8 sprays (as shown in Table 23 scenario analyses of the spasticity evidence review). De Trane S, Buchanan K, Keenan L, Valentine C, Liddicut M, Stevenson V, Farrell R. 2016. P1292 Nabiximols has a beneficial effect on self report of MS related spasticity. Multiple Sclerosis Journal 22 (Supp 3), 684. De Trane S, Buchanan K, Keenan L, Simeoni S, O'Brien L, Stevenson V, Farrell R. 2017. P1898 THC: CBD (Nabiximols) has a beneficial effect on resistant MS related spasticity and reduces the need for Intrathecal baclofen. Multiple Sclerosis Journal 23 (Supp 3), 1012–1013. De Trane S, Buchanan K, Keenan L, Valentine C, Liddicut M, Stevenson V, Farrell R. 2017. PO123 THC: CBD (Nabiximols) has a beneficial effect on multiple sclerosis related spasticity and delays the need for intrathecal baclofen. Journal of Neurology, Neurosurgery & Psychiatry 88 (Supp 1), A44.
Bayer plc	Evidence Review C	20	General	THC:CBD Oromucosal Spray is indicated as treatment for symptom improvement in adult patients with moderate to severe spasticity due to multiple sclerosis (MS) who have not responded adequately to other anti-spasticity medication and who demonstrate clinically significant improvement in spasticity related symptoms during an initial trial of therapy.[1] It should be made clear that THC:CBD Oromucosal Spray does not have a marketing	Thank you for your comments. An explanation that Sativex does not currently have marketing authorisation for motor neurone disease or spinal cord injury has now been added to the introduction of the evidence review (in the Interventions section).

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				authorisation for motor neurone disease using the wording as outlined in the NICE guidelines manual.[2] 1. GW Pharma Ltd. Summary of Product Characteristics - Sativex Oromucosal Spray. Last updated: 24/08/2018. Last accessed: 22/08/2019. Available from: https://www.medicines.org.uk/emc/product/602. 2. National Institute for Health and Care Excellence. Developing NICE guidelines: the manual. Last updated: 10/2018. Last accessed: 02/09/2019. Available from: https://www.nice.org.uk/process/pmg20.	
Bayer plc	Evidence Review C	23 174	42-45 18-20 & 25-30	We do not agree that it is appropriate to use the odds ratio derived from this meta-analysis to derive the treatment effect of THC:CBD Oromucosal Spray compared to placebo. We propose that the odds ratio derived from Novotna *et al.* 2011[1] and Markova *et al.* 2019[2] ("THC:CBD Spray within the licensed dose", 4.17) should be used as the base case. The enrichment design of the studies by Novotna *et al.* 2011[1] and Markova *et al.* 2019[2] reflects the licensed use of THC:CBD Oromucosal Spray e.g. only in those *"who demonstrate clinically significant improvement in spasticity related symptoms during an initial trial of therapy,"*[3] and also importantly, is aligned to clinical practice in accordance with the 'pay for responder' rebate scheme. Indeed the MHRA PAR agrees that *"the difference between active and placebo [in the study by Novotna et al 2011[1]] should be a fair reflection of efficacy in the population that will be treated with Sativex in the medium to long term."*[4] The studies by Collin *et al.* 2007[5] and 2010[6] represent a treatment strategy which is not consistent with use in accordance with the SmPC, and whilst the mean daily number of sprays in the active treatment group in these studies was 9.4 and 8.5 respectively and therefore lower than 12 sprays per day, doses as high as 22 sprays per day were administered in the trial by Collin *et al.* 2010,[6] which is outside the licensed indication. The results of these studies are therefore not representative of the use of THC:CBD Oromucosal Spray in UK clinical practice, and should not be used to inform the economic modelling. 1. A. Novotna, et al. A randomized, double-blind, placebo-controlled, parallel-group, enriched-design study of nabiximols* (Sativex®), as add-on therapy, in subjects with refractory spasticity caused by multiple sclerosis. European journal of neurology. 2011;18(9):1122-31. 2. J. Markova, et al. Sativex® as add-on therapy vs. further optimized first-line ANTispastics (SAVANT) in resistant multiple sclerosis spasticity: a double-blind, placebo-controlled randomised clinical trial. The International journal of neuroscience. 2019;129(2):119-28. 3. GW Pharma Ltd. Summary of Product Characteristics - Sativex Oromucosal Spray. Last updated: 24/08/2018. Last accessed: 22/08/2019. Available from: https://www.medicines.org.uk/emc/product/602. 4. Medicines and Healthcare products Regulatory Agency (MHRA). Public Assessment Report. Decentralised Procedure. Sativex Oromucosal Spray. UK/H/2462/01/DC. UK license no: PL 18024/0009. GW Pharma Limited. Last updated: 16/03/2014. Last accessed: 21/08/2019. Available from: http://www.mhra.gov.uk/home/groups/par/documents/websiteresources/con084961.pdf. 5. C. Collin, et al. Randomized controlled trial of cannabis-based medicine in spasticity caused by multiple sclerosis. European journal of neurology. 2007;14(3):290-6. 6. C. Collin, et al. A double-blind, randomized, placebo-controlled, parallel-group study of Sativex, in subjects with symptoms of spasticity due to multiple sclerosis. Neurological research. 2010;32(5):451-9.	Thanks for your comments. No network meta-analysis (NMA) was conducted for this question; rather, RCTs comparing THC:CBD spray were combined in pairwise meta-analyses. The enriched enrolment trials were highlighted in the forest plots (see spasticity evidence review) and brought to the attention of the committee. This was not to dismiss the evidence but to generate discussion over the methods which are different to a traditional RCT. While there was discussion over the potential for these studies to overestimate the treatment effect, it was also argued, as you suggest, that this trial design better reflects clinical practice. As a result, these findings were still considered as a part of the evidence base and helped to form the committee's opinion that THC:CBD spray appears to have benefits for people with spasticity. It is notable that, despite some a priori grounds for suspecting heterogeneity of effect between trials of different design, there was no evidence that results were statistically different between enriched-enrolment and conventional RCTs for any outcome (see 'test for subgroup differences' in each forest plot – appendix F). After publication of the consultation draft of the guideline, the manufacturer reduced the list price of THC:CBD spray, and this had an important impact on our assessment of its cost effectiveness. In light of stakeholder comments, the committee also reviewed their estimates of likely resource use associated with spasticity symptoms. The committee are now able to make a more positive recommendation. We acknowledged the limitations of the heterogeneity of the 4 RCTs. Hence, the economic analysis reported sensitivity analysis which tested different treatment effects (ORs), such as pooled OR from two enriched trials only and pooled OR from two non-enriched trials only. As explained in the 'model structure' section of appendix M, the initial cycle of the economic model simulates the 4-week run-in phase that is used in clinical practice. Patients enter the model before trying THC: CBD spray and then receive treatment for 4 weeks. Most non-responders are assumed to discontinue treatment; however, the model allows a small proportion of patients to continue treatment as the trials on which its estimate of response is based had more restrictive response criteria (30% improvement) than the 20% improvement criteria specified within SPC. The committee was also aware that Collin et al. 2007 and 2010 did not have a restrictive dose of a maximum of 12 THC: CBD sprays per day. As you pointed out, the mean daily dose of THC: CBD spray in Collin et al. 2007 and 2010 were lower than 12 sprays per day (9.4 and 8.5 respectively). Therefore, the committee agreed that the population from Collin et al. 2007 and 2010 are still relevant to the clinical and cost-effectiveness analyses. We acknowledged that there might be some patients used daily dose above 12 per day. Therefore, a sensitivity analysis was reported when excluding Collin et al. 2007 and 2010.
Bayer plc	Evidence Review C	24 189	28-31	The selection of 25% of costs from the publication by Stevenson *et al.* 2015[1] being attributable to spasticity appears to be completely unsubstantiated. The aim of the study by Stevenson *et al.* 2015[1] was to *"quantify the impact of spasticity on health care resources and the associated costs at different levels of spasticity severity in people with MS (PwMS) living in the United Kingdom (UK)."* The methodology describes that	Thank you for your comments. Based on committee consensus, the committee agreed that the resource use estimated in Stevenson et al. 2015 cannot be said to be 100% attributable to spasticity alone. The committee felt that the vignette from the health care professional survey could be misleading as it explicitly stated that the disability described in the health states was caused by spasticity only. The committee agreed that some of the physical

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				the *"online survey was designed in order to understand the resources used in the management of spasticity,"* and that the requirements for care and for specialised equipment were considered in the context of *"spasticity-related problems"*. An examination of the health state descriptions also shows that there was an attempt to attribute disability to stiffness. For example, in the most severe state (NRS 9 or 10), the phrase *"The stiffness completely dominates my life."* is included and in the least severe state (NRS 0 to 2) only the phrase *"I have little or no problem with stiffness in my limbs."* is used. Therefore, there is reason to believe that respondents were, in choosing the percentage of patients who they believed would use any particular resource, attributing this to the disability arising as a result of spasticity (stiffness), as opposed to any other aspect of the disease. The above suggests all costs reported by Stevenson *et al.* 2015[1] should be considered directly attributable to spasticity. Given that these results have been published in a peer-reviewed journal any reduction is arbitrary and not evidence based. 1. V. L. Stevenson, et al. The high cost of spasticity in multiple sclerosis to individuals and society. Multiple sclerosis. 2015;21(12):1583-92.	disability specified in the vignette, particularly in the most severe health states, would have involved multiple other features of the underlying MS. Based on published evidence and the committee's experience, the committee does not think treating spasticity would have a major impact on underlying disability associated with MS (measured by EDSS). Therefore, the committee concluded that Stevenson et al. 2015 overestimated the amount of resource use that is solely attributable to medically modifiable spasticity. However, the committee was sensitive to comments such as this, and did not want to underestimate the possible benefits of THC:CBD spray. Therefore, the committee made a consensus to change this parameter to 50%. The committee agreed that this parameter is highly uncertain, and it should be tested in the sensitivity analysis. This parameter has been modified in the model, tested extensively and reported in the spasticity evidence review chapter (Table 23). When doubling the background management costs (assuming 100% of costs from Stevenson et al. 2015 are attributable to spasticity alone), the cannabis strategy became dominant. When halving the background management costs (assuming 25% of costs are related to spasticity), the ICER is around £35,000. The modelling approach you propose would be attractive if any data were available for either the effectiveness of THC:CBD spray in influencing transit between spasticity health states or for the resource use independently associated with any such health states. As no such data are available, the model structure adopted made use of best-available evidence regarding the effectiveness of THC:CBD spray and the resource use associated with spasticity. After publication of the consultation draft of the guideline, the manufacturer reduced the list price of THC:CBD spray, and this had an important impact on our assessment of its cost effectiveness. In light of stakeholder comments, the committee also reviewed their estimates of likely resource use associated with spasticity symptoms. The committee are now able to make a more positive recommendation.
Bayer plc	Evidence Review C	24 189		Furthermore, the EDSS score[1] is known to be the main driver of cost in managing MS, and the EDSS is overwhelmingly driven by pyramidal symptoms (i.e. walking ability). Pyramidal symptoms are the result of damage to the corticospinal tract that carries motor nerves from the brain down the spinal cord to the muscles, and the signature feature of pyramidal damage is spasticity. Indeed the great reliance of the EDSS on walking distance/pyramidal symptoms (especially from EDSS 4.0 and beyond) is widely acknowledged to be one of its major deficiencies and there are many publications on this topic.[2] A study from Newcastle[3] supports the high prevalence of spasticity in MS, and the negative impact on function. The cost of managing MS is driven by EDSS[4] especially higher scores of EDSS, and pyramidal symptoms (i.e. spasticity, weakness) are the main driver of EDSS score from 4.0 onwards. Spasticity is therefore highly likely to be a significant driver of MS costs. Whilst there are few data supporting clear improvement in gait or EDSS as a result of treating spasticity,[5] this may be in part because of the relatively poor treatment options for spasticity historically available. 1. J. F. Kurtzke. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology. 1983;33(11):1444-52. 2. C. E. van Munster, B. M. Uitdehaag. Outcome Measures in Clinical Trials for Multiple Sclerosis. CNS drugs. 2017;31(3):217-36. 3. M. P. Barnes, et al. Spasticity in multiple sclerosis. Neurorehabilitation and neural repair. 2003;17(1):66-70. 4. M. B. Patwardhan, et al. Cost of multiple sclerosis by level of disability: a review of literature. Multiple sclerosis (Houndmills, Basingstoke, England). 2005;11(2):232-9. 5. G. B. Orsnes, et al. Effect of baclofen on gait in spastic MS patients. Acta neurologica Scandinavica. 2000;101(4):244-8.	Thank you for your comments. The committee reviewed EDSS evidence from RCTs (Killestein 2002, Markova 2018, van Amerongen 2018, Zajicek 2012). It agreed that the evidence does not show that CBMPs are associated with improvement of EDSS. Based on their experience, the committee agreed that this reflects the current clinical experience of treating MS patients. Therefore, the committee decided to keep the current model assumption of constant EDSS of 6.5 regardless of NRS spasticity improvement. This assumption was tested in the sensitivity analysis. The committee acknowledged that EDSS is the main driver of the costs of managing MS. Committee-members were cautious about the potential overlapping resource use of managing MS and MS spasticity (see responses for spasticity-related resource use). After publication of the consultation draft of the guideline, the manufacturer reduced the list price of THC:CBD spray, and this had an important impact on our assessment of its cost effectiveness. In light of stakeholder comments, the committee also reviewed their estimates of likely resource use associated with spasticity symptoms. The committee are now able to make a more positive recommendation.
Bayer plc	Evidence Review C	31 79 83	36-38	Assessment of Bias The trials by Novotna *et al.* 2011[1] and Markova *et al.* 2019[2] have been assessed as being at a high risk of bias for the following reason: *"RCT phase was an enriched enrolment design*	Thank you for your comments. As mentioned in the evidence review, the enriched enrolment trials were highlighted in the forest plots and brought to the attention of the committee when the data for spasticity was presented. This was used as a way to generate discussion over the methods which are different to a traditional RCT. While there was discussion over the

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		137		*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."* Whilst it is acknowledged in the MHRA PAR for THC:CBD Oromucosal Spray *that "enrichment designs can over-estimate the magnitude of the mean treatment effect and are therefore discouraged in most situations"* it goes on to state in this document that *"in this case* [Novotna et al 2011] *the enrichment design reflects proposed clinical practice and in principle the difference between active and placebo should be a fair reflection of efficacy in the population that will be treated with Sativex in the medium to long term."* This also applies to the design of the trial by Markova *et al.* 2019[2] In accordance with the SmPC, THC:CBD Oromucosal Spray is indicated as treatment for symptom improvement in adult patients with moderate to severe spasticity due to multiple sclerosis (MS) who have not responded adequately to other anti-spasticity medication *and who demonstrate clinically significant improvement in spasticity related symptoms during an initial trial of therapy*.[3] Therefore as opposed to being at 'high risk of bias', due to the enriched enrolment design, the trials by Novotna *et al.* 2011[1] and Markova *et al.* 2019[2] are those relevant to the labelled population, and are also reflective of clinical practice, as those who do not respond after an initial trial (covered by the 'Pay for Responder scheme') are not eligible to continue with treatment and would discontinue. For this reason these trials should not be considered as at high risk of bias due to their enrichment deign as they are directly applicable to the population in question, and the quality of evidence should not be down-graded for this reason. The study by Novotna *et al.* 2011[1] was designed following formal consultation with European regulatory agencies during the Decentralised procedure. A detailed and independent assessment of the integrity and results of this study is publicly available as the 'Public Assessment Report', issued by the MHRA following approval of the medicine.[4] As a general point, the MHRA has noted in its public assessment report that all clinical studies were carried out in compliance with good clinical practice. 1. A. Novotna, et al. A randomized, double-blind, placebo-controlled, parallel-group, enriched-design study of nabiximols* (Sativex®), as add-on therapy, in subjects with refractory spasticity caused by multiple sclerosis. European journal of neurology. 2011;18(9):1122-31. 2. J. Markova, et al. Sativex® as add-on therapy vs. further optimized first-line ANTispastics (SAVANT) in resistant multiple sclerosis spasticity: a double-blind, placebo-controlled randomised clinical trial. The International journal of neuroscience. 2019;129(2):119-28. 3. GW Pharma Ltd. Summary of Product Characteristics - Sativex Oromucosal Spray. Last updated: 24/08/2018. Last accessed: 22/08/2019. Available from: https://www.medicines.org.uk/emc/product/602. 4. Medicines and Healthcare products Regulatory Agency (MHRA). Public Assessment Report. Decentralised Procedure. Sativex Oromucosal Spray. UK/H/2462/01/DC. UK license no: PL 18024/0009. GW Pharma Limited. Last updated: 16/03/2014. Last accessed: 21/08/2019. Available from: http://www.mhra.gov.uk/home/groups/par/documents/websiteresources/con084961.pdf.	potential for these studies to overestimate the treatment effect it was also argued, as you suggest, that this trial design better reflects clinical practice. The committee decided that these trials should still be included as part of the analysis but given some concerns over the method they were kept as high risk of bias studies. After publication of the consultation draft of the guideline, the manufacturer reduced the list price of THC:CBD spray, and this had an important impact on our assessment of its cost effectiveness. In light of stakeholder comments, the committee also reviewed their estimates of likely resource use associated with spasticity symptoms. The committee are now able to make a more positive recommendation. Sativex pay-for-responder scheme and first 3 vials free discount have been incorporated into the spasticity economic model. This has been described in the treatment cost summary in the model report (Appendix M of the spasticity chapter).
Bayer plc	Evidence Review C	32	10-14	We agree with the statement on page 32 *that "in comparison to a standard RCT, this study design is more similar to the process that would be followed in clinical practice"*, and not that *"this design may favour responders and result in more positive outcomes and fewer adverse events."* Please see comment number 1.	Thank you for your comments. Our discussion of the evidence reflects the discussion of the whole committee and therefore takes into account both the opinions in favour of the enriched enrolment design reflecting clinical practice and those with concerns about the potential for this type of trial design to overestimate the treatment effect.
Bayer plc	Evidence Review C	35	7-9	Under 'other factors the committee took into account', the draft guideline reports a committee discussion that it would be difficult to identify the cohorts that could benefit the most from treatment as *"there is currently no evidence to indicate who will or will not have a good and persistent levels of response to the use of cannabis-based medicinal products."* We suggest that in clinical practice these cohorts can be identified by trying THC:CBD Oromucosal Spray for 4 weeks. The trial by Novotna *et al.* 2011[1] showed that patients who	Sativex pay-for-responder scheme and first 3 vials free discount have been incorporated into the spasticity economic model. This has been described in the treatment cost summary in the model report (Appendix M of the spasticity evidence review C).

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				achieve a 20% response in the first 4 weeks derive benefit from continued treatment as stated in the MHRA PAR.[2] The current 'Pay for Responder scheme' enables THC:CBD Oromucosal Spray responders to be identified at no drug cost to the NHS. Under the scheme the first pack (3 x 10ml vials) of THC:CBD Oromucosal Spray is free of charge to the NHS for all new THC:CBD Oromucosal Spray patients initiated by a specialist in secondary care (within the licensed indication), provided continued funding for responder patients has been formally agreed at a local level. 1. A. Novotna, et al. A randomized, double-blind, placebo-controlled, parallel-group, enriched-design study of nabiximols* (Sativex®), as add-on therapy, in subjects with refractory spasticity caused by multiple sclerosis. European journal of neurology. 2011;18(9):1122-31. 2. Medicines and Healthcare products Regulatory Agency (MHRA). Public Assessment Report. Decentralised Procedure. Sativex Oromucosal Spray. UK/H/2462/01/DC. UK license no: PL 18024/0009. GW Pharma Limited. Last updated: 16/03/2014. Last accessed: 21/08/2019. Available from: http://www.mhra.gov.uk/home/groups/par/documents/websiteresources/con084961.pdf.	
Bayer plc	Evidence Review C	44	37	When discussing the minimal clinically important differences (MIDs), the draft guideline currently states that *"No MIDs were identified."* We would like to draw NICE's attention to a publication by Farrar *et al.* 2008[1] which determines the clinically important difference (CID) and the minimum clinically important difference (MCID) in the 0-10 NRS Spasticity Score. It was found that MCID in spasticity as measured by the NRS scale is approximately an 18% improvement from baseline. 1. J. T. Farrar, et al. Validity, reliability, and clinical importance of change in a 0-10 numeric rating scale measure of spasticity: a post hoc analysis of a randomized, double-blind, placebo-controlled trial. Clinical therapeutics. 2008;30(5):974-85.	Thank you for your comment and for sharing the reference. The suggested MID was considered by the committee and was deemed appropriate. The evidence review was amended accordingly.
Bayer plc	Evidence Review C	9 12-13	23-24	We are concerned by the statement suggesting that the design of the 'enriched enrolment trials' including clinical trial GWSP0604 (publication by Novotna *et al.* 2011[1]) *"may result in more favourable outcomes for the intervention and fewer cases of adverse events."* Whilst it is acknowledged in the MHRA Public Assessment Report (PAR) for THC:CBD Oromucosal Spray *that "enrichment designs can over-estimate the magnitude of the mean treatment effect and are therefore discouraged in most situations"* it goes on to state in the document that *"in this case* [Novotna *et al.* 2011[1]] *the enrichment design reflects proposed clinical practice and in principle the difference between active and placebo should be a fair reflection of efficacy in the population that will be treated with Sativex in the medium to long term."* Analysis of past studies including Collin *et al.* 2007[2] and 2010[3] generated the hypothesis that a clinically useful treatment effect in some patients might be partly masked by data 'noise' from non-responders, and that a 4-week trial with THC:CBD Oromucosal Spray could be used to identify those subjects likely to benefit from continued treatment. The clinical trial GWSP0604 (publication by Novotna *et al.* 2011[1]), was specifically designed to prospectively test the benefits of this approach, and was designed taking account of Scientific Advice from the MHRA and from AEMPS, the Spanish Competent Authority.[4] The design of the study reflects the way in which THC:CBD Oromucosal Spray is used in clinical practice - which minimises exposure to active drug in patients who have not shown capacity to respond - and measures effectiveness in the licensed population e.g. only in those *"who demonstrate clinically significant improvement in spasticity related symptoms during an initial trial of therapy,"*[5], in a randomised placebo-controlled trial setting. In demonstrating a highly significant difference in favour of THC:CBD Oromucosal Spray versus placebo in the difference in the mean spasticity Numeric Rating Scale (NRS), the results of this study support the 'therapeutic trial' approach to the use of THC:CBD Oromucosal Spray and show that patients who achieve a 20% response in the first 4 weeks derive benefit from continued treatment with THC:CBD, as stated in the MHRA PAR.[4]	Thank you for your comments. As mentioned in the evidence review, the enriched enrolment trials were highlighted in the forest plots and brought to the attention of the committee when the data for spasticity was presented. This was carried out to generate discussion over the methods which are different to a traditional RCT. While there was discussion over the potential for these studies to overestimate the treatment effect it was also argued, as you suggest, that this trial design better reflects clinical practice. As a result, these findings were still considered as a part of the evidence base and helped to form the committee's opinion that Sativex appears to have benefits for people with spasticity. After publication of the consultation draft of the guideline, the manufacturer reduced the list price of THC:CBD spray, and this had an important impact on our assessment of its cost effectiveness. In light of stakeholder comments, the committee also reviewed their estimates of likely resource use associated with spasticity symptoms. The committee are now able to make a more positive recommendation. Sativex pay-for-responder scheme and first 3 vials free discount have been incorporated into the spasticity economic model. This has been described in the treatment cost summary in the model report (Appendix M of the spasticity chapter).

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				Interestingly, an analysis of the response achieved in the subjects who were not classified as 'responders' and therefore not randomised to further treatment, shows that around 50% of these subjects achieved less than 5% improvement,[1] *"supporting the idea that there is a group refractory to treatment, while others can achieve large benefits."*[4] It should also be noted that a 'Pay for Responder scheme' is available which enables THC:CBD Oromucosal Spray responders to be identified at no drug cost to the NHS. Under the scheme the first pack (3 x 10ml vials) of THC:CBD Oromucosal Spray is free of charge to the NHS for all new THC:CBD Oromucosal Spray patients initiated by a specialist in secondary care (within the licensed indication), provided continued funding for responder patients has been formally agreed at a local level. Therefore rather than resulting in more favourable outcomes for the intervention, the design of this trial and that by Markova *et al.* 2019[6] rather demonstrates the treatment effect in the licensed population and therefore more closely reflects clinical practice. This approach also minimises the risk of adverse events by minimising exposure to active drug in patients who have not shown capacity to respond. 1. A. Novotna, et al. A randomized, double-blind, placebo-controlled, parallel-group, enriched-design study of nabiximols* (Sativex®), as add-on therapy, in subjects with refractory spasticity caused by multiple sclerosis. European journal of neurology. 2011;18(9):1122-31. 2. C. Collin, et al. Randomized controlled trial of cannabis-based medicine in spasticity caused by multiple sclerosis. European journal of neurology. 2007;14(3):290-6. 3. C. Collin, et al. A double-blind, randomized, placebo-controlled, parallel-group study of Sativex, in subjects with symptoms of spasticity due to multiple sclerosis. Neurological research. 2010;32(5):451-9. 4. Medicines and Healthcare products Regulatory Agency (MHRA). Public Assessment Report. Decentralised Procedure. Sativex Oromucosal Spray. UK/H/2462/01/DC. UK license no: PL 18024/0009. GW Pharma Limited. Last updated: 16/03/2014. Last accessed: 21/08/2019. Available from: http://www.mhra.gov.uk/home/groups/par/documents/websiteresources/con084961.pdf. 5. GW Pharma Ltd. Summary of Product Characteristics - Sativex Oromucosal Spray. Last updated: 24/08/2018. Last accessed: 22/08/2019. Available from: https://www.medicines.org.uk/emc/product/602. 6. J. Markova, et al. Sativex® as add-on therapy vs. further optimized first-line ANTispastics (SAVANT) in resistant multiple sclerosis spasticity: a double-blind, placebo-controlled randomised clinical trial. The International journal of neuroscience. 2019;129(2):119-28.	We have checked the refences provided and all the studies have been included in evidence review C. Markova et al 2019 - was published in February 2019 and our evidence review literature searches were carried out in December 2018 – January 2019. This paper will be considered in any future update of this guideline
Bayer plc	Evidence Review C	General	General	THC:CBD Oromucosal Spray is indicated as treatment for symptom improvement in adult patients with moderate to severe spasticity due to multiple sclerosis (MS) who have not responded adequately to other anti-spasticity medication and who demonstrate clinically significant improvement in spasticity related symptoms during an initial trial of therapy.[1] In in all other areas where evidence for THC:CBD Oromucosal Spray has been considered it should be made clear that THC:CBD Oromucosal Spray does not have a marketing authorisation for these indications using the wording as outlined the NICE guidelines manual.[2] 1. GW Pharma Ltd. Summary of Product Characteristics - Sativex Oromucosal Spray. Last updated: 24/08/2018. Last accessed: 22/08/2019. Available from: https://www.medicines.org.uk/emc/product/602. 2. National Institute for Health and Care Excellence. Developing NICE guidelines: the manual. Last updated: 10/2018. Last accessed: 02/09/2019. Available from: https://www.nice.org.uk/process/pmg20.	Thank you for your comments. An explanation that Sativex does not currently have marketing authorisation for motor neurone disease or spinal cord injury has now been added to the introduction of the evidence review (in the Interventions section).
British Association for	General	General	General	There is evidence that patients treated with the main conditions reported in the current draft experience a "high" and that this should be monitored. Firstly, to the subjective "high" it would	Thank you for your comment. The committee agreed that this is captured in recommendation 1.5.5 as a 'high' would be considered as potential harms.

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Psychopharmacology				be advisable to include a formal screening of the Mental State alterations expected when assuming THC. For instance paranoia scales and cognitive assessment especially measuring memory and new learning, both very relevant for young adults and of course children.	
British Association for Psychopharmacology	Guideline	10	21	The recommendations for other research is missing research into the risk of dependence associated with prescribed cannabinoids	Thank you for your comment. The current research recommendations in the guideline will take into account safety of CBMPs which may include dependence.
British Association for Psychopharmacology	Guideline	8-7	General	Clinicians should discuss the potential legal and health risks of using illicit cannabis based products for medicinal purposes. Many patients will have experience of using these, and may do so alongside or instead of prescribed cannabis-based products. The risk of using illicit products will be especially high when a prescription is not made, which will be the majority of cases within the current guideline. Clinicians should be aware of this issue and should discuss it with their patients to minimise the risks of legal or health related harms of using illicit products.	Thank you for your comment. The use of illicit cannabis-based products was out of scope for this guideline. Recommendation 1.5.7 takes into account the use of illicit cannabis when prescribing medicinal cannabis.
British Association for Psychopharmacology	Guideline	General and 9-10	General	Recommendations for research in psychiatric disorders are lacking. There is growing evidence that cannabis-based medicines are being used for psychiatric indications. This is despite good quality evidence of efficacy. I am therefore deeply concerned that psychiatric disorders have been excluded from this guideline and particularly the list of recommendations for research given the high levels of morbidity and mortality associated with these illnesses. Psychotic symptoms in children and young people need to be monitored	Thank you for your comment. Psychiatric disorders were out of scope for this guideline. The current research recommendations in the guideline will take into account safety of CBMPs which may include psychotic symptoms.
British Medical Association	Guideline	3	General	1.1 Intractable nausea and vomiting These will be complex acutely ill patients and the clinician responsible for their chemotherapy is responsible for prescribing to combat the adverse effects of this. Shared care is therefore unacceptable on the grounds of an inappropriate transfer of clinical responsibility.	Thank you for your comment. The committee considered your comment and highlighted that recommendation 1.5.2 only recommends shared care as an option if all parties feel confident on prescribing and agree with the shared care arrangement in place. Additionally, shared care agreements are disease specific and whether or not this should be implemented would be based on local determination
British Medical Association	Guideline	3	General	1.2 Chronic pain This is only recommended as part of a trial, so shared care is inappropriate as all prescribing needs to be done by the trialists.	Thank you for your comment. We agree that shared care would be inappropriate in this instance.
British Medical Association	Guideline	4	General	1.3 Spasticity This is only recommended as part of a trial, so shared care is inappropriate as all prescribing needs to be done by the trialists.	Thank you for your comment. The guideline recommends that all those receiving treatment before publication of this guidance can continue to receive treatment. The committee considered your comment and highlighted that recommendation 1.5.2 only recommends shared care as an option if all parties feel confident on prescribing and agree with the shared care arrangement in place.Additionally, shared care agreements are disease specific and whether or not this should be implemented would be based on local determination.
British Medical Association	Guideline	5	General	1.4 Treatment resistant epilepsy NICE recognise that there is no evidence for this population, so responsibility for prescribing must not be removed from the initiating clinician through shared care mechanisms, which must have a robust and accepted evidence base.	Thank you for your comment. The committee considered your comment and highlighted that recommendation 1.5.2 only recommends shared care as an option if all parties feel confident on prescribing and agree with the shared care arrangement in place. Additionally, shared care agreements are disease specific and whether or not this should be implemented would be based on local determination.
British Medical Association	Guideline	5	General	1.5.1 Who should prescribe? The prescriber signing the script would take on the responsibility should ever anything adverse happen. With such a new and specialist drug, it would not be appropriate for GPs to take over prescribing, even if it is under a shared care agreement.	Thank you for your comment. The committee agreed that this would not be the sole responsibility of the GP because the responsibility is shared between the GP and the specialist as part of the shared care agreement.
British Medical Association	Guideline	6	General	1.5.2 Shared care The prescriber signing the script would take on the responsibility should ever anything adverse happen. With such a new and specialist drug, it would not be appropriate for GPs to take over prescribing, even if it is under a shared care agreement.	Thank you for your comment. The committee considered your comment and agreed that recommendation 1.5.2 is not a strong recommendation but one that uses the word 'may' to enable this to be an option if the GP feels confident to continue prescribing under a shared care arrangement. The committee also considered the NHS England document 'Responsibility for prescribing between Primary & Secondary/Tertiary Care' that provides details about arrangements and considerations. The committee agreed to refer to this guidance to supplement recommendation 1.5.2.
British Medical Association	Guideline	General	General	Medicinal cannabis is a new and specialist drug that requires specialist assessment, drug initiation and monitoring by the appropriate specialist team. This would be the case for any	Thank you for your comment. The committee considered your comment and agreed that recommendation 1.5.2 is not a strong recommendation but one that uses the word 'may' to

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				very specialist drug. The way to improve access to assessment and treatment is to properly resource specialist services and enable hospital services to access electronic prescribing systems. Therefore, the BMA would oppose the introduction of GPs taking over subsequent prescriptions of this specialist drug under shared care arrangements. Please also see our comments on some specific paragraphs outlined below:	enable this to be an option if the GP feels confident to continue prescribing under a shared care arrangement. The committee also considered the NHS England document 'Responsibility for prescribing between Primary & Secondary/Tertiary Care' that provides details about arrangements and considerations. The committee agreed to refer to this guidance to supplement recommendation 1.5.2.
British Paediatric Neurology Association	Guideline		17	this should not say BPNA, it should refer to the NICE clinical guideline. It should say NICE clinical guideline [CG137]	Thank you for your comment. This cross reference has been corrected.
British Paediatric Neurology Association	Guideline	1	General	Need to define what is meant by severe treatment resistant epilepsy and in what context NICE is giving advice about – i.e. is this guideline relevant to less severe epilepsies. Are NICE saying that CBMPs should not be considered outside the context of "severe treatment resistant epilepsies". If that is the case – they should say so.	Thank you for your comment. Epilepsies other than severe treatment resistant epilepsy were beyond the scope of this guideline. Evidence review D has the following definition: Severe treatment-resistant epilepsy, or drug-resistant epilepsy, is defined by the International League Against Epilepsy as epilepsy that has not responded to trials of 2 tolerated and appropriately chosen and used anti-epileptic drug regimens (as monotherapies or in combination) to achieve sustained freedom from seizures.
British Paediatric Neurology Association	Guideline	10	10	Typo… Should read "neuropsychological" rather than "neurophysiological"	Thank you, the guideline has been amended accordingly.
British Paediatric Neurology Association	Guideline	10	9-12	This could be expanded to say… Does the addition of THC have an effect on development, neuropsychological and language development, mood or mental health?	Thank you for your comment. The research recommendation outlines the outcomes that the committee felt were most important to the question. Other outcomes such as adverse events and change in cognition are listed in the detailed research recommendation section in Appendix J of the evidence review for epilepsy.
British Paediatric Neurology Association	Guideline	16-17	General	Agree that this is a fair appraisal of the information/research	Thank you for your comment
British Paediatric Neurology Association	Guideline	17	24-26	Should also be advice to continue other prescribed AEDs unless otherwise advised by their tertiary hospital specialist	Thank you for your comment. The committee were unable to make a recommendation on the use of cannabis-based medicinal products, either alone or with other anti-epileptic medications, for severe treatment-resistant epilepsy as there was no good quality evidence available in this population.
British Paediatric Neurology Association	Guideline	18	2-7	Significant concern expressed that this section places the pressure back on clinicians. All comments received agree that there is insufficient evidence to warrant a practice recommendation but some are concerned that not making a recommendation against treatment (except in the context of clinical trials) means that clinicians will continue to be pressurised to prescribe treatments for which there is no evidence. Some felt that NICE had shirked their responsibility here and were afraid to make a recommendation against treatment until more evidence was available.	Thank you for your comment. The committee considered your comment and highlighted that recommendation 1.5.2 only recommends shared care as an option if all parties feel confident on prescribing and agree with the shared care arrangement in place. Additionally, shared care agreements are disease specific and whether or not this should be implemented would be based on local determination.
British Paediatric Neurology Association	Guideline	6	General	In terms of prescribing – it needs to be very clear who is funding the treatment and if the child moves areas what happens re funding. It also needs to state very clearly that initial prescriptions should not be given unless there is adequate provision for ongoing care and ongoing funding of treatment. This is a particular issue when an initial private prescription is written and funded and then the family expects the NHS service locally to then continue prescribing and pick up the cost.	Thank you for your comment. This will be determined by local CCG funding arrangements. Recommendation1.5.4 also outlines that share care arrangements should make provision for when the patient, initiating specialist prescriber or other prescriber moves location (including transition to adult services).
British Paediatric Neurology Association	Guideline	7	10-15	Agree with recommendation	Thank you for your comment
British Paediatric	Guideline	7	3-8	Agree – very helpful	Thank you for your comment

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Neurology Association					
British Paediatric Neurology Association	Guideline	7	7-17	Need to comment that there is a particular interaction with the AED clobazam. Also need to comment re necessary monitoring that needs to be undertaken when using a CBMP – especially liver function monitoring.	Thank you for your comment. Antiepileptics have been added to the recommendation. Recommendation 1.5.4 covers monitoring; specific monitoring requirements would depend on the cannabis-based medicinal product in question.
British Paediatric Neurology Association	Guideline	General	General	Should NICE be saying something about over the counter/internet products that are not of GMP standard and the risks involved in doing this.	Thank you for your comment. Recommendation 1.5.6 states that people should be advised to stop taking any non-prescribed cannabis products. More details about concerns over the risks associated with non-prescribed products are covered in the individual evidence reviews.
British Pharmacological Society	Guideline	18	6	It is now just "an interest" rather than a "specialist interest"; this is much broader as any consultant could have an interest in an area. Generally, we propose that the wording and description of who can prescribe should be tighter and should reference that the individual is not only on the specialist register but that they are on the specialist register for that indication (e.g. oncology, palliative care, neurology).	Thank you for your comment. This wording has been amended to reflect your comment.
British Pharmacological Society	Guideline	18	5	Specialist doctors on the 'Specialist Register' of the General Medical Council should only prescribe within their own area of practice.	Thank you for your comment. This recommendation has been amended following further discussion by the committee.
British Pharmacological Society	Guideline	20	10-12	The concerns about effects on brain development are fair, but in the case of poorly treated intractable epilepsy, this also has effects on normal brain development and this overall need is a balance between the two sets of risks and benefits; the text as it currently reads seems to focus on the harms of prescription only. This should be addressed.	Thank you for your comment. The wording of the rationale has been amended to reflect your comment.
British Pharmacological Society	Guideline	23	10	A product can only be described as "pure" if it contains no controlled cannabinoids (i.e. THC). In reality this is very difficult to achieve. In view of this, we recommend the term "pure" is avoided, and simply refer to 'CBD products for medicinal use'.	Thank you for your comment. Following further discussion by the committee, they agreed to keep the term 'pure' to describe highly purified cannabidiol that comes from the cannabis plant.
British Pharmacological Society	Guideline	5	10	We propose that this section should be split into two sections; Lennox-Gastaut and Dravet first (where there is evidence, and it is being appraised separately) and then "other treatment resistant epilepsies" second. We also suggest adding a comment about ongoing clinical trials in these areas (e.g. Retts syndrome). Otherwise it looks like the area where there is evidence is being ignored as it is only included at the end.	Thank you for your comment. The evidence review considered evidence on treatment-resistant epilepsies such as Lennox-Gastaut and Dravet syndromes, however they were unable to make recommendations as this will be covered by the technology appraisal guidance. Furthermore, the committee considered whether it would be possible to extrapolate the findings from the Lennox-Gastaut and Dravet populations but felt that this wouldn't be appropriate given the differences between different types of epilepsy.
British Pharmacological Society	Guideline	5	10	Section 1.4 is not as specific as the other sections in terms of bulleted recommendations for when to use it.	Thank you for your comment. Because of limited evidence the committee could not make any recommendations on the use of CBMP for people with epilepsy. As such, they could not include more detailed information on the use of these products.
British Pharmacological Society	Guideline	6	17	Section 1.5.4: We are assuming that a primary care or non-specialist doctor can decline to continue prescribing, as with other shared care agreements? The funding requires CCG approval, but they are not mentioned as responsible parties in the first bullet point. This point should be clarified.	Thank you for your comment. The recommendation is not meant to be exhaustive. Additional parties to include in the agreement would be down to local agreement.
British Pharmacological Society	Guideline	6	4	Section 1.5.1: it is not clear from reading the indications where it is recommended for use that will relate to individuals younger than 18 years, apart from in clinical trials. It seems that the regulation of prescribing to those under 18 is much more robust and limited than for those older than 18 years since any consultant could prescribe and there is only a "should" recommendation on having a specialist interest in the area being treated.	Thank you for your comment. The recommendation has been reworded following further discussion by the committee to reflect your comment.
British Pharmacological Society	Guideline	6	7-8	We suggest amending the final sentence to read "For Children and Young people under 18 years, the initiating prescriber should be a tertiary paediatric neurologist (or epilepsy specialist)". Further, we suggest amending from just "specialist", as all paediatric consultants in tertiary hospitals will fit this description. This is clarified on p 18, line 21, but it should be in the main section as well	Thank you for your comment. The aim of this recommendation is to cover prescribing for other conditions and not limiting it to epilepsy. We have amended the recommendation to make clear that it should be a specialist with a specialist interest in the condition being treated.
British Pharmacological Society	Guideline	7	8	Section 1.5.5: this should specifically refer to "synthetic cannabinoids" in terms of previous substances used. Also, patients may not consider use of a recreational drug as "misuse" and so this is probably not the best term to use.	Thank you for your comment. The broader definition of cannabis was used to capture synthetic and non-synthetic products. Substance misuse is used as standard terminology in NICE guideline.

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British Pharmacological Society	Guideline	7	24	Section 1.5.7: again this should refer to "synthetic cannabinoid" use being discontinued. Are other substances (recreational drugs and NPS) okay to continue then? Please clarify	Thank you for your comment. Adding 'synthetic' would limit other cannabis-based products that are not classed as synthetic. The term 'non-prescribed cannabis' takes into account a range of products. If the person is taking other substances as you describe in your comment, then this will be part of the medical history taking during prescriber-patient consultation and factors to take into account are listed in recommendation 1.5.5.
British Pharmacological Society	Guideline	7	9	Amend to "Over-the-counter CBD oil products for non-medicinal use".	Thank you for your comment. Wording was considered by the committee who agreed that the current wording is broad enough to capture your suggestion.
British Pharmacological Society	Guideline	7	17	Please add about asking about any allergies (some products are formulated in peanut oil).	Thank you for your comment. Wording was considered by the committee who agreed that checking allergy status would be part of routine clinical practice when prescribing any medicine
British Pharmacological Society	Guideline	7	17	Please add about travelling abroad, as CBPMs are not legal in other countries and patients will need to check the status of the drug with the embassy of the country they are travelling to.	Thank you for your comment. This has been added following further discussion by the committee
British Pharmacological Society	Guideline	8	5	Section 1.5.9: what about the impact of use in professions where use of cannabis is not allowed (e.g. train drivers, pilots, armed forces personnel); should they not be appropriately counselled about this?	Thank you for your comment. Recommendation 1.5.9 is about having the necessary discussion with the patient about the cannabis-based medicinal products and how it may affect them depending on their circumstances, particularly with their ability to drive. Advice and counselling would be part of this discussion.
British Pharmacological Society	Guideline	8	13	Please consider adding that the CBPMs may affect ability to use tools or machines (i.e. as per standard drug labelling for licensed products that may cause drowsiness).	Thank you for your comment. The committee discussed this further and agreed that this would be stated on the product packaging if there was an impact, therefore the committee agreed to not make this addition.
British Pharmacological Society	Guideline	9	12	Recommendations for research: there is no mention about use in chronic pain in adults apart from fibromyalgia or treatment resistant neuropathic pain. Other pain conditions should be considered and mentioned.	Thank you for your comment. With regards to adult studies, the economic analysis suggested that most types of chronic pain were not going to be cost-effective to manage using medicinal cannabis. However, if any types of chronic pain could be cost-effective to manage using medicinal cannabis, they are most likely to be fibromyalgia and treatment-resistant neuropathic pain.
British Pharmacological Society	Guideline	General	General	Please refer to cannabis-based products for medicinal use throughout, in-line with legislation and guidance.	Thank you for your comment. The broader definition of cannabis-based medicinal products was used to capture those products defined by Regulation 16A of The Misuse of Drugs (Amendments) (Cannabis and Licence Fees) (England, Wales and Scotland) Regulations 2018 AND products such as cannabidiol, Sativex and nabilone which are not captured by Regulation 16A. By just referring to the government definition of cannabis-based products for medicinal use would exclude cannabidiol, Sativex and nabilone. Our final scope included cannabidiol, Sativex and nabilone as well as those products that meet the requirements of Regulation 16A.
British Pharmacological Society	Guideline	General	General	There are significant gaps in knowledge of cannabinoids in the following areas, and we feel that these need to be added to the recommendations: • pharmacokinetics of cannabinoids when administered by different routes; • drug-drug interactions with cannabinoids, pharmacokinetic, pharmacodynamic and mixed • long term safety of cannabinoids, in particular on the risk of psychiatric disorders and cognitive function.	Thank you for your comment. Pharmacokinetics and drug-drug interactions did not form part of this evidence review. This would be considered when the product is undergoing clinical trials. The current research recommendations in the guideline will take into account safety of CBMPs which may include risk of psychiatric disorders and cognitive function.
Cannabis Patient Advocacy & Support Services	Acknowledgements	5	1	There is not a single patient or parent or carer representative on the NICE Guideline Committee. Since many 1000s of patients have been consuming these products for many decades CPASS believe it is both critical and essential that the voices of patients are included at all levels of inquiry and review into the appropriate use of CBMPs. This is a unique situation and opportunity and without it misses a unique opportunity to learn as much as possible from patient expertise and experience. Whilst CPASS believe that each and every medical category where cannabis products have proven effective for patients, we understand that this would be impractical and would like to formally request selection for performing this role on behalf of patients. CPASS's 2 directors have a joint experience of over 8 years in supporting and advocating for medical cannabis patients along with an individual lifetime of experience in their consumption and impact both physically and mentally.	Thank you for your comment. Our guideline committee had three lay representatives with personal or carer experience of the conditions examined in the guideline. The committee membership list can be found on the cannabis guideline webpage under project documents.

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Cannabis Patient Advocacy & Support Services	Acknowledgements	5	1	CPASS suggest that the NICE Guideline Committee would benefit from the inclusion of skilled professional resources from jurisdictions outside of the UK, specifically Canada, US, Australia, Israel and Germany. CPASS have good working relationships with suitable professionals including several of our own Clinical Steering Board members whom we believe would accept such a position and would be glad to assist in referrals	Thank you for your comment. The NICE guideline considered and included international guidelines as part of the evidence review. This included the Canadian guideline. However, the recommendation about who should prescribe is set out in UK legislation, The Misuse of Drugs (Amendments) (Cannabis and Licence Fees) (England, Wales and Scotland) Regulations 2018, regulation 16A which differs from that in Canada. Furthermore, NICE guidelines are written for the English healthcare system and so we look to ensure that we have professionals and lay experience in that system
Cannabis Patient Advocacy & Support Services	Evidence Review A	General	General	Whilst accepting that "Smoked cannabis-based products" are not permitted within the current UK laws and regulations for CBMPs, CPASS feel that with the limited availability of evidence for all other forms and with the plethora of evidence for this type, this limitation has an unproportionate impact on assessing both the benefits and the risks of CBMPs which will lead to low quality and inaccurate outcomes.	Thank you for your comment, This guideline is underpinned by legislation in terms of which cannabis based medicinal products can be considered. Therefore we only considered the following: • cannabis-based medicinal products as defined by the UK Government in November 2018 • the licensed products nabiximols (Sativex) and nabilone. • plant-derived cannabinoids such as pure cannabidiol. • synthetic compounds which are identical in structure to naturally occurring cannabinoids such as delta-9-tetrahydrocannabinol (THC), for example dronabinol.
Cannabis Patient Advocacy & Support Services	Evidence Review A	General	General	CPASS Recommend that special consideration also be given to patients with a diagnosed or suspected complex mental health condition, particularly Schizophrenia and other psychotic disorders. Specifically, around the dosage/ratio of THC:CBD	Thank you for your comment. Psychiatric disorders were out of scope for this guideline. The current research recommendations in the guideline will take into account safety of CBMPs which may include psychotic symptoms.
Cannabis Patient Advocacy & Support Services	Evidence Review A	General	General	CPASS are concerned that very limiting criteria have been set for acceptable evidence throughout all evidence reviews. Only 28 pieces of research were accepted for Nausea and Vomiting, from a total of over 13000 RCTs and Observational studies ruling out 99.8% of available evidence to draw all conclusions within this Guideline and feel that it would be helpful to understand why broader evidence has not been considered.	Thank you for your comment. During the development of the review protocol, the committee agreed that randomised controlled trials (RCTs) and systematic reviews of RCTs should be included. However, the committee also noted that there are certain population groups where RCT data may not be available. Therefore, it was agreed when adequate RCT data was not available, observational studies would be further explored. In the evidence review for intractable nausea and vomiting, 27 RCTs were identified, 3 of which were conducted in children. Due to the lack of RCT evidence in this population, observational studies were also explored. Based on this search 1 study was identified as being relevant and was included in this review. The evidence reviews for this guideline all contain a list of excluded papers, which were considered at full paper stage, with reasons for exclusion.
Cannabis Patient Advocacy & Support Services	Evidence Review A	General	General	As RCTs are not an effective measure for the effectiveness of CBMPs, CPASS challenge the Eligibility criteria for study design being limited to RCTs along and recommend a wider set of criteria, particularly to include direct discussions and feedback from patients who have been consuming for many years.	Thank you for your comment. NICE guideline recommendations are based on the best available evidence. Review questions guide the search for evidence, and the type of evidence used depends on the type of question. For example, a randomised controlled trial is often the most appropriate type of study to assess the efficacy or effectiveness (including cost effectiveness) of an intervention. The guideline has added a recommendation advising prescribers to record details of treatment, clinical outcomes and adverse effects for people prescribed cannabis-based medicinal products, using local or national registrys. This will enable feedback from patients to feed into the evidence base.
Cannabis Patient Advocacy & Support Services	Evidence Review B	213	9-21	It seems that productivity losses were excluded from the model, presumably because the NICE reference case suggests exclusion. Nevertheless, productivity costs can still be included as a sensitivity analysis and it may be relevant to consider how their inclusion might affect the main results? (Avalon Health Economics - John E. Schneider, PhD, Andrew Briggs, DPhil, Shawn Davies, MA)	Thank you for your comments. As per the manual for Developing NICE guidelines, the costs in a guideline are calculated in line with the NHS and PSS perspective but do not include the wider societal perspective such as loss of productivity. The reason for this is that productivity costs in our analyses would favour those interventions aimed at the working population. We would then discriminate against the elderly, children, unemployed people and people with disabilities.
Cannabis Patient	Evidence Review B	215; also "Treatme		We recognise some of the limitations of the clinical evidence, but what are the strengths and weaknesses of this approach, and of relying quite heavily on the Langford et al. and Portenoy	Thank you for your comments. Langford et al. 2013 and Portenoy et al. 2012 were used to validate the assumption on the normal distribution of NRS scores. These are the only studies

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Advocacy & Support Services		nt Effects" section of 218		et al. studies? (Avalon Health Economics - John E. Schneider, PhD, Andrew Briggs, DPhil, Shawn Davies, MA)	which provided useful data needed for the model to predict the natural history of the disease (mean & SD of changes from baseline). The efficacy is based on the clinical review meta-analysis and included many more studies.
Cannabis Patient Advocacy & Support Services	Evidence Review B	220	8-19	We are unsure of whether the calculation of the hazard ratio through the censoring of adverse events in the identical dataset and the application of a Cox proportional hazard model is the appropriate method to determine the discontinuation curve. In particular, we would recommend exploration of formal stopping rules in any modelling analysis based on observed response to treatment. This has the potential to improve the cost-effectiveness of treatment. (Avalon Health Economics - John E. Schneider, PhD, Andrew Briggs, DPhil, Shawn Davies, MA)	Thank you for your comments. The approach adopted was designed to make best use of available data. There are no long-term data on response to treatment in this or any other indication; however, we do have some data on discontinuation rates subdivided according to AEs and others. We used these data to infer likely discontinuation trajectories for people taking CBMP as well as loss of 'response' in the standard of care arm.
Cannabis Patient Advocacy & Support Services	Evidence Review B	222	1-21	We are concerned that in cases of chronic pain, a variety of non-invasive treatments, such as pharmacological treatments and physical therapy, could potentially be displaced by the use of CBMPs. This displacement to some extent may impact the model. The models appear to only consider changes in invasive procedures, such as radiofrequency denervation (RFD). In the models, RFD costs were only considered for low back pain. A more thorough consideration of potential changes in clinical pathways should be considered. (Avalon Health Economics - John E. Schneider, PhD, Andrew Briggs, DPhil, Shawn Davies, MA)	Thank you for your comments. As described in the economic model report, the target population is defined as people for whom all available standard chronic pain treatments have failed (Appendix I of the chronic pain evidence review). Medicinal cannabis is only considered as the last treatment option as an add-on to the standard of care before the invasive or surgical interventions in the economic model. As such, medicinal cannabis cannot displace any other standard treatments. The included RCTs did not show any benefit of CBMPs in reducing dosage of other medical analgesia. Further details can be found in the committee discussion section and Appendix I of the chronic pain evidence review.
Cannabis Patient Advocacy & Support Services	Evidence Review B	223		We have two concerns with the handling of adverse events: (1) while we recognize that adverse events are unlikely to have a large impact on the model results, the assumption that serious adverse events are homogeneous may be too aggressive, possibly resulting in additional discontinuations; and (2) the Wang 2008 study is more than 10 years old, and there may be some limitations to its application. (Avalon Health Economics - John E. Schneider, PhD, Andrew Briggs, DPhil, Shawn Davies, MA)	Thank you for your comments. The incidence rate of individual serious adverse event was not reported from Wang et al. 2008. Therefore, we considered the overall serious AE incidence in our analysis. We assumed that the treatment discontinuation has already included discontinuation associated with AEs. To avoid double counting of the discontinuation, we did not assign additional discontinuation associated with the AE calculations in the model. Hence, we do not agree that the assumption that serious adverse events are homogeneous results in additional discontinuations. We conducted a targeted review to identify incidence data for AEs and serious AEs across of medicinal cannabis versus placebo/ standard of care across all indications. Wang et al. 2008 is the only study that provided the appropriate data for the model. A more recent meta-analysis by Whiting et al. 2015 did not report incidence data. Observational studies of medicinal cannabis only reported AEs of medicinal cannabis, rather than comparison against standard treatments. We have validated the safety data with the committee as well as submitted the report for peer-review with additional clinical experts during the consultation. As such, we consider Wang et al. is still the most appropriate source for safety data in the model. Whiting PF, Wolff RF, Deshpande S, Di Nisio M, Duffy S, Hernandez AV, Keurentjes JC, Lang S, Misso K, Ryder S, Schmidlkofer S, Westwood M, Kleijnen J. Cannabinoids for Medical Use: A Systematic Review and Meta-analysis. JAMA. 2015 Jun 23-30;313(24):2456-73.
Cannabis Patient Advocacy & Support Services	Evidence Review B	General	General	Whilst accepting that "Smoked cannabis-based products" are not permitted within the current UK laws and regulations for CBMPs, CPASS feel that with the limited availability of evidence for all other forms and with the plethora of evidence for this type, this limitation has an unproportionate impact on assessing both the benefits and the risks of CBMPs which will lead to low quality and inaccurate outcomes.	Thank you for your comment, This guideline is underpinned by legislation in terms of which cannabis based medicinal products can be considered. Therefore we only considered the following: • cannabis-based medicinal products as defined by the UK Government in November 2018 • the licensed products nabiximols (Sativex) and nabilone. • plant-derived cannabinoids such as pure cannabidiol. • synthetic compounds which are identical in structure to naturally occurring cannabinoids such as delta-9-tetrahydrocannabinol (THC), for example dronabinol.
Cannabis Patient Advocacy & Support Services	Evidence Review B	General	General	CPASS Recommend that special consideration also be given to patients with a diagnosed or suspected complex mental health condition, particularly Schizophrenia and other psychotic disorders. Specifically, around the dosage/ratio of THC:CBD	Thank you for your comment. Psychiatric disorders were out of scope for this guideline. The current research recommendations in the guideline will take into account safety of CBMPs which may include psychotic symptoms.
Cannabis Patient	Evidence Review B	General	General	CPASS are concerned that very limiting criteria have been set for acceptable evidence throughout all evidence reviews (E.g. only 20 pieces of research for Pain, when we are aware	Thank you for your comment. NICE guideline recommendations are based on the best available evidence. Review questions guide the search for evidence, and the type of

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Advocacy & Support Services				of many 1000s of high quality, peer reviewed and published studies for CBMPs and Pain) in order to draw any and all conclusions within this Guideline (there are over 20000 studies of good quality already and easily available, as reviewed and summarised by Professor Mike Barnes report from 2016 and more recently, the comprehensive CBMPs in Pain study published by Nottingham University and The Centre for Medicinal Cannabis' cannabinoid researcher, Dr Saoirse O'Sullivan (https://www.thecmcuk.org/pain-policy) and feel that it would be helpful to understand why 99.98% of the available evidence has not been considered.	evidence used depends on the type of question. For example, a randomised controlled trial is often the most appropriate type of study to assess the efficacy or effectiveness (including cost effectiveness) of an intervention such as chronic pain. This is because all analgesia has a strong placebo effect. Therefore, studies should be double-blinded and randomised.
Cannabis Patient Advocacy & Support Services	Evidence Review B	General	General	As RCTs are not an effective measure for the effectiveness of CBMPs, CPASS challenge the Eligibility criteria for study design being limited to RCTs along and recommend a wider set of criteria, particularly to include direct discussions and feedback from patients who have been consuming for many years.	Thank you for your comment. NICE guideline recommendations are based on the best available evidence. Review questions guide the search for evidence, and the type of evidence used depends on the type of question. For example, a randomised controlled trial is often the most appropriate type of study to assess the efficacy or effectiveness (including cost effectiveness) of an intervention. The guideline has added a recommendation advising prescribers to record details of treatment, clinical outcomes and adverse effects for people prescribed cannabis-based medicinal products, using local or national registrys. This will enable feedback from patients to feed into the evidence base.
Cannabis Patient Advocacy & Support Services	Evidence Review C	170	33-35	It is indicated that the model does not consider productivity losses. Although this is consistent with the NICE Reference Case, a sensitivity analysis could be presented to see what the potential impact on results might be of including productivity costs. (Avalon Health Economics - John E. Schneider, PhD, Andrew Briggs, DPhil, Shawn Davies, MA)	Thank you for your comments. As per the manual for Developing NICE guidelines, the costs in a guideline are calculated in line with the NHS and PSS perspective but do not include the wider societal perspective such as loss of productivity. The reason for this is that productivity costs in our analyses would favour those interventions aimed at the working population. We would then discriminate against the elderly, children, unemployed people and people with disabilities.
Cannabis Patient Advocacy & Support Services	Evidence Review C	175	1 -29	The model relies quite heavily on a small number of clinical studies (e.g., Messina 2017; Patti 2016; Navotna 2011; Markova 2018). It is unclear whether the model estimates used to approximate cannabis response are consistent with other studies, or whether these might be considered reasonable given the preponderance of evidence. (Avalon Health Economics - John E. Schneider, PhD, Andrew Briggs, DPhil, Shawn Davies, MA)	Thank you for your comments. The model considered all studies that reported relevant clinical evidence identified in the evidence review. Only four RCTs provided relevant data for the response (30% improvement in NRS spasticity). In addition to the RCTs, the model also considered evidence from a long-term patient registry. These studies, as well as the model results, are consistent with other included RCTs and show some clinical benefit of THC: CBD sprays in treating spasticity. We have validated the model data with the committee as well as submitted the report for peer-review with additional clinical experts during the consultation. As such, we consider the model estimate to reflect best-available clinical evidence and experience.
Cannabis Patient Advocacy & Support Services	Evidence Review C	184	27 +	Similar to the comment above in the chronic pain model, it is unclear whether the model sufficiently takes into account the potential cost offsets that might be associated with CBMP use. (Avalon Health Economics - John E. Schneider, PhD, Andrew Briggs, DPhil, Shawn Davies, MA)	Thank you for your comments. As described in the economic model report, the target population is defined as people for whom all available standard spasticity treatments have failed (Appendix M of the spasticity evidence review). Medicinal cannabis is only considered as the last treatment option as an add-on to the standard of care before the invasive or surgical interventions in the economic model. As such, medicinal cannabis cannot displace any other standard treatments. The model has considered potential cost saving from the resource use of spasticity management.
Cannabis Patient Advocacy & Support Services	Evidence Review C	General	General	Whilst accepting that "Smoked cannabis-based products" are not permitted within the current UK laws and regulations for CBMPs, CPASS feel that with the limited availability of evidence for all other forms and with the plethora of evidence for this type, this limitation has an unproportionate impact on assessing both the benefits and the risks of CBMPs which will lead to low quality and inaccurate outcomes.	Thank you for your comment. This guideline is underpinned by legislation in terms of which cannabis based medicinal products can be considered. Therefore we only considered the following: • cannabis-based medicinal products as defined by the UK Government in November 2018 • the licensed products nabiximols (Sativex) and nabilone. • plant-derived cannabinoids such as pure cannabidiol. • synthetic compounds which are identical in structure to naturally occurring cannabinoids such as delta-9-tetrahydrocannabinol (THC), for example dronabinol.
Cannabis Patient Advocacy & Support Services	Evidence Review C	General	General	CPASS Recommend that special consideration also be given to patients with a diagnosed or suspected complex mental health condition, particularly Schizophrenia and other psychotic disorders. Specifically, around the dosage/ratio of THC:CBD	Thank you for your comment. Psychiatric disorders were out of scope for this guideline. The current research recommendations in the guideline will take into account safety of CBMPs which may include psychotic symptoms.

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Cannabis Patient Advocacy & Support Services	Evidence Review C	General	General	CPASS are concerned that very limiting criteria have been set for acceptable evidence throughout all evidence reviews (E.g. only 15 pieces of research for Spasticity, when we are aware of many 100s of high quality, peer reviewed and published studies) in order to draw any and all conclusions within this Guideline and feel that it would be helpful to understand why the overwhelming majority of the available evidence has not been graded and considered.	Thank you for your comments. The inclusion criteria for studies in each of our reviews is based on a protocol that is agreed during the scoping process and with the experience of the committee. The protocol for the spasticity review focused on RCT evidence and excluded any cannabis-based medicinal products that were in schedule 1 of the 2001 regulations. The full protocol, including the inclusion and exclusion criteria for studies can be found in Appendix A of the evidence review.
Cannabis Patient Advocacy & Support Services	Evidence Review C	General	General	As RCTs are not an effective measure for the effectiveness of CBMPs, CPASS challenge the Eligibility criteria for study design being limited to RCTs along and recommend a wider set of criteria, particularly to include direct discussions and feedback from patients who have been consuming for many years.	Thank you for your comment. NICE guideline recommendations are based on the best available evidence. Review questions guide the search for evidence, and the type of evidence used depends on the type of question. For example, a randomised controlled trial is often the most appropriate type of study to assess the efficacy or effectiveness (including cost effectiveness) of an intervention. The guideline has added a recommendation advising prescribers to record details of treatment, clinical outcomes and adverse effects for people prescribed cannabis-based medicinal products, using local or national regisstys. This will enable feedback from patients to feed into the evidence base.
Cannabis Patient Advocacy & Support Services	Evidence Review D	General	General	Whilst accepting that "Smoked cannabis-based products" are not permitted within the current UK laws and regulations for CBMPs, CPASS feel that with the limited availability of evidence for all other forms and with the plethora of evidence for this type, this limitation has an unproportionate impact on assessing both the benefits and the risks of CBMPs which will lead to low quality and inaccurate outcomes.	Thank you for your comment. This guideline is underpinned by legislation in terms of which cannabis based medicinal products can be considered. Therefore we only considered the following: • cannabis-based medicinal products as defined by the UK Government in November 2018 • the licensed products nabiximols (Sativex) and nabilone. • plant-derived cannabinoids such as pure cannabidiol. • synthetic compounds which are identical in structure to naturally occurring cannabinoids such as delta-9-tetrahydrocannabinol (THC), for example dronabinol.
Cannabis Patient Advocacy & Support Services	Evidence Review D	General	General	CPASS Recommend that special consideration also be given to patients with a diagnosed or suspected complex mental health condition, particularly Schizophrenia and other psychotic disorders. Specifically, around the dosage/ratio of THC:CBD	Thank you for your comment. Psychiatric disorders were out of scope for this guideline. The current research recommendations in the guideline will take into account safety of CBMPs which may include psychotic symptoms.
Cannabis Patient Advocacy & Support Services	Evidence Review D	General	General	CPASS are concerned that very limiting criteria have been set for acceptable evidence throughout all evidence reviews. Only 15 pieces of research were accepted for Epilepsy, from a total of over 13000 RCTs and Observational studies ruling out 99.8% of available evidence to draw all conclusions within this Guideline and feel that it would be helpful to understand why broader evidence has not been considered.	Thank you for your comments. The inclusion criteria for studies in each of our reviews is based on a protocol that is agreed during the scoping process and with the experience of the committee. The protocol for the epilepsy review included both RCT and observational evidence but excluded any cannabis-based medicinal products that were in schedule 1 of the 2001 regulations. This review focused on people with severe treatment-resistant epilepsy and not other forms of epilepsy. The full protocol, including the inclusion and exclusion criteria for studies can be found in Appendix A of the evidence review.
Cannabis Patient Advocacy & Support Services	Evidence Review D	General	General	As RCTs are not an effective measure for the effectiveness of CBMPs, CPASS challenge the Eligibility criteria for study design being limited to RCTs along and recommend a wider set of criteria, particularly to include direct discussions and feedback from patients who have been consuming for many years.	Thank you for your comment. NICE guideline recommendations are based on the best available evidence. Review questions guide the search for evidence, and the type of evidence used depends on the type of question. For example, a randomised controlled trial is often the most appropriate type of study to assess the efficacy or effectiveness (including cost effectiveness) of an intervention. The guideline has added a recommendation advising prescribers to record details of treatment, clinical outcomes and adverse effects for people prescribed cannabis-based medicinal products, using local or national registrys. This will enable feedback from patients to feed into the evidence base.

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Cannabis Patient Advocacy & Support Services	Evidence Review E	General	General	Whilst accepting that "Smoked cannabis-based products" are not permitted within the current UK laws and regulations for CBMPs, CPASS feel that with the limited availability of evidence for all other forms and with the plethora of evidence for this type, this limitation has an unproportionate impact on assessing both the benefits and the risks of CBMPs which will lead to low quality and inaccurate outcomes.	Thank you for your comment. This guideline is underpinned by legislation in terms of what cannabis based medicinal products can be considered. Therefore we only considered the following: • cannabis-based medicinal products as defined by the UK Government in November 2018 • the licensed products nabiximols (Sativex) and nabilone. • plant-derived cannabinoids such as pure cannabidiol. • synthetic compounds which are identical in structure to naturally occurring cannabinoids such as delta-9-tetrahydrocannabinol (THC), for example dronabinol. Furthermore, the guideline has added a recommendation advising prescribers to record details of treatment, clinical outcomes and adverse effects for people prescribed cannabis-based medicinal products, using local or national registrys. This will enable feedback from patients to feed into the evidence base.
Cannabis Patient Advocacy & Support Services	Evidence Review E	General	General	CPASS Recommend that special consideration also be given to patients with a diagnosed or suspected complex mental health condition, particularly Schizophrenia and other psychotic disorders. Specifically, around the dosage/ratio of THC:CBD	Thank you for your comment. Psychiatric disorders were out of scope for this guideline. The current research recommendations in the guideline will take into account safety of CBMPs which may include psychotic symptoms.
Cannabis Patient Advocacy & Support Services	Evidence Review E	General	General	CPASS are concerned that very limiting criteria have been set for acceptable evidence throughout all evidence reviews (E.g. only 20 pieces of research for Pain, when we are aware of many 1000s of high quality, peer reviewed and published studies for CBMPs and Pain) in order to draw any and all conclusions within this Guideline (there are over 20000 studies of good quality already and easily available, as reviewed and summarised by Professor Mike Barnes report from 2016 and more recently, the comprehensive CBMPs in Pain study published by Nottingham University and The Centre for Medicinal Cannabis' cannabinoid researcher, Dr Saoirse O'Sullivan (https://www.thecmcuk.org/pain-policy) and feel that it would be helpful to understand why 99.98% of the available evidence has not been considered.	Thank you for your comment. NICE guideline recommendations are based on the best available evidence. Review questions guide the search for evidence, and the type of evidence used depends on the type of question. For example, a randomised controlled trial is often the most appropriate type of study to assess the efficacy or effectiveness (including cost effectiveness) of an intervention such as chronic pain. This is because all analgesia has a strong placebo effect. Therefore, studies should be double-blinded and randomised.
Cannabis Patient Advocacy & Support Services	Evidence Review E	General	General	As RCTs are not an effective measure for the effectiveness of CBMPs, CPASS challenge the Eligibility criteria for study design being limited to RCTs along and recommend a wider set of criteria, particularly to include direct discussions and feedback from patients who have been consuming for many years.	Thank you for your comment. NICE guideline recommendations are based on the best available evidence. Review questions guide the search for evidence, and the type of evidence used depends on the type of question. For example, a randomised controlled trial is often the most appropriate type of study to assess the efficacy or effectiveness (including cost effectiveness) of an intervention. The guideline has added a recommendation advising prescribers to record details of treatment, clinical outcomes and adverse effects for people prescribed cannabis-based medicinal products, using local or national registrys. This will enable feedback from patients to feed into the evidence base.
Cannabis Patient Advocacy & Support Services	Guideline	1	7	CPASS fail to understand the benefit in limiting "nausea and vomiting" to "intractable" and only related to "chemotherapy-induced" All medical professionals we have consulted have said that if there is the potential for a CBMP to work for a symptom, then that potential covers ALL conditions where the symptom is being experienced?	Thank you for your comment. During the development of the scope, intractable nausea and vomiting was identified as a key issue. Therefore, review questions were drafted to look at the effectiveness, safety and harms of cannabis based medicinal products in people with intractable nausea and vomiting. During the development of the review, the majority of evidence identified examined chemotherapy induced nausea and vomiting and only 1 study was identified for radiotherapy induced nausea and vomiting. Based on the available evidence the committee made recommendations for chemotherapy induced nausea and vomiting but did acknowledge the lack of evidence for other causes of intractable nausea and vomiting and drafted a research recommendation.
Cannabis Patient Advocacy & Support Services	Guideline	1	7	CPASS fail to understand why epilepsy is limited to severe treatment-resistant types only? We are in agreement with all medical professionals we have consulted that if there is the potential for a CBMP to work for a symptom, then that potential covers ALL conditions where the symptom is being experienced?	Thank you for your comments. The scope of this guideline was to examine the effectiveness of CBMP for the people who it was thought would have the most benefit and so severe treatment-resistant epilepsy was identified. The committee discussed whether the results of the research could be applied to other types of epilepsy. However, they were concerned that although different types of epilepsy may have some common mechanisms, there are differences in underlying pathologies that mean they could not confidently apply the results to other epilepsy syndromes.

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Cannabis Patient Advocacy & Support Services	Guideline	10	3	I think recommendation for further research can be broader and include effectiveness and safety of all CBMPs, including synthetic compounds, plant derived, whole plant extracts, oils and flower, and the guidelines could specifically recommend the use of a Phase IV clinical trial registry/surveillance study of clinical practice in terms of different types of CBMPs, prescribed in concordance between patients and healthcare providers, in England or the UK. A registry could facilitate the prescription and access of CBMPs while at the same time build up the evidence base in terms of benefits and risks across a range of conditions in a real world setting, rather than the limited evidence obtained from the restricted samples and environment of Phase I-III clinical trials of specific CBMP compounds. It is important that research is not just conducted with products developed and marketed by pharmaceutical companies, but that cost-effectiveness studies consider the use of other products that come at a much lower price-point. (I can speak both as a researcher - my credentials are PhD, CPsychol and over 10 years experience) and from experience as a patient or carer)	Thank you for your comment. The scope of this guideline included cannabis-based medicinal products: • cannabis-based products for medicinal use as set out by the UK Government in the 2018 Regulations • the licensed products delta-9-tetrahydrocannibinol and cannabidiol (Sativex) and nabilone • plant-derived cannabinoids such as pure cannabidiol (CBD) • synthetic compounds which are identical in structure to naturally occurring cannabinoids such as delta-9-tetrahydrocannabinol (THC), for example, dronabinol. All other cannabis-based products were excluded from the scope of this guideline. The committee agreed that an additional recommendation on a national or local registry was needed. This will facilitate an improved evidence base for CBMPs.
Cannabis Patient Advocacy & Support Services	Guideline	10	5	I think recommendation for further research can be broader and include effectiveness and safety of all CBMPs, including synthetic compounds, plant derived, whole plant extracts, oils and flower, and the guidelines could specifically recommend the use of a Phase IV clinical trial registry/surveillance study of clinical practice in terms of different types of CBMPs, prescribed in concordance between patients and healthcare providers, in England or the UK. A registry could facilitate the prescription and access of CBMPs while at the same time build up the evidence base in terms of benefits and risks across a range of conditions in a real world setting, rather than the limited evidence obtained from the restricted samples and environment of Phase I-III clinical trials of specific CBMP compounds. It is important that research is not just conducted with products developed and marketed by pharmaceutical companies, but that cost-effectiveness studies consider the use of other products that come at a much lower price-point. (I can speak both as a researcher - my credentials are PhD, CPsychol and over 10 years experience) and from experience as a patient or carer)	Thank you for your comment. The scope of this guideline included cannabis-based medicinal products: • cannabis-based products for medicinal use as set out by the UK Government in the 2018 Regulations • the licensed products delta-9-tetrahydrocannibinol and cannabidiol (Sativex) and nabilone • plant-derived cannabinoids such as pure cannabidiol (CBD) • synthetic compounds which are identical in structure to naturally occurring cannabinoids such as delta-9-tetrahydrocannabinol (THC), for example, dronabinol. All other cannabis-based products were excluded from the scope of this guideline. The committee agreed that an additional recommendation on a national or local registry was needed. This will facilitate an improved evidence base for CBMPs.
Cannabis Patient Advocacy & Support Services	Guideline	10	8	I think recommendation for further research can be broader and include effectiveness and safety of all CBMPs, including synthetic compounds, plant derived, whole plant extracts, oils and flower, and the guidelines could specifically recommend the use of a Phase IV clinical trial registry/surveillance study of clinical practice in terms of different types of CBMPs, prescribed in concordance between patients and healthcare providers, in England or the UK. A registry could facilitate the prescription and access of CBMPs while at the same time build up the evidence base in terms of benefits and risks across a range of conditions in a real world setting, rather than the limited evidence obtained from the restricted samples and environment of Phase I-III clinical trials of specific CBMP compounds. It is important that research is not just conducted with products developed and marketed by pharmaceutical companies, but that cost-effectiveness studies consider the use of other products that come at a much lower price-point. (I can speak both as a researcher - my credentials are PhD, CPsychol and over 10 years experience) and from experience as a patient or carer)	Thank you for your comment. The scope of this guideline included cannabis-based medicinal products: • cannabis-based products for medicinal use as set out by the UK Government in the 2018 Regulations • the licensed products delta-9-tetrahydrocannibinol and cannabidiol (Sativex) and nabilone • plant-derived cannabinoids such as pure cannabidiol (CBD) • synthetic compounds which are identical in structure to naturally occurring cannabinoids such as delta-9-tetrahydrocannabinol (THC), for example, dronabinol. All other cannabis-based products were excluded from the scope of this guideline. The committee agreed that an additional recommendation on a national or local registry was needed. This will facilitate an improved evidence base for CBMPs.

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Cannabis Patient Advocacy & Support Services	Guideline	10	22	I think recommendation for further research can be broader and include effectiveness and safety of all CBMPs, including synthetic compounds, plant derived, whole plant extracts, oils and flower, and the guidelines could specifically recommend the use of a Phase IV clinical trial registry/surveillance study of clinical practice in terms of different types of CBMPs, prescribed in concordance between patients and healthcare providers, in England or the UK. A registry could facilitate the prescription and access of CBMPs while at the same time build up the evidence base in terms of benefits and risks across a range of conditions in a real world setting, rather than the limited evidence obtained from the restricted samples and environment of Phase I-III clinical trials of specific CBMP compounds. It is important that research is not just conducted with products developed and marketed by pharmaceutical companies, but that cost-effectiveness studies consider the use of other products that come at a much lower price-point. (I can speak both as a researcher - my credentials are PhD, CPsychol and over 10 years experience) and from experience as a patient or carer)	Thank you for your comment. The scope of this guideline included cannabis-based medicinal products: • cannabis-based products for medicinal use as set out by the UK Government in the 2018 Regulations • the licensed products delta-9-tetrahydrocannibinol and cannabidiol (Sativex) and nabilone • plant-derived cannabinoids such as pure cannabidiol (CBD) • synthetic compounds which are identical in structure to naturally occurring cannabinoids such as delta-9-tetrahydrocannabinol (THC), for example, dronabinol. All other cannabis-based products were excluded from the scope of this guideline. The committee agreed that an additional recommendation on a national or local registry was needed. This will facilitate an improved evidence base for CBMPs.
Cannabis Patient Advocacy & Support Services	Guideline	11	6	I think recommendation for further research can be broader and include effectiveness and safety of all CBMPs, including synthetic compounds, plant derived, whole plant extracts, oils and flower, and the guidelines could specifically recommend the use of a Phase IV clinical trial registry/surveillance study of clinical practice in terms of different types of CBMPs, prescribed in concordance between patients and healthcare providers, in England or the UK. A registry could facilitate the prescription and access of CBMPs while at the same time build up the evidence base in terms of benefits and risks across a range of conditions in a real world setting, rather than the limited evidence obtained from the restricted samples and environment of Phase I-III clinical trials of specific CBMP compounds. It is important that research is not just conducted with products developed and marketed by pharmaceutical companies, but that cost-effectiveness studies consider the use of other products that come at a much lower price-point. (I can speak both as a researcher - my credentials are PhD, CPsychol and over 10 years experience) and from experience as a patient or carer)	Thank you for your comment. The scope of this guideline included cannabis-based medicinal products: • cannabis-based products for medicinal use as set out by the UK Government in the 2018 Regulations • the licensed products delta-9-tetrahydrocannibinol and cannabidiol (Sativex) and nabilone • plant-derived cannabinoids such as pure cannabidiol (CBD) • synthetic compounds which are identical in structure to naturally occurring cannabinoids such as delta-9-tetrahydrocannabinol (THC), for example, dronabinol. All other cannabis-based products were excluded from the scope of this guideline. The committee agreed that an additional recommendation on a national or local registry was also needed This will facilitate an improved evidence base for CBMPs.
Cannabis Patient Advocacy & Support Services	Guideline	12	1	The guideline states that there was a lack of evidence on longer-term adverse events, such as dependence and the development of psychological disorders but has not provided any rationale on why this considered such a special concern for CBMPs. There is no evidence that in balanced (Eg: Sativex) or moreover low doses of THC (which is found naturally in Hemp seed Oil) has any associated risk and it is surely not standard practise to apply risks associated with chronic use of an illicit drug to that of a quality, standardised medicine under the supervision of a medical professional? CPASS request that this is reviewed	Thank you for your comment. Long-term adverse events are considered for all pharmacological interventions. Cannabis-based medicinal products as defined by the government are unlicensed medications and the safety and efficacy has not been established for products other than nabilone and Sativex. The international guidelines included as part of the review all list risk of dependence as a treatment factor and the guideline committee made a recommendation for this to be a factor to think about when prescribing.
Cannabis Patient Advocacy & Support Services	Guideline	13	14	CPASS are concerned that ALL recommendations are based on a very limited selection of published, quality and peer reviewed evidence from around the world. The Guideline states, for instance, that "some evidence showed that cannabis-based medicinal products reduce chronic pain, but the treatment effect was modest." and adds that in spite of the overwhelming evidence to the contrary from around the world that the evidence reviewed did not show a reduction in opioid use in people prescribed medicinal cannabis. Frankly, this is highly inaccurate and ill-informed. This appears to relate only to limited RCT data which are inappropriate for measuring the efficacy of CBMPs. If only one formulation of CBMP is trialled against placebo, the results will always be limited, however, where a range of balances has been offered in alternative trials, efficacy is seen to improve from ~20% to ~80%. There is good quality evidence, increasing over time that shows where US States and other jurisdictions have introduced an easy access medical cannabis policy, opiate-related deaths and addiction have reduced by an average of 24.8%.	Thank you for your comment. NICE guideline recommendations are based on the best available evidence. Review questions guide the search for evidence, and the type of evidence used depends on the type of question. For example, a randomised controlled trial is often the most appropriate type of study to assess the efficacy or effectiveness (including cost effectiveness) of all pharmacological treatments across different conditions including chronic pain. This is because all analgesia has a strong placebo effect. Therefore, studies should be double-blinded and randomised. Our systematic review of RCTs found that the outcomes for opioid usage were not statistically significant.

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				https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/1898878 Further studies have since validated these results and it can be seen that these benefits are continuing to increase. We request that should NICE be unwilling to accept and include this evidence then a rationale should be provided to explain to patients as to why? The number of deaths and other related issues with Opiate medications is on the rise in the UK and this represents an enormous and critical opportunity to address this before it becomes any worse. Almost without exception, our patients tell us that the consumption of a CBMP (whether legally sourced or not) has immediately and significantly reduced their use of and dependency on other more harmful medications. This can be evidenced by the results and patient feedback during two UK patient surveys in 2016 and 2018 the raw data from which CPASS would be happy to provide for analysis. Here is a list of the Top 25 Medications that patients report reducing or in most cases replacing with Cannabis: Tramadol (10% of ALL medical cannabis patients) Gabapentin Pregabalin Amitriptyline Sertraline Codeine Paracetamol Naproxen Citalopram Diazepam Amitriptyline Morphine Mirtazapine Anti-depressants Duloxetine Fluoxetine Co-Codamol Pain-killers Co-co-codamol Ibuprofen Omeprazole Oramorph Dihydrocodeine Propranolol Baclofen One producer we have spoken to in the US, Columbia Care, whom we would be happy to introduce you to, has data on over 40000 patients in the US for whom 99% have successfully transitioned from opiates to CBMPs and are managing their pain more effectively and with significantly less unwanted side-effects.	
Cannabis Patient Advocacy & Support Services	Guideline	13	19	The Guideline states that because the number of people who might benefit is large and the cost potentially high, an economic model was developed to compare benefits with the potential costs. In all cases, the potential benefits offered were small compared with the high and ongoing costs, and so the products were not an effective use of NHS resources and adds that the evidence showed benefits of THC:CBD spray (licensed product in UK: Sativex®) for	Thank you for your comments. The economic model is based on the best available evidence in spasticity, which is mostly on THC: CBD spray (Sativex). NICE welcomes the upcoming

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				treating spasticity" but since Sativex® is little more than a 1:1 THC:CBD biological extract CBMP (it is made from full plant), CPASS suggest recommending one of the many other similar products that are currently available at less than 1/5th of the price of Sativex as this would radically change this recommendation? CPASS is currently in the process of producing an economic case for CBMPs with qualified health economists which we will publish and share with NICE in due course, but for now, as a most pertinent example: In the US where Multiple Sclerosis (MS) patients, who constitute just 6% of those who report benefit, have access to cannabis, around 25% replace their existing suite of medications. The average MS patient costs ~£30k per year in medications alone and the cost of cannabis is ~£6k per year, representing a saving of £24k per patient per year. The UK has ~100k MS patients so represents a potential saving of (£24k * 25% of 100k) £600m per year to the NHS for prescription medications alone. Imagine what the saving might be if this included the other 94% of patients? Of course, when your existing processes only take a single symptom into consideration rather than looking at how cannabis can help manage multiple conditions simultaneously and if the only figures you use for costs are based on a product costing 5 to 10 times more than other similar and available products (Sativex®) it is going to be impossible to make this case. CPASS strongly recommend to NICE that they review how these calculations are made and perform another review as soon as possible.	CBMPs in the near future. However, until there is published clinical evidence to show the effectiveness of these products, NICE cannot consider them in our analysis. After publication of the consultation draft of the guideline, the manufacturer reduced the list price of THC:CBD spray, and this had an important impact on our assessment of its cost effectiveness. In light of stakeholder comments, the committee also reviewed their estimates of likely resource use associated with spasticity symptoms. The committee are now able to make a more positive recommendation.
Cannabis Patient Advocacy & Support Services	Guideline	15	31	The Guideline goes on to state that other CBMPs should not be used to treat spasticity unless used in the context of a clinical trial. This recommendation was apparently needed to ensure that other products were not used as an alternative to THC:CBD spray (Sativex®) without sufficient evidence of their effects and associated costs. This is not a reasonable rationale and seems to us to be rather protective of a single product. There are many other products with almost the same makeup as Sativex®. What is the rationale for treating this differently? Sativex® is simply a very expensive CBMP. The safety data will be identical in all similar products?	Thank you for your comment. After publication of the consultation draft of the guideline, the manufacturer reduced the list price of THC:CBD spray, and this had an important impact on our assessment of its cost effectiveness. In light of stakeholder comments, the committee also reviewed their estimates of likely resource use associated with spasticity symptoms. The committee are now able to make a more positive recommendation.
Cannabis Patient Advocacy & Support Services	Guideline	16	17	The guideline states that current research is limited and of low quality, making it difficult to assess just how effective these products are for people. CPASS, along with many qualified experts and medical professionals in this field suggest that we MUST move beyond our exclusive reliance on RCT data and given that this was raised with NICE many months ago during the scoping consultation, we are very disappointed that seems to have been completely ignored.	Thank you for your comments. We included evidence from a number of observational studies within our review but the committee were concerned that these were low quality studies which did not include any control groups. The committee appreciated that some people have shown benefits from the use of cannabis-based medicinal products and so they did not make a recommendation against their use. However, they did not feel that current evidence was sufficient to confidently recommend their use either. Although the committee did not make a recommendation for the use of cannabis-based medicinal products they did make research recommendations to investigate the effectiveness of CBD and of CBD:THC for the treatment of epilepsy. These research recommendations are aimed at improving the quality of evidence so that future committees will be able to make more evidence-based decisions on the use of cannabis-based medicinal products.
Cannabis Patient Advocacy & Support Services	Guideline	4	4	This should definitely be used with chemotherapy. Anything which can help patients undergoing treatment. (I can speak from experience as a qualified medic)	Thank you for your comment.
Cannabis Patient Advocacy & Support Services	Guideline	4	12	There is very little effective treatment out there for patients. The data, although not in the correct type, i.e, RCT does suggest that CBMPs are useful and effective in managing chronic / persistent pain. Patients are increasingly frustrated and upset with the current state of chronic pain provision and management. (I can speak from experience as a qualified medic)	Thank you for your comment. RCTs are the best studies for assessing medicinal cannabis. This is because all analgesia has a strong placebo effect. Therefore, studies should be double-blinded and randomised.
Cannabis Patient	Guideline	4	4	A core tenant of NHS England's commitment to providing patient/person centred care is to	Thank you for your comment and for providing ESMO's guidance for the prevention of chemotherapy induced nausea and vomiting. The NICE guideline committee recommended

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Advocacy & Support Services				involve patients in their treatment decisions. To do this, all treatment options should be presented and discussed with the patient so that the most suitable combination for that individual is prescribed. Patients who are suffering from chemotherapy-induced nausea and vomiting, two of the most distressing side-effects of cancer chemotherapy, who are interested in trying a CBMP to alleviate their suffering should have the right to do that. The option of adding a CBMP onto an existing treatment regime with other conventional antiemetics should also be considered. There is no justification for forcing those patients who could benefit from CBMP, and who would like to try a CBMP alone or in combination with conventional antiemetics, onto other treatment combinations for prolonged periods of time, which risk causing unnecessary and avoidable suffering with significant impact on health related quality of life. Indeed, ESMO's clinical practice guidelines for the management of chemotherapy induced nausea and vomiting recommends "Antiemetics are most effective when used prophylactically. Therefore, it is preferable to use maximally effective antiemetics as first-line therapy rather than withholding more effective antiemetics for later use at the time of antiemetic failure" (Roila, F., et al. Ann Oncol (2016) 27 (suppl 5): v119-v133). In addition, for patients who develop an anticipatory response through the repeated experience of chemotherapy induced nausea and vomiting, the nausea and vomiting becomes difficult to control by pharmacological treatment. Therefore, ESMO states that the best approach for the prevention of anticipatory nausea and vomiting is the best possible control of acute and delayed nausea and vomiting up front (Roila, F., et al. Ann Oncol (2016) 27 (suppl 5): v119-v133). The draft NICE guidelines are providing recommendations for NHS England that are in direct opposition to European clinical practice guidance. To limit the recommendation to nabilone only is an oversight from NICE about the potential benefits of other plant derived and whole plant products, which often come at a lower price-point and have the potential benefit of the combined effect from the broad spectrum of cannabinoids, terpenes and flavonoids of the whole plant. Like with any other pharmacological treatment, different treatments work for different people, and prescribers and patients have to work together to figure out what works for an individual. Patients should have the same right to try different CBMPs that could be made available if facilitated by legal and regulatory process, synthetic compounds, plant derived, whole plant extracts, oils and flower, to find the formulation that best fit their needs and individual response to the CBMPs.	to consider nabilone as an add-on treatment if nausea and vomiting persists with optimised conventional antiemetics. This does not contradict the ESMO guidance and other guidance available which specify treatment options for antiemetic therapy, as nabilone is recommended to be considered as an add-on treatment if nausea and vomiting persists after optimised antiemetic therapy. The recommendation is a consider recommendation, and the person and healthcare practitioner should discuss and consider all treatment options. Furthermore, the scope of this guideline included the following cannabis-based medicinal products: • cannabis-based products for medicinal use as set out by the UK Government in the 2018 Regulations • the licensed products delta-9-tetrahydrocannibinol and cannabidiol (Sativex) and nabilone • plant-derived cannabinoids such as pure cannabidiol (CBD) • synthetic compounds which are identical in structure to naturally occurring cannabinoids such as delta-9-tetrahydrocannabinol (THC), for example, dronabinol. Evidence on the use of following products for intractable nausea and vomiting was found: • Tetrahydrocannabinol (THC) • Tetrahydrocannabinol (THC) plus prochlorperazine • Dronabinol • Dronabinol plus prochlorperazine • Nabilone Based on the available evidence and their clinical experience, the committee recommended for nabilone to be considered as an add-on treatment if nausea and vomiting persists after optimised antiemetic therapy. Other products were not recommended due to a lack of or poor-quality evidence.
Cannabis Patient Advocacy & Support Services	Guideline	4	12	CPASS feel that if any progress is ever to be made in helping patients to access CBMPs then, to offer a direct instruction NOT to prescribe them should be reconsidered to reflect less absolute wording, such as "NICE do not recommend" rather than "Do not offer"	Thank you for your comment. A 'do not use' recommendation was based on the evidence which showed that the potential benefits of these products were small compared with the high and ongoing costs. Therefore, the committee recommended that nabilone, dronabinol, THC and a combination of CBD and THC should not be offered.
Cannabis Patient Advocacy & Support Services	Guideline	4	12	A core tenant of NHS England's commitment to providing patient/person centred care is to involve patients in their treatment decisions. To do this, all treatment options should be presented and discussed with the patient so that the most suitable combination for that individual is prescribed. Chronic pain is very difficult to manage and the available treatments cause sever and debilitating side effects. Patients who are suffering from chronic pain who have been using, or are interested in trying a CBMP, including synthetic compounds, plant derived, whole plant extracts, oils and flower, to alleviate their suffering should have the right to do that. There is no justification for forcing those patients who could benefit from CBMP,	Thank you for your comment. Some of the cannabis preparations listed are out of scope for this review. Recommendation 1.5.10 in the guideline outlines the importance of shared decision making. The RCT data that we reviewed favours some types of medicinal cannabis for managing chronic pain compared to placebo. However, although this reaches statistical significance, the effect size is so small that individual people are unlikely to notice any difference. For example, pain intensity is measured on a scale of 0 to 10, 0 being no pain and 10 being maximum pain. In order for a person to notice any difference, analgesia should reduce pain

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				and who would like to try a CBMP alone or in combination with other treatments, onto other treatment combinations for prolonged periods of time, which risk causing unnecessary and avoidable suffering with significant impact on health related quality of life. (I can speak both as a researcher - my credentials are PhD, CPsychol and over 10 years experience) and from experience as a patient or carer)	intensity by at least 2 or even 3 points. Most pain intensity effect sizes were either statistically insignificant (oral delta-9-THC, oromucosal THC, vaporised THC (minimal CBD), vaporised THC:CBD, vaporised CBD (minimal THC)), or they caused less than a 2 point pain intensity drop (oromucosal CBD:THC) or the 95% confidence interval crossed the 2 point pain intensity drop threshold (oral nabilone). The cost of medicinal cannabis for chronic pain is around 6 times greater than the NHS would normally deem an efficient use of resources.
Cannabis Patient Advocacy & Support Services	Guideline	5	1	The field would benefit from more data being collected on the prescribing, use, effectiveness and safety of all CBMPs, including synthetic compounds, plant derived, whole plant extracts, oils and flower, and the guidelines could specifically recommend the use of a Phase IV clinical trial registry/surveillance study of clinical practice in terms of different types of CBMPs, prescribed in concordance between patients and healthcare providers, in England or the UK. A registry could facilitate the prescription and access of CBMPs while at the same time build up the evidence base in terms of benefits and risks across a range of conditions in a real world setting, rather than the limited evidence obtained from the restricted samples and environment of Phase I-III clinical trials of specific CBMP compounds. (I can speak both as a researcher - my credentials are PhD, CPsychol and over 10 years experience) and from experience as a patient or carer)	Thank you for your comment This guideline is underpinned by legislation in terms of what cannabis based medicinal products can be considered. Therefore we only considered the following: • cannabis-based medicinal products as defined by the UK Government in November 2018 • the licensed products nabiximols (Sativex) and nabilone. • plant-derived cannabinoids such as pure cannabidiol. • synthetic compounds which are identical in structure to naturally occurring cannabinoids such as delta-9-tetrahydrocannabinol (THC), for example dronabinol. The guideline has added a recommendation advising prescribers to record details of treatment, clinical outcomes and adverse effects for people prescribed cannabis-based medicinal products, using local or national registrys. This will enable feedback from patients to feed into the evidence base.
Cannabis Patient Advocacy & Support Services	Guideline	5	1	CBD is safe and unlikely to cause any significant harm to patients. There should definitely be trials especially in a primary care setting. (I can speak from experience as a qualified medic)	Thank you for your comment.
Cannabis Patient Advocacy & Support Services	Guideline	5	4	To limit the recommendation to Sativex only is an oversight from NICE about the potential benefits of other CBMPs, including plant derived and whole plant products, which often come at a lower price-point than compounds marketed by pharmaceutical companies, and have the potential benefit of the combined effect from the broad spectrum of cannabinoids, terpenes and flavonoids of the whole plant. Like with any other pharmacological treatment, different treatments work for different people, and prescribers and patients have to work together to figure out what works for an individual. Patients suffering from plasticity from MS should have the same right to try different CBMPs that could be made available if facilitated by legal and regulatory process to find the formulation that best fit their needs and individual response to different CBMPs. (I can speak both as a researcher - my credentials are PhD, CPsychol and over 10 years experience) and from experience as a patient or carer)	Thank you for your comment. After publication of the consultation draft of the guideline, the manufacturer reduced the list price of THC:CBD spray, and this had an important impact on our assessment of its cost effectiveness. In light of stakeholder comments, the committee also reviewed their estimates of likely resource use associated with spasticity symptoms. The committee are now able to make a more positive recommendation.
Cannabis Patient Advocacy & Support Services	Guideline	5	7	The field would benefit from more data being collected on the prescribing, use, effectiveness and safety of all CBMPs, including synthetic compounds, plant derived, whole plant extracts, oils and flower, and the guidelines could specifically recommend the use of a Phase IV clinical trial registry/surveillance study of clinical practice in terms of different types of CBMPs, prescribed in concordance between patients and healthcare providers, in England or the UK. A registry could facilitate the prescription and access of CBMPs while at the same time build up the evidence base in terms of benefits and risks across a range of conditions in a real world setting, rather than the limited evidence obtained from the restricted samples and environment of Phase I-III clinical trials of specific CBMP compounds. (I can speak both as a researcher - my credentials are PhD, CPsychol and over 10 years experience) and from experience as a patient or carer)	Thank you for your comments. We agree that more evidence is needed on the effectiveness and safety of cannabis-based medicinal products. For this reason we have included 8 research recommendations, each designed to increase understanding of the effectiveness of these products for the conditions covered in this guideline. The research recommendations can be found in the Recommendations for Research section of the guideline. The committee agreed that an additional recommendation on a national or local registry was needed. This will facilitate an improved evidence base for CBMPs.

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Cannabis Patient Advocacy & Support Services	Guideline	5	1	CPASS feel that if any progress is ever to be made in helping patients to access CBMPs then, to offer a direct instruction NOT to prescribe them should be reconsidered to reflect less absolute wording, such as "NICE do not recommend" rather than "Do not offer"	Thank you for your comment. The RCT data that we reviewed favours some types of medicinal cannabis for managing chronic pain compared to placebo. However, although this reaches statistical significance, the effect size is so small that individual people are unlikely to notice any difference. For example, pain intensity is measured on a scale of 0 to 10, 0 being no pain and 10 being maximum pain. In order for a person to notice any difference, analgesia should reduce pain intensity by at least 2 or even 3 points. Most pain intensity effect sizes were either statistically insignificant (oral delta-9-THC, oromucosal THC, vaporised THC (minimal CBD), vaporised THC:CBD, vaporised CBD (minimal THC)), or they caused less than a 2 point pain intensity drop (oromucosal CBD:THC) or the 95% confidence interval crossed the 2 point pain intensity drop threshold (oral nabilone). The cost of medicinal cannabis for chronic pain is around 6 times greater than the NHS would normally deem an efficient use of resources.
Cannabis Patient Advocacy & Support Services	Guideline	5	4	CPASS feel that if any progress is ever to be made in helping patients to access CBMPs then, to offer a direct instruction NOT to prescribe them should be reconsidered to reflect less absolute wording, such as "NICE do not recommend" rather than "Do not offer"	Thank you for your comment. After publication of the consultation draft of the guideline, the manufacturer reduced the list price of THC:CBD spray, and this had an important impact on our assessment of its cost effectiveness. In light of stakeholder comments, the committee also reviewed their estimates of likely resource use associated with spasticity symptoms. The committee are now able to make a more positive recommendation.
Cannabis Patient Advocacy & Support Services	Guideline	5	7	CPASS feel that if any progress is ever to be made in helping patients to access CBMPs then, to offer a direct instruction NOT to prescribe them should be reconsidered to reflect less absolute wording, such as "NICE do not recommend" rather than "Do not offer"	Thank you for your comment. After publication of the consultation draft of the guideline, the manufacturer reduced the list price of THC:CBD spray, and this had an important impact on our assessment of its cost effectiveness. In light of stakeholder comments, the committee also reviewed their estimates of likely resource use associated with spasticity symptoms. The committee are now able to make a more positive recommendation.
Cannabis Patient Advocacy & Support Services	Guideline	6	3	General Practitioners with an interest in Pain Management should be able to prescribe. (I can speak from experience as a qualified medic)	Thank you for your comment. This recommendation is underpinned by legislation in terms of who can start the treatment. Once the specialist has started treatment, this may then be taken over by the GP as part of a shared care arrangement.
Cannabis Patient Advocacy & Support Services	Guideline	6	4	General Practitioners should be able to prescribe. We deal with the majority of prescription in the NHS. We are the experts in prescribing. (I can speak from experience as a qualified medic)	Thank you for your comment. This recommendation is underpinned by legislation in terms of who can start the treatment. Once the specialist has started treatment, this may then be taken over by the GP as part of a shared care arrangement.
Cannabis Patient Advocacy & Support Services	Guideline	6	10	Shared care drugs already have a role in primary care. (I can speak from experience as a qualified medic)	Thank you for your comment
Cannabis Patient Advocacy & Support Services	Guideline	6	14	Safety mechanisms are already embedded in computer software in Primary Care. (I can speak from experience as a qualified medic)	Thank you for your comment
Cannabis Patient Advocacy & Support Services	Guideline	6	3	CPASS are pleased to see that it has been made clear that prescribing is not limited to specialists so that under their supervision, other healthcare professionals such as GPs have the right to prescribe but make the point that unlike the introduction of any other medicine into our healthcare system, cannabis has been consumed by many thousands of patients for many years and their expertise must be sought, accepted and explored. The most efficient way for this to happen will be where patients meet front-line healthcare services such as nurses, pharmacists and GPs as that is where the most productive therapeutic conversations between patients and our health care system take place. CPASS strongly recommend that education into CBMPs be made available to all levels within our healthcare systems.	Thank you for your comment. Health Education England have developed a training package for clinicians to support them when prescribing cannabis-based medicinal products.

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Cannabis Patient Advocacy & Support Services	Guideline	7	24	I think the guidelines should instead make the recommendation that potential drug-drug-interactions is investigated and that appropriate advice in terms of other products is based on that. If needed, monitoring of potential adverse interaction should be done by healthcare provider and that strategies for managing these are discussed with the patient. (I can speak both as a researcher - my credentials are PhD, CPsychol and over 10 years experience) and from experience as a patient or carer)	Thank you for your comment. The recommendation has been amended to reflect your comment.
Cannabis Patient Advocacy & Support Services	Guideline	7	8	CPASS highlight that from many years' experience working with self-medicating cannabis patients, it is highly likely that patients will continue to supplement their prescribed medications with illicit and/or other sources of cannabis-based products. The associated risks of this should be taken into consideration: 1: The lack of information on strength and quality 2: the risks that continued exposure to the criminal market will subject the patent to Ultimately any decision not to prescribe a CBMP to a patient constitutes a decision to leave the patient exposed to these risks, which should be considered in any risk/benefit analysis.	Thank you for your comment. According to NHS England, cannabis-based products for medicinal use are only prescribed to people where there is an unmet clinical need and established treatment options have been exhausted. Clinicians work with their individual patients or their carers to agree the best treatment, taking into account the clinical evidence base, GMC prescribing guidance on licensed, off label and unlicensed medicines, and local medicines governance systems. This is in line with normal clinical practice.
Cannabis Patient Advocacy & Support Services	Guideline	7	20	The guideline makes strong references to the potential impact on psychological, emotional and cognitive development and on structural and functional brain development, however, there is no quality evidence of any such impact from low THC dose CBMPs and in fact, all of the research that has highlighted these risks is based on smokable forms of cannabis with unknown quality and strength and in the vast majority of cases, mixed with tobacco. CPASS request that an appropriate and detailed rationale be published in order to help manage the expectation of patients.	Thank you for your comment. The rationale for the recommendation you refer to has been amended to reflect your comment.
Cannabis Patient Advocacy & Support Services	Guideline	7	24	CPASS feel that it would be of benefit, both to the patient and for the creation of useful clinical data that should a patients should be encouraged to report their intention to continue to supplement their non-prescribed cannabis to their healthcare team and should be guided to record their consumption along with detailing its impact on their health and well-being including any adverse side-effects. Drawing on years of experience supporting and advocating for medical cannabis patients, CPASS have already produced a form for these purposes which we would be happy to share. Please note that CPASS are currently working on a "Patient Guide", drawing from over 20 years of experience from medical professionals in other countries which will include an updated form for recording their consumption along with the benefits and adverse side-effects. There are also several online and mobile applications that could also be adopted for this specific purpose which could easily be adapted for the UK patient population.	Thank you for your comment. The guideline focused on prescribed cannabis-based medicinal products that can be prescribed legally. Non-prescribed cannabis was not within the scope for this guideline.
Cannabis Patient Advocacy & Support Services	Guideline	8	7	CPASS recommend that evidenced-based advice is given by healthcare professionals and to that end there should be guidance as to the benefits, risks and harms so as to eliminate unevidenced opinions based on bad quality research and inaccurate mainstream media stories over the last 40 years that along with the general public, our doctors have also been exposed. CPASS strongly request that we should apply the same standards for evidence to measure risks and harms as we expect for measuring the benefits in order to produce the very best benefit/risk analysis and advice.	Thank you for your comment. The guideline is based on evidence and committee expertise. When the committee considered and discussed the evidence, they looked at the risks and harms of treatment.
Cannabis Patient Advocacy & Support Services	Guideline	9	15	I think recommendation for further research can be broader and include effectiveness and safety of all CBMPs, including synthetic compounds, plant derived, whole plant extracts, oils and flower, and the guidelines could specifically recommend the use of a Phase IV clinical trial registry/surveillance study of clinical practice in terms of different types of CBMPs, prescribed in concordance between patients and healthcare providers, in England or the UK. A registry could facilitate the prescription and access of CBMPs while at the same time build up the evidence base in terms of benefits and risks across a range of conditions in a real world setting, rather than the limited evidence obtained from the restricted samples and environment of Phase I-III clinical trials of specific CBMP compounds. It is important that research is not just conducted with products developed and marketed by pharmaceutical companies, but that cost-effectiveness studies consider the use of other products that come	Thank you for your comment. The scope of this guideline included cannabis-based medicinal products: • cannabis-based products for medicinal use as set out by the UK Government in the 2018 Regulations • the licensed products delta-9-tetrahydrocannibinol and cannabidiol (Sativex) and nabilone • plant-derived cannabinoids such as pure cannabidiol (CBD) • synthetic compounds which are identical in structure to naturally occurring cannabinoids such as delta-9-tetrahydrocannabinol (THC), for example, dronabinol. All other cannabis-based products were excluded from the scope of this guideline. The committee agreed that an additional recommendation on a national or local registry was needed. This will facilitate an improved evidence base for CBMPs.

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				at a much lower price-point. (I can speak both as a researcher - my credentials are PhD, CPsychol and over 10 years experience) and from experience as a patient or carer)	
Cannabis Patient Advocacy & Support Services	Guideline	9	15	The prevalence of chronic pain is sky rocketing. Fibromyalgia management is poor in primary care. More primary care based research is needed. (I can speak from experience as a qualified medic)	Thank you for your comment. The economic analysis suggested that most types of chronic pain were not going to be cost-effective to manage using medicinal cannabis.
Cannabis Patient Advocacy & Support Services	Guideline	9	22	I think recommendation for further research can be broader and include effectiveness and safety of all CBMPs, including synthetic compounds, plant derived, whole plant extracts, oils and flower, and the guidelines could specifically recommend the use of a Phase IV clinical trial registry/surveillance study of clinical practice in terms of different types of CBMPs, prescribed in concordance between patients and healthcare providers, in England or the UK. A registry could facilitate the prescription and access of CBMPs while at the same time build up the evidence base in terms of benefits and risks across a range of conditions in a real world setting, rather than the limited evidence obtained from the restricted samples and environment of Phase I-III clinical trials of specific CBMP compounds. It is important that research is not just conducted with products developed and marketed by pharmaceutical companies, but that cost-effectiveness studies consider the use of other products that come at a much lower price-point. (I can speak both as a researcher - my credentials are PhD, CPsychol and over 10 years experience) and from experience as a patient or carer)	Thank you for your comment. The scope of this guideline included cannabis-based medicinal products: • cannabis-based products for medicinal use as set out by the UK Government in the 2018 Regulations • the licensed products delta-9-tetrahydrocannibinol and cannabidiol (Sativex) and nabilone • plant-derived cannabinoids such as pure cannabidiol (CBD) • synthetic compounds which are identical in structure to naturally occurring cannabinoids such as delta-9-tetrahydrocannabinol (THC), for example, dronabinol. All other cannabis-based products were excluded from the scope of this guideline. The committee agreed that an additional recommendation on a national or local registry was needed. This will facilitate an improved evidence base for CBMPs.
Cannabis Patient Advocacy & Support Services	Guideline	9	14	CPASS recommend that based upon 2 UK Medical Cannabis Patient Surveys which were run in 2016 (623 Patients) during the APPG Inquiry and again in 2018 (1750 patients), CPASS recommend that research should be prioritised into the most common 10 conditions and/or symptoms that patients report cannabis as helping them to manage: These patient survey results are reflected in all countries where similar surveys are performed. 1: Chronic Pain (20%) 2: Depression (17%) 3: Anxiety (16%) 4: Insomnia (9%) 5: Arthritis (7%) 6: Fibromyalgia (7%) 7: Muscle-Spasms (7%) 8: Irritable Bowel Syndrome (and other gastrointestinal issues: Cronhs, IBD, Endometriosis, Etc) (6%) 9: Migraines (6%) 10: Headaches (5%) These are the areas most likely to produce positive trial results and address the needs of the highest proportion of patients in the shortest time.	Thank you for your comment. The guideline scope focused on chronic pain, epilepsy, nausea and vomiting and spasticity as these were identified by NICE and stakeholders as conditions with the greatest need for guidance and where there was evidence of effectiveness.
Cannabis Patient Advocacy & Support Services	Guideline	General	General	CPASS would like to point out that this Guideline highlights a number of fundamental issues of our medicines approval systems which we feel is due to an intransigent adherence to existing policies, procedures and responsibilities which will never be appropriate for the uniqueness of CBMPs and as such, all recommendations should be reviewed carefully and policy changes recommended through full cross-organisation collaboration	Thank you for your comment.
Cannabis Patient Advocacy & Support Services	Guideline	General	General	CPASS states that it is critical that the expertise of patients, their voices, their issues, their pain and their priorities should be engaged, heard and seriously considered.	Thank you for your comment. The committee included patients and a carer. In addition, the draft guideline has been through a consultation process that includes patient organisations as registered stakeholders. Furthermore, recommendation 1.5.10 in the guideline outlines the importance of shared decision making.
Cannabis Patient	Guideline	General	General	Whilst CPASS understand that each organisation in this process (NHS England, Dept Health, Home Office, MHRA, FSA, etc....) has well defined scope, expectations and accountabilities,	Thank you for your comment.

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Advocacy & Support Services				if significant progress is ever to be made in making CBMPs accessible to patients through our NHS, we need more flexibility, adaptability, end-to-end collaboration, ownership and innovation from all organisations with the priority being the needs of patients as opposed to blindly following current systems and rules that do not make adequate allowance for this new and unique category/classification of medicines.	
Cannabis Patient Advocacy & Support Services	Guideline	General	General	CPASS would like to state that patients with chronic and debilitating conditions deserve so much better than this and unless our healthcare system innovates appropriately for CBMPs, as has already been seen in other countries then the UK are going to get left far behind and will no longer be able to claim that they are world-class.	Thank you for your comment.
Cannabis Patient Advocacy & Support Services	Guideline	General	General	CPASS state that he vast majority of the estimated 1.1 million patients already benefiting from their consumption of cannabis as medicine will have no choice but to continue to source the relief they seek for a better quality of life that is free from pain, from the criminal market and be exposed to all associated risks, quality, lack of medical support and potential criminalisation. Every decision NOT to prescribe a legal, regulated, quality controlled, standardised CBMP to a patient, under the supervision of qualified and skilled healthcare professionals, IS a decision to send the patient back to the criminal market to access low quality substances on unknown origin, and strength whilst continuing to expose them to all associated risks. This must be considered in any risk/benefit analysis.	Thank you for your comment. At the time of guideline development, most of the cannabis-based medicinal products were not licensed and so the quality of these may vary from product to product.
Cannabis Patient Advocacy & Support Services	Guideline	General	General	CPASS are concerned that very few pieces of research have been reviewed in order to draw any and all conclusions within this Guideline when we know there are over 20000 studies of good quality already and easily available, as reviewed and summarised by Professor Mike Barnes report from 2016. More recently, the comprehensive CBMPs in Pain study published by Nottingham University and The Centre for Medicinal Cannabis' cannabinoid researcher, Dr Saoirse O'Sullivan (https://www.thecmcuk.org/pain-policy) provides another excellent summary of the available quality evidence and we and the patients we represent feel that it would be helpful to understand why ~99.8% of the available evidence has not been considered.	Thank you for your comment. NICE guideline recommendations are based on the best available evidence. Review questions guide the search for evidence, and the type of evidence used depends on the type of question. For example, a randomised controlled trial is often the most appropriate type of study to assess the efficacy or effectiveness (including cost effectiveness) of an intervention such as chronic pain. This is because all analgesia has a strong placebo effect. Therefore, studies should be double-blinded and randomised.
Cannabis Patient Advocacy & Support Services	Guideline	General	General	Whilst accepting that "Smoked cannabis-based products" are not permitted within the current UK laws and regulations for CBMPs, CPASS feel that with the limited availability of evidence for all other forms and with the plethora of evidence for this type, this limitation has an unproportionate impact on assessing both the benefits and the risks of CBMPs which will lead to low quality and inaccurate outcomes moreover especially as all evidence of risks and harms associated with cannabis has been for smokable forms by mostly self-reported consumption where neither the quality nor the strengths can be guaranteed.	Thank you for your comment. This guideline is underpinned by legislation in terms of which cannabis based medicinal products can be considered. Therefore we only considered the following: • cannabis-based medicinal products as defined by the UK Government in November 2018 • the licensed products nabiximols (Sativex) and nabilone. • plant-derived cannabinoids such as pure cannabidiol. • synthetic compounds which are identical in structure to naturally occurring cannabinoids such as delta-9-tetrahydrocannabinol (THC), for example dronabinol.
Cannabis Patient Advocacy & Support Services	Guideline	General	General	NICE need to design a more appropriate process for evaluating CBMP as the existing approach to evaluating evidence and cost-effectiveness is clearly lacking in terms of being able to assess the potential benefits and risks of the full range of CBMPs, including synthetic compounds, plant derived, whole plant extracts, oils and flower, that could be made available to patients in need. The cost-effectiveness arguments within these guidelines clearly would not hold up if low-cost products such as home grown flower is taken into account. To simply a apply a framework for evaluating evidence and cost-effectiveness that has been developed specifically for medical products developed by pharmaceutical companies is playing in the hands of the pharmaceutical industry, rather than in favour of patients and families who are suffering and prescribes who would like to provide the care and treatment options that patients and their families deserve. Rather than recommend a large number of narrowly specified clinical studies, a national CBMP registry could recommended/be set up to monitor prescribing practice, products used, medical conditions treatment, patient profiles, effectiveness and safety signals. Training and knowledge sharing for healthcare providers and prescribes could incorporated into the registry set up. This approach could amass the evidence needed across conditions, while simultaneously ensure access for patients in need.	Thank you for your comment. This guideline is underpinned by legislation in terms of which cannabis based medicinal products can be considered. Therefore we only considered the following: • cannabis-based medicinal products as defined by the UK Government in November 2018 • the licensed products nabiximols (Sativex) and nabilone. • plant-derived cannabinoids such as pure cannabidiol. • synthetic compounds which are identical in structure to naturally occurring cannabinoids such as delta-9-tetrahydrocannabinol (THC), for example dronabinol. The guideline has added a recommendation advising prescribers to record details of treatment, clinical outcomes and adverse effects for people prescribed cannabis-based

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				NICE could be pioneering and forward thinking in their approach to CBMP if they choose to. (I can speak both as a researcher - my credentials are PhD, CPsychol and over 10 years experience) and from experience as a patient or carer)	medicinal products, using local or national registrys. This will enable feedback from patients to feed into the evidence base.
Cannabliss Ltd	General	General	General	We would like to thank NICE for having the opportunity to comment on these guidelines	Thank you.
Cannabliss Ltd	Guideline	1	7	In the description of what the guideline covers, we believe the statement "plant-derived cannabinoids such as pure cannabidiol (CBD)" should be removed as this is already covered by the description of Cannabis resin in the Misuse of Drugs Act 1971 and therefore the 2018 Regulations on CBPM's. The guidelines should make it clear that plant derived CBD is a form of Cannabis resin as defined by the Act.	Thank you for your comment. The text you refer to is an example and is not meant to be an exhaustive list of all plant-derived cannabinoids. The guideline does not exclude natural THC as this is included in the 2018 regulations and so products that meet the requirements of this regulation were included. Canabidiol on the other hand is not a controlled drug and so this would not be captured by the 2018 regulations which is why it was specifically mentioned under plant-derived and was also included. As a result any product that had a combination of THC:CBD was included in this guideline as part of the evidence review.
Cannabliss Ltd	Guideline	4	1	Given the huge media attention Medical Cannabis has received, we would expect a great number of patients to be asking specifically about the use of Cannabis for medical purposes. Given the content of the guidelines it is clear most will be advised they cannot receive these on prescription. So that patients can make informed decisions about their own well-being we feel that they should be informed there are alternative routes for accessing Medical Cannabis Products by way of licencing. It is our understating that people have the right to self-medicate and this should be made clear even if it goes against the advice or wishes of their health care professionals.	Thank you for your comment. NICE were commissioned to look at the clinical and cost effectiveness of cannabis-based products for medicinal use for spasticity, severe treatment-resistant epilepsy, intractable nausea and vomiting and chronic pain. The guideline did not look at non-prescribed access to these medicines and self-medication. As most of these medicines are currently not licensed in the UK, the quality, safety and efficacy cannot be guaranteed. The committee agreed that we need more evidence to assess the safety and effectiveness of these medicines which is why they made a number of research recommendations to find out more to enable safe use. The NHS document on Barriers to accessing cannabis-based products for medicinal use on NHS prescription makes recommendations on how organisations will be working together to enable safe access to these medicines.'
Cannabliss Ltd	Guideline	4	10	Consider inserting 'do not offer cannabis based medical products for intractable nausea and vomiting'	Thank you for your comment. The committee found evidence that nabilone can be considered as an add-on treatment for adults with chemotherapy-induced nausea and vomiting which persists with optimised conventional antiemetics. Consequently, the committee made a positive recommendation.
Cannabliss Ltd	Guideline	4	13	For Choric pain, we recommended adding 'Cannabis based medical products' to the list of "do not offer"	Thank you for your comment. There was no evidence for the use of CBD alone (either as a pure product or containing traces of THC). Therefore, the committee recommended that CBD should not be offered unless as part of a clinical trial.
Cannabliss Ltd	Guideline	5	1	Consider removing 'CBD' or changing to 'plant derived pure cannabidiol'	Thank you for your comment. The committee felt it appropriate to specify CBD as this was the CBMP for which there wasn't any evidence.
Cannabliss Ltd	Guideline	7	7	Considering including a section of the risk of diversion by both patient and carer	Thank you for your comment. The third bullet point in recommendation 1.5.5 includes taking into account the risk of diversion and this applies to the patient or carer who may support with taking medicines.
Cannabliss Ltd	Guideline	General	General	NICE have compiled a very robust set of draft guidelines in a situation that is entirely unique. On the whole we concur with the evidential findings and the subsequent rationale behind the recommendations presented. We would, however, recommend that the definition of 'Medical Cannabis' be made much clearer for the purpose of informing patients, carers and healthcare professionals. Products that are widely on general sale containing CBD have repeatedly been referred to in the media as 'Medical Cannabis' and it appears that a wider public perception has evolved that CBD is Medical Cannabis where is THC is not – this is clearly false and needs to be robustly address in the guidelines	Thank you for providing this information. This guideline is underpinned by legislation in terms of what cannabis based medicinal products can be considered. Therefore the definition of CBMP used in this guideline was: • cannabis-based medicinal products as defined by the UK Government in November 2018 • the licensed products nabiximols (Sativex) and nabilone. • plant-derived cannabinoids such as pure cannabidiol. • synthetic compounds which are identical in structure to naturally occurring cannabinoids such as delta-9-tetrahydrocannabinol (THC), for example dronabinol. This can be found in the terms used in the guideline section.
Cannabliss Ltd	Question 1			NA	Thank you.
Cannabliss Ltd	Question 2			No	Thank you.

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Cannabliss Ltd	Question 3			We believe a full definition of Medical Cannabis is urgently needed	Thank you for your comment. This guideline is underpinned by legislation in terms of what cannabis based medicinal products can be considered. Therefore we only considered the following: • cannabis-based medicinal products as defined by the UK Government in November 2018 • the licensed products nabiximols (Sativex) and nabilone. • plant-derived cannabinoids such as pure cannabidiol. • synthetic compounds which are identical in structure to naturally occurring cannabinoids such as delta-9-tetrahydrocannabinol (THC), for example dronabinol.
CBD Science Group		14	General	"There was no evidence for intractable cancer-related pain or pain associated with painful childhood diseases. The committee agreed that cannabis-based medicinal products could potentially offer additional benefits for this group, for example, by allowing them to receive their care in an outpatient rather than an inpatient setting. The research recommendation to explore clinical and cost effectiveness would be useful here across the board and not just in children.	Thank you for your comment. With regards to adult studies, the economic analysis suggested that most types of chronic pain were not going to be cost-effective to manage using medicinal cannabis. However, if any types of chronic pain could be cost-effective to manage using medicinal cannabis, they are most likely to be fibromyalgia and treatment-resistant neuropathic pain.
CBD Science Group	General	General	General	In cancer related chronic pain only pain outcome was measured, social aspects such as activity/mobility, pain medication levels, physician/ER visits, sleep quality, mood, and medication side-effects were not considered. The NICE statement reiterates the position of the Royal College of Physicians from 31 October last year and again calls for more research, which we agree to.	Thank you for your comment. The committee agreed that the most important outcome was pain intensity. This is because it is ubiquitous and therefore allows comparison using a meta-analysis. The other outcomes included are ones that are most consistently reported on. We did include pain medication levels. However, it is not commonly reported and when it is, it is often measured in different ways. For the research recommendations, the committee acknowledged that favoured functional pain measurement tools change all the time. Therefore, we have included the outcome: "A validated functional pain measurement tool".
CBD Science Group	General	General	General	Need for a shared care policy to be developed with academic centres	Thank you for your comment. This would be for local determination.
CBD Science Group	General	General	General	We support NICE recommendation for more research in the clinical and public arena	Thank you for your comment.
CBD Science Group	General	General	General	We believe that the trials that have been selected for this review by NICE are not reflective of the real world and indeed many are inconclusive and not conducted accurately and therefore drawing conclusions and cost effectiveness will not reflect accurately. We believe more robust clinical data is needed in the form of real world evidence and that this is then used for future decisions rather than waiting for RCTs which will take longer. There are limitations in the studies used including short follow up times and no economic burden impact measured.	Thank you for your comment. NICE guideline recommendations are based on the best available evidence. Review questions guide the search for evidence, and the type of evidence used depends on the type of question. For example, a randomised controlled trial is often the most appropriate type of study to assess the efficacy or effectiveness (including cost effectiveness) of an intervention. The guideline has added a recommendation advising prescribers to record details of treatment, clinical outcomes and adverse effects for people prescribed cannabis-based medicinal products, using local or national registries. This will enable feedback from patients to feed into the evidence base.
CBD Science Group	General	General	General	The current modelling of Cannabis has been done on current cannabis based treatments that are available and hence these costs have been used. The new CBMPs are likely to be much cheaper on cost of product as the research is based on real world evidence so the QALYs will work out in favour of the manufacturer with lower ICERs If we use the new costs of potential treatments and add in the economic burden of eg Opiods in pain we would get a different result.	Thank you for your comments. NICE acknowledges the upcoming research on CBMPs in the near future. However, until there is published clinical evidence to show the effectiveness these products, NICE cannot consider them in our analysis. The clinical evidence review did not identify evidence supporting opioid use reduction in the included RCTs. Therefore, we cannot consider the benefit in the opioid use reduction or preventing opioid dependence or mortality.
CBD Science Group	Heading, Recommendation for research			"In children and young people with intractable cancer-related pain and pain associated with specific diseases ….what is the clinical and cost effectiveness of cannabis-based medicinal products as an add-on to standard treatment to improve symptoms in comparison to treatment with standard care? Only studies looked at were improvement in pain and not improvement in symptoms	Thank you for your comment. The committee agreed that the most important outcome was pain intensity. This is because it is ubiquitous and therefore allows comparison using a meta-analysis. We did include functional pain measurement tools: the McGill pain questionnaire and Brief Pain Inventory. However, they were not frequently reported. For the research recommendations, the committee acknowledged that favoured functional pain measurement tools change all the time. Therefore, we have included the outcome: "A validated functional pain measurement tool".
CBD Science Group	Heading, who should prescribe			"….highlighted a clear need for shared care arrangements, which could involve other healthcare professionals such as GPs and non-medical prescribers."	Thank you for your comment.

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	in shared care				
Change, Grow, Live	Evidence Review E	General	General	There are many references to "dependence" and a few to "psychosis". There is minimal reference as to what to do about them – prevention and treatment. This should be corrected	Thank you for your comment. The treatment and prevention of dependence and psychosis associated with cannabis-based medicinal products is out of scope for this guideline.
Change, Grow, Live	Expert report (Freeman)	General	General	Expert advice regarding "potential for dependence, diversion and misuse" is needed – e.g. when the person cannot stop using the medication even though it interferes with many aspects of his or her life.	Thank you for your comment. Issues about diversion and misuse are addressed further in the controlled drugs guideline which is cross-referenced in recommendation 1.5.9
Change, Grow, Live	Expert report (Freeman)	General	General	Expert advice is needed regarding the mechanism of cannabis dependence, e.g. CB1, dopaminergic and opioid pathways.	Thank you for your comment. These areas were considered outside of the scope for this guideline.
Change, Grow, Live	Guideline	7	12	Guidance is required regarding "potential for dependence, diversion and misuse". These are managed variably with e.g. benzodiazepines, gabapentinoids, and opioid analgesia.	Thank you for your comment. Issues about diversion and misuse are addressed further in the controlled drugs guideline which is cross-referenced in rec 1.5.9
Change, Grow, Live	Guideline	General	General	There is insufficient guidance regarding the psychological (pleasure) and psychotomimetic (altered state) reinforcers for cannabinoid misuse (primarily abuse and/or dependence). Similarly, a "health warning" is needed regarding the popular conflation of "recreational" use of cannabis products and its medicinal use (as for most classes of prescribed drugs liable to misuse and diversion).	Thank you for your comment. The recommendation around factors to consider takes into account the potential for misuse. In addition, there is a recommendation that takes into consideration non-prescribed cannabis-based products including those that are used recreationally.
CLEAR Cannabis Law Reform	Guideline	22	4	There is little evidence of potential for harm for cannabis for any medical condition. Given the enormous numbers using cannabis in its most potent form as a recreational drug and/or self-medicating (estimated at 250 million regular users worldwide) there are far fewer adverse events or incidents of harm than for common over-the-counter medicines	Thank you for your comment. The section you refer to is not saying that there is more harm with cannabis-based medicinal products, but is making a general comment about all medicines having the potential to cause harm.
CLEAR Cannabis Law Reform	Guideline	4	15	This denies the actual long-term experience of millions of people worldwide that THC is safe and effective for chronic pain	Thank you for your comment. For the chronic pain population, THC was not found to be clinically and cost effective.
CLEAR Cannabis Law Reform	Guideline	4	16	This denies the actual long-term experience of millions of people worldwide that CBD with THC is safe and effective for chronic pain	Thank you for your comment. For the chronic pain population, CBD with THC was not found to be clinically and cost effective.
CLEAR Cannabis Law Reform	Guideline	5	1	This denies the actual long-term experience of millions of people worldwide that CBD is safe and effective for chronic pain. In the UK, millions use over-the-counter CBD food supplements for chronic pain and find it safe and effective. There is no evidence of any harm, significant negative side effects or adverse events from the use of CBD so there is no risk, it is very low cost compared to other medications and patients should be offered it to see if it works.	Thank you for your comment. No evidence was found for CBD alone for the treatment of chronic pain. Therefore the guideline recommends that CBD alone should not be used to manage chronic pain in adults unless as part of a clinical trial
CLEAR Cannabis Law Reform	Guideline	5	7	This denies the actual long-term experience of millions of people worldwide that cannabis-based medicinal products are safe and effective for spasticity.	Thank you for your comment. After publication of the consultation draft of the guideline, the manufacturer reduced the list price of THC:CBD spray, and this had an important impact on our assessment of its cost effectiveness. In light of stakeholder comments, the committee also reviewed their estimates of likely resource use associated with spasticity symptoms. The committee are now able to make a more positive recommendation.
CLEAR Cannabis Law Reform	Guideline	5	11	There is excellent observational evidence and real-world experience that cannabis-based medicinal products are safe and effective for severe treatment-resistant epilepsy. In particular, side effects and adverse events are far fewer and less severe than with other medicines.	Thank you for your comments. We included evidence from a number of observational studies within our review but the committee were concerned that these were low quality studies which did not include any control groups. The committee appreciated that some people have shown benefits from the use of cannabis-based medicinal products and so they did not make a recommendation against their use. However, they did not feel that current evidence was sufficient to confidently recommend their use either. Although the committee did not make a recommendation for the use of cannabis-based medicinal products they did make research recommendations to investigate the effectiveness of CBD and of CBD:THC for the treatment of epilepsy.
CLEAR Cannabis Law Reform	Guideline	6	6	Training in the use of cannabis-based medicinal products should be given equal importance to a special interest in the condition being treated	Thank you for your comment. Health Education England have developed a training package to support prescribers. Training was out of scope for this guideline.

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CLEAR Cannabis Law Reform	Guideline	6	15	Dose adjustment is a continuing requirement with cannabis-based medicines. As part of a shared care agreement, a secondary prescriber should be able to adjust doses as these medicines are extremely low risk.	Thank you for your comment. This may be part of the shared care agreement and would need to be agreed locally.
CLEAR Cannabis Law Reform	Guideline	7	23	There is no evidence of any potential impact on structural and functional brain development at the doses concerned, particularly not under supervision. This is nothing more than unjustified scaremongering.	Thank you for your comment. Based on their clinical experience of the committee were mindful of the harms of not treating the underlying condition optimally. They agreed that from a patient safety perspective, it is in the child's best interest to highlight to their family or carer the unknown effects on brain and cognitive development and the effect of sedation in the absence of data.
CLEAR Cannabis Law Reform	Guideline	9	17	Based on widespread patient experience this recommendation should consider THC and CBD as a first line treatment	Thank you for your comment. No evidence was found for CBD alone for the treatment of chronic pain. Therefore the guideline recommends that CBD alone should not be used to manage chronic pain in adults unless as part of a clinical trial. Evidence was found for CBD in combination with THC therefore a research recommendation was made CBD alone.
CLEAR Cannabis Law Reform	Guideline	9	25	Based on widespread patient experience this recommendation should consider THC and CBD as a first line treatment	Thank you for your comment. No evidence was found for CBD alone for the treatment of chronic pain. Therefore the guideline recommends that CBD alone should not be used to manage chronic pain in adults unless as part of a clinical trial. Evidence was found for CBD in combination with THC therefore a research recommendation was made CBD alone.
CLEAR Cannabis Law Reform	Guideline	General	General	The entire guideline is characterised by a failure to consider observational evidence and real-world experience. Cannabis is the oldest medicine known to mankind and failure to give substantial weight to real-world experience of its safety and efficacy is nothing short of absurd. Given its illegality over the past 100 years, the wild scaremongering about its recreational use and therefore the lack of formal clinical evidence, this is simply setting it up to fail. It is irresponsible in the extreme to fail to consider the enormous benefit at very low cost and the very few adverse events associated with illicit cannabis.	Thank you for your comment. NICE guideline recommendations are based on the best available evidence. Review questions guide the search for evidence, and the type of evidence used depends on the type of question. For example, a randomised controlled trial is often the most appropriate type of study to assess the efficacy or effectiveness (including cost effectiveness) of an intervention. The guideline has added a recommendation advising prescribers to record details of treatment, clinical outcomes and adverse effects for people prescribed cannabis-based medicinal products, using local or national registries. This will enable feedback from patients to feed into the evidence base
CLEAR Cannabis Law Reform	Guideline	General	General	Further to comment 11, the weight given throughout the guideline to the potential for harm of cannabis is wildly disproportionate. There is no evidence of any significant harm from cannabis when used as a medicine, especially when under the supervision of a medical professional. At least 10,000 years of human experience shows that cannabis is essentially safe. Seeking to evaluate its safety in the same way as a new, experimental medicine, synthesised in a lab for which there is no real-world experience is a fundamentally flawed approach. Unlike potentially dangerous or unsafe medicines, cannabis can and should be offered to patients on a 'try it and see' basis. Instead of being over-cautious, clinicians should welcome this approach and can be certain that it will benefit patients whether or not in proves effective in individual cases.	Thank you for your comment. The guideline is based on evidence and committee expertise. When the committee considered and discussed the evidence, they also looked at the risks and harms of treatment and noted that the potential for harm must be weighed up against the potential for benefit for individual patients. Given the lack of robust evidence on the use of CBMPs the committee took a measured and considered view regarding safety.
Cochrane Pain, Palliative and Supportive Care		26 - 27	6	Quality of evidence for cannabis for cancer-related pain and disability is rated high, but only based on one study with 16 participants. Even by their own methods, this should be low-quality at a minimum as they downgrade due to imprecision if sample size is less than 40 participants (page 46 – 47, line 9).	Thank you for your comment. You are correct. We have revised our GRADE tables. However, no recommendation was affected by this revision.
Cochrane Pain, Palliative and Supportive Care	Evidence Review B	General	General	: I have some major concerns with NICE approach in general and with this guideline in particular. They make very detailed analyses of single studies but they do not make a quantitative analysis, e.g. for neuropathic pain. The inclusion and exclusion criteria are not well worked out (perhaps I did not find them in the multiple appendices). Why did they exclude studies with smoked cannabis? Why did they exclude a study with smoked cannabis because the wash out period was < 1 week? What is the rationale to include experimental studies of 24 hours, e.g. the one of van de Donk on fibromyalgia (in PaPaS we require 2 or 4 weeks double blind duration)? Why didn't they include studies available in clinicaltrials.gov? Why didn't they calculate response rates (30% and 50% pain relief or more) from means and standard deviations (SDs) as we do? They did not mention our review on cannabinoids in fibromyalgia (Walitt et al. 2016). The NICE guideline is not an appropriate reflection of the evidence for neuropathic pain. Their position is too strict. I think that the European Pain Federation (EFIC) position paper (Hauser 2018) – individual therapeutic trial after established treatment options have failed – is much more adapted to routine clinical care.	Thank you for your comment. We looked at the effects of medicinal cannabis on neuropathic pain: Neuropathic pain was a subgroup analysis on the meta-analyses. The effect of medicinal cannabis on neuropathic pain was no different compared to other types of pain. Smoked cannabis and its wash out period was not included in the scope for this guideline. When the review's protocol was written, the committee did not include a follow-up duration because it was not entirely known what studies were available. The committee employed at inclusive approach and were keen to consider all studies regardless of their follow-up period. The finding that there was an RCT with a short follow-up period (van de Donk) was useful information because this further endorsed the need for research recommendations that had a longer follow-up period. Our surveillance team does keep track of studies of interest on the clinicaltrials.gov website. However, the data needs to be peer reviewed and published before they can be considered.

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				References: Walitt B, Klose P, Fitzcharles M-A, Phillips T, Häuser W. Cannabinoids for fibromyalgia. Cochrane Database of Systematic Reviews 2016 , Issue 7 . Art. No.: CD011694. DOI: 10.1002/14651858.CD011694.pub2 Häuser, W, Finn, DP, Kalso, E, et al. European Pain Federation (EFIC) position paper on appropriate use of cannabis-based medicines and medical cannabis for chronic pain management. Eur J Pain.. 2018; 22: 1547– 1564. https://doi.org/10.1111/ejp.1297	We did assess 30% and 50% response rates when they were published. However, this data was not often provided. Furthermore, we do not calculate response rates. Response rates are data that investigators should collect from participants during the study. Calculating response rates involves making assumptions. For example, assuming the data conforms to normal distributions. It is possible to calculate a mean and a standard deviation even though there is not a normal distribution. Ideally, the committee should not be making any assumptions. We have considered Walitt 2016 however this review was excluded as it is not a focused systematic review and it does not examine studies on medicinal cannabis vs placebo. The RCT data that we reviewed favours some types of medicinal cannabis for managing chronic pain compared to placebo. However, although this reaches statistical significance, the effect size is so small that individual people are unlikely to notice any difference. For example, pain intensity is measured on a scale of 0 to 10, 0 being no pain and 10 being maximum pain. In order for a person to notice any difference, analgesia should reduce pain intensity by at least 2 or even 3 points. Most pain intensity effect sizes were either statistically insignificant (oral delta-9-THC, oromucosal THC, vaporised THC (minimal CBD), vaporised THC:CBD, vaporised CBD (minimal THC)), or they caused less than a 2 point pain intensity drop (oromucosal CBD:THC) or the 95% confidence interval crossed the 2 point pain intensity drop threshold (oral nabilone). The cost of medicinal cannabis for chronic pain is around 6 times greater than the NHS would normally deem an efficient use of resources.
Cochrane Pain, Palliative and Supportive Care	General	General	General	I also disagree with rating evidence as anything other than very low quality when only one study is included in the analyses and the findings have not been replicated. All studies rated as moderate or high have only one study included, and cannot be rated for inconsistency (and therefore are only judged on three categories rather than four). The vast majority of analyses that include more than one study are rated as low or very low. Therefore, from the offset, it seems that more evidence lowers our confidence in this field. Size should be taken into account.	Thank you for your comment. We graded the outcomes according to NICE's manual. If 1 RCT is conducted well enough and is large enough, it could produce outcomes that are of high quality. In order for such outcomes to be high quality, the RCT would have to be large enough such that the effect sizes do not cross minimally important differences. At NICE, the committees assess our grading. Sometimes they pick up on differences between how a study was conducted and UK practice. In these instances, the evidence is downgraded for indirectness and we write an explanation. We have revised our GRADE tables because we realise that we did not take the small size of the studies into account.
Cochrane Pain, Palliative and Supportive Care	General	General	General	Overall, the evidence is so heterogeneous that it's difficult to derive anything from these analyses.	Thank you for your comment.
College of Mental Health Pharmacy	Guideline	7	13	The recommendation about caution in mental health patients should be stronger or expanded to highlight risk of psychosis in patients with schizophrenia when exposed to cannabis based medicinal products, in particular THC.	Thank you for your comment. Psychiatric disorders were out of scope for this guideline. The current research recommendations in the guideline will take into account safety of CBMPs which may include psychotic symptoms.
Devon, Cornwall and the Isles of Scilly Police	General	General	General	I am concerned that none of the recommendations you have made reflect the current challenges users face in accessing medicinal cannabis. These need to be addressed before any proposed extension to the use of medicinal cannabis to prevent those eligible under the guidelines from feeling betrayed. Residents of Devon and Cornwall have written to me to express their concern. They have advised that they suffer from a serious medical condition, one which is currently listed under the Clinical Interim Guidelines as suitable for the prescription of medicinal cannabis, and yet they are unable to actually obtain the medicine from the NHS. If a doctor prescribes it, patients have to pay for their own prescriptions which I am advised can cost thousands of pounds a month. This is financially impossible for most people whether they are on a salary or are unemployed e.g. due to disabilities. This means they cannot access the medicine legally, despite the fact they believe it could drastically improve their condition, and are lobbying Police and Crime Commissioners to allow them to grow their own. They believe their only other alternative is to access the black market, where there is no quality control and where they are at risk from criminal organisations. I cannot	Thank you for your comment. Local funding arrangements are outside the scope of this guideline.

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				endorse their proposal to adopt a scheme which allows them to grow their own, this would require legislative changes to the Misuse of Drugs Act 1971; this places them at risk of a criminal conviction for cultivating cannabis. NICE need to consider how prescriptions can be funded, before they consider additional guidelines for its extended use.	
DrugScience	General	General	General	Another significant issue in the case of these childhood epilepsies is the fact that cannabidiol by itself isn't always particularly efficacious, many of the successful UK outcomes have come from the use of cannabis oil which contains other molecules such as d9THC and THCV that are also anti-epilepsy. Developing and testing the such combinations would be extremely challenging and expensive and, given none may ever be reimbursed by NICE, ultimately futile. This is why no mainstream pharmaceutical companies are in the field. To conduct efficient research, DrugScience would suggest to enter all overseas patients using medical cannabis into a trial using the N=1 methodology (please see details below) that would rapidly determine if the medicines were effective.	Thank you for your comments. Only the products described in Appendix A of the evidence review for epilepsy were considered for this guideline. Other products were outside the scope of this review and therefore the committee could not make comments on these.
DrugScience	Guideline	13	17	US observational data shows that often there is a reduction in opioid use in people prescribed medical cannabis. In light of the severity of the opioid epidemic there, and the known addictive potential of opioids, this is a vital finding not to be dismissed. Whilst medical cannabis is not risk free, its risks pale into insignificance compared with the well established risks of opioid use.	Thank you for your comment. RCTs are the best studies for assessing medicinal cannabis. This is because all analgesia has a strong placebo effect. Therefore, studies should be double-blinded and randomised. Our systematic review of RCTs found that the outcomes for opioid usage were not statistically significant.
DrugScience	Guideline	14	9-14	On the one hand, the guidelines highlight that CBMPs might improve safety in the chronic pain group by replacing standard care or reducing doses of other medicines, whilst on the other hand it is noted that the recommendations might reduce the number of these prescriptions, effectively choosing NOT to potentially improve patient safety?	Thank you for your comment. We have amended the guideline and evidence review in line with your comments removing the reference to standard care,
DrugScience	Guideline	16	21	While DrugScience agrees with the perceived lack of RCTs, this does not mean that there is no evidence. Rather, there is a notable pattern of evidence emerging from patient testimonies and strong lived experience. We need to learn from parents who have gone overseas to find experts to treat their children and have seen remarkable results. Their UK doctors are allowed or prescribed medical cannabis yet less than 10 NHS prescriptions have been written to date. At the very least, these children who were hoping for Epidiolex to improve their quality of life should now have their specialists prescribe it as a matter of urgency.	Thank you for your comments. Given the lack of RCTs we included evidence from a number of observational studies within our review. However, the committee were concerned that these were low quality studies which did not include any control groups. The committee appreciated that some people have shown benefits from the use of cannabis-based medicinal products and so they did not make a recommendation against their use. However, they did not feel that current evidence was sufficient to confidently recommend their use either.
DrugScience	Guideline	17	11	This decision is the same as the one that NICE made for Sativex in Multiple Sclerosis. Getting pure extracts of plant cannabis products into the NHS now seems a lost cause. It must now be clear to NICE and the public that medical cannabis isn't suitable for traditional pharmaceutical development programmes in part because of their high costs and low likelihood of returns for investors.	Thank you for your comment. The products that were considered for this guideline are described in the protocol in Appendix A of each evidence review. Other products were outside the scope of this review and therefore the committee could not make comments on these. After publication of the consultation draft of the guideline, the manufacturer reduced the list price of THC:CBD spray, and this had an important impact on our assessment of its cost effectiveness. In light of stakeholder comments, the committee also reviewed their estimates of likely resource use associated with spasticity symptoms. The committee are now able to make a more positive recommendation.
DrugScience	Guideline	18	13	The fact that different countries have different health care systems should not unduly impact their applicability to the prescribing of CBMPs in the UK. These countries have access to the same (generally international) scientific evidence as the UK. If the scientific evidence warrants prescribing in one country, it is difficult to see how this can not be the case for another country. Please do not hesitate to contact DrugScience for a review of current medical cannabis regulatory regimes.	Thank you for your comment. The section you refer to is about the process of prescribing rather than the clinical efficacy. Processes for prescribing and access to medicines differ outside of the UK.
DrugScience	Guideline	General	General	There are multiple individual pieces of evidence for medical cannabis. The fact that the FDA has approved cannabidiol (in the form of Epidiolex) shows that these treatments work. NICE does not dispute that but cannot recommend because of the benefit/cost ratio for what are life-long disorders.	Thank you for your comment. Evidence for the use of cannabidiol for other types of epilepsy (Epidiolex for Dravet and Lennox-Gastaut syndromes) are currently being considered by our technology appraisals team, due to be published later this year.
DrugScience	Question 1			Which areas will have the biggest impact on practice and be challenging to implement? The draft NICE guidelines on medical cannabis restrict support for medical cannabis products for almost all indications, in contrast to the evidence available to date. Drug Science accepts that the current evidence base requires strengthening, but does not believe randomised	Thank you for your comment. NICE guideline recommendations are based on the best available evidence. A randomised controlled trial is often the most appropriate type of study to assess the efficacy or effectiveness (including cost effectiveness) of an intervention.

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				clinical trials are the only solution at this time; due to the unique properties of the product, and the existing positive benefit/risk profile in certain conditions. The draft prescribing guidelines make it unlikely that doctors will prescribe medical cannabis to patients in need. Indeed, there is likely to be even less prescribing than before as doctors are unlikely to go against the guidelines. Unfortunately, the perceived lack of controlled efficacy data overrides strong lived experience from patients or carers and international evidence of effectiveness. This is an unethical approach. If there is a continued sole focus on RCTs, it will take many years for research results to be available- yet patients could benefit from the medicine now, making it potentially unethical NOT to prescribe. It is important to balance harm minimization against patient need. This balance of legitimate patient need against potential harms is vital in the context of novel medicines (a category for which cannabis substances qualify in a contemporary evidence-based medical culture, despite the many centuries of use). The long history of uses of, the limited scientific evidence, and the recent public demand for cannabis and cannabinoids collectively suggest that these substances provide relief for a range of significant problems. The reasons why people turn to the family of cannabis substances for relief varies from good to bad; e.g. there may be indications for which these substances are indeed more effective or more easily tolerated than available treatments – this would be a good reason. Despite the limited RCT evidence for their efficacy, many patients who request cannabis have not responded to standard treatments and are desperate to find something that helps ease their symptoms. In such cases, the fact that other treatments are statistically more effective may not be relevant as a contra-indication to use of cannabinoids.	The committee agreed that an additional recommendation on a national or local registry was needed. This will facilitate an improved evidence base for CBMPs.
DrugScience	Question 2			Would implementation of any of the draft recommendations have significant cost implications? The draft prescribing guidelines mean that patients face increased challenges in acquiring medicines, which will have negative cost implications (both financial and otherwise) for patients. Patients who can afford it, will be able to receive their medicine from private clinics, highlighting further ethical issues in that only the wealthy have legal access to a vital medicine to relief their suffering. If they are unable to receive medical cannabis through a private prescription, patients are likely to source from the back market, with all the risks this entails. This prohibitionist approach fuels a burgeoning illicit market, whilst concurrently increasing public health harms by driving vulnerable people to the illicit market flooded with products of unknown constituents and safety profiles. Other non-financial costs implications include patients risking a criminal record because they have to purchase illegally and patients having to stick with other less effective (and potentially more harmful) medicines, such as opioids, even though medical cannabis might be able to help. DrugScience agrees with the very many thousands of patients who see CBPMs as providing a significant advance in medical treatment for those in whom current medicines are either ineffective or poorly tolerated. Less restrictive guidelines would offer the potential for significant costs savings to the NHS in terms of reduced patient hospital stays and lowered prescribing of other medicines, particularly opioids for chronic pain. The failure of the medical and pharmacy professions to embrace their being made "legal" 8 months ago is a great worry to patients and carers and will already have led to more preventable deaths from conditions such as epilepsy. DrugScience hopes that policy makers and prescribers can improve the challenges to prescribing and develop approaches to overcome the current highly unsatisfactory situation.	Thank you for your comments. The reason that no population level recommendations were made was because of a lack of evidence of clinical and cost effectiveness. The research recommendations were therefore made with the aim of improving the evidence base to help inform recommendations in future updates. The guideline recommends that all those receiving treatment before publication of this guidance can continue to receive treatment. Clinicians can also still make their own individual prescribing decisions in the best interest of their patients. .
DrugScience	Question 3			What would help users overcome any challenges?	Thank you for your comment. We will pass these onto our implementation and field team for their consideration regarding the implementation of this guideline.

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				Drug Science believes that the benefit/risk profile of medical cannabis in certain disorders, and as a treatment for certain conditions, is favourable. Drug Science does however recognise that there are significant data gaps in some areas which warrant further research, and proposes the following additional policy solutions: • Instigate a series of pilot N-of-1 trials in key therapeutic areas to collect real world data through registries to assess the efficacy, safety, QALYs and patient reported outcomes of CBPMs (cannabis-based products for medicinal use), modelled on DrugScience's TWENTY21 initiative. Ideally these would be reimbursed by the NHS and funded similarly to the innovative Cancer Drugs Fund. • Remove CBPMs from the "specials" category. At a minimum, ensure importers can order and hold more than the current maximum of 25 doses. • Whilst CBPMs are categorised as "specials", NHS clinical insurance should protect prescribers in the same way as other medicines prescribed within the NHS. • Simplify the prescriber pathway. • Enable GPs to initiate prescribing, rather than having to do so under consultant supervision. • Reassure prescribers that to recognise and accept the value of patients' self-reported outcomes with "illegal" cannabis is neither unlawful nor bad practice. • Improve educational materials on medical cannabis available to undergraduate and postgraduate doctors. There are many other ways to improve the data gaps through wider evidence, rather than only focussing on RCTs. Many other forms of clinical evidence should be taken into account. Drug Science has developed a solution to the perceived lack of efficacy data, widely accepted as the main hurdle of access to medical cannabis: • Project TWENTY21 is the UK's first national pilot for medical cannabis, aiming to enrol 20,000 patients before the end of 2021. • Project TWENTY21 will collect clinical data to document the efficacy, safety, QALY and patient-reported outcomes of medical cannabis during the pilot phase. It will support evidence for licensing individual medical cannabis treatment options and help inform NICE to what degree these new treatment options should be widely funded within the NHS. • Drug Science network leads will support the implementation of the project by providing oversight into the appropriate protocols to collect real world data over two years. • Project TWENTY21 is moulded on the existing UK best practice models, The Cell and Gene Therapy Catapult and the Cancer Drugs Fund. It provides an innovative solution through partnership between academics, patient groups and industry.	The committee have also made a number of research recommendation to help advance the evidence base for CBMPs.
DrugScience	Question 3 (cont..)			The N-of-1 trial N-of-1 trials are the core of medical practice. It should be obvious to all medical professionals that every time they prescribe a medicine [or any other intervention] they are conducting an N-of-1 experiment. For almost all medicines the experiment fails in some patients, either they do not respond or the adverse effects outweigh the therapeutic benefit. One might therefore expect that doctors would welcome patients who have conducted successful self-treatment with cannabis since it's almost certain that prescribing medical cannabis to these will work, providing a win for both patient and prescriber! The resurrection of CBPMs, following their international banning by the UN Conventions and WHO, is directly attributable to N-of-1 trials. The first in the USA was Charlotte Web, which inspired parents of other children with severe childhood epilepsies such as Alfie Dingley and Billy Caldwell in the UK. These children were facing death or brain damage from multiple seizures having proved resistant to a range of licensed treatments. CBPMs have restored them to close to normality and also allowed them to come off other medicines. In the case of Billy, the proof of efficacy was inadvertently and dangerously established by the confiscation of his medical cannabis by UK customs officials which led to a life-threating episode of status epilepticus that required admission to intensive care. The public outcry over such harsh treatment by the UK government was the immediate cause of the rescheduling of medical	Thank you for your comment.

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				cannabis in November 2018. This meant he was allowed to restart his treatment from which he was rapidly restored to health. In scientific terms he was the subject of an N-of-1, A-B-A-B design, one of the most powerful methodologies for examining a medical intervention. The A's define the baseline before and after treatment B, with the final B a re-administration of the treatment if a clinically relevant level of improvement for that patient was established by the first B trial. Scientific support for ABA trials is well established in educational, behavioural and psychological assessment but is less so in medical research (Elizabeth O Lillie, 2011). An ABA(B) trial design is well-suited for determining whether medical cannabis is efficacious, which explains why the UK government was prepared to accept that in these cases of epilepsy self-treatment CBPMs worked. So why would any prescriber resist similar claims in their patients, particularly if they had seen their own previously prescribed treatments fail? In such cases to deny a patient a CBPM simply because they are using an "illegally" sourced preparation is illogical and could be construed as being unethical. Germany took this view when they decided to make medical cannabis available. The GMC guidance on good medical practice makes it quite clear that all registered doctors must take into account and respect patients' views and experience. We suggest that NICE does as well. A major advantage of N-of-1 trials is that they are much cheaper than RCTs as they are much more powerful statistically. Subjects are their own controls, so the resulting data are less noisy than in RCTs, and the return of a successful treatment to the individual patient is an efficient and ethical approach to individualised medicine. Further, a Bayesian analysis of several N-of-1 trials can turn the data into information about the probability that a new patient will respond to the treatment.	
DrugScience	Question 3 (cont..)			NICE's assertion that they can only give guidance based on RCTs is blinkered and disingenuous as there are many other forms of clinical evidence they should take into account. The insistence on traditional efficacy trials before giving a license for a specific indication won't work if pharmaceutical companies don't conduct them, which they won't if their shareholders believe that this is not commercially viable. It is also a long process taking around ten years and in order to recoup their huge investment companies have to charge a lot for the medication. In the past decade only one CBPM [Epidiolex®] has been taken through this route and has only last month been declared not value for money by NICE so is not being made available on the NHS. There are many different medical disorders that CBPMs are a treatment for [Germany recognises over 50] so it is very unlikely that each will be submitted to such trials. NICE and other UK regulatory bodies such as the MHRA need to accept that if they pursue this "gold standard" approach patients currently breaking the law to get medical benefit from cannabis will probably never see a licensed CBPM in their lifetime. They need to consider new regulatory and data assessment approaches, and properly interrogate the international data on CBPMs. Another important advance in treatment research in recent years is the recognition of the critical value of patient-reported outcomes [PROs]. These have received immense investment from the USA National Institute of Health [NIH] and many new scales have been developed for this purpose. PRO measures are now required as elements of outcome measures for clinical trials funded by the NIH [https://commonfund.nih.gov/promis/index]. UK progress in this direction has led to the setting up of a special centre in Cambridge for patient-led research in the clinical trials unit. https://www.cuh.nhs.uk/clinical-trials/cambridge-clinical-trials-unit-cctu/patient-led-research-hub	Thank you for your comment. NICE guideline recommendations are based on the best available evidence. Review questions guide the search for evidence, and the type of evidence used depends on the type of question. For example, a randomised controlled trial is often the most appropriate type of study to assess the efficacy or effectiveness (including cost effectiveness) of an intervention. The guideline has added a recommendation advising prescribers to record details of treatment, clinical outcomes and adverse effects for people prescribed cannabis-based medicinal products, using local or national registries. This will enable feedback from patients to feed into the evidence base.

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				There is a large body of experience from other countries which can help users as well as prescribers in the UK. DrugScience has prepared a report evaluating regulatory regimes in the following countries: Germany, Italy, the Netherlands, Canada, Israel and Australia. All of these countries have comparatively well established medical cannabis regimes, which can provide valuable lessons for the UK. Please do not hesitate to contact Drugscience for the full report. As an example, in the Netherlands, the Office for Medical Cannabis (OMC) ensures responsible production of cannabis for medical and scientific purposes and for the supply to pharmacies, universities and research institutes. Medical cannabis can be produced and distributed in commission by the government to ensure quality and patient safety. Nabiximol-containing medicinal products (such as Sativex) are available as medicines. Doctors are also permitted to prescribe medical cannabis for conditions such as (but not limited to): MS, HIV, cancer, pain, Tourette syndrome. Generally, the doctor is allowed to judge whether cannabis might be beneficial to treat a condition. However, cannabis should only be prescribed when the standard treatments have not helped or cause too many side effects. Dutch medical cannabis is produced by Bedrocan to meet quality standards, complying with the strictest requirements, then dispensed by a pharmacist to patients with medical prescription. It is available in several varieties, one of them being as strong as 22% THC. Moreover, registering patients' details anonymously contributes to a large real-world database to be analysed and followed up. In the UK, there is the need for a broader view, incorporating real world data, to look at patterns of evidence so that patients are able to try cannabis medicine now. Different methodologies can be applied to move the evidence base forward. Despite research limitations and evidence gaps at present, there is a need to maximise clinical research and patient benefit, in a safe, cautious and ethical manner, so that the medicine can reach patients in need.	
Dystonia Society	General	General	General	The Dystonia Society response to consultation on cannabis-based medicinal products Thank you for inviting comments to the recently published draft guidance on cannabis-based medicinal products. This comment is from The Dystonia Society, the UK charity representing people affected by dystonia. The Dystonia Society is a registered stakeholder of NICE. The Dystonia Society's comment is under three headings: context about dystonia and The Dystonia Society; comment to the draft guidelines; and ongoing involvement of people affected by dystonia as NICE and NHS England develop their plans.	Thank you for your comments.
Dystonia Society	General	General	General	About dystonia and The Dystonia Society Dystonia is the term used to describe uncontrollable and sometimes painful muscle spasms caused by incorrect signals from the brain. It is estimated to affect at least 70,000 people in the UK. It is a lifelong condition that can change over time. There are a large number of different types of dystonia which affect people in widely differing ways. The severity of symptoms can vary from day to day. Unfortunately, there is not yet a cure. The Dystonia Society is the UK charity for people affected by dystonia. Our mission is a world without dystonia. To achieve this mission, we support and advocate for people living with the impact of dystonia to ensure they experience the best quality of life for all of their life while we drive forward towards critically needed treatments and ultimately a cure. We do this by raising awareness; by supporting and advocating for those affected by dystonia – including via a network of local support group; and by facilitating research into critical advances in treatments and ultimately the search for a cure.	Thank you for your comments.

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Dystonia Society	Guideline	General	General	The Dystonia Society's comment to this draft guideline This consultation follows the re-classification last year of cannabis-based medical products to allow specialist doctors to prescribe them where the clinical needs of patients cannot be met by licensed medicines. Following input from our medical advisors, the Dystonia Society agrees with the conclusion in your draft guideline (relating in particular to spasticity) that, sadly, there is insufficient clinical trial evidence in the use of cannabis-based medicinal products to reduce spasticity. This is a tragedy for people with dystonia, as generally treatment options are poor and not very effective. There is very little trial evidence for dystonia and cannabis-based therapies; 2 dated trials of THC and nabilone, both underpowered in terms of numbers. In addition, an as yet unpublished study of cannabinoids (Sativex) in childhood spasticity where the control group responded as well as the trial group (Turner, 2017) The Dystonia Society supports further evidence through properly controlled and funded trials. This is for cannabis-based therapies among other orphan/experimental therapies.	Thank you for your comments. We agree that more evidence is needed on the effectiveness and safety of cannabis-based medicinal products. For this reason we have included 8 research recommendations, each designed to increase understanding of the effectiveness of these products for the conditions covered in this guideline. The research recommendations can be found in the Recommendations for Research section of the guideline.
Dystonia Society	Guideline	General	General	Involving people affected by dystonia As the only UK wide organisation for people affected by dystonia, The Dystonia Society is in a position to help NHS England and NICE bring to this conversation the voice of people living with dystonia, their families, and their healthcare professionals. This includes via our network of local support groups throughout the UK. Thank you for inviting comment to the draft guidelines. Please keep us informed of progress	Thank you for your comments and support for this guideline.
End Our Pain	Evidence review C	General	General	**<u>Misunderstandings or mistakes in the draft guideline and rationale</u>** It is not clear why NICE rejected such large volumes of evidence identified in its review. Some of the reasons which *are* given appear inappropriate. For example, no reason has been given for the exclusion of 23 observational studies.(14) Furthermore, one piece of evidence was rejected for being in a foreign language.(15) It is unclear whether NICE has directly considered the evidence which underpinned the CMO's recommended rescheduling of CBMPs. Nor does it appear to have considered the experience of other jurisdictions, where use of CBMPs is clinically recommended in appropriate cases. Further detail of this is contained in the review by Professor Barnes, which is included with this consultation response. The draft guideline appears to underplay the effectiveness of CBMPs in reducing seizures. It states that there are "some reports" of individual patients having fewer seizures, but in fact all of the RCT and "single-arm" studies reviewed appear to find reductions in seizures.(16) Furthermore, NICE appears not to have reviewed or considered some important studies, including Tzadok et al (2016), Pamplona (2018) and Mitelpunkt (2019). These are summarised in Professor Barnes' review. In relation to adverse events, the draft guideline also states as follows: *"People with these epilepsy syndromes also report a very high rate of adverse events. Open-label studies (clinical trials in which the treatment and placebo groups are not disguised) of cannabis-based medicinal products in other types of epilepsy have also shown a very high level of adverse events*	Thank you for your comment. NICE guideline recommendations are based on the best available evidence. Review questions guide the search for evidence, and the type of evidence used depends on the type of question. For example, a randomised controlled trial is often the most appropriate type of study to assess the efficacy or effectiveness (including cost effectiveness) of an intervention. Two of the observational studies (McCoy and Tzadok) were included as part of this review. The results of these can be found in Appendix K of the epilepsy review. The Pamplona review article was considered and the references were checked to ensure we hadn't missed any articles that would meet our inclusion criteria. The Mitelpunkt article was published after the development of this guideline but the results would not change the committee's decision on recommendations or research recommendations.

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				(in up to 98% of people) but it was not possible to determine how many of these were due to the cannabis-based products." However, this does not reflect the weight of evidence, which is that the rate of side effects is relatively low. This is demonstrated in the studies highlighted by Professor Barnes. It also does not recognise the serious side effects of standard pharmaceutical anti-epilepsy drugs. The statement is, in any event, inappropriate, because the guideline committee admits that it is not possible to determine how many of the events were due to the CBMPs. The draft guideline also takes account of considerations that do not appear relevant to whether the evidence supports the efficacy of CBPMs. For example: *"There was limited evidence on who should prescribe and monitor cannabis-based medicinal products. Studies were conducted in Australia and Canada, and 1 study included participants from 8 different European countries. These countries have different healthcare systems, funding streams and legislation, which raised questions about their applicability to the prescribing of cannabis-based medicinal products in England. It was also not clear whether all products could be considered cannabis based products for medicinal use as defined in the 2018 Regulations."* Clearly, the funding streams and legislation of foreign jurisdictions bears no relevance to the clinical evidence within those studies as to the efficacy of CBMPs. It does not seem to us to be reasonable to reject those studies on this basis. (14) See page 41 of the Evidence Review (15) Page 74 of the Evidence Review (16) See page 16 of the draft guideline and Appendix G and K	
End Our Pain	Evidence review D	General	General	[redacted] **– Evidence review on behalf of EoP (evaluation of evidence)** The NICE committee reviewed the literature on CBMPs in epilepsy. They reviewed 19,491 trials and reviews but then dismissed the overwhelming majority and finally only reviewed 4 randomised controlled and 11 observational trials. The latter were dismissed as "the committee agreed that the very low quality of evidence and absence of a control arm for comparisons meant that these results could not be used to make any recommendations". In other words the committee has only assessed the evidence resulting from the 4 randomised controlled trails. This is despite the prior chair of NICE - Professor Sir Michael Rawlins- stating in his 2008 Harveian Oration that: *Randomised controlled trials (RCTs), long regarded at the 'gold standard' of evidence, have been put on an undeserved pedestal. Their appearance at the top of "hierarchies" of evidence is inappropriate; and hierarchies, themselves, are illusory tools for assessing evidence. They should be replaced by a diversity of approaches that involve analysing the totality of the evidence-base.* In summary, the committee found 9,341 RCTs and RCT systematic reviews and dismissed 9,303 based just on the title or abstract and a further 34 based on review of the full article. That left the 4 studies referred to above. They found 4,028 observational studies and systematic reviews and rejected 3,994 based on title /abstract and a further 23 based on the full article, leaving 11 studies. Of the 34 RCT studies rejected this seems to be have been on grounds of being a conference poster or abstract (may still contain valid data), not being in the English language or by being a review article or an observational trial (Appendix I in NICE guideline). No reason has been given for the exclusion of 23 observational studies and reviews (see page 41 of the	Thank you for your comments. The committee assessed the evidence form both the RCTs and the observational studies that were included in this review. The committee discussed the evidence from the observational studies and then decided that the evidence was too low quality to be able to confidently make recommendations. Articles for this review were assessed based on the protocol developed at the beginning of this review and the exclusion of articles such as conference abstracts is standard NICE policy. The RCTs in relation to Dravet and Lennox-Gastaut syndromes were out of scope for this review as they are part of the NICE technical appraisals process, due to be published later this year. The quality of the evidence for severe-treatment resistant epilepsy was therefore referring to the observational studies which were classified as low or very low-quality. Two of the observational studies (McCoy and Tzadok) were included as part of this review. The results of these can be found in Appendix K of the epilepsy review. The Pamplona review article was considered and the references were checked to ensure we hadn't missed any articles that would meet our inclusion criteria. The Mitelpunkt article was published after the development of this guideline but the results would not change the committee's decision on recommendations or research recommendations.

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				Guideline). No information is given as to how many of the rejected studies (over 13,000) were rejected for being in a foreign language (as one study has been in Appendix I). According to Professor Dame Sally Davies' Cannabis Scheduling Review from June 2018, the 2017 scientific review by the Health Products Regulatory Authority (HPRA) of the Republic of Ireland on the medical use of cannabis *"concluded that based on the compelling anecdotal evidence and the (limited) scientific evidence, cannabis has potential therapeutic benefits, but that they need to be defined through peer-reviewed clinical research"* (para. 7.1). The HPRA advised that CBMPs should only be made available for the treatment of patients with specific medical conditions including *"severe, refractory (treatment-resistant) epilepsy that has failed to respond to standard anticonvulsant medications whilst under expert medical supervision"* (para. 7.2c). It is unclear whether the evidence underlying the HPRA review has been considered by the committee or why, if so, the Committee cannot make a recommendation for the use of CBMPs for treatment-resistant epilepsy, whereas HPRA were able to do so. Similarly, according to Professor Dame Sally Davies' review, the WHO Expert Committee on Drug Dependence (ECDD) reviewed cannabidiol, cannabis and related substances in June 2018 and found that *"the most advanced clinical use of cannabidiol is for the treatment of some forms of epilepsy, with one pure cannabidiol product currently in Phase III clinical trials and multiple other smaller clinical studies demonstrating efficacy"* (para 8.2). It is unclear whether these trials were considered by the Committee. The 4 studies reviewed all utilised a pure CBD isolate (Epidiolex) by GW Pharma. The studies were positive with regard to the efficacy of the active medicine in drug-resistant Dravet and Lennox-Gastaut syndromes. (See Nice Appendix E). The committee say that there are "some reports" of individual patients having fewer seizures with CBMPs, but all the RCT and "single-arm" studies reviewed in ERD appear to find reductions in seizures (see pp.15-18 of the Guideline; Appendix K of the Evidence Review). This characterisation of the evidence is misleading and it seems crucial to the decision not to recommend CBMPs. The committee summarises the evidence as "low quality", which does not appear to be a fair summary of the quality of the evidence because in fact two of the four RCTS reviewed (Devinsky 2018 and Thiele 2018) were assessed as "moderate" quality. The Committee have failed to consider many useful observational studies. We appreciate that more research is needed but key information to inform a balanced decision has been dismissed. To illustrate this point the following 4 papers are relevant: **1. McCoy B, Wang L, Zak m et al. A prospective open label trial of a CBD/THC cannabis oil in Dravet syndrome. Ann Clin Transl Neurol 2018: 5; 1077 -1088** This study included 19 children with Dravet treated with a product containing 100mg/ml CBD and 2mg/ml THC. The mean dose achieved was 13.3 mg/kg /day of CBD and 0.27 mg/kg/day THC. Median seizure reduction was 70.6% with a 50% responder rate of 63%. There were statistically significant improvements in quality of life and reduction in EEG spike activity. These children were on an average of 2.9 other AEDs. Adverse events included somnolence, anorexia and diarrhoea. Liver enzyme abnormalities were noted in some who were on valproate. No major adverse events were reported and no child withdrew from the trial due to adverse events. **2. Tzadok M, Uliel-Siboni S, Linder I et al. CBD-enriched medical cannabis for intractable paediatric epilepsy; The current Israeli experience. Seizure 2016: 35; 41-4.** A retrospective study of the use of CBD enriched medical cannabis in children with epilepsy. 74 patients were included with intractable seizures resistant to at least 7 AEDs. 66% had also	

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				failed a ketogenic diet a vagal nerve stimulator or both. The product was a 20:1 CBD:THC formula. 89% of the children reported reduced seizures with 18% reporting 75-100% reduction and another 34% a 50-75% reduction. Five (7%) reported worsening of seizures . There were improvements in behaviour, alertness, language, communication, motor skills and sleep. Adverse reactions included somnolence and fatigue, gastrointestinal disturbances and irritability leading to withdrawal in 5 patients. **3. Pamplona FA, Rolim de Silva L, Coan AC. Potential clinical benefits of CBD rich cannabis extracts over purified CBD in treatment-resistant epilepsy: Observational data meta analysis. Front Neurol 2018; 9: 759** A meta-analysis of observational clinical studies in 11 papers involving 670 patients. Average dose ranged from 1 to 50 mg/kg/day. 64% reported improvement in seizure frequency and more reported improvement with CBD rich (full extract) products (71%) compared to pure CBD products (36%). Patients with CBD rich extract had a lower average dose (6.1 mg/kg/day) than pure CBD products (27.1 mg/kg/day). Mild and severe side effects were also less in the CBD rich group. Mild side effects included appetite disturbance, sleepiness, gastrointestinal disturbance, fatigue and nausea. Rare and more serious side effects were low platelet count, respiratory infections and alteration of liver enzymes. (13% incidence of major side effects and 43% incidence of mild effects) Secondary effects were improvements in awareness, sleep, mood, behaviour / aggression, language and cognition and motor skills. **4. Mitelpunkt A, Kramer U, Hausman m et al. The safety, tolerability and effectiveness of PTL 101, an oral cannabinoid formulation in paediatric intractable epilepsy: A phase II open label single centre study. Epilepsy and Behaviour 98: 233-237, 2019** This study assess a cannabidiol product (93% pure CBD) in drug-resistant epilepsy and found the medicine to be safe and efficacious. *"Sixteen patients (age: 9.1 ± 3.4) enrolled in the study; 11 completed the full treatment program. The average maintenance dose was 13.6 ± 4.2 mg/kg. Patient adherence to treatment regimens was 96.3 ± 9.9%. By the end of the treatment period, 81.9% and 73.4 ± 24.6% ($p < 0.05$) reductions from baseline median seizure count and monthly seizure frequency, respectively, were recorded. Responders' rate was 56%; two patients became fully seizure-free. By study end, 8 (73%) caregivers reported an improved/very much improved condition, and 9 (82%) reported reduced/very much reduced seizure severity. Most commonly reported treatment-related adverse effects were sleep disturbance/insomnia, (4 (25.0%) patients), followed by somnolence, increased seizure frequency, and restlessness (3 patients each (18.8%)). None were serious or severe, and all resolved.* *Conclusions* *PTL-101 was safe and tolerable for use and demonstrated a potent seizure-reducing effect among pediatric patients with TRE".* These 4 examples of the literature show reasonable efficacy in a very difficult- to-treat population with relatively few side effects.	
End Our Pain	Guideline	16	24 - 29	[redacted] **– Evidence review on behalf of EoP (side effects)** The NICE draft guideline states that *"People with these epilepsy syndromes also report a very high rate of adverse events. Open-label studies (clinical trials in which the treatment and placebo groups are not disguised) of cannabis-based medicinal products in other types of epilepsy have also shown a very high level of adverse events (in up to 98% of people**) but it was not possible to determine how many of these were due to the cannabis-based products"** (MB emphasis)*	Thank you for your comment. The committee discussed the adverse events as they considered this to be one of the key concerns when considering prescribing CBMPs. The committee were also aware of the side-effects of seizures, however the low-quality evidence that is currently available made it difficult to compare both the benefits and harms of CBMPs. This has led to the development of the research recommendations.

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				This statement is disingenuous. The accepted rate of side effects is quite low as confirmed in the 4 example papers and in other publications. Most side effects are minor and transient. Clearly, as with any medicine, there are some serious adverse events. However, CBD is remarkably safe. THC medicines have more side effects according to the THC content but it should be remembered that CBD counteracts the effects and side effects of THC. Epilepsy cannabis medicine will always contain CBD. The Committee admits that they cannot be sure that the reported side effects are secondary to the cannabis-based products. The serious side effects of the other AED "standard" medication needs to be borne in mind, particularly when used in combination in a polypharmacy regime.	
End Our Pain	Guideline	18	12 - 16	[redacted] **– Evidence review on behalf of EoP (other jurisdictions)** 50 countries have now adopted medical cannabis legislation. Lessons need to learnt from these countries and the NICE report does not refer to any prescribing guidelines in other jurisdictions. Australia, for example, has published their guidelines for practitioners. Their recommendations are as follows: 1. Epilepsy treatment with medicinal cannabis or cannabinoids is only recommended as an adjunctive treatment - that is, in addition to existing anti-epileptic drugs. 2. Should the treating physician elect to initiate medicinal cannabis therapy in epilepsy patients, it is recommended that CBD be used as adjunctive therapy to existing AEDs in children or young people aged up to 25 years, with the primary aim of decreasing seizure frequency and improving overall quality of life. Achieving full seizure remission is likely to be rare. There is insufficient evidence to provide recommendations for adults aged over 25 years. 3. Patients and prescribing clinicians should be aware of likely adverse events such as diarrhoea, drowsiness, and changes to appetite. Adverse events such as a worsening of seizures, convulsions, severe diarrhoea or behavioural difficulties may affect the aims of the epilepsy treatment and increase the likelihood of treatment withdrawal, and should be evaluated on a case by case basis. If treatment is likely to be long-term, it is important that any side-effects from medicinal cannabis are not greater than side effects experienced with other AEDs, and that their response to treatment is regularly assessed. 4. In the absence of strong evidence for dosing and specific preparations of cannabis or cannabinoids in epilepsy treatment, it is recommended that should the treating physician elect to initiate medicinal cannabis therapy in epilepsy patients, patients should be re-evaluated after 12 weeks for evidence of response to treatment. 5. In the absence of strong evidence for dosing and specific preparations of medicinal cannabis in epilepsy treatment, it is recommended that CBD be used and re-evaluated after twelve weeks of therapy, to ascertain whether there has been any benefit from its introduction. 6. Prescribing clinicians should also be aware of the potential drug-drug interactions with CBD and anti-epileptic drugs. The Australia report drew on 22 studies, both observational and randomised trials. Their conclusions appear reasonable and balanced. Cannabis for epilepsy use is now legal in 34 of the 50 USA states as well 5 of the G7 nations. In those states and G7 nations cannabis prescription for epilepsy is allowed. In all bar two of the 50 countries that have adopted medical cannabis legislation prescription for epilepsy is allowed.	Thank you for your comments. The NICE guideline also considered and included international guidelines as part of the evidence review. This included guidelines from Canada, Ireland, Australia and the Netherlands. Furthermore, NICE guidelines are written for the English healthcare system and so we look to ensure that we have professionals and lay experience in that system

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End Our Pain	Guideline	5	11 - 20	EoP considers that the first part of paragraph 1.4 of the draft guideline should be changed from how it is proposed to be drafted, to read as follows: *"~~Because there is no good quality evidence in this population, the committee were unable to make a recommendation on~~ Consider the use of cannabis-based medicinal products for severe treatment-resistant epilepsy. ~~Therefore, they~~ The committee have made research recommendations to promote further research and inform future practice."* The reasons why EoP considers that these changes should be made are as follows: 1. The comment as to the lack of good quality evidence is inappropriate as part of the recommendation. Recommendations 1.1, 1.2 and 1.3 do not contain any information as to the adequacy of the evidence-base, nor any explanations as to the reasons for the recommendations. They are, appropriately, confined to the recommendations themselves. Recommendations should be just that – recommendations. Providing reasoning as part of recommendations is liable only to create confusion for clinicians: in this case by suggesting that there is a recommendation against the use of CBMPs. Supporting reasoning for recommendations can be presented elsewhere. 2. Our families' consistent experiences show that without a recommendation positively encouraging practitioners to consider the use of CBMPs, patients will continue to be denied NHS prescriptions, even where one is merited in a particular case. The simpler wording that we propose at paragraph 1.4, starting with "Consider", is consistent with recommendation 1.1.1. 3. It is untrue that there is "no good quality evidence in this population". There is a considerable body of evidence to support the prescription of CBMPs in appropriate cases. That is why Parliament changed the law to allow precisely that. The key problem with the draft recommendation is that it has the intention or effect of discouraging practitioners even from considering prescribing CBMPs in appropriate cases, thereby defeating the intention of Parliament in enacting the change to the law (as discussed further below). In this respect, it is disappointing to find that this restrictive approach appears to follow the interim guidance previously issued by the BPNA, which contained serious errors. (6) We emphasise that the difference between the recommendation which EoP is seeking, and the current draft recommendation, is small but absolutely crucial. EoP is not asking for a recommendation that CBMPs should always be prescribed in all cases of severe drug-resistant epilepsy. Instead, what it is asking for is that (in the mould of the other recommendations in the same draft guideline) it be positively recommended that clinicians consider prescribing in appropriate cases. This is particularly appropriate given the evidence of decreasing efficacy of existing pharmaceuticals once one pharmaceutical anti-epilepsy drug has failed. We note that NICE has disclaimed that it is making a recommendation against prescriptions in certain cases: its position is rather that it is not prepared to make a recommendation either way. If, as NICE would appear to recognise, consistently with the history of the legislation by which CBMPs can now lawfully be prescribed, there are at least certain cases in which CBMPs would be appropriately described, then that should be reflected in the guideline. This will crucially give clinicians the assurance which in practice doctors do not feel they have, even in those cases. In short, NICE should make a positive – albeit modest – recommendation, rather than adopting a supposedly neutral stance which is at odds with its own rationale, and which will continue to limit access to CBMPs for those in desperate need.	Thanks for your comments. The information in section 1.4 for epilepsy is not a specific recommendation but is instead guidance on why the committee decided they could not make a recommendation. The committee did not feel that they could make a recommendation to consider the use of cannabis-based medicinal products because of the current low-quality evidence base. Although there were some RCTs which are considered higher quality evidence, these were in relation to Lennox-Gastaut and Dravet syndromes which were not in the scope of this guideline. Results of the technology appraisal for these syndromes will be published later this year. Although the committee did not feel that they could make a recommendation based on current evidence, they did not want to prevent people being prescribed cannabis-based medicinal products if a clinician felt it was appropriate for a particular patient. This is why the committee did not make a recommendation against the use of these products for epilepsy. However there was not sufficient evidence to be able to state specific populations that would most benefit from this. More information on the committee's discussion around this can be found in the evidence review D.

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				(6) For example, the BPNA relied on a study conducted into the effects of THC on adolescents who smoked cannabis recreationally. That is inappropriate, where the issue is the efficacy of pharmaceutical grade CBMPs on patients with severe treatment-resistant medical conditions.	
End Our Pain	Guideline	General	General	This document forms the response of End Our Pain ("EoP") to the consultation on NICE's draft guideline on cannabis-based medicinal products ("CBMPs"). EoP is a registered stakeholder in the development of this guideline. We are a campaigning organisation set up to help secure legislation for access to wholeplant medical cannabis for patients in the UK, to help them gain relief from their distressing symptoms. EoP provides the Secretariat services to the All-Party Parliamentary Group on Medical Cannabis under Prescription and is the most powerful voice in Westminster on this issue. The campaign represents patients suffering from all conditions who seek medical benefit from access to medicinal cannabis. The campaign has a particular emphasis on patients – many of them infants and young children – with severe, drug-resistant, intractable epilepsy who represent the most urgent need. We therefore have a particular interest in the aspects of the draft guideline which address these conditions. It is those aspects which are the focus of this consultation response. This consultation was open for four weeks, almost all of which fell during the August school holidays. EoP requested that the consultation period be extended by two weeks, in order to allow the families we represent proper time to give a full and meaningful response to the draft guideline. Although NICE allowed EoP one additional week to submit its response, this still did not give us the time we consider to be fair and necessary. This document represents all that has been possible in the limited time afforded to us.	Thank you for your comments.
End Our Pain	Guideline	General	General	**<u>The significance of the change in the law</u>** NICE will be well aware that the background to the guideline is the recent change in legislation by which CBMPs can now lawfully be prescribed. The key point here is that that change in law has reflected an intention on the part of Parliament that there will be at least certain cases in which such prescriptions should be given. Were it otherwise, the change in the law would not have made any sense. EoP calls on NICE accordingly to reflect the intention of Parliament in its guideline, in the way set out above: whilst CBMPs will not always be appropriate for all cases, they absolutely are appropriate for some, and it is crucial that in those cases doctors feel able to prescribe with the backing of a recommendation of the above type. In more detail the recent history is as follows. Until 1 November 2018, CBMPs were listed in Schedule 1 of the Misuse of Drugs Regulations 2001 ("2001 Regulations"). That meant they could not be lawfully prescribed to patients in the UK. Following the high-profile case of Alfie Dingley, whose mother Hannah Deacon was supported by EoP, the Government agreed to commission a review to consider a change to the law preventing the prescription of CBMPs. In June 2018, the Chief Medical Officer for England and Chief Medical Advisor to the UK Government, Professor Dame Sally Davies ("the CMO"), conducted a review of the evidence of the therapeutic and medicinal benefits of cannabis-based products ("the Review"). The purpose of the Review was to *"advise on the appropriateness of [cannabis-based products'] place within Schedule 1 of the Misuse of Drugs Regulations 2001…" (7)*	Thank you for your comment. We recognise that the CMO identified sufficient evidence to reschedule CBMPs. NICE considers cost-effectiveness evidence as well as clinical effectiveness when determining which treatments to recommend on a population-wide basis. For the chronic pain population, the evidence showed that CBMPs were not clinically and cost effective. For the epilepsy population, the committee did not feel that there was sufficient evidence available to make a positive or negative recommendation. Clinicians can still make their own individual prescribing decisions in the best interest of their patients.

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				The CMO's central conclusion is contained in paragraph 1.4 of the Review: "*There is now…conclusive evidence of the therapeutic benefits of cannabis based medicinal products for certain medical conditions and reasonable evidence of the therapeutic benefit in several other medical conditions. This evidence has been reviewed in whole or in part, and considered robust, by some of the leading international scientific and regulatory bodies, as well as the World Health Organisation (WHO)…**I therefore recommend that the whole class of cannabis based medicinal products be moved out of Schedule 1** [of the Misuse of Drugs Regulations 2001]" (8)* The CMO was clear about the purpose of the change to the legislation: *"[m]oving these drugs out of Schedule 1 would allow them to be prescribed under controlled conditions by registered practitioners for medical benefit." (9)* The Committee is correct to recognise that many patients in this population benefit from treatment with CBMPs. However, NICE's failure to make a recommendation of the sort required (see above) is making it impossible for our families to obtain NHS prescriptions, causing unconscionable risk to the health of the children affected and an impact on families' finances which can be impossible to manage. Several families risk criminalising themselves in order to personally transport these products into the UK from abroad. They do this because they simply cannot afford to pay the huge costs charged by private importers in the UK. In other words, these families face an impossible dilemma. A recommendation to <u>consider</u> the use of CBMPs in cases of severe treatment-resistant epilepsy would more accurately reflect the reality that some patients in this population group can benefit from treatment with CBMPs. Were such a recommendation to be made, it would still be for individual doctors to make individualised decisions in the best interests of their patient. Indeed, that is the only approach that can work with CBMPs, which are highly personalised medicines. Doctors would feel greater confidence in making those individualised decisions knowing that there is clear guidance from NICE that they should <u>consider</u> prescribing CBMPs in appropriate cases. The Review was based upon evidence reviews from outside the UK. The CMO considered evidence collated in Australia, Ireland and the USA, as well as reviews by WHO. She regarded this evidence as conclusive or at least reasonable to support changing the legislation. The CMO reported that WHO considered the evidence to be "robust." For example, the CMO draws upon a 2018 review of evidence commissioned by the Australian Commonwealth Department of Health, which found that there is *"limited but high quality evidence for the use of medicinal cannabis products in epilepsy." (*10) Parliament accepted the CMO's recommendation, and changed the law. It enacted the Misuse of Drugs (Amendments) (Cannabis and Licence Fees) (England, Wales and Scotland) Regulations 2018, which moved CBMPs out of Schedule 1 of the 2001 Regulations and into Schedule 2, with effect from 1 November 2018. (11) The change meant that for the first time CBMPs could be prescribed in the UK. In October 2018, when laying the amended legislation before Parliament, then Home Secretary Sajid Javid said in a written ministerial statement: "*I have been clear that my intention was always to ensure that patients have access to the most appropriate course of medical treatment. I stressed the*	NICE guideline recommendations are based on the best available evidence. Review questions guide the search for evidence, and the type of evidence used depends on the type of question. For example, a randomised controlled trial is often the most appropriate type of study to assess the efficacy or effectiveness (including cost effectiveness) of an intervention. The NICE guideline also considered and included international guidelines as part of the evidence review. This included guidelines from Canada, Ireland, Australia and the Netherlands,

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				importance of acting swiftly to ensure that where medically appropriate, these products could be available to be prescribed to patients. I have been clear that this should be achieved at the earliest opportunity whilst ensuring that the appropriate safeguards were in place to minimise the risks of misuse and diversion. *Building on the expert advice we have received, first from the Chief Medical Adviser to the UK Government and then the Advisory Council on the Misuse of Drugs (ACMD), the regulations we have laid today give effect to my commitments."*(12) However, despite the clear intention behind the change in the law, to our knowledge only two patients have been granted NHS prescriptions for CBMPs to date. From the experience of the families we represent, we know that – despite the change in the law – many doctors still feel they cannot prescribe CBMPs because of the terms in which the available guidance is cast. Even where their own professional opinion is that a CBMP would be medically appropriate and beneficial for a particular patient, doctors fear negative repercussions from their regulator. That is why the content of the draft guideline matters so much to the families EoP represents, and to all patients suffering with severe drug-resistant epilepsy. The Committee has explicitly recognised that there are patients who are currently benefitting from treatment with CBMPs. The Committee states as follows: *"Not making a recommendation against their use means that people who are currently benefitting from the use of CBMPs can continue with treatment, and specialists, people with epilepsy and their carers will not be prevented from making individualised treatment decisions."*(13) *(Emphasis added)* The Committee is correct to recognise that many patients in this population benefit from treatment with CBMPs. However, NICE's failure to make a recommendation of the sort required (see above) is making it impossible for our families to obtain NHS prescriptions, causing unconscionable risk to the health of the children affected and an impact on families' finances which can be impossible to manage. Several families risk criminalising themselves in order to personally transport these products into the UK from abroad. They do this because they simply cannot afford to pay the huge costs charged by private importers in the UK. In other words, these families face an impossible dilemma. A recommendation to consider the use of CBMPs in cases of severe treatment-resistant epilepsy would more accurately reflect the reality that some patients in this population group can benefit from treatment with CBMPs. Were such a recommendation to be made, it would still be for individual doctors to make individualised decisions in the best interests of their patient. Indeed, that is the only approach that can work with CBMPs, which are highly personalised medicines. But doctors would feel greater confidence in making those individualised decisions knowing that there is clear guidance from NICE that they should consider prescribing CBMPs in appropriate cases. (7) *Cannabis Scheduling Review Part 1: The therapeutic and medicinal benefits of Cannabis based products – a review of recent evidence,* para 1.2: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/722010/CMO_Report_Cannabis_Products_Web_Accessible.pdf (8) Emphasis in the original (9) Para 1.5	

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				(10) See para 9.1 of the Review. The Australian review drew on 22 studies, including both observational studies and randomized controlled trials: https://www.tga.gov.au/epilepsy-randomised-controlled-trials-and-other-studies (11) See regulation 7 of the 2018 Regulations (12) https://www.parliament.uk/business/publications/written-questions-answers-statements/written-statement/Commons/2018-10-11/HCWS994/ (13) NICE, *Cannabis-based medicinal products: evidence reviews for epilepsy DRAFT [August 2019]*, pg. 20, lines 28-32.	
End Our Pain	Guideline	General	General	**The evidence of benefit** As above, it appears that NICE already recognises the benefit that CBMPs can bring in certain cases. For that reason alone, NICE's position that there is "no good quality evidence" to support a positive recommendation of any sort is one we find difficult to understand. However, if NICE has been under any doubt as to the sufficiency of evidence to support the modest recommendation we consider should be made, that should no longer be so. As summarised below, there is a very large amount of evidence to support the making of that modest recommendation. First, there is the evidence of the parents whose children continue to be affected by severe treatment-resistant epilepsy. Of the parents EoP supports who access CBMPs for their children, almost all do so through expensive private prescriptions, either issued in the UK or in Holland. The only exception is [redacted], whose son [redacted] is one of only two patients with an NHS prescription for CBMPs. These families will be directly affected by this guideline. If the draft recommendation in paragraph 1.4 becomes the final recommendation, the guideline will continue to entrench the restrictive approach adopted by the BPNA, which fails to take into consideration the exceptional clinical circumstances of children with intractable epilepsy, the devastating side effects they experience on pharmaceutical medication, and the extraordinary effect the CBMPs have had on their health and wellbeing. This has been nothing short of life-changing for these families. The children of the families we support have the most extreme, if not entirely novel, forms of intractable epilepsy and have exhausted most, if not all, pharmaceutical medication available on the NHS. They are exceptional cases, with exceptional clinical need who have demonstrated under private prescription that CBMPs do more to alleviate their symptoms than any medication they have been given to date. Their experiences provide the best evidence of CBMPs working in patients, in a clinical setting, all monitored and cared for by their clinicians. They demonstrate a profound change in the severity, type and duration of the seizures, changes that has never been replicated by pharmaceutical medication. These experiences should not be discounted simply because they have not been identified in a clinical trial setting. These experiences should operate to educate and encourage doctors that, when all reasonable alternatives have been tried, they should consider all treatment options available to them, including CBMPs. In the case of [redacted], the clinical team had exhausted all standard pharmaceutical medication including unlicensed drug combinations, invasive brain surgery and the ketogenic diet, with limited if no improvements in [redacted] condition. In this particular circumstance, the family no longer had any viable pharmaceutical alternatives to control [redacted] 100 seizures a day. In the case of [redacted], he is the only child in the	Thank you for taking the time to share details of the care received by children affected by severe treatment-resistant epilepsy. On an individual level there appears to be evidence that CBMPs have a role. Clinicians can make their own individual prescribing decisions in the best interest of their patient taking into account their values and preferences. However the committee agreed there wasn't sufficient quality and quantity of evidence to make population level recommendations. Research recommendations were made to promote the evidence base in this area. This should include the views of patients, carers and families. The committee agreed that a national or local registry of prescribing practices of CBMs was also needed.

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				world with the particular genetic mutation which causes his epilepsy. There will never be an RCT which can appropriately study his condition, balance the risks and reach a conclusion which can be applied to a broader patient base, as there is not one. His care should be conducted on an individual basis, reviewing his response to medication and any applicable side effects. It is clear that the drafting of the guideline could operate to prevent children such as [redacted] and [redacted] accessing any further treatment which may help control their condition, and that they will continue to suffer on a daily basis. Importantly, the changes in the quality of life are not just felt by the children whose epilepsy is better controlled. There could be a real improvement in the health and wellbeing of close family members and carers, who are constantly in fear of the risks and side effects of their child's care. Many of the families have other children who struggle to understand the severity of their sibling's condition, and are frightened and scared by the symptoms they see. In the case of [redacted], his family have had to seek primary mental health support and social worker care for their other son, [redacted], in order to help him cope with severity of [redacted] condition. The principal point which can be drawn together from the families' submissions is that their children are suffering. These are all circumstances of intractable epilepsy where conventional treatment has been ineffective and exposes their children to high doses of dangerous, off-licence and commonly untested (on the child population) adult medication which inflicts high volumes of adverse effects. The families have, after reviewing the draft guideline, prepared responses to outline their own individual experiences, which are found at comment number 7 – 19 of this submission. However, a summary of their different experiences between pharmaceutical medication and CBMPs include: 1. [redacted] After being on over 15 different medications and seeing little to no change in his more than 100+ seizures a day, the prescription of CBMPs (progressively weaning off other pharmaceuticals) has resulted in [redacted] having fewer than 10 seizures a day, walking and drinking independently, and no longer attending hospital on a frequent, if daily, basis. 2. [redacted]: After responding negatively to five separate anticonvulsants over a 2-year period, [redacted] has been weaned off her pharmaceutical medications and relies solely on CBMPs. There has been a marked improvement in the type, duration and severity of her seizures, with improvements in her quality of sleep, attention span and gait. [redacted] has not been on any other daily medication, pharmaceutical or otherwise, for [redacted]. It should be pointed out that the prevailing approach has caused the [redacted] family huge emotional and financial hardship, given the enhanced risk of mortality for their child. Only very recently [redacted] medication, obtained in Holland, under prescription issued by a British Paediatric Neurologist, was confiscated only to be returned later with significant additional costs. The prospect of this child being deprived of effective medication, when all conventional drugs have failed, should not be countenanced by NICE. A track record of [redacted]' success should be ample proof that her cannabis oil has greatly mitigated her symptoms, justifying an NHS prescription. 3. [redacted]: Before starting CBMPs, [redacted] would have at least 5-20 seizures a day, lasting an average of 5 minutes. Since starting CBMPs in [redacted], [redacted]a has had 19 seizure free days over a 29-day period, is more alert and can focus on people's faces. 4. [redacted]: After being prescribed Bedrolite in May 2019, [redacted] seizure frequency has reduced by 85% and he is now a happy and responsive [redacted] year old boy. This is a marked improvement from the side effects he	

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				experienced on pharmaceutical medication, which left him heavily sedated and miserable. 5. [redacted]: During the course of her treatment, [redacted] did not respond to the combination of four different anti-epileptics and surgical installation of a vagal nerve stimulator. After starting treatment with CBMPs in [redacted], [redacted] has had a huge reduction in the frequency in her seizures and marked improvements in her quality of sleep. 6. [redacted]: [redacted] suffered with over 600 daily myoclonic jerks and had life-threatening side effects from his treatments with anticonvulsants, including excessive weight gain, blood transfusions, and being inadvertently forced into a medically induced coma. After spending almost the entirety of his life after his diagnosis in hospital, since starting CBMPs in [redacted] has now been seizure free for over 11 weeks and no longer needs to wear his protective helmet. 7. [redacted]: [redacted] struggled to control his seizures and responded negatively to whatever combination of 18 pharmaceutical medication options provided, including attending hospital for intravenous delivery of the drugs and not responding to up to three rescue medications given whilst in seizure. The severity of [redacted] seizures has frequently resulted in severe injuries and broken bones. The delivery of CBMPs has had a marked improvement on [redacted] life, he can interact and play with other children his age, he can speak more clearly, he has better co-ordination and balance, and he no longer needs frequent ambulance delivery/intervention or hospital stays. 8. [redacted]: Over [redacted] years, [redacted] has had all the normally prescribed antiepileptic medication, tried the ketogenic diet and had a vagus stimulator installed with limited success. Since starting CBMPs in [redacted], [redacted] daily seizures have reduced by 80%, she is more alert, and no longer needs a wheelchair when leaving the house. In the year since starting on CBMPs, there have been no reported side effects. 9. [redacted]: [redacted] was a very happy, intelligent and active little boy until he was diagnosed with complex epilepsy at the age of [redacted]. Since then, his treatment with pharmaceutical anti-epileptics was unsuccessful, painful and he stated that he would rather die than ever be given IV phenytoin ever again. The addition of CBMPs to his treatment has resulted in [redacted] having seizure free days for the first time in [redacted] years and he is able to read, write, and attend school, which he would not have been able to do previously. 10. [redacted]: Despite being prescribed a range of primary anti-epileptics, secondary pharmaceutical medication, and the ketogentic diet, [redacted] continued to suffer hundreds of seizures a day. Upon commencing treatment with CBMPs and ceasing treatment with pharmaceutical medication, [redacted] seizures have become manageable and he has begun to thrive, including recognising and reaching for his parent's faces and demonstrating emotions – something they never expected after the severity of his diagnosis. 11. [redacted]: [redacted] is an [redacted] boy who is the only recorded case in the world of an [redacted] gene mutation which is attributed with causing his intractable epilepsy. The severity of [redacted] seizures, and the frequency in which he entered status epilepticus, has required him to be placed into a medically-induced coma on more than one occasion, of which one coma lasted for three weeks. After starting CBMPs in [redacted], [redacted] has not required hospital	

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				admission for his seizures and their frequency has plateaued; a marked difference to the first year of his life which required constant hospital intervention. Additionally, [redacted] has not entered into status epilepticus since starting treating with CBMPs. 12. [redacted]: After being diagnosed with intractable epilepsy at age 4, alongside a rare chromosomal disorder, [redacted] suffered up to 300 seizures a day with one episode requiring admission to intensive care for over 6 weeks. In order to manage her condition, [redacted] has been prescribed a combination of 15 different pharmaceutical medications, as well as surgical installation of a vagal nerve stimulator, with little to no impact on her seizures. After starting CBMPs, [redacted] has had a remarkable improvement in the severity and frequency of her seizures, enabling her to be re-learning how to walk and talk. 13. [redacted] [redacted] : [redacted]` is [redacted] of only [redacted] boys in the world who has been diagnosed with intractable epilepsy attributable to a [redacted] mutation. By the age of [redacted], [redacted] suffered up to 500 seizures a month which could not be controlled by any combination of the 15 different pharmaceutical medications that he had been prescribed to date. After starting CBMPs in [redacted] [redacted] has experienced much better seizure control, including going [redacted] completely seizure-free. Whilst he is currently experiencing some relapses whilst a new CBMPs regime is established, his seizures are much smaller, less frequent and easier to control. In view of the compelling evidence of the positive impacts of CBMPs outlined above, it would be appropriate for NICE to make a recommendation which states that CBMPs should be considered. Such a recommendation has the potential to make a huge difference to the lives of children like those highlighted in this document. Many pharmaceutical anti-epilepsy drugs which have been unsuccessfully tried by these families have severe side effects. In the experience of the families we represent, any risks involved in using CBMPs have been far outweighed by the improvements they are seeing in their children's health and overall quality of life. <u>Secondly, there is the evidence of expert clinicians.</u> Professor Mike Barnes is a neurologist and rehabilitation physician. He was involved in the EoP campaign that culminated in the first cannabis licence in the UK, for [redacted], in [redacted]. He remains the consultant looking after the cannabis prescription for [redacted]. Professor Barnes has conducted a review of the draft guideline, which is included in the appendix to this consultation response. He identifies the trial-and-error approach which is required to treat severe treatment-resistant epilepsy. As he notes, the evidence demonstrates that where a patient in this population has not responded positively to their first regime of anti-epilepsy drugs, there is a diminishing likelihood of success with subsequent regimes of standard drugs. He also notes the complex and severe side effects associated with multi-drug treatment regimes, many of which are themselves "off-label" and tested by few randomised controlled trials. He further notes the undue weight given which the guideline committee appears to have given to the side effects of CBMPs, without also considering the serious side effects of regimes which include multiple anti-epilepsy drugs. In the circumstances, Professor Barnes highlights that any potential new medicine for this population, such as CBMPs, should have a low threshold for clinical use, particularly if it has a good safety profile.	

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				As Professor Barnes states, cannabis is a highly personalised medicine, which does not readily fit into the pharmaceutical model of randomised, placebo-controlled trials. It is therefore appropriate for observational studies to be considered. He points to several observational studies which do not appear to have been considered by NICE. Professor Barnes further highlights the experience of other jurisdictions in which the approach to CBPMs better reflects the evidence base. This includes the balanced and reasonable guidance for the prescription of CBMPs in Australia. The Australian experience was drawn upon in the June 2018 review by the CMO, which resulted in Parliament changing the law in this country. In developing the draft guideline, NICE does not appear to have given proper consideration to the Australian approach, or that of other jurisdictions.	
End Our Pain	Guideline	General	General	The families represented by EoP recognise the need for further research as to the efficacy and risks of CBMPs. Nevertheless, there is clear evidence of its efficacy, recognised by our own Parliament, the governments of Ireland, Australia, Holland, Canada and the USA, and by WHO, which the NICE Committee appears to have rejected without giving any, or any adequate, reasons. In the meantime, the draft guideline, if it is published in its current form, will mean that these families will continue to be prevented from accessing CBMPs without unacceptable financial cost and personal risk, even though they are shown to be helping their children. Their stories show that CBMPs have reduced seizures, hospital admissions and side effects and improved quality of life for their desperately sick children, with the attendant cost savings to the NHS. They also show that, despite these manifold benefits, NHS clinicians remain unwilling to prescribe CBMPs without a positive recommendation supporting their use for severe treatment-resistant epilepsy. The draft guideline would mean that our families would have no way of escaping from a nightmare in which they must meet the crippling cost of private prescriptions or risk allowing their children to experience horrendous suffering, permanent injury, or death. Amending the guideline in the manner proposed is the only way in which the intentions of the NICE committee, to ensure that *"specialists, people with epilepsy and their carers will not be prevented from making individualised treatment decisions"*, can be met.	Thank you for your comment. NICE guideline recommendations are based on the best available evidence. Review questions guide the search for evidence, and the type of evidence used depends on the type of question. For example, a randomised controlled trial is often the most appropriate type of study to assess the efficacy or effectiveness (including cost effectiveness) of an intervention. The NICE guideline also considered and included international guidelines as part of the evidence review. This included guidelines from Canada, Ireland, Australia and the Netherlands.
End Our Pain	Guideline	General	General	[redacted] **– Evidence review on behalf of EoP (general comments)** NICE, on August 2019, produced draft guidelines for consultation on Cannabis-Based Medicinal Products (CBMPs). The guidelines include a "No Recommendation" advice on the use of CBMPs for severe treatment-resistant epilepsy: *"Because there is no good quality evidence in this population, the committee were unable to make a recommendation on the use of cannabis-based medicinal products for severe treatment-resistant epilepsy. Therefore, they made research recommendations to promote further research and inform future practice"* We contest that this lack of any recommendation is unnecessarily restrictive and will effectively preclude prescription of CBMPs on the NHS despite the suggestion from the Committee that: *"Given the limited amount of research currently available for the use of CBMPs for treatment-resistant epilepsy, the committee decided that making no recommendation was preferable to making a recommendation against the use of CBMPs. Not making a recommendation against their use means that* ***people who are currently benefitting*** *(my bold highlight) from*	Thank you for your comments. As you mention the committee decided not to make a recommendation against the use of CBMPs because they did not want to prevent people who are currently benefitting from the use of CBMPs from continuing to receive treatment. By not making a recommendation against the use of CBMPs, this also means that people can still be prescribed CBMPs if the clinician feels that they may benefit. However, the committee did not feel they could make a wider recommendation for people with severe treatment-resistant epilepsy given the limited, low-quality, evidence base. There was no evidence that met the inclusion criteria for our review that assessed specific polypharmacy combinations incorporating CBMPs and so the committee could not comment on this.

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				the use of CBMPs can continue with treatment, and specialists, people with epilepsy and their carers will not be prevented from making individualised treatment decisions". **<u>Drug resistant epilepsy</u>** Most people, adults and children, with epilepsy are well controlled on standard anti-epilepsy drugs (AEDs). Overall, about 70-80 % of people with epilepsy are controlled on a single anti-convulsant. However, the remainder require a trial and error approach in order to maximise their treatment regime. Unfortunately, if individuals fail the first treatment regime there is a diminishing likelihood of success after the 2nd and subsequent regimes. In one study, as an illustration, (Ramos-Lizana et al Seizure 18: 620-624; 2009), 61% of people responded well to the first regime but only 8% to the second regime, 3% to the third and 1% to the fourth regime. The usual course of action in drug resistant cases is to eventually use a polypharmacy regime utilising several AEDs – with very limited chance of satisfactory seizure control. There have been very few studies of optimal polypharmacy regime in such circumstances. There have been a few studies assessing the efficacy of adding a third AED to an existing two drug regime, such as the addition of stiripentol to an existing regime of clobazam and valproate in Dravet syndrome (Chiron et al, Lancet 356: 1638-42; 2000). However, in clinical practice the overwhelming number of polypharmacy regimes have not been subject to any rigorous academic assessment by, for example, randomised controlled trial and are usually a matter of clinical judgement by the prescribing physician. There are considerable side effects problems when multiple AEDs are used. The seriousness of drug-resistant epilepsy should not be understated. There are complex and serious side effects often associated with multi-drug regimes. There is the major factor of reduced quality of life for the person with epilepsy and their family. There is an increased risk of death from uncontrolled seizures. Drowning in epilepsy in general, for example, is 15-19 times more likely than the general population and there is an increased risk of death from suicide, drug overdose and other accidents. These risks are all further increased in uncontrolled epilepsy and in particular the risk of Sudden Unexplained Death in Epilepsy Syndrome (SUDEP) is much higher in drug-resistant epilepsy and is related to the number of drugs prescribed and frequency of dose change and the residual frequency of the seizures. In summary, drug resistant epilepsy in childhood, as well as in adulthood, is a serious and life threatening issue with very limited evidence of the correct course of action to guide the prescribing physician other than trial and error use of the available AEDs. The great majority of the AEDs used in such circumstances have not been subject to clinical trials in such multi-drug regimes and many used in childhood are used "off-label" as so few studies have been conducted in the childhood drug-resistant epileptic population. Thus any potential new medicine should have a low threshold for clinical use, particularly if there is a good safety profile.	
End Our Pain	Guideline	General	General	**[redacted] – Evidence review on behalf of EoP (concluding remarks)** The NICE committee draft guidelines have adopted a negative stance for the prescription of cannabis-based medical products for epilepsy. They have rejected the evidence from all but 4 studies and specifically excluded from their consideration all observational studies and other sources of evidence. It is accepted that there is a paucity of randomised controlled trials as yet in this field although it is worth pointing out that as cannabis is a family of medicines and not a single molecule medicine it does not readily fit into the pharmaceutical model of randomised, placebo-controlled trials. It is a very personalised medicine that requires patience and skill to prescribe one of many products specifically tailored to the individual patient. It should not be forced into a pharmaceutical pigeon hole into which it does not fit. Many jurisdictions have realised this and established an Office of Medical Cannabis to assess evidence more appropriately to the product and monitor quality and supply.	Thanks for your comments. The independent guideline committee considered evidence from 11 observational studies as well as the 4 RCTs. However, they decided that this was too low quality to be able to confidently make a recommendation in favour of the use of cannabis-based medicinal products for severe treatment-resistant epilepsy. The committee decided not to make a recommendation against the use of CBMPs because they are aware that some people who are prescribed them do experience benefits. However, without higher quality evidence they were unable to fully assess both the benefits and harms of CBMPs, and therefore make a recommendation for their use. The committee discussed the variety of CBMPs and how the different constituents may have varying effects on epilepsy. This led them to make research recommendations for the use of different types of CBMPs. The aim of these research recommendations is to provide higher

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				The committee acknowledges that *"CBMPs...had the potential to generate significant gains in quality of life"* (Evidence Review D p.20) but its decision not to recommend CBMPs does not reflect this. In particular, the lack of any positive recommendation means that the stated aims of the committee (ensuring that *"people who are currently benefiting from the use of CBMPs can continue with treatment, and specialists, people with epilepsy and their carers will not be prevented from making individualised treatment decisions"* and "preventing "an increase in patients and carers using unprescribed (over the counter/internet) CBMPs" (Evidence Review D, p.20)) are incapable of being met, because NHS doctors will not prescribe without a positive recommendation to consider the use of CBMPs. The guidelines fail to understand the subtlety of cannabis medicine. As an example, they do not appear to understand the fundamental difference between pure isolate CBD and full plant extract CBD and other full extract products. We consider that: • Given the serious and life threatening nature of drug-resistant childhood epilepsy syndromes • Given the good safety profile of CBD cannabis products • Given that existing AEDs for such epilepsy have mainly not been assessed through randomised trials when polypharmacy is initiated • Given the side effect profiles of existing AEDs in multiple combinations • Given the plethora of studies showing evidence of efficacy and a good safety profile (albeit not randomised clinical trials but "real world" data) Then it is reasonable to suggest that cannabis-based medicinal products should be allowed on NHS prescription. We suggest that physicians should learn from the ongoing prescription experience by actively enrolling patients in to observational studies so we can learn more about the products whilst not disadvantaging the patients in need of treatment who would otherwise wait several years for a full trial programme to be completed and evaluated. The UK should learn from other jurisdictions that have adopted this approach.	quality evidence to allow future committees to make more informed decisions when this guideline is updated.
End Our Pain	Guideline	General	General	**Individual Family Submissions 1 –** [redacted] Dear Paul Chrisp, My name is [redacted] and I have been campaigning for the use of medicinal cannabis in intractable epilepsy for over a year recently with End Our Pain. My son is [redacted] he is [redacted] years old and has intractable epilepsy, substantial developmental delay, Autism, left hemisphere brain atrophy, right sided cerebral palsy. [redacted] has been on clobazam, clonazepam, lamotrigine, levetiracetam, phenobarbital, phenytoin, topiramate, sodium valproate, zonisamide, steroids, ethosuximide, chloral hydrate, diazepam, buccal midazolam, Epidiolex. Most have been used twice or more and we were told that as tolerance is built up to a drug it's swapped for another drug, or another added. Unfortunately for [redacted] none have worked. We have also used the ketogenic diet and over 12 months later it was doing nothing to control the 100+ seizures a day. We also explored brain surgery with Professor [redacted], she said [redacted] was at a huge risk of SUDEP due to his bad seizure control, yet surgery was reported to be a palliative option which would leave [redacted] further disabled creating other health conditions. We found out about cbd oil in 2014 when there was talk of [redacted] started trials and we were seeing it's results for epilepsy and other conditions via the internet. We did some research and asked [redacted] about access to the drug, but were told [redacted] does not have	Thank you for taking the time to share details of the care received by your child affected by severe treatment-resistant epilepsy. On an individual level there appears to be evidence that CBMPs have a role. Clinicians can make their own individual prescribing decisions in the best interest of their patient taking into account their values and preferences. The committee considered the evidence in the area. The RCT evidence focused on treatment for particular epilepsy syndromes and the committee agreed that these findings couldn't be extrapolated to other forms of epilepsy. The committee also considered observational studies but agreed that these were of very low quality due to the high risk of bias. Overall, the committee agreed there wasn't sufficient good quality evidence to make population-level recommendations. Research recommendations were made to promote the evidence base in this area. This should include the views of patients, carers and families. The committee agreed that a national or local registry of prescribing practices of CBMs was also needed.

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				any syndrome they are aiming the research at, to get the drug passed, just brain damage from birth. Even though epilepsy is a symptom not a syndrome. We then tried a few well known cbd products in [redacted] with little success due to inconsistency as there was a high demand of good products. We then got a Canadian whole plant medication from a Canadian clinic and used it from early [redacted] successfully, with a reduction of seizures to just 6 a day using very little, until September when we were running out, we were then given Epidiolex in [redacted], 6 ml a day, which was failing by [redacted], so we discussed the use of bedrocan medications with our neurologist and he asked if he could prescribe these as [redacted] met all of the 5.2 BPNA guidance, and he felt [redacted] had exhausted all other treatments and he said Professor [redacted] [redacted] outlines that fact in her letters about [redacted] and the treatments he had received, he was told NO and a refusal letter was sent. At the end of [redacted] my son was having 300 tonic seizures a day and nearly died. Access to medication was still refused by senior staff because of the guidance put out by the BPNA that said they did not advise it being prescribed due to not enough evidence. So regardless of meeting the 5.2 guidance to be prescribed, and other guidance they have decided to not prescribe on an individual basis to anyone until there is further evidence, as this is what the guidance says. We were told to get a second opinion. We got an independent second opinion in early [redacted] and started Bedrolite(cbd) and bedica(thc) medication in [redacted]. Since then we have weaned Epidiolex, reduced phenobarbital and we are currently weaning clonazepam, We will then just be on 16ml Keppra per day and 5ml phenobarbital per day, along side the bedrolite and bedica. [redacted] seizures have reduced from 100-300 per day each lasting a few minutes to just 3-12 a day lasting no more than 10 seconds. Since starting the medication he can walk again, drink unaided, play with toys, interact with others, see the world and not spend time in hospital from drop seizure severe injuries, requiring CT scans or long hospital stays due to uncontrollable increased seizures of 300 a day. [redacted] would have injuries everyday and ambulances called out for serious head injuries often a few times a month. Our consultant Neurologist has written letters to our GP to say how well [redacted] is now doing since starting the whole plant cannabis medication and Professor [redacted] also said he would endorse how well [redacted] was on the medication. Yet still we can not access the medication via the NHS due to restrictive guidance. Since weaning some of the anti epilepsy medications my son is more alert to the world around him, and has better seizure control, than he did before starting Epidiolex, and finishing his previous whole plant cannabis medication. He also has no bald patches from AED medications and is no longer sedated and drooling unable to feed or drink unaided. [redacted] has never had such good seizure control, before trying cannabis medication the best control was on 4 epilepsy medications and the ketogenic diet and he was seen to have 87 seizures in less than 24 hours on telemetry eeg. Professor [redacted] at [redacted] told us we may as well not use any AEDs as they just didn't work for [redacted]. Whole plant Cannabis medications have so far been the most effective treatment we have used to date to reduce our sons seizures. Giving him a quality of life and the ability to live a full life, with there being less chance of suffering SUDEP. We were also concerned when we were told that neurologists don't know the long term effects of multiple AEDs on the developing brain. We were never told this when they prescribed and adding up to 4 AEDs a day. We have gone down every avenue possible to obtain an NHS prescription for the medication that works for our son. We have been blocked at every turn by [redacted]. Our GP would like to help as our Neurologist would but he has had no training yet to be able to do so under a shared care scheme, the CCG will not fund it either, yet they are for one child I know of. The hospital would not sign off on the paperwork filled in last year for the expert panel and they are doing the same for an IFR and our Neurologist has been threatened with disciplinary action if he goes against the trust. Recently we were told that they would like to take my son off the cannabis medication he is doing well on, wash it out of his system, putting him back	

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				into 100s seizures a day and in two years time put him into a RCT. I'm not sure when it became acceptable to experiment on disabled children again, I thought this was stopped when the war ended. Also my child has a mental capacity of a 10 month baby, the placebo effect is not likely to work with [redacted] since he will not have an understanding of the treatment and therefore the effect is nullified. I know far too much about cannabis as a medicine so I would know instantly if we were given the placebo, or an ineffective isolate. What we do see though is health professionals seeing the difference in my son and documenting it, monitoring of his bloods also, via the NHS. So they want the data but expect me to pay for the medicine that is enabling them to do so. We are now left after seeking an independent second opinion, the NHS Trust told us to get, paying £6300.00 per month privately in the UK or forced to criminalise ourselves to pay £1948,00 in Holland per month. We are left with no choice due to bad guidance leaving Hospital Trusts legally unable to allow NHS Neurologists to prescribe. We are also continually fundraising and asking others to pay to keep our child alive. As 300 a day seizures do irreparable damage to the developing brain. We are scared of having to go abroad as we have been forced to do once before. I am a mother going to a foreign country, buying just under three months supply of medication worth £5,844.00. I could be robbed, arrested upon entering the UK or face getting a criminal record, just to keep my child alive and well. Yet people that live in these countries can bring in 3 months supply yet we can't, even though we have a UK private prescription. My other children can no longer have holidays, fun summer days out and little luxuries they had before as we are putting every penny we have into the pot to keep our son alive. We have been forced to use monies from our business account, putting us into huge financial loss. I am constantly writing emails and letters for help also, leaving us with little time as a family and us missing years of memorable time with our children. I would now like to see the children and adults using this right now be given NHS access immediately, to these medications under a shared care arrangement to help families like us. As I have said before to NHS England, MPs and the Department of health, the yellow card scheme could be utilised to gain experience of any adverse effects people may have, yet no one has ever died yet from taking cannabis, and two children have had it paid for through the NHS for over 12 months, with no adverse effects. I would also like to see a number of doctors trained immediately at a central place in the UK where cannabis based drugs could be administered and vital data collected. Children are dying and these drugs are not even being used as a last resort. In our experience they would rather use unlicensed drugs like, Chloral hydrate which we proved didn't work for seizures when it was given to my son whilst on telemetry EEG. We have tried unlicensed drugs for his age, in the hopes it would help ease his suffering and reduce seizures. We have been given drugs that have caused seizures also. Now we have found an effective treatment we feel no one is helping us access this. We can not sustain the costs for long term use of the drug helping him, I don't think anyone could afford it. We don't want our child back to 300 a day seizures lay in a hospital bed, or experimented on. I have lots of video evidence, seizure spreadsheets and dosing documentation that could be helpful yet no one has asked to see it. We now urgently ask N.I.C.E to step in and give excellent guidance to help my child and others using these medications now, using all data possible. It is not fair that we are being left to fund an effective treatment, saving the NHS thousands a month. Especially when it is already being prescribed to two children via the NHS. [redacted]	

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				Yours sincerely [redacted]	
End Our Pain	Guideline	General	General	**Individual Family Submissions 2 –** [redacted] My name is [redacted]. [redacted] is my [redacted] year old daughter. She was diagnosed with Dravet Syndrome around [redacted] old. Since the age of [redacted] started suffering debilitating seizures that very quickly controlled her life and ours. [redacted] was blue lighted to hospital weekly , with no luck in controlling her seizures, I was scared she was going to die with doctors not giving Me much hope for the future. I have set out a chronology of events based on [redacted] medical notes. Because I do not feel decisions are being made on what is best for the parents our children. In actual fact it seems like full clinically denial. [redacted] life before using bedrolite was heart-breaking and destroying to watch our child suffer continuously. [redacted] has been on no other AEDS since [redacted] as they failed to work and gave her horrible side effects. [redacted] • [redacted] was born. • [redacted] began experiencing seizures when she was 4 months old and in [redacted] she was prescribed Buccal Midazolam. This medication is a benzodiazepine and is used to treat a number of different conditions including seizures. • An additional medication was introduced which [redacted] e took daily – Carbamazepine. This is an anticonvulsant. • [redacted] did not react well to Carbamazepine so she was prescribed Sodium Valproate, another anti-epileptic drug. • There is an association with taking Sodium Valproate and liver dysfunction (especially in children under 3 years old). • A short course of Clobazam was also tried around this time but [redacted] became very agitated and had poor sleep so it was not re-prescribed. [redacted] • The dose of Sodium Valproate was increased again and Phenobarbital was introduced for administration if cluster seizures continued after giving [redacted] Buccal Midazolam. • Phenobarbital a central nervous system depressant which is primarily used as a sedative hypnotic and also as an anticonvulsant in subhypnotic doses. • Side effects can include (at an unknown frequency) anxiety; hallucination; hypotension; megaloblastic anaemia; severe cutaneous adverse reactions (SCARs); thrombocytopenial. [redacted] • [redacted] continued to have seizures despite being on a fairly high dose of Sodium Valproate. She was not experiencing any known side effects from Sodium Valproate so it was continued but another medication was added – Lamotrigine, an anti-epileptic drug. • Initially, there were concerns that [redacted] was developing an ataxic gait but these symptoms improved and she experienced better seizure control for a few months. [redacted] • [redacted] seizures worsened and [redacted] doses of Sodium Valproate and Lamotrigine were increased.	Thank you for taking the time to share details of the care received by your child affected by severe treatment-resistant epilepsy. On an individual level there appears to be evidence that CBMPs have a role. Clinicians can make their own individual prescribing decisions in the best interest of their patient taking into account their values and preferences. The committee considered the evidence in the area. The RCT evidence focused on treatment for particular epilepsy syndromes and the committee agreed that these findings couldn't be extrapolated to other forms of epilepsy. The committee also considered observational studies but agreed that these were of very low quality due to the high risk of bias. Overall, the committee agreed there wasn't sufficient good quality evidence to make population-level recommendations. Research recommendations were made to promote the evidence base in this area. This should include the views of patients, carers and families. The committee agreed that a national or local registry of prescribing practices of CBMs was also needed.

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				• [redacted] seizures dramatically increased again and Lamotrigine was stopped. Dr [redacted] ([redacted] Consultant Paediatrician at [redacted] reported that: ○ "[redacted] is on her 5th anti epileptic medication with no sign of adequate seizure control. She merits a referral for a Ketogenic diet (KD), however, a trial of Stiripentol should be undertaken beforehand". Stiripentol was prescribed. • Dr [redacted] also stated that "The results of the trial using Cannabidiol were encouraging. Although safety and efficacy results were good, further trials are needed before this is made available as a prescription drug". [redacted] • Around this time we started giving [redacted] Cannabidiol oil. Dr [redacted] ([redacted] consultant paediatric neurologist [redacted]) stated that: "Parents recently started her on Cannabidiol on their own and report that since starting this she is much better in terms of her seizure frequency and they also mention that she is more active and able to learn new things". [redacted] • At that time [redacted] was taking Sodium Valproate 260mg twice daily, Stiripentol 300mg twice daily and self- administered Cannabidiol. • Medical notes recorded that there was a good initial response to the Cannabidiol but that seizures continue to occur on a regular basis, mainly Tonic Clonic seizures during sleep. [redacted] • [redacted] seizures worsened again and she experienced a significant neurocognitive decline and consideration was given to prescribing an additional anticonvulsant. [redacted] • Initially Stiripentol was stopped and then a drug holiday was agreed with Dr [redacted] and [redacted] was weaned off Sodium Valproate as well. [redacted] has not been on any medication other than Cannabidiol since approximately. • During this time there were regular discussions between ourselves and Dr [redacted] regarding CBD and other possible treatments. [redacted] • Dr [redacted] reported that [redacted]: "has now been off [Sodium Valproate] for the last two months. There has been no appreciable improvement in cognitive skills. Parents notice generalised tonic/clonic seizures once every 3 to 4 nights that last 1 to minutes at most". [redacted] • We declined Ketogenic diet therapy, preferring to explore cannabis-based products. [redacted] • It was reported by Dr [redacted] that: "On CBD oil her seizures have reduced in frequency and there are longer gaps between clusters. She used to have between 3 to 4 seizures a week and now she can go up to 8 days between seizures. Total seizure count is also reduced with 6 seizures in the last 37 days". [redacted]	

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				• We took [redacted] to Holland where she was seen by Dr [redacted], a consultant Neurologist. Dr [redacted] prescribed [redacted] her current medication – Bedrolite and Bedica – to treat the symptoms of her Dravet Syndrome. These are higher quality cannabinoid medications than those that we had previously obtained. [redacted] • We applied to the Home Office for a licence for Bedrolite, with the assistance of Dr [redacted]. Initially we were informed that you could not make the application because [redacted] had not tried the ketogenic diet but it was later considered. [redacted] • The Expert Panel at the Home Office recommended that a time-limited licence for Bedrolite be granted. The conditions on the licence required that as soon as practically possible [redacted] treatment should be changed to Epidiolex. [redacted] • Cannabis-based medicinal products were moved from Schedule 1 to Schedule 2 of the Misuse of Drugs Regulations 2001 making it legal for specialist doctors to lawfully prescribe and for pharmacists to lawfully supply cannabis- based products. • We hoped that this would allow [redacted] to receive a prescription for Bedrolite and Bedica from the NHS. [redacted] • Dr [redacted] reported in a letter to Dr [redacted], Consultant Paediatric Neurologist [redacted]. ○ "[redacted] is now 4.5 months into treatment using CBD (Bedrolite and Bedica) without any other [anti-epileptic drugs]. Her seizures are better compared to when she was on multiple AEDs and the diary shows 6 [generalised tonic-clonic seizures] in [redacted], none prolonged. The recovery from seizures is much quicker with no panic/confusion in the postictal phase. The quality of her sleep is much improved as is her attention on tasks and gait. There is also better eye contact and social interaction prepared to before. ○ There have been multiple meetings with parents for the use of CBD starting from applying to the expert panel, going over to the new guidance from the BPNA which formulated to use. I am waiting to hear whether Epidiolex will be dispensed from [redacted]. This preparation was advised by Dr [redacted], the expert panel and in the BPMA guidance. ○ Parents are using a different preparation of CBD (Bedrolite and Bedica) prescribed by Dr [redacted], consultant neurologist based in Holland. This is currently self-funded. A seizure reduction of up to 50% from the baseline is being noted, and so they do not want to switch to Epidiolex. In fact, they would like to continue using Bedrolite and Bedica for a year or until they are no longer able to fund it. There are concerns about Epidiolex compared to Bedrolite from their own research. The fear is that the benefit to both Bedrolite and Bedica is due to the composition of several cannabidiol with THC, whereas Epidiolex only has one cannabidiol. ○ [redacted] parents are asking me to prescribe Bedrolite and Bedica. They have approached Professor [redacted], consultant neurologist, privately in this regard who has written to me asking me to do the same. However, I am duty bound to follow the guidance of the paediatric neurologist and the medical director, and so I regrettably cannot prescribe this medication. ○ Her parents are also asking me to explicitly state that I support the use of Bedrolite and Bedica for [redacted]. They would like to send a letter in support	

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				to the local MP, The [redacted] for discussion in Parliament. I would like to take the advice from a medical director, as well as the GMC and Medical Protection Society to know where I stand in respect of writing a letter to this effect. I shall be in contact with the parents following the outcome of the discussions." [redacted] • Dr [redacted], Consultant Paediatric Neurologist at [redacted], wrote in a letter to us: "We discussed the cannabinoids and I am sorry that I was unable to supply the versions that you are presently giving her, and did feel you were in a difficult position, particularly bearing in mind the great cost. I have explained that [redacted]is one of the limited number of children within the region for whom we could prioritise prescription of Epidiolex on the basis of her underlying diagnosis and ongoing seizures." [redacted] • [redacted], [redacted]dad, noted the following regarding an improvement in [redacted]seizure control: "We have continued our seizure diary and in February we had 4 tonic/clonics and we had much bigger gaps between seizures. 12 days seizure free and then a small cluster of one tonic and two partials over two days then 20 days seizure free and then day 21 small cluster, no tonic/clonics, 2 partials. Now we are at 28 days without tonic/clonic so it seems they are slowly petering off with less severity. I am hopeful this will continue with still no panic attacks and no insomnia and no nocturnal seizures for months". [redacted] • [redacted]visited [redacted] Hospital due to an increase in her seizures. She had been experiencing at least two per day. The medical records state that: "THC stopped 4 days prior to the increased seizures frequency". In fact we did not stop administering Bedica altogether, but we no longer give [redacted] Bedica every day. [redacted]was prescribed a 5 day course of Co-Amoxiclav (an antibiotic). [redacted] • Dr [redacted] reported in a letter to Dr [redacted] ([redacted]GP at [redacted]) that: ○ "[redacted] was admitted with a non-specific illness a few days back. Although a urinary infection was suspected it was difficult to collect a urine sample for culture. In the meantime she improved without any specific antibiotic treatment. A genital swab did not show growth of any organisms or candida. Coincident with this illness, an increase in generalised tonic/clonic seizures was seen (from 2 days before admission till a day after discharge). They have stopped after a single stat dose of THC administered by parents. Prior to this she had gone a full 28 days without any generalised tonic/clonic seizures. ○ Looking at the seizure diaries she has had 10 GTCS and 3 [Complex Partial Seizures] in January, 4 GTCS and 2 CPS in February, 19 GTCS and 6 CPS in March. All the GTCS have been 1 to 2 minutes in length at most and she has not needed a dose of Buccal Midazolam for over a year. Complex partial seizures consist of staring, raising of one arm, head and eye deviation to one side and then oro motor automatisms. This are preceded by hyperventilation and on occasion her parents have been able to terminate a progression to a seizure by blowing on her face. She has not had any nocturnal seizures, myoclonic jerks or absences for several months now.	

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				○ Her parents continue to administer Bedrolite (CBD oil) but stopped Bedica (THC) around 2 weeks back to see what effect, if any, this was having on her seizures. They want to hold off restarting this till they get a good idea of any changes to the seizure pattern. ○ [redacted]continues to have an ataxic gait but this does not cause her any difficulties in the sense that she doesn't fall. There has been no loss of motor skills. After the THC was taken out her autistic traits have become more prominent, especially repeated touching and increased display of emotions. She was experiencing mild side effects to the CBD and THC such as dry eyes requiring hydration drops, reduced oral secretions (a side benefit) and slightly increased appetite. The latter has not resulted in excess weight gain. She was slightly less vibrant on this medication but not enough to make her drowsy. She is not experiencing any GI side effects. The LFTs are normal. ○ Once again parents asked if they needed to make any changes to the treatment regimen. I advised that the Ketogenic Diet was the next option and parents should adopt it when they feel ready. ○ [redacted]continues to be seen by Dr [redacted]with respect to her developmental progress, and I will oversee the management of her seizure disorder. There is a forthcoming meeting with [redacted], Paediatric Neurologist and the MP for this area [redacted]later to discuss the funding of [redacted] medication." [redacted] • Dr [redacted] [redacted] (consultant paediatric neurologist) from the [redacted] Hospital wrote a private prescription for Bedrolite only. • I understand that Dr [redacted] made an application for the cost of this prescription be paid for by the NHS (possibly in the form of an Individual Funding Request, although these are usually made by GPs to CCGs). • On [redacted]a meeting of the Drugs and Therapeutics Committee was held at [redacted] Trust to discuss prescribing Bedrolite for [redacted]. The record of this meeting says: ○ "Patient: [redacted]Indication: Dravet syndrome Requestor: Dr [redacted] ○ Dr [redacted] was present for this discussion. This request is for a specific cannabidiol preparation (Bedrolite) for the treatment of Dravet syndrome in a child who has not responded to standard anticonvulsant management. ○ The committee was of the opinion that based on the current national guidance on prescribing cannabis-based products this request may not be relevant to the [redacted], as the trust does not currently have a doctor who would be allowed to prescribe the drug (guidance suggests a Consultant Paediatric Neurologist). Therefore this cohort of care would be through [redacted] as a local tertiary centre. However, it was felt that in view of the current issues surrounding prescribing of these products it would be useful to discuss the request in principal. ○ The trust's policy for the use of unlicensed medicines states that unlicensed medicines are only used when no licensed alternative exists. Bedrolite is an unlicensed "special" which carries minimal assurance in terms of GMP (good manufacturing practice) and MHRA guidance. Whilst no licensed alternative is available in the UK at present another cannabidiol preparation (Epidiolex) is currently progressing through the licensing process in the UK and is the preparation referenced in current guidance. In summary, based on this information the committee was not able to support the request for Bedrolite for two main reasons. Firstly the trust does not have a consultant paediatric neurologist to supervise the safe prescription and administration of this class of medication, and secondly if it did the preferred cannabidiol preparation for us in the UK is currently Epidiolex."	

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				• Subsequently we approached our GP, Dr [redacted], to see if he would consider prescribing Bedrolite and Bedica. Dr [redacted] agreed to look into it but said that assistance would be required from a specialist. • [redacted] Hospital informed us that Dr [redacted] could not assist Dr [redacted]. We do not understand their position as he has recently assisted us in making a Specialised Services Individual Funding Request. Conclusion: [redacted] has not been blue lighted to hospital for seizures for 14 months, this is not coincidental. We simply cannot continue like this and without a NHS prescription [redacted] will suffer as we cannot continue to find the people to fund this medication. But we shouldn't have been put in this position on the first place. [redacted]	
End Our Pain	Guideline	General	General	**Individual Family Submissions 3 – [redacted]** Our Daughter [redacted] is [redacted] years old. She was diagnosed with Cardio-faicio-cutaneous Syndrome at [redacted] old. She suffered her first status epilepticus at [redacted] old. She has complex refractory epilepsy, pulmonary stenosis, developmental delay, sever reflux, fed via gastrostomy, hypotonia, bilateral hearing impairment, and she has recently developed hyponatraemia. CFC is a multisystem disorder associated with cardiac anomalies, delayed development and intellectual disability. It is associated with neurological findings such as low muscle tone (hypotonia), seizures and other brain anomalies. Poor growth is a problem as well as thickened dry itchy skin. We originally wanted to try Bedrolite because [redacted] had poor seizure control, poor quality of life, failure of conventional anti-epileptic medication, risk of drug toxicity. Drug toxicity is a concern which has been raised by Dr [redacted] and Dr [redacted] and the Neurology team at [redacted]. [redacted] started Bedrolite and Bedica on the [redacted] and has been used in combination with the medication listed in the table on page 1. We found that since taking Bedrolite the ferocity of [redacted] seizures has been significantly less, [redacted] has experienced an unusual amount of seizure free days and [redacted] alertness has been greatly improved. [redacted] has only had one hospital admission since starting Bedrolite and Bedica, during which she was given a dose of 5mg midazolam which broke the seizure as the ambulance arrived. She was then taken into hospital as a pre-cautionary measure and needed no further treatment. This is unheard for [redacted] as prior to this she is frequently admitted and treated with paraldehyde, lorazepam, Diazepam, phenytoin infusions etc…and would usually be admitted to CICU. [redacted] has been able to engage socially in a way that we have not seen before. [redacted] had only ever given eye contact on a couple of occasions, her eyes typically roll around in her head, but we have noticed she has since been able to focus on faces and keep her eyes steady as she observes her surroundings. We have also experienced her smiling socially as she focuses on a face. She has been stronger in her core movements ([redacted] suffers Hypotonia, is unable to sit unaided and has very poor head control) and we have been able to put her in her standing frame and carry out exercises as per her physiotherapy programme. Prior to medicinal cannabis she was so poorly she was rarely able to take part in many of the physiotherapy and Occupational therapy sessions.	Thank you for taking the time to share details of the care received by your child affected by severe treatment-resistant epilepsy. On an individual level there appears to be evidence that CBMPs have a role. Clinicians can make their own individual prescribing decisions in the best interest of their patient taking into account their values and preferences. The committee considered the evidence in the area. The RCT evidence focused on treatment for particular epilepsy syndromes and the committee agreed that these findings couldn't be extrapolated to other forms of epilepsy. The committee also considered observational studies but agreed that these were of very low quality due to the high risk of bias. Overall, the committee agreed there wasn't sufficient good quality evidence to make population-level recommendations. Research recommendations were made to promote the evidence base in this area. This should include the views of patients, carers and families. The committee agreed that a national or local registry of prescribing practices of CBMs was also needed.

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				[redacted] is prescribed Chloral Hydrate and melatonin due to chronic sleep disturbances, which preceded severe seizures. Prior to [redacted] when we started her Bedrolite treatment[redacted]could go for as long as four nights with no sleep whatsoever, we had to administer Chloral Hydrate almost every night to get her to sleep, we have since only administered Chloral on 3 separate occasions since we started her cannabis treatment. Her overall quality of life and progression has been drastically and notably improved. [redacted] receives care from community [redacted] nurses who have expressed that they observe a dramatic improvement in her general alertness. During every clinic and Neurologists ward rounds from [redacted] I would raise the question of medicinal cannabis, however, they raised the issues of it's illegal status and inability to prescribe. When the law was changed in [redacted] I discussed with Doctors my concerns that seizure control has not yet been obtained, that [redacted] quality of life is poor and that she is either in seizure or zombie like and unaware of the world around her, I voice concerns of toxicity as do her Doctors. I suggest that we should explore medicinal cannabis in light of its legalisation, but Doctors inform me that BPNA guidelines and a lack of evidence means they are unable to prescribe it and refer us to the out of date BPNA statement on use of marijuana (cannabis) related products in the treatment of complex epilepsies (4th July 2018). Below are the documented requests as written in clinicians' letters where we as parents ask them to prescribe medicinal cannabis on compassionate grounds: Dr [redacted] (Consultant Paediatric Neurologist- [redacted]) [redacted]– [redacted]mum also enquired about CBD oil, and we discussed regarding the pros and cons and legal issues surrounding it." Dr [redacted] (Consultant Paediatric Neurologist- [redacted]) [redacted]– "Mum also enquired about CBD oil and we discussed the pros and cons and legal issues surrounding it. We discussed that once it has been approved by the NHS then we can discuss further regarding CBD oil for [redacted]." Dr [redacted] (Consultant Neonatologist- [redacted]) [redacted]- "During the course of this consultation, mother also asked me about cannabinoids oil as a possible adjuvant to her current treatment. The family have been looking into this. Unfortunately, I have no experience of the use of cannabinoid oil, but would be happy to try and find out what is available, although I understand it is currently not available in the UK for routine use, except under special license. If I do get any further information I will of course discuss this with the family" Letters to our MP-[redacted] -I meet [redacted]with regards to the issues accessing medicinal cannabis on the NHS for [redacted]. He writes a letter to the Dr [redacted] [redacted] (Head of[redacted]), Dr [redacted] responds on [redacted] with the following: "Your request has been discussed with the Paediatric Neurology team in [redacted] and there is a universal consensus not to prescribe the drug until it is approved by NHS England and NICE. This is in accordance with a statement published on 4th July by the BPNA" Dr [redacted] (Specialist Doctor to Dr [redacted]Paediatric Neurologist- [redacted]) [redacted]– "Once again there was a discussion about prospective availability of Cannabidiol for use in epilepsy. Dr [redacted]explained to Father the statement from BPNA which explains about the evidence about the use so far and recommendation of the BPNA at this stage." Doctors in the NHS were telling us they were unable to prescribe CBD and THC. So we turned our attentions to a private Clinician Dr [redacted], Paediatric Neurologist who prescribed [redacted]and Bedrolite on compassionate grounds. We had also seen Dr	

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				[redacted]who expressed concerns over the amount of medication [redacted] was on at such a young age, he was concerned about toxicity. When I asked Dr [redacted] "is it a race between the medication killing [redacted] and the seizures killing her?" he replied "yes". We asked if he felt Medicinal Cannabis could be an alternative and he was expressly against the use of medicinal cannabis because of the "lack of research in the UK". Since starting the treatment on the [redacted], we have spent a total of £2,235. [redacted] is still on a very low dose and we expect the cost to rise dramatically in the coming weeks. We do not have the financial means to buy this medication. [redacted] requires 24/7 care, that along with spending a significant amount of time campaigning has meant I am no longer able to work full time which has meant our family income has dramatically reduced as a result. We rely wholly on charitable donations in order to purchase [redacted] medication. We have to dedicate a huge amount of time fund raising, this financial burden on top of our grief for our daughter is inconceivable and cannot be sustained. This in turn puts a tremendous amount of strain on our marriage. We are also concerned about [redacted] Neurology team at the [redacted] being unwilling to discuss [redacted] prescription for Medicinal Cannabis in relation to clobazam and other medications which they are still managing. I was told by Dr [redacted] that he would not discuss [redacted]medicinal cannabis when I asked about possible interactions with other medication and feel there is a huge disconnect in treatment. I would like to see [redacted]neurology team and Dr [redacted] embark in a shared care scheme. So that we can arrive at the best care plan for [redacted]. At present I feel the neurology team are trying to push the "supposed' success of the Ketogenic diet which I don't feel has been as successful as they have documented, I have observed a higher amount of seizures since she has been on the ketogenic diet program. Because I did not feel the diet was working effectively enough we sought advice from Doctor [redacted] and then Bedrolite and Bedica were prescribed. It is since we commenced Bedrolite and Bedica that we have seen dramatic improvements and only 1 brief admission with no further rescue medication beyond a 5mg dose of Buccal midazolam. [redacted] date of birth is [redacted]. During pregnancy at our 12 weeks scan she was found to have a high nuchal translucency. The silence during the scan from the sonographers was palpable and they were deeply concerned. We were taken into a memorial room where a nurse discussed the possibility that the pregnancy may not be viable. We agreed to a CVS to screen for Patau's, Edwards or Down's syndrome. Results from that screening indicated that there was a low chance of being affected by the above-mentioned syndromes. We continued with the pregnancy and had scans almost fortnightly as there were further concerns over our daughter's development, excessive weight gain, heart development and polyhydramnios. At about 38 weeks' gestation concerns were growing over [redacted] evident heart condition and polyhydramnios, to further complicate matters I had also tested positive for Group B Strep. It was agreed and arranged that the baby would be induced on the [redacted] due to the evident risks detected. I went into labour naturally two days earlier, there were many complications including Meconium aspiration syndrome and an emergency C-section was necessary. As a neo-nate [redacted] was taken away immediately as she had contracted respiratory disease. I didn't meet her until I was out of theatre, it was brief as she was immediately taken to NICU. I woke up alone in a room, without my baby and unaware of what had happened or where she was. I struggled to walk after the C-section, I had to walk from my ward to another level and an agonising distance to try and feed [redacted] in that first week. We remained in hospital with [redacted] for 7 days as there were further concerns such as feeding, her systolic heart murmur, subtle craniofacial dysmorphism, and failure of her new-born hearing test. The	

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				9 months leading up to [redacted] birth from pregnancy through to birth were incredibly stressful and traumatising and something I'm finding very difficult to re-live and write about. After the birth of [redacted], I did not feel hope or joy at becoming a parent, I felt scared and anxious at what may be coming for us next. There were still so many un-answered questions and issues causing doctors concern. For the first two months of [redacted] life I tried to breast feed her, our health visitor and I were very concerned that [redacted] was not gaining weight. At [redacted] months we were both hospitalised and she looked skeletal, while many tests were carried out and nurses, speech and language therapists, and dieticians observed her it became increasingly obvious all was not well. We battled for hours trying to feed [redacted], following the dieticians plans, it was exhausting as we tried to feed her day and night. [redacted] also had severe reflux and vomiting which contributed to her failure to thrive. At [redacted] old [redacted] underwent an echocardiogram where she was diagnosed with a mild pulmonary stenosis. She is to be monitored 6 monthly. At [redacted] old [redacted] had her first tonic clonic seizure. She was screaming and convulsing over and over, her eyes were rolled up and flickering and she was going blue. I could hear her heart pounding without needing to put my ear close to her heart. We called an ambulance and were blue lighted into [redacted]. My husband and mother were present, and we were all horrified, we had never witnessed suffering as violent and scary as this. We had never witnessed a seizure before, we thought she was going to die. [redacted]was admitted to CICU after she was loaded with lorazepam, Phenytoin and Phenobarbitone as per APLS guideline but still continued to have seizures when she was given pyridoxine under EEG when the movements finally stopped. During her first admission for seizures the stress and trauma caused me to stop developing breast milk, as a result of this and [redacted] failure to thrive it was decided that [redacted] would be fed with use of NGT. My Husband and I were trained in basic life support, Buccal midazolam, NGT and administering anti-epileptic medication, Phenytoin, Phenobarbital and Levetiracetam. Including Ranitidine for severe reflux and issues with vomiting. We were devastated at what was unfolding and shocked to find ourselves with a new role, we were no longer parents but nurses. History of Medical interventions and Hospital admissions: • Admission dates [redacted]-Elective admission, under investigation due to poor feeding, reduced weight gain, abnormal neurodevelopment-MRI scan under sedation, neurometabolic and other investigations were also carried out. • Admission dates [redacted] -Emergency- It is discussed that [redacted] may need to go on life support. Fortunately, this is not necessary. Due to prolonged status epilepticus lasting hours-the following anticonvulsants were prescribed, phenytoin, phenobarbital and levetiracetam. • Admission-[redacted] -Admitted with vomiting, coughing and being investigated for seizures-original medication is increased. • Admission dates: [redacted] -Emergency Admission, due to recurrent seizures, likely secondary to viral illness. [redacted] had prolonged seizures and was admitted to CICU It is discussed that [redacted] may need to go on life support. Fortunately, this is not necessary. She is given iv midazolam that improved her seizures. She is later	

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				moved to HDU. She also started Clobazam in addition to her other anti-epileptic medication which were also increased. • Admission dates: [redacted] -Emergency admission, due to prolonged seizure, her medication phenobarbitone and phenytoin doses were increased. • Diagnosis date: [redacted] -results indicate a significant variant in the BRAF gene and is given a diagnosis of Cardio-facio-cutaneous syndrome (CFC). • Admission date: [redacted] Emergency admission, due to prolonged seizures. Chloral Hydrate prescribed due to sleep disturbance triggering seizures and Levetiracetam dose is increased. • Admission date: [redacted] -Emergency admission, prolonged seizure triggered by severe sleep disturbance, 4 days without sleep. Chloral Hydrate dose is increased. • Admission date: [redacted] -Emergency A&E admission, due to seizures not subsiding on regular medications. Treated with Buccal midazolam, and iv phenobarbital, levetiracetam, paraldehyde. Neurologist increases Levetiracetam and clobazam. • Admission date: [redacted] -Emergency A&E admission, [redacted] is admitted due to increased seizures, experiencing multiple episodes in the department, associated with desaturations. She was treated with x2 doses of midazolam and a loading dose of phenytoin. Her seizures stopped after this. • Admission date: [redacted] Emergency A&E admission, due to prolonged seizures needing CICU admission. It is discussed that [redacted] may need to go on life support. Fortunately, this is not necessary. She received x2 buccal midazolam, diazepam, phenytoin half loading dose, and paraldehyde after which seizures stopped. Once [redacted] was transferred to a ward she continued to have frequent episodes of short seizures lasting from 30seconds to 5 mins. She also had two further prolonged seizures for about 15 minutes and needed buccal midazolam on [redacted] of admission. TTO'S increase clobazam evening dose and continue ketogenic diet. • Admission date: [redacted] -Emergency A&E admission, [redacted] was admitted due to recurrent seizures around 10 times on [redacted]. In hospital she continued to have recurrent seizures, some episodes were focal, and others were generalised tonic clonic seizures for which she was given Buccal midazolam, infusions of lorazepam, paraldehyde and phenytoin. Phenobarbitone is increased and an additional midday dose of clobazam is added to [redacted] plan. • Admission date: [redacted] -Emergency A&A admission, due to recurrent epileptic seizures. Movements relating to gastro-oesophageal reflux we also observed, and lansoprazole has been started. Levetiracetam dose is increased further. Await video telemetry. Ketogenic diet to continue. • Surgery date: [redacted] `Admitted for surgery, procedure laparoscopic nissen fundoplication and gastrostomy. • Admission date: [redacted] Emergency A&E admission, after a prolonged seizure lasting 11 mins at home, further seizures in A&E requiring 2 further doses of buccal midazolam, rectal paraldehyde and iv phenytoin infusion. It is discussed that [redacted] may need to go on life support. Fortunately, this is not necessary. Advised	

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				to re-start midday clobazam dose as it is still early days on the ketogenic diet and there has been a significant breakthrough seizure. • Neurologist telephone conversation with Doctor [redacted] [redacted] -seizures are worse even after increased dose of clobazam. With regards to ketogenic diet where ketones are 2's-5's, It is discussed that a plan to increase ketones at this time would not be appropriate. Dr [redacted] puts forward a plan to introduce MCT fat to [redacted] diet. Because [redacted] has not responded to several anti-epileptic he suggests a trial of Perampanel a medicine that is not licenced in very young children. I refuse to add further medication to [redacted] list of medicine especially after our private appointment with Dr [redacted] [redacted] at [redacted] hospital, where he expresses concerns over adding medication without weaning the medications that are not working, and the risk of toxicity. • Admission date: [redacted] Emergency A&E admission, due to prolonged seizures. Bucculam midazolam is given at home, seizures continue, and emergency department give a loading dose of phenytoin. She is then admitted to PICU and started on a midazolam infusion as seizures were not controlled by phenytoin. It is discussed that [redacted] may need to go on life support. Fortunately, this is not necessary. Investigations find [redacted] has a low sodium level and she is started on a Sodium Chloride supplement and Potassium effercitrate is also started. • [redacted]: Private prescription medicinal cannabis Bedrolite and Bedica are started. • Admission date: [redacted], due to prolonged seizure lasting 14 minutes. Buccol midazolam is given and there are no further seizures. No changes to anti-epileptic medication. [redacted] is having increased mucus/oral clear secretions, she is choking frequently and turning blue and does not have fever/cough/coryzal symptoms. Glycopyrronium Bromide medication is started to help with secretions. We are discharged after 1 day. • From [redacted] , [redacted] seizures are marginally under control. She still has daily seizures which are short in length, typically under 2 minutes. However during this period, she was significantly more drowsy and zombie like. There was very little interaction with the world around her. Her issue with vomiting was worse and weight gain a worry. I felt strongly that the pharmaceutical medication [redacted] was on was seriously affecting her ability to develop and had poor control over her seizures. It is documented that [redacted] has complex refractory epilepsy with poor AED control. We have been told that [redacted] diagnosis and continued failure to control seizures means it is unlikely she will live beyond her teenage years. We have been referred to [redacted] hospice for respite in light of this and also have a continuing care grant which allows us two [redacted] Nurses to visit our home and care for [redacted] two days per week. We originally had an allowance for 1 nurse but due to the severity of her seizures the [redacted] Service felt it was essential she have two carers present at all times. [redacted] private prescription from Dr [redacted] is Bedrolite has a concentration of 10% CBD and 1% THC (100mg CBD per ml) and Bedica has a concentration of 2% THC (20mg THC per ml) manufactured by Bedrocan. [redacted] current dose is as follows Bedrolite 0.24ml and Bedica 0.02ml. We have seen a positive effect on [redacted] since commencing CBPM. With seizure free days, less aggressive seizures and minimal hospital admissions. [redacted] started CBPM on [redacted] and is still taking the same anti-epileptic medication and ketogenic diet plan as set out by her Consultant Neurologist, [redacted].	

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				Neurologists at [redacted] are keen to prevent withdrawal syndrome or destabilisation of the limited seizure control we have. Therefore, they are holding back on reducing medication for a further month or two when they will re-evaluate. The reduction in seizures is hard to measure as a percentage as [redacted] still has some days where she has many small seizures lasting as long as 30 seconds. However, she is having many days seizure free. For example, when we started the CBPM in [redacted] she had 19 out of 29 days seizure free, when prior to this she was having as many between 5 and 20+ seizures per day with seizures lasting an average of 5mins. [redacted] has also developed an improved sleep pattern. Sleeping well at night while awake and alert during the day. I am hopeful that in light of these improvements (while [redacted] is still on a very low dose of CBPM) if we can continue to improve [redacted] health as we reach her optimum dose we can start to wean the other anti-epileptic medications safely under the supervision of her Neurologist at [redacted]. So far doctors say it is too early to start weaning her due to fears of destabilising her. Our local MP [redacted] has been incredibly supportive, writing letters to the Department at [redacted] as well as through social media and attending the End Our Pain Campaign in Parliament earlier this year offering his signature in support. He continues to work with us and has attended Sir Mike Penning's urgent question in parliament to ask the Secretary of State for Health and Social Care why patients are being denied access to medicinal cannabis despite the law change in November. We are concerned as fundraising is not a sustainable solution for our family to pay for [redacted] CBPM. With each prescription we pay for each month our financial situation becomes worse. We are now considering going to Holland in order to obtain her next month's prescription, as we simply cannot afford the hundreds of £'s in import and license fees applied to each bottle. The journey to Holland will put a huge strain on our family as [redacted] needs 24/7 care. My husband works long hours and is our only source of income at present. I would have to go to Holland with [redacted] alone as we can't afford for [redacted] not to work. This would be dangerous as [redacted] could suffer seizures during our flight over to Holland. The Hopes and expectations evoked by 1.11.18 decision to move Cannabis from Schedule 1 to Schedule 2 was that families like ours would have an opportunity to give our children the best possible chance in life, we were elated. That is an increasingly distant emotion and we continue to struggle through and pay extortionate fees in order to obtain a medicine we had hoped would be available to all families, but instead we find it is only available to those who have the financial means to obtain it. I see this as discrimination, and it forces us into a financially unstable position. Double Blind RCT are wrong for [redacted] – her medicine Bedrolite and Bedica is working. It is morally wrong to wash out and then risk deterioration, death or irreversible brain damage by RCT (Placebo) or to trial a pharmaceutical product when Bedrolite is working. My child's life will be put at risk if double blind RCT cannabis when conventional drugs (which haven't worked) are being prescribed as "specials" for [redacted], an infant of the tender age of [redacted], for whom many of the drugs she has been given have not been tested or designed for her. I would like NICE to be open minded. Look at the positive impact of CBPM'S on our daughter thus far and how at least three conventional efforts have already failed my daughter. How many more pharmaceutical drugs are thrown at her. My daughter is in danger of toxicity that was confirmed by Dr [redacted] and indeed is a concern of her consultant neurologist. We need to arm our doctors with more options. Please adopt CBPM's where conventional efforts	

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				are failing, back observational trials for our families with NHS funding and please act on our evidence, [redacted] and our family have had many traumatising experiences in the [redacted] years she has had on this earth, we need hope.	
End Our Pain	Guideline	General	General	**Individual Family Submissions 4 – [redacted]** Dear Sirs [redacted] pregnancy was normal, no issues or concerns and baby developing well. During very early labour [redacted] felt something wasn't quite right and [redacted] movements were decreased. As a precaution [redacted] and baby were monitored at hospital. As the waters broke, meconium was found to be present in the waters which was cause for concern. Monitoring of the baby continued whilst a decision was made as to whether a C-section should be carried out. [redacted] heart rate did not recover after a contraction and [redacted] was rushed into theatre to undergo an emergency C-Section. On delivering of [redacted] the umbilical cord was found to be around his neck. Once delivered [redacted] was "grunting" and was immediately moved to NICU for assessment. They found him to have caught a virus and so two antibiotics were administered over the following four days. Once [redacted] blood Indicators were at an acceptable limit both he and [redacted] were discharged. [redacted] then developed what we thought was colic, his body would go tense and bend over, like he had severe wind, and it was always around feeding after waking up. We filmed an episode of what we thought was colic and made an appointment with the GP for the same day. The GP had not seen anything like this before and called the hospital. [redacted] was admitted to the [redacted] in the Children's Assessment Ward immediately. [redacted] was diagnosed with Infantile Spasms when he was approximately [redacted] old at the end of [redacted] [redacted] seizures were increasing in frequency and severity causing him distress and he was given rescue medicine. He was then given Prednisolone and Vigabatrin, which controlled his seizures. He was given an EEG at the end of [redacted], which was clear and we had high hopes that [redacted] would fully recover. Unfortunately, upon the wean off of both medications in [redacted] returned and since then we have struggled to gain control of them. [redacted] is our first, everything was new to us, we weren't expecting anything like this. This condition is so severe and detrimental to his development which could affect the rest of his life and ours. We thought we would lead a normal life, seeing him say his first word, walk for the first time, dropping him off for his first day at school. All the normal expectations and milestones you look forward to had been taken from	Thank you for taking the time to share details of the care received by your child affected by severe treatment-resistant epilepsy. On an individual level there appears to be evidence that CBMPs have a role. Clinicians can make their own individual prescribing decisions in the best interest of their patient taking into account their values and preferences. The committee considered the evidence in the area. The RCT evidence focused on treatment for particular epilepsy syndromes and the committee agreed that these findings couldn't be extrapolated to other forms of epilepsy. The committee also considered observational studies but agreed that these were of very low quality due to the high risk of bias. Overall, the committee agreed there wasn't sufficient good quality evidence to make population-level recommendations. Research recommendations were made to promote the evidence base in this area. This should include the views of patients, carers and families. The committee agreed that a national or local registry of prescribing practices of CBMs was also needed.

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				us. No one could or can tell us his future, we do not know how much damage or delay the epilepsy has caused now which will affect his future. It was and is very anxious, frightening and completely overwhelming process to go through. To then learn about SUDEP and that [redacted] was at risk, completely destroyed both of us. [redacted] was prescribed Oxcarbazapene and a vitamin B trial. The EEG at this time showed epileptic activity from the right hand side of his brain which matched the symptoms of not using his left hand or arm and the right hand side of his face having less tone. Over these period he continued to have clusters of spasms daily reaching up to a 100 spasms a day. We at this point were constantly anxious and filled with fear as nothing was helping him. We requested an emergency second opinion from a paediatric neurologist who immediately prescribed another round of Prednisolone and arranged for us to be admitted to [redacted] and [redacted] to be started on the Ketogentic diet. The neurologist also confirmed that Oxcarbazapene is not a drug which is normally prescribed for Infantile Spasms. [redacted] was left for around two months on this drug before we requested a second opinion. Three months passed, and neither the vitamin B or the Ketogenic diet helped. Over the remainder of [redacted] [redacted] was prescribed Vigabatrin, Sodium Valproate, Clobazam and Toprimate. We had physio at this point to help strengthen his arms and legs, we had walking therapy and [redacted] was completely out of it, the combination of 4 very potent and toxic drugs were taking their toll, he was barely conscious all day, just wanting to sleep, and when he was awake he was still having clusters of spasms and looked miserable the clusters were also beginning to really upset him. [redacted] has been prescribed Prednisolone, Vigabatrin, Oxcarbazepine, Sodium Valporate, Clobazam, Pyridoxene, Topirimate, Ketogenic diet. Below are a list of the side effects associated with the prescribed drugs [redacted] has received. [redacted] has been prescribed four unlicensed drugs. Sodium Valproate is clinically proven to cause cortical thinning in the parietal lobes in the brain (study: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3908352/) Abdominal pain; agitation; alopecia (regrowth may be curly); anaemia; behaviour abnormal; concentration impaired; confusion; deafness; diarrhoea; drowsiness; haemorrhage; headache; hepatic disorders; hypersensitivity; hyponatraemia; memory loss; menstrual cycle irregularities; movement disorders; nausea; nystagmus; seizures; stupor; thrombocytopenia; tremor; weight increased Alertness decreased; anxiety; ataxia (more common in elderly); confusion (more common in elderly); depression; dizziness; drowsiness; dysarthria; fatigue; gastrointestinal disorder; headache; hypotension; mood altered; muscle weakness; nausea; respiratory depression (particularly with high dose and intravenous use—facilities for its treatment are essential); sleep disorders; suicidal ideation; tremor; vertigo; vision disorders; withdrawal syndrome. Alopecia; anaemia; appetite abnormal; asthenia; behaviour abnormal; cognitive impairment; concentration impaired; confusion; constipation; cough; depression; diarrhoea; dizziness; drowsiness; dry mouth; dyspnoea; ear discomfort; eye disorders; feeling abnormal; fever (in children); gait abnormal; gastrointestinal discomfort; gastrointestinal disorders; haemorrhage; hearing impairment; hypersensitivity; joint disorders; malaise; memory loss; mood altered; movement	

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				disorders; muscle complaints; muscle weakness; nasal complaints; nasopharyngitis; nausea; oral disorders; pain; seizures; sensation abnormal; skin reactions; sleep disorders; speech impairment; taste altered; tremor; urinary disorders; urolithiases; vertigo(in children); vision disorders; vomiting (in children); weight changes (source https://bnf.nice.org.uk/drug/) [redacted] into early [redacted] we were referred to [redacted] for an extended EEG, 3T MRI and PET Scan, into whether brain surgery was a possibility. [redacted] have confirmed that abnormalities are present on both sides of [redacted] brain which rules him out for brain surgery. I would draw to your attention the catastrophic impact Infantile Spasms has on a developing brain. Constant chaotic brain activity prevents the child's brain from developing. It has always been made very clear to us by [redacted] Neurologist and Paediatric Consultant that it is imperative that seizures are controlled. It is therefore urgent that [redacted] epilepsy is brought under control. We began to investigate alternative therapies. We became aware of cannabis via the news and the stories of Hannah Deacon and her son Alfie. We began to research it for use in epilepsy and found many studies worldwide in countries like Israel, Canada, America, and Europe. We learnt about the endocannabinoid systems and how cannabis interacts with it, we learnt about the history of cannabis, why and how it came to be schedule 1, how it's been used as a medicine for thousands of years and how it treats the symptoms of epilepsy. We learnt about the thousands of strains available, the cannabinoids and terpenes found in cannabis. We spoke with parents here in the UK using it, we looked at forums worldwide, and spoke with clinics in America and Spain. [redacted] meets the requirements of the BPNA Guidelines and therefore as the law changed in November 2018 he should receive a prescription for medicinal cannabis via the NHS. [redacted] started Bedrolite at the end of [redacted] after receiving a private prescription from a UK based Neurologist. Since that time we have noticed a drop in seizures from 50 to 100 a day to, currently less than 10. [redacted] is happier, alert, taking an interest in generic plastic toys, far more vocal and constantly babbling. His Paediatric Consultant has noticed a difference and indeed would prescribe, however after speaking to [redacted] neurologist confirmed that if he prescribed it would open the floodgates and it therefore becomes unmanageable. [redacted] quality of life has greatly improved. In conjunction with Bedrolite, [redacted] is currently taking three antiepileptic drugs (AED); Vigabatrin, Sodium Valporate and Clobazam. We administer the Bedrolite two hours apart from the AEDs. [redacted] bloods and liver function are monitored by his Paediatric Consultant and these are clear. We would draw to your attention the interactions of AEDs used together. Currently there is no study or evidence of what these combinations together have on the developing brain. It is a normal course of treatment for bloods to be monitored because of the toxic nature of these standard drugs prescribed on the NHS. The cost is significant and unsustainable in the long term. For us to purchase Bedrolite through a UK pharmacy it is £466/10ml bottle. A bottle of Bedrolite lasts [redacted] five days at his current dose. We are therefore left in the position where we have to break the law and pick up [redacted] medication ourselves and bring it into the country. A bottle of Bedrolite purchased in Holland costs €178. A vast cost saving. We saved £7,200 by travelling to Holland and purchasing 3 months worth of oil, which cost £3,500. If we were to purchase the same quantity via our local pharmacy it would cost £10,700. We sought a private prescription for Medicinal Cannabis so that [redacted] is given a pharmaceutical grade GMP product with consistency. Introduced in 2014, Bedrolite is the	

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				brand name for the cultivar Cannabis sativa L. 'Rensina', derived from a Sativa strain and Ruderalis strain of cannabis. Cannabis sativa L. 'Rensina' is a so-called CBD-only product, with less than 1% THC and 10% CBD. The virtual absence of THC means it does not have psychoactive properties. It is a GMP full extract cannabis oil which contains all the major and minor cannabinoids, terpenes (found in vegetables and fruit) and Flavanoids. Its carrier is Peanut oil with the allergens removed. Bedica was Introduced in 2011, Bedica, is the brand name for the indica cultivar Cannabis sativa L. 'Talea'. Cannabis sativa L. 'Talea' was developed in response to mounting evidence of a real difference in the effects of sativa and indica types. Characteristic differences between indica and sativa cultivars can be found in the presence of aromatic compounds (terpenes) in the plant. Bedica contains a high amount of the myrcene terpene, which is known to have a calming effect. Bedica contains 14% THC with less than 1% CBD. Again GMP approved, and developed under pharmaceutical GMP conditions. We are weaning [redacted] off Sodium Valporate, we are not sure whether it is helping him and he has been on this medication since [redacted]. We then intend to wean him off Vigabatrin because, again we are unsure as to whether this is helping him, and it can cause tunnel vision. We note within your Draft Guidance that you state "it is difficult to assess just how effective cannabis-based medicinal products are for people with epilepsy". We are confused as to why it is difficult to assess the effectiveness of medicinal cannabis. Please clarify your statement? We are using medicinal cannabis and are confirming to you that our child's life quality has improved significantly with a 85-90% reduction in seizures. There are numerous worldwide studies that medicinal cannabis is an effective treatment in epilepsy. Why does NICE refuse to take these studies into account? A recent study from The Beckley Foundation found that:- 'Our research on cannabis, the first to use MRI brain imaging technology in order to gauge how different strains of cannabis impact brain function in different ways, has been published today in the Journal of sychopharmacology. Initiated by Amanda Feilding in collaboration with Matt Wall at UCL, the study compared two strains of cannabis, both with equal levels of THC (the psychoactive compound in cannabis), but one of them was high in cannabidiol (CBD) while the other strain contained negligible levels of CBD.' We found that the strength of the subjective effect was correlated to the disruptions to the posterior cingulate area of the brain in the default mode network, with the high THC / low CBD strain impairing the functional connectivity in the brain's default mode and salience networks. The high-CBD strain caused only a minimal disruption to these areas, suggesting that the CBD acts as a buffer against some of THC's negative effects. Disruptions to the brain's salience network have been implicated with both psychosis and addiction, thus this study adds to the evidence that supports CBD's anti-psychotic potential observed in previous research': • https://journals.sagepub.com/doi/10.1177/0269881119841568 A further study provides justification for adding in the THC. If there is insufficient response to a CBD/low THC product: • https://onlinelibrary.wiley.com/doi/10.1002/acn3.621 This study adds justification to the use of CBD/THC combination and that this may lead to behavioural improvement and is safe and well tolerated: • https://www.nature.com/articles/s41598-018-37570-y	

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				We note further that with your Draft Guidelines NICE states that people with Dravets and Lennox Gastaut Syndrome "report a very high rate of adverse events". Could you please confirm which report you are referring to and that you are not confusing Epidiolex with Full Extract Medicinal Cannabis. These are two separate products. The known side effects of THC are; dry mouth, dry red eyes, increased appetite, sleepiness and lethargy, impaired memory. Known side effects of CBD appear minor, below is a study published in 2017: • https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5569602/ Cannabis doesn't treat a particular syndrome of epilepsy, it works in conjunction with the endocannabinoid system within the human body and the receptors. Within our group of parents, we have an array of syndromes, different causes and different types of seizures ranging from infantile spasms to rare genetic disorders. In addition to the above, children treated with epilepsy are typically treated with a high level of CBD compared to THC which counteracts any psychoactive effects. Our son [redacted] is at present on 200mg CBD and 0.8mg THC. It is also obvious that any side effects from Full Extract Medicinal Cannabis are negligible when compared to the array of side effects caused by drugs prescribed on the NHS. [redacted] has had no side effects from Medicinal Cannabis. We are confused as to why NICE, the NHS and clinicians refuse to take note of parent experience and worldwide evidence. We are faced with a situation where our child could die and could suffer greatly throughout his life. [redacted] and others should have access to Medicinal Cannabis. It has been made clear on numerous occasions by parents and campaigners and indeed to [redacted] himself that randomised controlled trials are not suitable for medicinal cannabis, nor is it suitable to undertake these trials on specific syndromes, for reasons stated earlier in our letter. It is fundamentally morally and ethically wrong to give children placebos in a randomised controlled trial when seizures could cause death, brain damage, suffering and distress. It is fundamentally wrong to take a product that is working effectively for [redacted] and flush it out of his system to become part of a trial. Our son is not a guinea pig and will not be used as such. Even your own guidelines state this. The open label study which is used by the BPNA links smoking high THC strains long term to psychosis, and concerns about THC and the developing brain. As already stated we don't know the risks of three or more anti epileptics used in conjunction. It is a nonsense to compare different products. There have been numerous studies linking the consumption of cannabis and psychosis to genetics and that the risk is relatively low, you'd need to stop 23,000 people from consuming cannabis to prevent 1 from developing psychosis. • https://www.sciencedaily.com/releases/2017/04/170420132334.htm • https://www.sciencedaily.com/releases/2016/02/160216111357.htm When a balanced view is taken, taking into consideration that the amount of THC used for epilepsy is very small (0.8mg per day in our case) and that his quality of life is greatly improved, seizures significantly reduced and the risk of psychosis very small. His bloods are clear and liver function normal. In conjunction with the known side effects of his current medication (stated above) which haven't been able to control his seizures. Taking into account that seizures do cause brain damage and could kill him, we feel it is fair to say that any associated risk of taking cannabis is outweighed by the benefits we are seeing. Taking into account worldwide studies and what we are seeing in our own children, the fact that cannabis has been used by humans for 3000 years, the guidelines should reflect this.	

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				Yours faithfully, [redacted]	
End Our Pain	Guideline	General	General	**Individual Family Submissions 5 –** [redacted] Name of child : [redacted] Date of birth: [redacted] Dear Professor, [redacted] has multi-drug resistant intractable epilepsy. Her EEG suggests an epileptic encephalopathy probably genetic, but no diagnosis yet. After [redacted] first seizure (age [redacted]) she was prescribed Keppra as an anti-epileptic medication, this was later weaned once on other anti epileptic medication as it was apparent it wasn't having any positive effect. It did seem to affect her behaviour in a negative way. We have also tried the ketogenic diet which did not help. [redacted] current medication is clobazam, sodium valproate, sultiame and ethosuximide, along with medicinal cannabis Bedrolite. A cocktail of four anti-epileptic drugs I don't feel is benefitting [redacted]. She is very subdued and sleeps a lot of the time. Her most recent EEG showed 70% background seizure activity so why are we pumping her with pharmaceutical drugs that can be so dangerous to her health with so little benefit? [redacted] has had two courses of steroids the second of which was ineffective and made her gain an excessive amount of weight. In [redacted] this year [redacted] had a vagal nerve stimulator fitted I don't believe such an invasive surgery should be performed before having the opportunity to try medicinal cannabis. The settings on the stimulator are being adjusted at intervals to see if this can help with seizure activity. We desperately wanted the opportunity to try Bedrolite for [redacted] as our options are low to none. I am not prepared to sit around and watch [redacted] disappear without fighting and visiting every option. I have already lost so much of my daughter to epilepsy. We started Bedrolite on [redacted]. Previous to this prescription [redacted] has been taking CBD oil since [redacted] and we have not been admitted to hospital because of her seizures since! [redacted] is back to a healthy weight and off steroids. Sleep has improved massively for [redacted] as before she would have trouble staying asleep and would just nap 24/7. I used to describe [redacted] as 'being in a fog' this has cleared and we have seen a massive reduction in clinical seizures. The most important thing to me is giving [redacted] and my family the best quality of life possible, these benefits are seen by parents that are caring for their children every day and managing to stay out of hospital. I feel very strongly about the two syndromes being named (Lennox gastaut syndrome and dravet syndrome) there are many epileptic encephalopathies, medical cannabis works with our own endocannabinoid system not against a syndrome. This was one of the reasons our neurologist gave for not prescribing [redacted] medicinal cannabis, the two children that have an NHS prescription for full extract medicinal cannabis do not have these syndromes. My hospital trust, [redacted], said in a letter to my local MP [redacted] [redacted] that there is a universal consensus not to prescribe the drug until it is approved by NHS England and NICE. I find this utterly barbaric as children in the UK already revive an NHS prescription for this, it's being used across the world there are lots of studies, in the mean time we are competing with irreversible damage caused by seizures. We had to fundraise to allow [redacted] to try this medication, now we have used the fundraised money we have to find that money from somewhere. I would sell my house if I had	Thank you for taking the time to share details of the care received by your child affected by severe treatment-resistant epilepsy. On an individual level there appears to be evidence that CBMPs have a role. Clinicians can make their own individual prescribing decisions in the best interest of their patient taking into account their values and preferences. The committee considered the evidence in the area. The RCT evidence focused on treatment for particular epilepsy syndromes and the committee agreed that these findings couldn't be extrapolated to other forms of epilepsy. The committee also considered observational studies but agreed that these were of very low quality due to the high risk of bias. Overall, the committee agreed there wasn't sufficient good quality evidence to make population-level recommendations. Research recommendations were made to promote the evidence base in this area. This should include the views of patients, carers and families. The committee agreed that a national or local registry of prescribing practices of CBMs was also needed.

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				to if it gave [redacted] and my family a better quality of life. We need to increase the dose so we reach a therapeutic level but with this comes more cost! Please help us and produce guidelines that take into account children like [redacted] with severe intractable epilepsy for whom this is the only medicine that could help them. Yours sincerely, [redacted] [redacted]	
End Our Pain	Guideline	General	General	**Individual Family Submissions 6 – [redacted]** [redacted] [redacted] Age [redacted]. (mother). has 2 siblings, aged [redacted] and [redacted]. [redacted] has Doose Syndrome / Myoclonic Astatic Epilepsy Medications tried: • Sodium Valporate – caused red blood cells to stop working. This was logged by neurologists in [redacted] endured 5 blood transfusions due to this medication. Lumbar punctures, tests also. • Clobazam – did not help • Keppra – Did not help • Steroids – Did not help. Caused [redacted] to gain 2 stone in weight over 3 months. He was unrecognisable. His friend was too scared to visit him in hospital as he said 'that's not [redacted]'. The weight gain caused considerable amount of stress and devastation on the whole family. • Zonisamide – Still currently taking 75mg twice daily and has not helped. Side effects causing jumbled up speech and poor communication skills. • Lamtrogine – Still currently taking 5mg twice daily and has not helped. • Ketamine – for status – did not work – Lay like a zombie for 5 days • IV Keppra – for rescue medication when in status epilepticus – does not work • Midazalam – for rescue medication – does not work • Loading doses of phenobarbitone for status epilepticus. (Induced coma) • Ketogenic Diet – refused to eat this and starved for 2 days. Attempted this 3 times. • Epidiolex – Stopped daytime seizures only for 3 months. Side effects – chronic diarrhoea which prevented him from attending school. • Bedrolite – Cannabis oil (cbd based) – currently taking – very effective and no side effects • Bedica – Cannabis oil (thc based) – currently taking – very effective and no side effects [redacted] suffers from tonic clonic, absences, drops and myoclonic jerks. His condition worsened in [redacted] when he started medication then soon went into status epilepticus and was put into HDU. This was how his life progressed up until [redacted]. He had over 50 drop seizures in [redacted]. One resulting in him having to get his head glued back together. [redacted] has been taking Bedrolite since [redacted] and Bedica daily since [redacted]. He had been in hospital over the course of 2 years, prior to [redacted], getting home for a week then an ambulance back into hospital. He was in status epilepticus for a lot of this time. Since starting Bedrolite and very slowly increasing the dose and then adding in Bedica his seizures reduced then stopped. [redacted] has been seizure free since [redacted].	Thank you for taking the time to share details of the care received by your child affected by severe treatment-resistant epilepsy. On an individual level there appears to be evidence that CBMPs have a role. Clinicians can make their own individual prescribing decisions in the best interest of their patient taking into account their values and preferences. The committee considered the evidence in the area. The RCT evidence focused on treatment for particular epilepsy syndromes and the committee agreed that these findings couldn't be extrapolated to other forms of epilepsy. The committee also considered observational studies but agreed that these were of very low quality due to the high risk of bias. Overall, the committee agreed there wasn't sufficient good quality evidence to make population-level recommendations. Research recommendations were made to promote the evidence base in this area. This should include the views of patients, carers and families. The committee agreed that a national or local registry of prescribing practices of CBMs was also needed.

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				Bedrolite started [redacted] whilst in hospital suffering status epilepticus. Bedica started twice daily in [redacted]. This is when major improvements started. The evidence is that since starting these cannabis oils, [redacted] seizures reduced in length and frequency then stopped completely. He was having constant seizures for over a year and there is no other medication that could have helped reduce/stop the seizures. This is a fact. [redacted] paediatric neurologist will not prescribe cannabis oils. He said that he 'can't and won't prescribe' due to there being no guidance, trials etc for these oils. He said that he 'does not want to the first to prescribe the oils' and also even if he did prescribe it would get blocked higher up. ([redacted] I visited a doctor in Holland who prescribed the oils. I brought them back unnoticed to Scotland. I then obtained a private prescription from a private neurologist in England. I now have an importer in Scotland bringing the oils in at cost. It is costing over £1,000 per month. I spend every waking moment fundraising to pay for these oils. I would like an emergency fund put in place to pay for the cannabis oils. I would also like to see training given to our doctors in order that they can support us. My pregnancy was normal. Delivery was quick and normal (no pain relief). His neo-natal period was normal, no complications [redacted] was a normal happy baby. When [redacted] was [redacted], he suffered his first tonic clonic seizure. These doubled each year until he was[redacted] years old. In [redacted] he suffered 12 tonic clonic seizures and was given the Doose diagnosis and put on anti-epileptic medication. We would have to call an ambulance when [redacted] had a seizure. At first these lasted over 5 minutes. His brother would cry in a corner under extreme panic. I had to keep calm to assure [redacted] and his siblings that he would be okay. Unfortunately no anti-epileptic medication ever helped [redacted]. In fact they did more harm than good. When epidiolex was introduced the daytime seizures stopped (and myoclonics, absences and drops). He still suffered up to 6 tonic clonic seizures throughout the night. He suffered from chronic diarrhoea as a side effect. After 3 months the epidiolex stopped working and [redacted] went downhill very quickly. He ended up in status epilepticus for weeks. The doctors were unable to help him and there was nothing else they could try. [redacted] breathing deteriorated and he had no muscle tone. We thought he was going to die. ([redacted] to [redacted]). This is the reason I went to Holland and illegally brought back the cannabis oils. There was nothing else the doctors could do for him except watch him slip away. [redacted] was constantly in an ambulance. He was hardly at home between [redacted] – [redacted]. He maybe got home for a few days or a week and then was in an ambulance to hospital with stays as long as 3 months each time. I wish the anti-epileptic medications had worked for [redacted]. Unfortunately, all they did were make the seizures worse and gave him nasty / life threatening side effects.	

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				I research everything. [redacted] suffered from all the major (and minor) side effects listed in every single medication he was given. This is all documented in his hospital records. I read a story about Hannah Deacon's child, Alfie. Upon reading that cannabis oils helped control his seizures I began to investigate cannabis as an alternative medication for [redacted]. I started to research online and contact other parents who were treating their children with (illegal) cannabis oils My motivation to continue seeking cannabis oils for [redacted] was due to the fact that every single person / parent I spoke to were delighted that their child's seizures were reducing due to using cannabis oils. I begged [redacted] neurologist several times to write a prescription for the cannabis oils. He declined as he said that 'thc would damage [redacted] brain' I asked him what evidence he had that it would. He could not answer me apart from quoting the BPNA guidelines. I thought [redacted] was going to die during [redacted] I had NO choice but to obtain the cannabis oils myself. (thank god I did or [redacted] would be dead). It was a very easy choice. I would die for my child. I travelled to Holland for an appointment with a doctor. I took [redacted] medical notes and medications he had tried and was currently taking. [redacted] was given a prescription for Bedrolite and Bedica. As advised, I slowly dosed the cannabis oil then added in bedica twice daily. The difference was remarkable. Some may say a miracle. The seizures reduced and eventually stopped. [redacted] was in status epilepticus in [redacted] (he was lying in a hospital bed in a vegetative state. He couldn't move, talk, eat). He had a very long period of recovery and rehabilitation (learning to walk and eat again). He then went downhill again very quickly, back into status in [redacted]. He had EEGs done in [redacted] and [redacted] whilst in status. After another long recovery process, he went downhill again in [redacted], however he was taking bedrolite by this point. He had an EEG taken in [redacted] and the results were showing the same as the 2 previous EEG's whilst he was in status. This time however [redacted] was walking about the doctors office talking to him and able to eat. The neurologist was amazed. After this I started giving [redacted] bedica twice daily. He recovered from this cluster very quickly. Since this date he has suffered no clusters and has not been back to stay in hospital. He has required no rescue medication. There is no other explanation than the cannabis oils are effective. He suffers from no side effects therefore the cannabis oils are safe. To keep [redacted] healthy and out of hospital it is costing me approx. £1,300 per month (depending on exchange rate). This cost is minus plane and train fayres. I am extremely stressed trying to fundraise constantly. Worrying constantly how I am going to afford the next months prescription. Bedrolite is a cbd based cannabis oil with a very small amount of THC (0.6%). One 10ml bottle lasts [redacted] 4 days. Bedica is a thc based cannabis oil. One 10ml bottle lasts [redacted] 6 weeks. It is made by Bedrocan in Holland. There are certificates on the Transvaal Apotheeks website detailing each batch. Bedrocan's CBP's are Pharmaceutical grade oils – GMP Approved. [redacted] had no quality of life before cannabis oils. He could not attend school. He lived in hospital, as I did. His siblings hardly saw me. [redacted] is still taking zonisamide (even though his neurologist has stated he knows these pills are not helping [redacted]). [redacted] is also still taking a very small amount of lamtrogine. The doctors say that the quantity given will not be effective. As [redacted] is seizure free I am too scared to adjust or remove any of his medications. Before [redacted] [redacted] could suffer up to 600 myoclonic jerks/ absences on a daily basis. He has suffered 25 tonic clonic seizures in a 10 hour period. He also suffered from	

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				approximately 50 drop seizures last year and therefore had to wear a protective helmet at all times. He has had no seizures in 11 weeks (since starting bedica) and does not wear his protective helmet anymore. [redacted] has not been in an ambulance nor back to hospital since starting Bedica. In fact, he has not even needed any rescue medication. [redacted] now has no side effects – apart from jumbled speech problems due to the zonisamide. In Scotland I have been told by the NHS trust and my health secretary that if I can obtain an NHS prescription for the cannabis oils that they will honour it. Unfortunately no doctor on the specialist register will give me a prescription. [redacted] NHS Neurologist will not even note his cannabis oil medication in his hospital notes! He does not view the CBP's as a suitable anti-epileptic medication. My MSP and MP have been very helpful, however everybody could be helping our children more. [redacted] would have certainly died or be left with brain damage if I had not intervened and started giving him the cannabis oils. The seizures were constant. I feel angry that I had no NHS assistance through this period and anxious that this should not happen to any more parents/children. This help MUST be given. When the law was changed in November 2018 I had hoped that children (and adults) would be able to access cannabis medication through their doctors. Unfortunately, this evidently has not been the case and it is very disappointing and also devastating to parents like myself. I am devastated that [redacted] neurologist will not support us. He could not do anything to help [redacted]. In fact he caused more damage to [redacted] by prescribing the anti-epileptic drugs. (Especially keeping [redacted] on the sodium valproate for 6 months after we repeatedly said that we thought it was the sodium valproate causing [redacted] red blood cells to stop working). [redacted] endured 5 blood transfusions before the neuro took him off off this. [redacted] red blood cell count immediately returned to normal). I absolutely would not put [redacted] through an RCT. He is well now therefore I will not risk stripping him of his cannabis oil medication to enter into a trial. I will not gamble with my son's life to prove a point. I truly believe (due to the evidence in front of me), that without cannabis oils [redacted] would go back into status epilepticus. The doctors thought he was going to die last time. I will not put my son's life at risk. NICE could make a considerable difference to the lives of many in the UK. After 3 anti-epileptic drugs have been tried (and failed) the probability of other drugs working reduces in percentage. I know this from research and what [redacted] neurologist has told me. Would it not be a sensible approach to offer CBP's at this point? Especially as cannabis oils are clearly helping a lot of children and adults with debilitating conditions. RCTs will never work with cannabis. It would be a costly disaster. Observational trials are definitely the way to proceed. For children like [redacted] however, they have already been put through a very successful observational trial. The right guidance would be to provide funding for the children in [redacted] situation. This would ease the financial stress and burden for parents like myself. [redacted]	
End Our Pain	Guideline	General	General	**Individual Family Submissions 7 – [redacted]** Parents: [redacted] and [redacted] Child Affected: [redacted] Date Of Birth: [redacted] Current Age: [redacted] years Siblings: [redacted] Date Of Birth: [redacted] Current Age: [redacted] years	Thank you for taking the time to share details of the care received by your child affected by severe treatment-resistant epilepsy. On an individual level there appears to be evidence that CBMPs have a role. Clinicians can make their own individual prescribing decisions in the best interest of their patient taking into account their values and preferences. The committee considered the evidence in the area. The RCT evidence focused on treatment for particular epilepsy syndromes and the committee agreed that these findings couldn't be extrapolated to other forms of epilepsy. The committee also considered observational studies but agreed that these were of very low quality due to the high risk of bias. Overall, the

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				Our son has Global Learning Delays, Speech and Language Difficulties, and has a slow moving bowel due to the drugs he is taking so he is on laxatives, he also has eczema on his face, hair and in the creases of his arms and legs. He also has enlarged gums which is the side effect from the Phenytoin. [redacted] also has numerous allergies, Feather, Fur, Dust, Dust Mites, Pollen, Tree, and Grass.We need access to wholeplant medical cannabis (CBD and THC) because we have exhuasted all the other medications, [redacted] has a VNS implant, and tried the ketogenic diet. This Medication has to be available more easily and as quickly as possible our neurologist will not prescribe FECO due to the very restrictive BPNA guidelines. I fear that the NICE guidelienes could just entrench these guidelines. I pray this does not happen. We need cannabis oil just as much as those that have given an NHS prescription before the law changes. Because my child is equally at risk as those children are. [redacted] was born ventouse delivery and after a traumatic birth he was a healthy baby boy reaching all his milestones and learning to count and learn his colours in welsh. Although he had really awful colic as a baby and irregular sleeping pattern. We were extremely happy & elated first time parents looking forward to the future & building a happy family. As a year previous [redacted] had an accident at work that could have been catastrophic we didn't want to wait any longer in saving to get married then start a family – life was too short. At [redacted] years old we woke to the sound of [redacted] choking we phoned an ambulance. To see your baby convulse in distress turning blue is the most terrifying experience you hold your breath as they hold their breath hoping wishing they will come around. That the colour in their face will go back to a flushed red instead of blue & purple. The biggest fear was there was nothing we could do to help [redacted] but to phone for the ambulance & follow their instructions to keep him safe until they arrived. That first seizure will always imprinted in our minds but this was the calm before the storm, little did we know the worst was yet to come. That night the doctors diagnosed a febrile convulsion related to high temperature although we took his temperature and it was normal and [redacted] didn't have any cold or virus symptoms but we were relieved but still unsure and on edge that this could happen again. Much to our heartache these convulsions continued to happen [redacted] was admitted to hospital again and they gave us some medication before being discharged. We asked them what the medication was for and they said for [redacted] epilepsy, they didn't even tell us that was what they had diagnosed him with. At this moment looking back we were in shock we had not been given any information on epilepsy, didn't have any idea what this meant for [redacted] and his future and our future as a family was it hereditary, was it his birth, what caused it we had some many questions that we needed answers to Why [redacted]? A few weeks later we were then referred to a Pediatric Specialist Dr [redacted] [redacted] at [redacted]. Over the next few months [redacted] would have more seizures and they gained in severity and duration. We tried different drugs but they would either stop working, make his seizures worse or give him horrific side effects. From here on [redacted] seizures become more frequent and violent he was having Tonic Clonic Seizures, then they progressed into Drops Seizures, Absent Seizures, Myoclonic Jerks, Partial Seizures all these happening throughout the day and night. As the years passed we tried different medications as nothing would control the seizures, we were phoning an ambulance every week as [redacted] rescue medication would not stop the seizures they were relentless. Dr [redacted] [redacted] then told us that he had come to the end of this knowledge and drug base so he was referring us to a Pediatric Neurologist Dr [redacted] [redacted] at [redacted], as [redacted] was also experiencing sde effects from a lot of	committee agreed there wasn't sufficient good quality evidence to make population-level recommendations. Research recommendations were made to promote the evidence base in this area. This should include the views of patients, carers and families. The committee agreed that a national or local registry of prescribing practices of CBMs was also needed.

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				the drugs he has already tried. At this point [redacted] seizures became more uncontrolled and prolonged even 3 lots of rescue medications failed to bring him out of the seizures. He was being admitted into hospital on a weekly basis into PICU & ICU loaded up with obscene amounts of drugs to stop the uncontrolled seizures. Again, we tried more drugs which came with more side effects of head to toe rashes, hair loss, weight loss, aggression, rages, toxicity, decreased appetite, hallucinations, unable to sleep the list was endless. [redacted] has been admitted into PICU as the prolonged cluster seizures could not be stopped by further rescue medication and his airways became compromised. Once [redacted] recovered Dr [redacted] [redacted] asked if we would try the ketogenic diet, we agreed and met with [redacted] [redacted] Dietician at [redacted] who advised us and started [redacted] on the ketogenic diet. This proved exceptionally hard for [redacted] as he was [redacted] years-old and was enjoying normal food. Unfortunately [redacted] became very sick on the diet he went into rapid ketosis and we could not keep his glucose and ketones at safe levels, he was admitted into [redacted] and given chicken nuggets and chips to get him well as the Doctors at [redacted] didn't know anything about The Ketogenic Diet and they could not get hold of any Dietian at [redacted] Hospital. After being discharged we contacted [redacted] and we had to start the diet from scratch again, by this time [redacted] was vomiting daily, having to have bloods taken hourly and urine tests throughout the day and again we could keep his glucose & ketone at a safe Level and with no support in the community we had to stop the diet. [redacted] had to have a EEG which showed a diagnosis of Lennox Gastaut Syndrome so again there were more drugs we could try relating to this form of Epilepsy. The next form of treatment was vagal nerve stimulator, so [redacted] had the operation and it seemed to stop the small absent/head drop seizures. Although [redacted] would still endure daily seizures, the drop seizures would literally fling him from one end of the room to another almost like he had an electric shock. He would be having seizures during the day and the night being his worse time. [redacted] would still be having an ambulance into hospital every week from either seizure related or injuries from a seizure and then admitted on HDU as they could not stop his seizures he would then go into Status. The drugs he would have to take would deplete his system so he would have to have fortnightly loading doses intreveniously along with other cocktails of drugs, we were constantly interchanging drugs in and out on a weekly basis. Which as you can imagine gave horrific side effects, if there was a rare side effect to that drug [redacted] would have it. Dr [redacted] [redacted] also contacted Dr [redacted] [redacted] at [redacted] and asked to look at [redacted] case and see if brain surgery would be an option, her reply was no as [redacted] seizures are Generalized so he would not be a candidate for Surgery. [redacted] was admitted into hospital in status again and they loaded him up with various emergency drugs and he didn't wake up for 3 days. he had to have a catheter, feeding tube, drips, cannulas, his veins were shutting down and he wasn't responding. Dr [redacted] [redacted] sat us down and told us that he didn't know if [redacted] would wake up the [redacted] we knew or if at all. He said his basket of drugs were empty and he had nothing left to try it was a waiting game. Thankfully [redacted] did wake up after three days although he was still having seizures again we would just have to keep interchanging drugs. It was at this point that [redacted] and I decided to try Charlotte's Web CBD oil as [redacted] had been researching it for a few years, and a friend of our also mentioned it to us. We thought we have nothing left to try and then found a stockiest in Kent and went to purchase it. That weekend we gave Charlotte's Web CBD oil his first dose of Charlotte's Web Everyday Advanced and it was like a light switched back on, he was aware of his surrounding, he was able to hold conversations, and after a few weeks his drop seizures	

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				were less frequent and the severity of his tonic clonic seizures subsided. He even went out to the garden picked up his scooter and started to ride it and interacting with all the other children in the street. [redacted] over the next two years felt confident to go without wearing his helmet. We also requested an EEG to see if Charlotte's Web made a difference to seizure activity and yes it had showed less spiking to that of the EEG before taking Charlotte's Web. Also, we experienced no hospital stays throughout two years, no loading doses of Phenytoin and no increases in medication.. He had rapid growth spurts, (he was always below the growth centile line) he was looking healthier and his hair was growing thicker. However, [redacted] plateaued on the CBD only product.During the next year we saw [redacted] deteriorate rapidly and the benefits from Charlotte's Web plateaued. [redacted] had to have another battery replacement in his [redacted] was suffering tremendously and all his seizure types came back with a vengeance throughout the day and night. Even when he was sitting down you could feel his whole body pulsate, his hands were crooking inward and so is was one leg, putting pressure on his knee giving him alot of pain in the process. He was having constant absent and head drop seizures which caused him to trip and fall over. He was in a state of confusion and wandered around not knowing what to do with himself. There are fleeting moments of our [redacted] who has a kind hearted soul and wicked sense of humor. But we were losing him piece by piece and he was sleeping throughout the day and the seizures were draining his every being. Dr [redacted] [redacted] wanted to try the new Keppra Drug which has less aggressive side effects but we refused as[redacted] and his body has had enough. We have now agreed to bring [redacted] off one of the drugs, Clonazepam as it has stopped working so we are decreasing this very slowly as we have tried to decrease previously with horrendous withdrawal side effects. [redacted] has recently had a liver function test which has come back normal. But the Phenytoin Levels were 28.1 so we have had to reduce the evening dose. His vitamin D was also low so he is taking supplements for this too. The side effects of his cocktail of toxic medications included: aggression, frustration, inability to walk, weight loss, slurred speech, hair loss, rashes, oversized gums, sleepiness, hallucinations the list is endless. Our NHS Neurologist actually said he wanted us to revisit drugs that have given [redacted] horrific side effects, that he would like him to go back on steroids and he said that [redacted] quality of life had gone. The impact on Our Family is immense our son [redacted] who is [redacted] yrs old has been gravely affected he suffered from absent seizures as a toddler but is now seizure free. But seeing his brother suffer every day from seizures is something no child should ever see it has made him anxious, distant unable to express his emotions, he won't cry or discuss how poorly his brother is, he is scared and fears that we might not be here in the morning when he wakes up, as he has been left with relatives when we've had to take [redacted] into Hospital. [redacted] seems to get side-tracked when we have to care for [redacted] we often see him in the back round looking in on the seizure that is hurting his brother. Many trips have been cancelled and the simplest daily routines are a struggle as [redacted] has been too poorly to leave the house. [redacted] resorts to making himself vomit and soils himself daily due to the stress of seeing what [redacted] and us parents go through on a daily basis he cannot except or comprehend why this is happening to us all it is all too painful to face. When we travel in the car [redacted] has to sit in the front now as he is having servere seizures that have broken his leg and caused tissue damage, he also falls over onto [redacted] whilst having a seizure which are that strong he slips out of the belt. The terror and panic I see in [redacted] eyes at that moment is unbearable I feel like getting out the car and running as far away as possible because I cannot bear the horrific pain & suffering I see affecting my family every single hour of every single day. It is crushing my heart and soul. I sincerely don't know how we as a family find the strength to combat each day when all its filled with is pain & suffering. There is nothing more I can do but comfort him [redacted], I cannot explain why this has happened to	

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				our family, why we are not like every other family, I have no words or explanation as to why nobody is helping us and that we have done nothing wrong. It simply is hell on earth. It is unbearable because [redacted] has very recently broken down and told us he wants to Commit Suicide & hates his life because of [redacted] seizures we are now having to seek help from Social Workers & Primary Mental Help & CAMS. [redacted] has seizures throughout the day, during the Night and when he falls asleep the Seizures become more frequent and vicious so with [redacted] or I have to sleep in with him because he may not recover from a seizure, he could suffocate and die. So a lot of the time our Family Life is split into two parts of the house with either parent with [redacted] or [redacted]. We NEED Access to Medicinal Cannabis Oil because we have exhumed all the medications, [redacted] has a VNS implant, and tried the Ketogenic Diet. Since [redacted] has been taking Charlottes Webb CBD Oil it has shown improvements on his EEG. This Medication has to be available more easily and as quickly as possible our Neurologist will not prescribe FECO due to the very restrictive BPNA guidelines and them also recommending they do not prescribe please see attached letters from Chief Executive of [redacted] our second opinion Neurologist [redacted] Our Neurologist of [redacted] years has refused to prescribe [redacted] full-extract Cannabis Oil, we have filed a complaint to the NHS Trust and another 2nd opinion was arranged, he has seen [redacted] and looked over his case and the guidelines that have been written and he has also refused to prescribe [redacted]. We have also had a conversation with Head Neurologist at our hospital and she also said that she was unable to prescribe as she helped write those guidelines, so I had replied that those guidelines stated that they could prescribe Tilray & Bedrocan Products and and felt she could not go back on them now. She didn't even know that this part of the guidelines had been updated even though she had various meetings with BPNA. She also informed us that if one neurologist said no to prescribe then all other would say no too, so our second opinion that was arranged for us by Dr [redacted] was always going to be a no. We were offered Epidiolex but the CBD oil [redacted] is on is far better grade than Epidiolex because it is a full-extract oil. [redacted] would most definitely deteriorate if changed over to Epidiolex. We feel like neurologists are being misinformed and are being threatened with losing their jobs which is preventing them from doing "What is in the Best Interest of The Patient". Each day we grieve because the next seizure could take his life it could be now as I am writing this or tomorrow, next week, it is a ticking time bomb. But what we do know every day he has 100s of seizures and everyday those seizures kill brain his brain cells, taking a piece of our son away from us and away from this world. We cannot bear to see the deterioration any longer not in [redacted] or any other Child or human being when Full Extract Oil can elevate their condition and or give them a better quality of life forever how long they have left or prolong a happier Life. We now have a private prescription for Bedrolite & Bedica Medical Cannabis which we have to fundraise, basically beg, steel & borrow to pay for. We cannot sustain the £4000 per month costs of this private prescription we have one wage coming into the household as I am a full time carer to [redacted] & [redacted]. I had to give up my job as a Bank Clerk due to the profound care needed for both my sons Due to Epilepsy. Because of the extreme cost of honouring the prescription in the UK we are now having to criminalize ourselves by going abroad to bring [redacted] prescription back to the UK.	

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				Having to break the law is not something that we have ever done it doesn't sit well with us. It is causing extreme stress which we cannot bear as we already have a very a sick child. But we know that we have to do this to keep our son aive, safe and well because we are being let down, ignored and let to fend for ourselves. If other medications worked for [redacted], or he only had a small and manageable number of seizures. We wouldn't be doing this. [redacted] has been on Bedrolite (pure CBD) for nearly three months and the improvements are staggering. [redacted] is holding conversations & initiating them, his personality has returned, he is able to stay awake through the day until 4pm most days. He is playing with his toys in an imaginative way, he is able to vocalize what he wants and what he doesn't want, he is aware of his surroundings, he is enjoying all of his favorite tv programs and the laughter from him is so infectious, he is building a relationship again with his brother which brings tears to our eyes. He is trying so hard to regain his feeding skills, he is lucid and repeats and engages in conversations with us. We can still introduce Bedica (THC) if the clusters and tonic clonics continue to be aggressive but we shall see how he goes within the next few weeks. There are many more I can list but more importantly he has a significant reduction in seizures. Although the tonic clonics he does have are still really vicious and affect his breathing they are short lived and he recovers a lot quicker and he is able to walk, talk afterwards they do not wipe him out for the rest of the day. So we have what we have always wished for [redacted] & our family and that is auality of life and happy times together. In conclusion, we were elated when the law changed on 1 Nov 2019 for Medical Cannabis to be prescribed on NHS but we have been extremely let down and abandoned by NHS, Government for not following through on many processes that should have been addressed at the time. We are having to fight tirelessly to obtain this medicine on NHS Prescription. . Very soon our funds will run out & [redacted] seizures will return and his life will be held in balance once again. Due to the barbaric behaviors of Our Government, NHS, Various Establishments failing to finish what they started when they changed the Law for Medical Cannabis to be prescribed. We now have to keep fundraising to keep [redacted] alive & well, a price has been put on his life, [redacted] is entitled to a right to a life. our whole family is living on a knifes edge, [redacted] suffers from high blood pressure due having to keep down a full-time stressful job -and having to take turns sleeping in with [redacted] and keep him safe. i ([redacted]) have had to take anti-depressant tablets for 15 years to try and cope with looking after a sick child and now having to fight within an inch of our lives for a medicine that is legally allowed to be prescribed on the NHS. Due to all this stress anxiety and having to campaign and fight I now suffer from hemiplegic migraines brought on by stress. We cannot withstand this any longer something will break very soon. We have to relive all the uncomprehenable pain & suffering that we have shut away so we can cope with looking after a sick child to prove why we need an NHS prescription. Its not something we want to be doing it. Especially when its clear why he needs a prescription. The medicine that is making him well, saving the NHS money by not having weekly visits to hospital, no loading doses of drugs, no increases of drugs, no HDU stays, how many more reasons due we have to give. We welcome whole heartily that trials, tests have to be done but there is worldwide evidence of cannabis medicine and just because they are not licensed does not mean they are not safe or effective, [redacted] has consistently been given medicine that has not been used or tested in children and are unlicensed and have to be approved by medical board for use, so that is not a justified response. We don't think it unreasonable for us to have a Shared Care system with our private Neurologist and for our NHS Neurologist be granted permission/guidelines to observe and collect data whilst being on Medical Cannabis funded on NHS Prescription, as [redacted] has already been on Medical Cannabis and it is working for him.	

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				Whilst we have been waiting for Government to answer our pleas [redacted] and many other children have done their trials, they have given you evidence, they have waited and suffered enough. We cannot go through anymore horrific pain, suffering, stress anxiety having to Fundraise for RCT,s, Observational trials to be set up even. For our children to be put into a trial they have to be stripped of their current drugs & cannabis oil which would be catastrophic & unethical, which could take months/years as this has to be done slowly, then what products would be used and in what ratios every child has different diagnosis and tolerates different dosages and then who gets the placebo? We will not put [redacted] through this is would simply be inhumane & torture. [redacted] needs an NHS Prescription for Medical Cannabis to keep him alive, safe & well. So he can live his live for now, for however long he is on this earth, we want to live as a family without burden, pain & suffering creating happy, loving memories. We simply don't have the luxury of time! Please act with common sense and compassion in our cases, and recognize that we have the most extreme and urgent need, as well as the evidence it works for [redacted]. Yours sincerely, [redacted], [redacted], [redacted] and [redacted]	
End Our Pain	Guideline	General	General	**Individual Family Submissions 8** [redacted] (age [redacted]... [redacted]) Name of Parents: [redacted] & [redacted]. [redacted] has [redacted] Siblings : [redacted]) [redacted] has LGS (Lennox Gastaud Syndrome) the symptoms of which are well known. She had her first seizure at age [redacted] and is now [redacted]. Her epilepsy is characterised by multiple daily seizures of various types and severity. Over a [redacted] period we have tried all the normally prescribed AED's, none of which had an effect and some exacerbated the condition by making her drowsy and sometimes unresponsive in addition to the seizures. She also has had a VNS fitted, with only marginal success. Alternative treatments such as surgery had been ruled out early-on as an MRI showed multiple areas of a migrational disorder that was too widespread in the brain. [redacted] pregnancy with [redacted] was normal. [redacted] delivery was normal (38 weeks). Her neo-natal period was normal. The first indication of [redacted] illness was at age [redacted] on first day of school. We had a call from school saying is she prone to seizures. First real full blown seizure with [redacted] when ambulance called and after seeing local doctors was transferred to [redacted] under the care of [redacted]. Probably the worst few days of our lives as we had no diagnosis and no plan of a way forward. [redacted] attended various MLD Schools and over the next [redacted] tried every AED that was on the market. The epilepsy diagnosis soon became intractable epilepsy, and after an MRI we were told that an operation was not feasible. We were advised that during pregnancy there had been a 'migrational disorder' and some cells in the brain had 'migrated' to the wrong location. There was a thickening of the walls of the speech and language centres which had caused the learning difficulties and the Epilepsy. Finally diagnosed with LGS (confirmed by Dr [redacted]). Fitted with a Vagal Nerve Stimulator (LGS) which was only marginally effective. Constantly on the internet searching for any hope of progress anywhere in the world. Meanwhile [redacted] continued to have between 5-10 seizures a day. During a tape-test at	Thank you for taking the time to share details of the care received by your child affected by severe treatment-resistant epilepsy. On an individual level there appears to be evidence that CBMPs have a role. Clinicians can make their own individual prescribing decisions in the best interest of their patient taking into account their values and preferences. The committee considered the evidence in the area. The RCT evidence focused on treatment for particular epilepsy syndromes and the committee agreed that these findings couldn't be extrapolated to other forms of epilepsy. The committee also considered observational studies but agreed that these were of very low quality due to the high risk of bias. Overall, the committee agreed there wasn't sufficient good quality evidence to make population-level recommendations. Research recommendations were made to promote the evidence base in this area. This should include the views of patients, carers and families. The committee agreed that a national or local registry of prescribing practices of CBMs was also needed.

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				[redacted] Hospital over a 24 hour period, it was shown that [redacted] was actually suffering 100s of seizures, but mostly too small to register. As parents we have always been highly interested in any medical developments that would potentially assist [redacted]. When we saw reports on the News 15 months ago how Cannabis Oil has been helping people all over the world with many different ailments (MS, Pain, Epilepsy and even Cancer) we researched the subject in greater detail. The highlight was Alfie Dingle who had gone from hundreds of seizures a month to zero and more research showed this was not a one-off and there was multiple examples all over the world with success, so we followed the path after taking advice. As Cannabis Oil was illegal in the UK we met a doctor in Holland who recommended Bedrolite. [redacted] started taking Bedrolite in [redacted] under a Dutch doctor. The advice was to take it in conjunction with her existing meds as there was no contra-indications with them. She continues to take the other AED's which are: Clobazam, Inovalin, Lamotrigine. We have successfully weaned her off a forth AED which was Topiramate, with no adverse effect. After [redacted] started taking Bedrolite we saw an 80% reduction over a 3 month period. This persuaded our consultant to apply for a licence under the home office licencing scheme in October 2018, but this was disbanded when the law changed in November 2018. [redacted] supported an IFR request....but this was refused under the exceptionality rule. [redacted] now takes Bedrolite and her seizures are 90% less than at their peak. Her dosage vs weight ratio suggests the dose could increase, but the cost is unaffordable. We spend over £2000 out of earned income and have remortgaged the house to pay for the oil. [redacted] has gone from multiple daily seizures (between 5 and 10 a day) to less than 1 per day on average. She is far more alert now her brain is allowed to recover from the seizures, her IQ has improved and her speech and language is at a totally different level. Her quality of life has improved immeasurably. She no longer needs to take a wheelchair when leaving the house and is far more involved in the day to day conversations around her. THERE HAS BEEN NO ADVERSE EFFECTS FROM THE CANNABIS OIL IN OVER A YEAR OF TAKING IT. In [redacted] we had a consultation with [redacted] Neurologist Dr [redacted] at the [redacted] which is part of [redacted], where he heads up the research department. We showed him the exceptional results from the 3 months that [redacted] had taken the Bedrolite, and he agreed to support an application for a licence to the Home Office which was the system at the time. A week later the law was changed, the panel disbanded and it was assumed that an NHS prescription would then be forthcoming. It was not. After discussion [redacted] they agreed to support an IFR due to the results, which was rejected. We continue to self fund a prescription in Holland even though we have obtained a UK private prescription. The fact we have obtained a private prescription shows that we have support from a neurologist that it is felt to be needed. The sole reason that we fund a private prescription in Holland rather than the UK is cost. [redacted] is on 1.3ml of Bedrolite x3 a day and therefore uses 1 bottle every 2.5 days. The cost of this is £2,000 a month in Holland whereas it would be over £6,000 in the UK. We make this trip once a month and chose to criminalise ourselves to keep our daughter well, rather than let her return to her previous condition. Apart from the financial cost as explained I have to take 1 day per month off work (thus destroying any likelihood of family holidays, which are unaffordable anyway),the risk and	

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				stress of being stopped at the airport. This is having a compound effect on the family and affecting my other two children. It is my hope that we will be able to secure an NHS prescription for Bedrolite. This will be able to take the pressure and worry that [redacted] will not be able to access the only medication that has worked in the last 20 years. Further our family will be able to mend without the stress and the financial pressures that we are having to endure. It is my fervent hope that once this medication becomes mainstream that [redacted] will be able to wean off the other AED's. I find it difficult to comprehend the current NHS stance. This medication will save a fortune on many AED's that don't work for people with intractable epilepsy, cut down substantially on hospital admissions, ambulance call outs, and improve the health and well being of many people including my daughter. Once off the other AED's the cost to the Health budget will be positive rather than negative. It is a Win/Win/Win situation. It has had a severely detrimental effect on our family and our marriage has suffered to the extent that we are now separated. We have proved beyond any reasonable doubt that the Bedrolite Oil works and yet we are being denied it. We would like to wean [redacted] off the other 3 AEDs which I suspect would save the NHS more than it would cost to fund the oil. I have recently increased the THC element and can report a reduction in the level of seizures. This is only slight, but the level of THC is small and there have been no adverse effects. 2 final points. I believe double blind trials are both cruel and ineffective. Firstly I would not want [redacted] to come off the medicine which has proved beneficial for her.... effectively to multiple her seizures by a factor of 10. Then to have a 50% chance of her receiving a placebo..... I would know after 1 week if she was receiving the medication or a substitute and I would act accordingly! Secondly I would ask NICE to act in a rational way rather than a restrictive way and agree to an observational trial for [redacted], this reaping the rewards of detailing a success story and recording the results accordingly. This would help [redacted], It would help our family (financially and emotionally), and help the NHS collect vital data. Doing anything else would result in[redacted] deteriorating, becoming ill, more return trips to hospital (which is becoming a distant memory) I urge NICE to look at their rules, and decide that people already having a success and with the backing of a consultant, be allowed to continue taking the Medication on the NHS. [redacted] **and** [redacted]	
End Our Pain	Guideline	General	General	**<u>Individual Family Submissions 10 –</u>** [redacted] My name is [redacted], and I am married to [redacted]. We have [redacted] children, [redacted]. [redacted] is now [redacted] years old, he was born on the [redacted] by emergency caesarian section at the [redacted] Hospital [redacted]. [redacted] is [redacted] years old, and he was born on the [redacted] by an elective caesarian section, also at [redacted]. During my pregnancy with [redacted] I was diagnosed with polyhydramnios, as a result of which I had weekly ultrasound scans, and was induced early. This induction failed and I ended up having to deliver [redacted] by section. This was far from the home birth I imagined.	Thank you for taking the time to share details of the care received by your child affected by severe treatment-resistant epilepsy. On an individual level there appears to be evidence that CBMPs have a role. Clinicians can make their own individual prescribing decisions in the best interest of their patient taking into account their values and preferences. The committee considered the evidence in the area. The RCT evidence focused on treatment for particular epilepsy syndromes and the committee agreed that these findings couldn't be extrapolated to other forms of epilepsy. The committee also considered observational studies but agreed that these were of very low quality due to the high risk of bias. Overall, the

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				As it had taken a little while longer than we'd imagined to fall pregnant with [redacted] we started trying for a sibling fairly soon, but again found it hard to fall pregnant. Over the next three years I had two miscarriages, and was eventually referred for an IVF consultation. We then found out I was pregnant, and were of course beyond delighted. I worked hard to stay fit and healthy in my pregnancy, as I was desperate for a more positive and natural birth. My bump was again large, but I avoided a second polyhydramnios diagnosis. at 35 weeks gestation I had two episodes of unexplained pain and cramping, and then went into suspected early labour. In the end it turned out I was not in labour, but the midwife felt my bump was too big, and scheduled a scan. I told my husband not to come, as I'd had so many with [redacted], but he did. During the scan he asked the monographer if she was looking at the brain, once she confirmed he asked 'what is that black area'? In that instant our lives changed forever. I still find it incredibly hard to think about the next hour as different people filed into the room to talk to us. No one could tell us what this might mean for our son, or why it had happened. If he would live, or even possibly die. After the discovery of a large porencephalic cyst on the left side of our unborn son's brain as well as some other suspected issues an MRI was done, following which we met with a Paediatric Consultant at [redacted] to discuss the results. He told us that some of the issues raised were not noted on the MRI, and whilst they could not tell us how the cyst might effect our child he hoped that it might merely cause 'one sided muscle weakness' and we should try be 'quietly optimistic.' I was so frightened of any additional damage being done if the birth proved difficult that an elective section was planned and[redacted] was born fit and well. He was a little small, but perfect. He did everything he needed to do, including latching on and feeding beautifully. We took him home and tried to just enjoy him, but the fear and worry remained. A second MRI revealed some additional damage, but no likely outcomes were discussed until [redacted] was [redacted] old when we met his Paediatric Consultant Dr [redacted]. By [redacted] months [redacted] had been diagnosed with Cortical Visual Impairment (CVI), and right hemiplegia but was otherwise felt to be developing well if a little delayed. At [redacted] months, in [redacted] [redacted] was diagnosed with a rare and catastrophic type of epilepsy called Infantile spasms. This is treated as a medical emergency and he was immediately started on a medication called Vigabatrin, after two weeks and no improvement Prednisolone was added (not licensed for use with children under 6 years of age). When this too failed to work [redacted] was denied treatment using ACTH, another high dose steroid recommended in the NICE guidelines, on the basis of cost. This was by both the [redacted] and by [redacted]. Following this we sought a second opinion from [redacted], under whose care [redacted] remains today [redacted]. [redacted] has been prescribed a range of primary anti-epileptic drugs (AEDs) including Vigabatrin, Prednisolone and Epilim. He has also been prescribed secondary drugs including Pyridoxine, Clobazam, keppra - all I believe unlicensed for use in children under 6 years of age. [redacted] was also on the ketogenic diet for two years, and was assessed for brain surgery (a hemispherectomy) but was not a candidate. None of these pharmaceutical drugs or other therapeutic methods have had any long-term success in improving [redacted] condition. As such, his development has been significantly affected- he has been diagnosed as having Global Development Delay - and his quality of life is greatly diminished. From open and frank discussions with both Dr [redacted] and [redacted] we knew that [redacted] was going to be profoundly disabled, and would likely suffer from seizures throughout his life. They were both clear that once the first few anti epileptic medications have failed the likelihood of one working is substantially diminished to just a few percent. We were crushed, and desperately wanted[redacted] to have a brighter future, and one in which he did not seizure all day every day.	committee agreed there wasn't sufficient good quality evidence to make population-level recommendations. Research recommendations were made to promote the evidence base in this area. This should include the views of patients, carers and families. The committee agreed that a national or local registry of prescribing practices of CBMs was also needed.

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				As we approached a year of [redacted] suffering hundreds of seizures daily we began discussing trying CBD with Dr [redacted]. He could not advise us on it, nor prescribe it of course, but he felt that if we wanted to try he would at least document this in [redacted] records. We started [redacted] on a product called Haleigh's Hope (HH) in [redacted]. We saw some improvements immediately, and after a few months enjoyed a short period with no obvious seizures. They did return but never to the extent they had been (on average 2 clusters in 24 hrs as opposed to 8). Over the next year we tried different doses, a different product (Palmetto Harmony), and also added another AED (keppra) and weaned [redacted] off other treatments. CBD has been the only thing that has worked for [redacted], and we have used it to both keep him stable and to wean him off all the other medications as they were not doing anything. By Haleigh's Hope [redacted] was only on HH. Over the years [redacted] has gone on to develop additional seizure types, he still experiences myoclonic seizures daily, and has had focal seizures and a tonic clonic. The Infantile Spasms has resolved but he does still experience some epileptic spasms. In early [redacted] we followed the case of Hannah Deacon and her son Alfie closely, and decided that we too would take our son to Holland. We found a Neurologist in Holland we hoped to see, she needed a referral which Dr [redacted] agreed to do. The doctor eventually refused to take on any new cases from the UK, so we started publicly campaigning. In the following weeks Nick Hurd announced he was setting up an 'Expert Panel' for applications to be made for licences to use medicinal cannabis, Dr [redacted] agreed to apply despite the application criteria being framed in such a way as to deter applications. He was supported in the application by Prof [redacted]. In that time I also met with Nick Hurd personally, I explained my worry that the application was proving vey difficult to complete but he assured me that the panel was set to help patients and families like ours. After a number of weeks the application as refused, the two main reasons being that the application was not completed by a Neurologist, and [redacted] had not tried Epidolex. Epidiolex is of course not yet licensed nor available for prescription, however on the basis of the Panel's recommendations [redacted] Neurologist did help Dr [redacted] applying for compassionate access which was granted (despite [redacted] not having LGS or Dravet). At the time of the law change in November 2018 we finally received the Epidiolex. As with each medication we have tried we desperately hoped it would work and it did improve [redacted] seizure burden and eventually helped resolve the IS. However he was very unsettled and uncomfortable, and continued to have a lot of subclinical seizure activity (picked up on an EEG) as well as hundreds of myoclonics. We also experience 4 significant seizures (focal/tonic clonic) which resulted in us calling ambulances and being admitted, with rescue medications being given twice. This felt like the start of [redacted] seizures becoming more immediately dangerous and not just neurologically catastrophic. In [redacted] had a meeting with Dr [redacted] and the CEO of [redacted] who were both in theory happy to support a prescription, but Dr [redacted] was anxious about the BPNA guidelines, and the possibility of GMC involvement should a complaint by a more senior colleague be made. Not necessarily for him, but for [redacted] new Doctor as Dr [redacted] was due to retire at the end of [redacted]. Instead he had referred us again to Holland, and we got a prescription there and bought back medicinal cannabis for [redacted]. We were unhappy doing this as it is illegal, and we did not want Dr [redacted] to feel compromised by our decision. Fortunately within a week or two Dr [redacted] of the [redacted] Hospital agreed to see us and [redacted] now has a private prescription for bedrolite oral solution and bedica. He currently takes .7ml of bedroll 2 x daily and 0.01ml of the bedica. We have not seen any focal seizures or tonics, and just a few spasms. The myoclonic are also reduced though he still experiences some daily. He is happy, settled and sleeping though the night.	

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				Since [redacted] diagnosis we have worked tirelessly to care for him and to ensure we are fully informed on all aspects of his diagnosis including extensive research on medications and therapies that could improve his condition. Since he has been on his private prescription for bedrolite we have seen some things we never thought possible. Put quite simply [redacted] is thriving. At [redacted] years old the challenges [redacted] faces are huge, he cannot sit independently, nor walk or really stand. He is non verbal, and can not tell us if he is hungry, or tired, happy or sad, he relies completely on those around him to provide him with the care he needs. But of course he can communicate, more and more each day, with an infectious smile, or a big belly laugh. Or with big fat sad tears, or utter frustration. And he loves life. He has recently learnt how to do his first responsive action on demand, a high five, and delights in being asked to do so. He is picking up food, feeling it, and if it is not what he wants he just drops it on the floor - typical toddler behaviour we did not ever expect to see. But best of all he has started reaching for our faces, and pulling us close for kisses. And that, that is truly priceless. But beyond the benefits we are seeing our local Trust are also seeing savings. [redacted] is on no other medication, and the NHS have not paid for a routine prescription for [redacted] since [redacted]. And as above more recently [redacted] has started sleeping through the night, and we voluntarily reduced the overnight care [redacted] was receiving by 50%, saving our local trust £204 a week. And yet we are relying on our family, who have given [redacted] money, and our friends, to help us fundraise to meet the monthly costs of around £2000 for [redacted] medication. Before he retired Dr [redacted] applied to the Drugs and Therapeutics Committee at [redacted] to be allowed to apply for Individual funding for [redacted] (an IFR), this was refused. In his email following the refusal Dr [redacted] wrote the following; *"at least an attempt has been made to obtain NHS funding. Sadly, it didn't even get through the first hurdle of [redacted] committee and, I fear, it was even less likely to have been approved had it managed to go on to the [redacted]. Perhaps the situation might change after NICE produces its guidance later this year".* The publication of the interim NICE guidelines has decimated the tiny sliver of hope we had left left that one day he will receive an NHS prescription. [redacted] lies awake at night worrying about how we will maintain [redacted] prescription, and feels hugely responsible as the only breadwinner in our family. We worry about the cost currently that our friends and family help us to carry, how long can they be expected to do this? And we are terrified about the possible consequences of having to obtain from Holland once our funds run out. I have been unable to work since we had [redacted], but now in the hours he is in Nursery instead of focusing on our home I am constantly campaigning. When the boys get home I'm still often trying to cook, or tidy, or any of the other tasks running the house require. But [redacted] needs constant supervision, and between managing him, and also trying to be there for [redacted] it is often left to [redacted] to cook. I should have the time, but instead my time is used for countless phone calls, for campaining, meetings with media, MP's, and writing documents like this. We simply can not sustain this. Not the private prescription nor the constant fighting for [redacted]. He needs us, and we want to enjoy our time with him. He has a life limiting condition, and so we just want him to live his life as happily and with the best health he can have. When the Home Secretary Sajid Javid confirmed that the Misuse of Drugs (Amendments) (Cannabis and Licence Fees) (England, Wales and Scotland) Regulations 2018 would "reschedule cannabis-based products for medicinal use", we truly hoped that this would enable us to access medicinal cannabis. Unfortunately, despite the change in the law, this has not happened. We have been fortunate to have had an extremely supportive doctor in Dr [redacted], and so have a huge amount of documented evidence of [redacted] use of CBD, his improvements, and the many steps we have taken. We have documented evidence of our continued efforts to access medicinal cannabis through the various channels that have been	

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				created by Government at the time, and although we have followed the advice issued we still do not have access. We are calling on NICE to take a more holistic, open-minded approach, but also to be more honest and transparent about the reality of the current situation for children like [redacted]. [redacted] has severe intractable epilepsy, as such he has already been prescribed conventional AED's (which haven't worked). He has been prescribed drugs like clobazam that are being prescribed as "specials" for children/infants for whom they were not tested or designed. Within this framework the support for observational trials using the only medication that has helped [redacted] so far is not an unreasonable request. Medicinal cannabis has helped [redacted]. Nothing else has. [redacted] [redacted]	
End Our Pain	Guideline	General	General	**Individual Family Submissions 11 – [redacted]** To whom it may concern, My name is [redacted] and my partner is [redacted] we are the parents of [redacted]. [redacted] is [redacted] months old and was born on [redacted]. He is our only child. We are choosing to write this letter today during the NICE consultation period after reviewing the proposed guidelines. We thought it was imperative we do so, because although [redacted] is now having a better quality of life Thank youto Bedrolite a cannabis based medical product, unfortunately nobody has contacted us to give evidence. We feel that most of the medical profession is not looking at the progress [redacted]` has made and are only concentrating on the negative effects it MAY have in later life. Of course, there has not been any negative side effects, or we would not be campaigning so hard for a prescription. We thought it wise to give you some background information starting with my pregnancy. During pregnancy I experienced some difficulties and was diagnosed with Symphysis Pubis Dysfunction (SPD) or pelvic pain. I also then developed Carpal Tunnel Syndrome. Both were managed well with advice from a Physical therapist. In the later stages of pregnancy, I developed what was referred to as borderline Pre-eclampsia with raised blood pressure, severe nausea and vomiting, this condition can be extremely dangerous. It was classed as borderline as although my blood pressure was on the cusp of being dangerous quite frequently, it would regularly reduce by itself. I had to attend my local maternity ward on a couple of occasions, as advised by a midwife. Each time my blood pressure reduced however as it was a frequent occurrence, I was put under the care of a Consultant to guide me through the rest of my pregnancy. He decided that once I reached week 38 due to my body struggling, I would be taken in to induce the labour. This did have complications. I was oversensitive to the drug that was used to induce labour, and this had to be removed from my system. I was having too many contractions too quickly and [redacted] became distressed and heart rate dropped significantly. The midwife who was supposed to be monitoring me was not in the room and despite all alarms going off did not come to assist. I knew that the labour was not going to plan and found the midwife to lack bedside manner & wasn't communicating with me, and actually unprofessional for the times she was in the room. Therefore, I asked for her to get someone senior. This was eventually done and quite quickly the consultant who came to see me made the decision to go for a caesarean section. This was done as an emergency and in my opinion should have been done much sooner than it was. It was not only done as an emergency but [redacted] and I were becoming so poorly that the consultant explained to me that there was no time to wait for an epidural (20 minutes) and I was put to sleep as the baby needed to be delivered straight away for both of our safety. My blood pressure was dangerously high, and [redacted] was born extremely poorly with an Apgar score of 2 and needed oxygen. He recovered quite quickly so I was told, as unfortunately I was still too poorly to see him, and it was deemed he did not need any time in neo-natal care. I was in recovery most of that day in high dependency care. It was a truly traumatic experience. So	Thank you for taking the time to share details of the care received by your child affected by severe treatment-resistant epilepsy. On an individual level there appears to be evidence that CBMPs have a role. Clinicians can make their own individual prescribing decisions in the best interest of their patient taking into account their values and preferences. The committee considered the evidence in the area. The RCT evidence focused on treatment for particular epilepsy syndromes and the committee agreed that these findings couldn't be extrapolated to other forms of epilepsy. The committee also considered observational studies but agreed that these were of very low quality due to the high risk of bias. Overall, the committee agreed there wasn't sufficient good quality evidence to make population-level recommendations. Research recommendations were made to promote the evidence base in this area. This should include the views of patients, carers and families. The committee agreed that a national or local registry of prescribing practices of CBMs was also needed.

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				much so I was offered a debrief with a consultant to discuss how things could have been done differently. I have all medical records of [redacted]birth, as this has been looked into very closely. After the extremely traumatic birth, [redacted] entered the world and brought with him so much happiness and Joy. We had decided to wait to have our first child until we were both established in our individual careers and financially stable and had purchased our first home. [redacted] was the final piece of the puzzle and we could not have been more overjoyed at becoming parents. [redacted] seemed to be a perfectly healthy and happy little boy. He did not sleep well but I was advised by my health visitor and Dr's that this was perfectly normal. All babies take time to settle into a routine and during the day he was perfectly happy and meeting all milestones. I did have some concerns pretty much straight away about his lack of sleep. During the evening he became very unsettled in his sleep he would thrash about and look extremely uncomfortable. He would make strange noises and twitch and jerk very often. I did seek medical advice and took videos, and this was put down to reflux and medication was commenced and I changed his milk to a comfort milk. I personally now believe that [redacted] was experiencing nocturnal seizures at night from the beginning. Unfortunately, as a new mum I accepted the diagnosis of reflux at the time, I did not push this further. I believe that his birth played a major part in his severe epilepsy now. At the time I did seek medical advice and as already mentioned he was diagnosed with reflux. I now feel that this was not the case. Until recently I have not been able to look back at videos of [redacted] s first weeks of life, as we now have a very different child to what we had then. However, on looking back at those videos recently that I had taken of him at night I believe he was having seizures pretty much from the beginning but it was put down to normal baby movements and reflux. [redacted] first noticeable or major seizure happened when he was [redacted]old. I noticed his right arm was continually twitching whilst he was sleeping. It was persistent and abnormal. We called an ambulance and by the time they reached us [redacted] was in a generalised seizure effecting the whole of his body. I have never felt fear like it. We were rushed to hospital and it was then that I realised the severity of the situation. Approximately 9 people worked on my tiny baby for approximately 3 hours I believe. All the time I had hold of him on a hospital bed as it was thought this would keep him calm. They pumped various amounts of drugs into him trying to stop the seizure, but they couldn't. It was then that they placed him into a coma. This is the only way [redacted] seizures can be stopped when he goes into status. We know this now, as [redacted] has since been in a further 2 comas for seizure control as he is drug resistant. One of these comas lasted 3 weeks. As mentioned, [redacted] was just over [redacted] old. The next 3 months we had to live in hospital whilst I watched him deteriorate. The more drugs they gave him to prevent seizures the more poorly and unresponsive he became. I must point out that to my knowledge none of these drugs would have passed randomised controlled trials on a child of [redacted] age. So, it infuriates me and makes no sense as to why Cannabis based medical products is being treated so differently from these drugs, especially when it is the only thing [redacted] has responded to. During our 3 month stay, which was mainly in intensive care [redacted] was put through various tests to establish the cause of his severe seizures. We were asked when we were admitted about his previous health for example his birth. I told them that I felt his birth could be the only real reason he was experiencing these seizures as his oxygen levels had dropped so low for over 6 minutes. I was told that they felt this to be unlikely as it would be expected that [redacted] would have experienced seizures before he was [redacted] old. At the time I completely accepted this after all he was such a happy healthy boy in the daytime. As I have previously mentioned it was only recently looking back at videos, I now believe the reflux at night was actually seizures. So, his birth was ruled out by medical professionals at the time. [redacted] had blood tests to look for infection which were clear. He had brain scans to check for structural damage and his brain was perfectly formed. We were then told about genetic	

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				testing. [redacted] did have bloods taken and a mutation was found in his [redacted] gene. Both myself and [redacted] carry a mutation within this gene and [redacted] inherited both mutations. We were told that this gene is responsible for producing healthy Mitochondria. Dr's believe that this is a LIKELY cause for [redacted] severe epilepsy. We are not able to get a definitive diagnosis as the trouble is that [redacted] is the only recorded case in the world in medical journals with this mutation, so they cannot say for definite that this is the cause. When we where given this diagnosis, my world fell apart. Children with mitochondrial disorders do not tend to make it past their infancy. Not only this but there is so much uncertainty around [redacted] diagnosis and because the genetics team can not say to us for certain this is the cause or whether the mutation is purely coincidental, they are not able to help us with any further family planning, as of course and rightly so embryos have rights. So, we personally feel we can never go on to have future children in case they are as poorly as [redacted]. Although we will never know for sure. Life for us now is all about [redacted] and making him as well as he can be. During our 3 month stay in hospital there were times we did not think we would ever make it home. We had him christened in intensive care whilst in a coma. On 3 separate times I have thought [redacted] I was about to die. 1 of them was not even due to being in status or down to seizures. [redacted] became hugely bradycardic due to the obscene number of drugs given to him. At one period he was on ketamine for 6 weeks. We were in high dependency care at the time not long been transferred from intensive care and they could not wake [redacted] l up. He was unresponsive and I could see the look of concern on peoples faces and the fact that more and more people where coming to his bedside. I have seen that his heart rate was at 48 and Cardiology had been called. [redacted] had never been under cardiology, always just neurology. I was quietly told that [redacted] was really poorly. If his heart rate dropped below 40, they would have to think about prepping for resuscitation. I was asking them how can this be happening what has caused it? I remember the consultant from Cardiology questioning what he has had and saying I believe he is over sedated. How could it be that the drugs used to stop my child seizing were making him so unwell. I have said my final goodbyes to [redacted] on 3 separate occasions. It should never have been this way when cannabis can and does help him. A mother should not have to hold their tiny babies' body and whisper to them that, it will be ok now and if they need to stop fighting, they can and can go peacefully, because their tiny body can't take anymore. It is cruel and I will never recover from what I have been through, but I will fight for a medicine which has kept him well for the last 4 months. [redacted] has failed all pharmaceutical drugs they have tried. He is not a candidate for surgery, and it has been deemed that due to his suspected mitochondrial disorder the ketogenic diet is not suitable for him. He fulfils all criteria for medical cannabis. Here is a list of just some of the anti-epileptic drugs he has tried and failed: • Phenobarbitone • Sodium Valproate • Phenytoin • Carbamazepine • Topiramate • Clobazam • Steroids • Keppra We know as I have mentioned that [redacted] does not have a long-life expectancy and he has failed so many antiepileptic drugs and other non-conventional ones like ketamine. So, as he does not have a long-life expectancy, I was amazed by one of the reasons he was declined medical cannabis was due to worries about psychosis in later life. Surely the short term benefit we are seeing at present should outweigh a worry of his brain in adult years when he is not expected to make it to adult years. We have even been offered to talk to Palliative Care, in my opinion this is absurd. We have not even trialled full extract medical cannabis via	

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				the NHS and therefore do not feel it appropriate to discuss palliative care. [redacted] has actually not been admitted to hospital since [redacted] and has had only one real illness since starting his Bedrolite in [redacted] and that was very shortly after his vaccinations. Prior to this he was in hospital from [redacted] to [redacted]. He was admitted again in [redacted] and again in [redacted]. Although he has been poorly since, he has not needed to be hospitalised and we have not seen seizures increase which is in itself so positive. Within a week of [redacted] first seizure and admission to hospital back in [redacted]I began to ask about cannabis as a treatment. I spent night after night researching as best as I could when going through such a trauma. I was living in fear and desperation. I was told that they would not recommend it and advised that if I was to administer it myself, I could be prosecuted. Nothing was working for [redacted] other than putting him into a coma, surely this wasn't the only way they could treat him? I read report after report of not only how medical cannabis could help him but how the drugs, they were using had their own harmful side effects and I was witnessing them with raised liver function tests and extreme sedation. I decided to keep pushing on at his medical team and eventually on [redacted] we were granted the use of Epidiolex on a compassionate scheme. It was a victory to us, a small one as preferably we would have liked a whole plant product so [redacted] could benefit from the entourage effect. However shortly after starting to use this [redacted] needed his rescue medication of chloral hydrate (which has its own risks) much less frequently, at one stage we had to give it every 4 hours. We got down to once or twice a day with Epidiolex. We were able to wean his midazolam infusion, which of course was difficult due to [redacted] being addicted to it by then, so we had to go through withdrawal, again horrific to watch in such a [redacted]. We continued to see positive effects from Epidiolex. [redacted] was awake more and we moved from critical care to a ward. Eventually we were able to take [redacted] home. We never thought this would happen. We believe firmly this was due to Epidiolex. Once we were home we had to adapt to our new life. [redacted] was still having 100's of myoclonic jerks a day and up to 10 tonic seizures a day. However, since adding the Epidiolex he never went back into status and his seizures never materialised to the long-generalised ones that could only be controlled via intubation. It was then that I started looking further into medical cannabis as a treatment. Epidiolex was giving positive results but I learned that this was just a CBD isolate. I educated myself on the Endocannabinoid system. Never the less we were at home and managed to enjoy Christmas as best as we could with an extremely poorly child. By [redacted], we had noticed N[redacted] seizures increase again. I hadn't really thought much further into cannabis for a month or so as Epidiolex had given us a great run from [redacted] to [redacted] . However, come the new year and we were seeing him deteriorate again, I joined multiple parents discussion groups and found the many parents on the compassionate scheme had found the same as us and that their children had grown a tolerance to the CBD isolate within 4-6 months. Others of course found it worked well which is great. I do think Epidiolex is a good drug for some children it just unfortunately stopped working for [redacted]. I became depressed again and fearful, I could not let them pump him full of numerous harmful drugs that simply didn't work or for [redacted] or be in a position where I thought I could lose him again, so I approached his Hospital Trust and was declined. This was their reasoning: "The family discussed about other cannabis related medical products, particularly the ones containing tetrahydrocannabinol (THC). I discussed that we don't have any evidence from proper scientific studies that such products are helpful, and there are concerns about the long-term impact on brain development with THC. Also, products containing THC (like Bedrocan), may not be available as per the GMP and GDP guidelines set out by the MHRA for safe prescribing by clinicians. However, we expect that clinical trials on	

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				such products may start with the department of health inviting applications from researchers and should this be available we will inform the family about this. The family enquired about going to Holland to procure such products. We discussed about the need for discontinuing Epidiolex should they wish to proceed with this, in which case this may not be available again for [redacted] Also, there are difficulties in importing such products across borders, which may make it difficult for the family to give this to [redacted] on their return back to UK. In my opinion, we should continue with Epidiolex, which is researched scientifically in other epilepsies and which has shown improvement in [redacted] epilepsy. " So, it was clear I was not going to obtain a prescription from the NHS. when you are left with the stark choice of the death of your child potentially, or brain damage you have to do all you can as parents to fight for them and at least try a product that you have seen working for others. I followed the story of Alfie Dingley and his mother Hannah and I knew the success he was having, and I knew he was getting his prescription via the NHS. I am so pleased that this little boy is getting relief form his seizures, and so he should be but I think we need to ask the question why is it good for Alfie and the other 1 patient who has access via the NHS, but not for the thousands more who need it? Why is it not good for [redacted]? I decided to find a campaign group and fight for my son to have access and this is when I joined End Our Pain. We attended Parliament in March and met with the secretary of State for Health and he promised us he would help. We are still awaiting this help nearly 6 months on. In [redacted] I decided I could not live with myself if I had not at least tried this medication for [redacted]. After all what did we have to lose? The only thing I was worried about losing was [redacted], so we took him to see a private Dr in London. This Dr was well informed of the law change of November 2018 and knew it was her right as a Dr to make a clinical judgement as to whether a patient should be prescribed. This Dr's clinical letter said, "due to this Childs hopeless condition, I feel it is right to prescribe him with medical cannabis on compassionate grounds." We also all agreed that medical cannabis was a good option for [redacted] as he originally responded so well to Epidiolex a form of medical cannabis and had not responded to anything before that. After a thorough clinical assessment it was agreed that [redacted] would commence Bedrolite, (CBD)I had also looked into adding Bedica (THC) however this wonderful Dr thought it best we just commence on Bedrolite as it has a very small quantity of THC in anyway and I trusted her opinion, after all she was the only Dr willing to listen to me about medical cannabis. [redacted] is currently responding well on the small amount of THC he is getting from his Bedrolite CBD. He is responding better than he did to Epidiolex and I imagine this is due to Epidiolex being and isolate and Bedrolite being a whole plant product, but also crucially that it contains an element of THC. So, we commenced on 130mg of Bedrolite per day via a private prescription this cost us £2200 for 1 months' worth of medication. It was worth every single penny. As the difference to my child is immeasurable. [redacted] responded so well that in [redacted] we increased to 150mg per day meaning we needed an extra bottle per month and he would need 5 in total at a cost of £550 per bottle. How could we continue this? We were already fundraising to meet his medical bills but these prices were unsustainable. We knew that if we were to travel to Holland it is £180 per bottle, but then we would be criminalising ourselves. I am employed in the finance sector by a major bank and [redacted] is employed by a firm of solicitors, criminalising ourselves was not an opinion as instant dismissal would occur if we had a criminal record. Not to mention the worry of this now literally lifesaving medication being confiscated at Border Control. So we had to do it legally and in the U.K. I started approaching local pharmacies to see if they could do it cheaper than £550 and the lowest we got was £450. This month [redacted] prescription is going up to 180mg and we will need 6 bottles this	

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				will cost £2700. [redacted] story is followed by a charity, this charity was amazed by the progress in my son that they have offered to pay for the next few months of oil for [redacted] whilst we build up our savings pot through fundraising again, as from May to June we spent over £7000. Thank god this charity stepped in as we were just thinking about selling our family home to keep my son alive. The family home we saved so hard to buy before starting a family. I still live in fear of how we will carry on paying once the charity stops helping later this year and my family, friends and in fact perfect strangers hold regular fundraising events to build up his medication fund. This is an added stress to an already stressful life, at a time I should be able to enjoy my son and the progress he is making. We should not be begging for money off the general public to keep my son well. Experience post Bedrolite I believe this to be the most important part of this letter. This is imperative to our plea for Bedrolite on prescription. Since [redacted] has been using the product he is showing positive signs as you now know. From the diary we keep we noticed him becoming more alert almost immediately, however we did not want to get our hopes up. By day 5 there was no denying it so we recorded it in the diary. He began interacting more & vocalising. [redacted] never really vocalised since his hospital stay, as was so sedated from rescue medication. By the second week we noticed that his rapid eye movement was less rapid, still abnormal movement but was able to focus for longer periods & reacting to his sensory toys & us as his parents. It was also around this time that he started smiling more & we noticed he was generally happy. Also though [redacted] didn't really cry very often sometimes he could go weeks without crying & we noticed that he was crying appropriately, if tired or hungry. He also cries now when he has a tonic seizure which is new as he never did this before, again showing he is aware & has emotion. By week 3 we noticed his tonic seizures where less frequent however he was still having the same amount of myoclonic jerks. This was a massive milestone for us as since [redacted] needed Chloral Hydrate as a rescue when falling asleep every night. This was due to him just having repeated tonic seizures when falling asleep. Since being on Bedrolite [redacted] no longer needs Chloral every night due to the tonic seizures reducing. As I write to you today [redacted] has not needed Chloral Hydrate for over 4 weeks. He has not needed buccal midazolam since starting Bedrolite. He now falls asleep independently. So he no longer utilises his special prescription for Chloral Hydrate or midazolam as he no longer needs to be rescued from seizures. This is also a saving to the NHS. By week 4 his right arm had completely stopped the constant focal seizures & moving. We are now at a point where some days he has no tonic seizures at all. A huge improvement from up to 10 per day I hope you would agree. Reduced tonics and reduced myoclonic jerks. We have a happier more alert & vocal child. We also see [redacted] determined to lift his head when on tummy time which he has never done before & he is managing to support his head for short periods. He is making more appropriate movements with both his arms & legs & grasping my finger which he had not been doing for a very long time. He has recently passed his video fluoroscopy and we have introduced a pureed diet. To feed a child orally when you haven't for nearly a year is beyond a miracle. Despite all evidence supplied to [redacted] medical team we were declined a prescription again in [redacted] by a specialist panel that had been set up by his hospital Trust. There reasons are as follows:	

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				"You informed the Trust, via email, that [redacted] started treatment with Bedrolite (a THC containing CBMP) on [redacted]. The product was prescribed privately by Dr [redacted], a paediatric neurologist working at [redacted] Hospital in [redacted]. The members of the panel reviewed all the available evidence for the prescription of Bedrolite in children with drug resistant epilepsy. The panel also reviewed your statement, the statement of professionals involved in [redacted] care and videos of [redacted] that you sent us. Based on our review of the evidence of efficacy and safety of THC containing CBMP's in children with refractory epilepsy and in line with the BPNA guideline regarding CBMP's, the panel concluded that we are unable to continue this prescription from [redacted] Hospital." This came as a massive blow to us, as we also got statements from other medical professionals to confirm the change and positive progress he is making. His community matron very kindly wrote a statement outlining his progress. His physical therapist did and several nurses from the [redacted] where he attends respite. Despite these statements and my own statements and actual video evidence, These were ignored due to restrictive guidelines and as you can see the BPNA interim guidelines were quoted. My local MP has also been very supportive and even contacted the hospital himself to address the matter. He also had to address the issue that I was actually threatened by his current consultant with safeguarding when I informed her that I had commenced Bedrolite under a Private prescription from a paediatric neurologist with over 20 years' experience. Of course, safeguarding where never contacted because the threat was ludicrous and outrageous that we were subjected to such a threat, however I believe it is imperative you know what parents are dealing with. Trusts are stopping their Dr's from prescribing and setting up Panels within the trust, to take away the decision making from clinicians and these panels are declining based on the interim guidelines provided by the BPNA and no doubt will do the same now based on NICE guidelines if these issues are not addressed before the official release date. On 01/11/2018 hopes and expectations were raised for many families and sheer joy was felt by most including myself when the decision was taken to move Cannabis from Schedule 1 to Schedule 2 and it was finally recognised as having medical benefits. In reality though this has made no difference to families like my own. Not 1 single new prescription has been given for medical cannabis other than Epidiolex since that date to children with infractory epilepsy to my knowledge. The law was not changed to reflect Epidiolex is was changed to make medical cannabis accessible to those that need it but guidelines are preventing this. It became quickly apparent that the law change meant nothing and quickly the feeling and Sense of desolation and despair returned. My own mental health has been affected by the continuous refusal of a medication that is clearly working for my son and many others. I have thoroughly read the proposed NICE guidelines over and over and I have a major worry. There is a constant referral to the need of evidence via Double Blind Randomised Controlled Trials, whilst this may work for children who are not already benefiting from cannabis what about the ones that are? What about my son||? What happens when I can no longer finance £2500 a month? the medicine (Bedrolite) is working for [redacted]. I hope you would agree that it is morally wrong to wash this medication out and then risk deterioration, death or irreversible brain damage by commencing an RCT and potentially giving him a Placebo or to trial a pharmaceutical product when Bedrolite is working. I have already mentioned that I cannot understand the insistence of RCT's for cannabis anyway when conventional drugs (which haven't worked) are being prescribed as "specials" for children/infants of very tender age like [redacted] for whom they were not tested or designed. [redacted] has certainly been prescribed many of these medicines perhaps you could provide me with an explanation as to why Cannabis based medicines are being treated differently?	

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				Why are we not adopting the methods used in other countries around the world that have already built evidence? Finally, I would like to finish with a plea and how I feel we could move forward not only for [redacted] but for the other children from within the End Our Pain Campaign who are already benefiting from this medication. Also, for those children that have not been able to start CBMP'S because of financial restraints. I would please ask you to take an open-minded approach and use discretion to adopt CBPM's backed by observational trials funded by NHS and to act on the evidence from myself and other families' experience and offer them hope. Please treat my son as an individual and look at his case independently. We have come to the end of the line for him, we have tried and failed many anti-epileptic drugs, and endured many horrendous side effects. He is not suitable for brain surgery, and not a candidate for the ketogenic diet. There is nothing left to try for him. Although currently I do not need to try something else, as we are having success with Bedrolite a cannabis based medical prescription. I'm a mother in a vulnerable position but for the first time in a long time I go to bed each night not worrying if my son will be alive in the morning. If Dr's are correct and they think [redacted] will not be here for a long-time then please support us as a family by making his time with us as comfortable as possible. I can't continue to fund this medication once the charity stops helping us and as I have already mentioned spent over £7000 of money we raised in 3 months. Please do the right thing for my son and our family and end this living hell and let me enjoy being a mother for whatever time I have with my son. [redacted]	
End Our Pain	Guideline	General	General	**Individual Family Submissions 12 –** [redacted] **Name of Child** – [redacted] **D.O.B** – [redacted] **Age** – [redacted] **Parent** – [redacted] Background: I fell pregnant with [redacted] unexpectedly whilst awaiting IVF treatment. I had a normal pregnancy (apart from gestational diabetes). [redacted] was delivered by an emergency c-section at just under 42 weeks. Once she was born there were no complications Childhood: [redacted] was a miracle baby for me and I was overjoyed at the fact I was finally getting to be a mum, but things quickly indicated something wasn't quite right. [redacted] was very behind in hitting milestones. At first I thought she was blind as she didn't blink if you went a bit close to her face. [redacted] wasn't smiling or trying to roll over when she was expected to [redacted] was initially diagnosed with spastic quadriplegia and referred to our local paediatric unit. There she went under further tests and eventually they diagnosed her with a chromosome deficiency ([redacted]) and cerebral palsy. This was a huge blow to me. I had dreamt of having this beautiful perfect baby and now I was being told all my expectations were dashed. Her chromosome deficiency was so rare that doctors know nothing about it. It is only called [redacted] as it's an [redacted] – there isn't actually a name as it's too rare. The doctors told me [redacted] probably wouldn't roll over, never mind walk or talk. At that moment I honestly felt my heart break. I had no idea how my life was about to be thrown into such chaos. [redacted] didn't develop many skills until the age of about [redacted]. She started to walk and laugh, but had no communication or understanding. We were so grateful that she had developed these skills. But at the age of [redacted] epilepsy struck Epilepsy: [redacted] seizures started very suddenly and progressed rapidly. Her life was dramatically affected by her seizures. She lost all the skills she had learnt and was literally wheelchair	Thank you for taking the time to share details of the care received by your child affected by severe treatment-resistant epilepsy. On an individual level there appears to be evidence that CBMPs have a role. Clinicians can make their own individual prescribing decisions in the best interest of their patient taking into account their values and preferences. The committee considered the evidence in the area. The RCT evidence focused on treatment for particular epilepsy syndromes and the committee agreed that these findings couldn't be extrapolated to other forms of epilepsy. The committee also considered observational studies but agreed that these were of very low quality due to the high risk of bias. Overall, the committee agreed there wasn't sufficient good quality evidence to make population-level recommendations. Research recommendations were made to promote the evidence base in this area. This should include the views of patients, carers and families. The committee agreed that a national or local registry of prescribing practices of CBMs was also needed.

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				bound. When she had her first EEG she was immediately transferred to the care of a paediatric neurologist at [redacted]. The consultant said this was probably the worst EEG she had ever seen. I knew at that moment our lives were never going to be the same. My heart was broken yet again. The next few years are a blur. So much happened in regards to treatment and medications. Her medication over the last 6 years has included: • Sodium Valporate • Topirimate • Keppra • Lamotrogine • Lacosomide • Clobazam • Ethosuximide • Phenobarbitol • Phenytoin • Prednisolone • Rufinamide Recent: [redacted] has never responded well to any of the AED's she has been on. In [redacted] hit the worst time of her life. She had lost the minimal skills she had learnt over the years. At one time [redacted] could walk quite well, help feed herself, help get dressed and choose what she wanted between two photos. It was devastating that her seizures had robbed her of these skills that she worked so hard to get. Summer [redacted] was awful. [redacted] was having up to 300 seizures a day. She was requiring rescue medication about 3 times a week and was in hospital for a couple of days at least once sometimes twice a week. I was saying goodnight to [redacted] every night terrified that was going to be the last time. No parent should have to go through that [redacted] her body stopped responding to the rescue medication. She ended up being put in an induced coma (to stop the seizures and give her a chance to rest and recover) and transferred to [redacted] Paediatric Intensive Care Unit. The next day she was taken out of the coma and the seizures returned almost immediately. The doctors then pumped her full of multiple medications to try to stop the seizures, but nothing seemed to help. There was an incident on the ward and [redacted] was sent back to her local hospital for monitoring. That night, her seizures started to get out of control again and she didn't respond to the rescue medication. She was then put on a midazolam infusion and transferred to [redacted] Hospital Intensive Care Unit. This is where we stayed for the next six weeks. During this time it had been announced that the law was changing and medical cannabis would be legal from 2nd November. This was music to our ears. We asked [redacted] neurologist to prescribe and were informed they wouldn't be able to. I pushed for her to be given this medication and on the [redacted] when it was still being refused, I threatened legal action. The following day I was informed they had managed to secure the medication on compassionate grounds for [redacted]. This medication was Epidiolex [redacted] responded well and her awake seizures reduced. She was still having seizures when she slept but they were not severe enough to require any intervention. On [redacted] we were finally discharged from [redacted] Hospital and allowed home [redacted] continued to stay seizure free whilst awake until [redacted]. On this day her awake seizures returned and through the week she deteriorated again. She required rescue medication multiple times over the next few weeks. I then contacted her neurologist to ask if they would prescribe full extract medical cannabis and was told no again	

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				This led me to do things my own way. I was very open and honest with the doctors. I actually have an email from one of them recommending I travelled to Holland to get the medication. I found a paediatric neurologist in Rotterdam willing to see [redacted]. So on [redacted] we flew out to Holland to meet with her. She prescribed the required medication and I collected it from a pharmacy in The Hague. On our return into England on [redacted], Border Force officials were waiting for us. They approached me as I walked towards Passport Control and eventually confiscated the medication worth £4500. This was how desperate I was to help my little girl, I was breaking the law and risking prosecution As it was a [redacted], we couldn't do much about the confiscation. On the [redacted] we made various phone calls and enquiries to try and get the medication returned. [redacted] story was heard in the House of Commons as an urgent question on the [redacted] afternoon. I then received a phone call on the [redacted] from [redacted] hospital pharmacy to say they were expecting the medication to be passed to them in the next 24hours. Exactly a week after it was confiscated, I collected it from a London hospital pharmacy – with no charges <u>Post Medical Cannabis:</u> [redacted] has tried 15 different AED's, she has also had a VNS (vagal nerve stimulator) fitted. Nothing has helped her. The only thing that has reduced her seizures dramatically and given her a new lease of life is full extract medical cannabis. [redacted] is a now a new child. She is back running around the house and learning all the skills she lost last year. Her seizures have reduced from up to 300 per day to a maximum of 20 (on a bad day) [redacted] can now walk around the house again, she can play on her custom built slide in the garden, she just has the freedom and happiness that has been missing for so long. She is starting to re-learn how to help feed herself, how to assist with dressing – minimal things that we didn't think we were ever going to see again. Bedrolite has changed [redacted] life, and also ours too. Our family life is so much better now and I couldn't be more proud of how far she's come Her medication is called Bedrolite. It is made by the company Bedrocan. It is a full extract medical cannabis oil. It currently costs me £2500 per month to supply [redacted] with this medicine We really thought after the law change we would be able to get this on an NHS prescription but this is not the case. [redacted] paediatric neurologist has completed an IFR which was submitted to NHS England and rejected (as the product is not 'in tariff') The NHS are blocking mu daughter from having access to medication which is legal here in the UK but also is saving them thousands of pounds by keeping her out of hospital!! We are pleading with you to help our children. There are some doctors that want to help but they don't feel supported by their trust. This is wrong. What is it going to take? One of these children to die? [redacted]	
End Our Pain	Guideline	General	General	**<u>Individual Family Submissions 13 – [redacted]</u>** I am [redacted], the mother of [redacted]. [redacted] father is [redacted]. [redacted] is [redacted] years old; he has [redacted] epilepsy and his date of birth is [redacted] he has a sister called [redacted] who is [redacted], her date of birth is [redacted] and she is unaffected by [redacted] gene mutation. [redacted] is my first child. The pregnancy was normal, but the birth was difficult. I had a sweep which resulted in an onset of contractions which were all over the place. Due to him being my first child I didn't know they weren't right I do now have had another child. He was born blue with low Apgar score. But he was quickly sorted out and given to me, I breast fed	Thank you for taking the time to share details of the care received by your child affected by severe treatment-resistant epilepsy. On an individual level there appears to be evidence that CBMPs have a role. Clinicians can make their own individual prescribing decisions in the best interest of their patient taking into account their values and preferences. The committee considered the evidence in the area. The RCT evidence focused on treatment for particular epilepsy syndromes and the committee agreed that these findings couldn't be extrapolated to other forms of epilepsy. The committee also considered observational studies but agreed that these were of very low quality due to the high risk of bias. Overall, the

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				him fully for the first three months of his life. He was a settled baby, but I started to notice him becoming unwell at [redacted]. He was constantly sick, never slept well and seemed hungry all the time. I since found out he had a dropped palate bone in his mouth likely caused by his traumatic birth, but this hadn't been picked up. It made it so hard to breast feed and extremely painful. At [redacted]old, I decided to stop feeding him myself as it was so painful. A few days later he had his first seizure. I found him in his bed having a tonic clonic seizure. I had never seen anything like this before. I was terrifying and was the start of a four month stay in hospital. [redacted]did not respond to any anti-epileptic drugs or other interventions during his first cluster of seizures. It is only when we went to [redacted] Hospital, our third hospital during that four months, and they used IV methyl prednisolone, he stopped seizing. He was diagnosed with immune responsive epilepsy and we were sent home to try and get him better. They said it could be an isolated attack but wed must wait and see. [redacted] had no more seizures after that for [redacted], then he had another awful cluster which only responded to steroids again even though the doctors still tried other interventions we always went back to steroids. These clusters continued to get worse with age and by age [redacted] [redacted] was having a cluster every week, requiring IV steroids, at times long hospital stay, A and E, and ambulances. I was taking [redacted] into hospital every week in an ambulance at night, it was terrifying. He had to be quickly treated, the consultant would have to find a vein for his IV, whilst [redacted]was screaming and seizing. I was diagnosed with PTSD by a counsellor who I was seeing whilst I was pregnant with [redacted] in [redacted]. It was not post trauma it was current. He told me it's the gift that keeps on giving. He was right, the trauma never ended, the fear and worry of how [redacted] may survive what he lived through. We had no support at home other than our families, we had no social worker, no respite and no counselling. [redacted] was diagnosed with a condition called [redacted] when he was[redacted]. It is genetic condition that only usually effects girls, so he hadn't been tested for it. It is non-inherited, and only 9 boys are diagnosed in the world. It is extremely rare therefore, there is no research apart from low grade projects from the [redacted] in America. Most doctors I have spoken to know nothing or very little about [redacted], so I became the expert in his condition by living it every single day. [redacted] presents with extremely refractory epilepsy, learning difficulties, behaviour problems and speech delay. [redacted]has had the following medications prescribed to him: • Topiramax • Keppra • Steroids • Clobazam • Epilim • Phenobarbital • Lorazepam • Chloral Hydrate • Stirepentol • Zonisamide • Ketogenic diet • Immuglobulins • The above medications caused him the following side effects – • Hair growth • Swelling • Bruising • Bowel problems • Aggression • Hitting	committee agreed there wasn't sufficient good quality evidence to make population-level recommendations. Research recommendations were made to promote the evidence base in this area. This should include the views of patients, carers and families. The committee agreed that a national or local registry of prescribing practices of CBMs was also needed.

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				• Screaming • Risk adverse • Not drinking • Not sleeping • Sleeping too much [redacted] had clusters every 8 months, from the age of [redacted] until he was [redacted] At this time, he was on Keppra and pulse steroids. [redacted] condition is cyclical in nature, so it is hard to know whether these drugs helped. In summer [redacted] when [redacted] was put on Epilim and clobazam he was seizure free from may to [redacted]. But then in [redacted] the clusters came every week. We tried to put the dose up, but it didn't work, we added another AED phenobarbital that didn't help either. By age [redacted] [redacted] was in hospital every week having hundreds of seizures. He was having up to 25 doses of IV steroids every month. He had absolutely no quality of life. He was either very ill in hospital or at home coming down off drugs prescribed in hospital. Causing horrendous side effects. He simply could not engage in any sort of normal life. In [redacted] I started to research alternatives for steroids. [redacted] doctors kept saying to me if the seizures don't kill him the steroids would. I knew if he did die, I had to know I had done everything in my power to give him the best life possible and to keep him alive. I kept finding patients talking about using medical cannabis to treat seizures. In fact, the first noted us by a mainstream doctor was from Dr OShaunessy in 1878 where he showed epilepsy responded to cannabis oil. I started to talk to families from across the world who were using cannabis products with their children and seeing miraculous results. I started talking to [redacted] doctors about it. We were told about a trial for a product called epidiolex which was a cbd only medicine. I asked our neurologist to apply to use it for[redacted]. We tried three times and each time [redacted] was refused as he didn't fit the criteria. I then started looking at other countries and we found that [redacted] could be prescribed medical cannabis in Holland. Because it is part of the EU it meant any emergency care was free so it would be much easier to get there on a smaller amount of money if we didn't have to pay any health care costs like in Canadian. In [redacted] was prescribed Steripentol, this made him have seizures pretty much every day, this is when I snapped, I had, had enough of filling him with drugs that didn't work and made him much worse. We raised money from [redacted] to [redacted] and left on the [redacted] and we travelled to Holland to see the Paediatric Neurologist who we had found, and she was willing to treat [redacted]. The main reason we did this is to save our son, we could not watch him suffer or die without trying this treatment we would have never forgiven ourselves. When [redacted] became unwell, I started to really look at the drugs he was treated with. I started to question what he was given and why. I started to research many of the drugs he was given, and some were not licensed, and some were not for the indication that it was prescribed for. I started to feel very concerned that in fact the drugs were making [redacted]	

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				worse. The side effects of many of the drugs that [redacted] has taken are horrendous. Some in fact can cause psychosis and seizures. If they didn't work, I was now questioning why I was giving them to him with such awful risks attached to the prescribed drugs. [redacted] started on medical cannabis in [redacted] in Holland. We had used other CBD legal products in the UK with [redacted] which are made from hemp, but they did not help. When we arrived in Holland the paediatric neurologist told us to keep everything as it was and add in the CBD. At the time [redacted] was on a small dose of Epilim at 300mgs twice a day and 5mgs twice a day of Clobazam but no other drugs or interventions. When we arrived in Holland [redacted] was in hospital every week with seizures. We started Bedrolite CBD oil on [redacted]. You must start low and increase the dose slowly to ensure that you find the right dose and to give the receptors chance to work. Once we were five weeks into [redacted] treatment and we were at 150mgs of CBD oil he went 17 days without a cluster of seizures. As we continued to increase his dose he started going longer between seizures. We added in a very small dose of extra Bedica THC oil and the longest [redacted] went in Holland was 41 days without a seizure. Also, when he did have seizures, he would only have two or three seizures and they were very easy to stop he didn't need lots of medications. Cognitively he was improving too and playing more alone. From [redacted] he was completely seizure free until the following [redacted]. Since then we have seen some seizures, but they are still very small and easier to stop. This is due to possible tolerance to the CBD product as this can happen like any other drug with refractory epilepsy. Due to there being no industry in the UK [redacted] is not able to try another CBD. He is now prescribed THCA which non psychoactive and has stopped the THC bedica oil. He has so far responded well to the THCA and cannabis medication remains the only product which [redacted] responds to, but it does need adjusting which is why it is so important to have expertise in the UK to advise patients. We have seen absolutely no adverse side effects in [redacted] since he has been using medical cannabis. It has been noted that another CBD product has seen lots of side effects in the trial. This is most likely due to other ingredients in the medication not the CBD. The WHO have reported that CBD has little side effects. Before we went to Holland, we got the approval of our paediatric neurologist. He told us if we went and it helped, he would apply for a license and prescribe it. We were so happy as he was so supportive. We called him in [redacted] to tell him how well [redacted] had responded. He was overjoyed. We had an initial report from our Dutch neurologist, and he was happy with this. Two weeks after this calling our paediatric neurologist called us in Holland, he was nearly crying. He explained that he had be warned off from helping us and that he could lose his job or be up at the GMC if he tried to prescribe a full extract cannabis product. We were also very upset. We tried hard to engage with professional in the NHS and the Home Office through our MP, whilst we were in Holland but unfortunately, we didn't really get far. So, once we decided to take [redacted] off the THC element of his medicine and come back to the UK, we arranged another appointment with [redacted] new neurologist as unfortunately his old one had to go on long term sick leave. We met with the new neurologist and showed him the report we had from our neurologist in Holland. It was extensive and showed a clear improvement in [redacted] symptoms. Our new doctor was open to trying to help us, but we had to meet a very senior clinician with him first at Great Ormond Street Hospital. During that meeting I explained the huge improvement in [redacted] whilst in Holland. I was told that [redacted] could have Epidiolex now, I explained that he was refused three times before we went to Holland. I asked why now he fits the criteria no one could answer this. The doctor we met told me I would never get a prescription on the NHS for the medicine [redacted] was on. Our neurologist happily agreed with us that [redacted] should have a prescription and he applied to the hospitals internal medicines board to see if he could prescribe just the Bedrolite	

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				CBD which we had agreed with him we were happy to use without the extra thc as a compromise. This was turned down and we were told we must use Epidiolex only. It is worth noting that Epidiolex has no RCT data for [redacted] condition also it is against GMC guidance to remove a patient from a medicine which is working to another one without hard evidence it could be helpful to the patient. During our campaign when we were home, we managed to meet the Prime Minister Theresa May, who agreed that [redacted]doctors could apply for a license through the Home Office for personal use of the medicine he was on in Holland. Our doctor at our hospital was not allowed to help us so we then met [redacted]who was happy to carry out the licensing process along with our importer, local paediatrician, pharmacist and GP all who were supportive of [redacted] having this medicine. [redacted] was issued the first license for medial cannabis on [redacted]and this was transferred to an NHS prescription on the 1st November 2018 when the law changed. We now have an NHS prescription which is obtained through our local pharmacist as per any other prescribed medicine. Bedrolite CBD is 100mg per ml of CBD, 0.3mgs of THC per ml and has other minor cannabinoids and terpenes which help with the entourage effect. It is made by Transvaal apotheek to GMP standards and the flower is provided by Bedrocan. We fund raised from [redacted]through to [redacted]when we returned home. We spent £30K whilst we were in Holland. This also included our life savings and family money given to us. We lived in Holland for five months to prove this helped [redacted]. We left our friends and family. [redacted] shut down his business. We spent every penny we had. It was extremely stressful leaving our support network and having no one to help us in Holland. It put a huge amount of pressure on the whole family and the children. They missed their family, and both missed time at school and nursery. The guidance which has been issued to date surrounding medical cannabis have been very restrictive and do not fairly represent the facts about medical cannabis. I would like to see the NICE panel consult with colleagues around the world where medical cannabis is legal to understand their views on prescribing. I would like to see guidance from NICE which truly represents the urgent need for patients like my son [redacted], there are over 21K children in the UK with refractory epilepsy. They have nothing more to try. Medical cannabis should be available to them. To me NICE do not understand the impact of the negative guidance they have released. They may say that clinicians can still prescribe but they simply will not without more support from NICE, the GMC, NHS England and the Government. The Government changed the law and the Home Secretary made a promise to the UK people that this medicine would be available to patients who urgently needed it. The reality is that this has not happened, so I would like to see all agencies involved working together to ensure that patients can get access. Especially for those families who have now secured private prescriptions for their children at great expense. These children are getting better, they are the evidence and their parents should not have to find thousands of pounds a month to keep their children safe. [redacted]	
Epilepsy Action	Guideline	10	3 - 14	See comments 7 & 8 below	Thank you for comments. Responses to each of your comments are included in the table below.
Epilepsy Action	Guideline	16	25 - 29	We are concerned that this comment is not representative of the available evidence around potential adverse events in trials of cannabis-based medicines for the treatment of epilepsy. The Chen (2018) open label cohort study from which the statistic seems to be taken is deemed by NICE to be of 'very low' quality (Evidence Review D, Appendix K). The abstract of the original article (https://onlinelibrary.wiley.com/doi/abs/10.5694/mja18.00023) notes that of the thirty-nine patients reporting at least one adverse event 'many were deemed unrelated to cannabidiol treatment'. Epilepsy Action would recommend removing this statistic from the draft guidance.	Thank you for your comments. The discussion over adverse events represents an overview of what was reported in each of the included studies in addition to the committee's discussion and clinical experience. This section includes the statement that it was not possible to determine how many of the adverse events were due to cannabis-based medicinal products in order to highlight that not all adverse events may have been as a result of treatment.

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Epilepsy Action	Guideline	17		We would encourage the inclusion of a recommendation around monitoring and capturing data of patients with severe and treatment-resistant epilepsy who are currently accessing CBMPs on the NHS or who subsequently receive such treatments through alternative access routes. The lack of evidence, specifically over a longer time period, is a persistent barrier and whilst likely to be of low-quality, any such additional evidence should be gathered. We would also encourage any recommendations around monitoring and data capture of paediatric patients accessing CBMPs to include prospective monitoring of neurodevelopment. Anecdotal evidence suggests that some specialist clinicians have specific concerns about the potential impact of CBMPs on the developing brain (https://www.england.nhs.uk/wp-content/uploads/2019/08/barriers-accessing-cannabis-based-products-nhs-prescription.pdf, para 26). Much of the available research around the potential neurodevelopmental impact of cannabis use in young people related to recreational cannabis use (https://ajp.psychiatryonline.org/doi/10.1176/appi.ajp.2018.18020202). Recreational cannabis is not directly comparable to CBMPs as per the legislative definition. Such monitoring and subsequent reporting would help address the gap in clinical research in this area and support specialist clinicians to feel confident in prescribing CBMPs, where clinically appropriate.	Thank you for your comment. The committee discussed the need for a national register and recommended that prescribers should record details of treatment, clinical outcomes and adverse events for people prescribed cannabis-based medicinal products in a local or national registry.
Epilepsy Action	Guideline	17	16 - 23	We would recommend broadening the scope of research recommendations in the longer term to include other active compounds found in the cannabis plant such as THCA. There are over eighty active compounds present in cannabis and necessary research should be done to explore the therapeutic potential of as many relevant compounds as possible. This would also be within the remit of the guidelines given the legal definition of CBMPs as • A product that is or contains cannabis, cannabis resin, cannabinol or a cannabinol derivative • It is produced for medicinal use in humans; and • It is a product that is regulated as a medicinal product, or an ingredient of a medicinal product.	Thank you for your comment. While there may be benefit in looking at the other active compounds, the committee felt there were other priorities for research at this stage.
Epilepsy Action	Guideline	5	11	There is some high-quality clinical evidence of safety and efficacy in this population although such evidence is limited to randomised controlled trials (RCTs) of cannabidiol/ CBD (Epidyolex) for Dravet syndrome and Lennox-Gastaut syndrome. While acknowledging that cannabidiol/ CBD (Epidyolex) for these indications is not in the scope of these draft guidelines, this would still be considered relevant to the defined scope and should be appropriately referenced.	Thank you for your comments. Although this guideline could not comment directly on the use of CBD for people with Dravet and Lennox-Gastaut syndromes, this evidence was still considered by the committee. A cross reference to the technology appraisal for epidiolex will be added when published. More information on these studies, and the committee discussion relating to this, can be found in the evidence review for severe treatment-resistant epilepsy.
Epilepsy Action	Guideline	5	10 - 20	While acknowledging that the committee have been unable to make a recommendation on the use of cannabis-based medicines for severe and treatment-resistant epilepsy there remains a need for some guidance. The current draft recommendation, as set out in this draft guidance document, does not rule out prescribing cannabis-based medicines for some epilepsies on the NHS. Some guidance for clinicians who may wish to explore prescribing these drugs through NHS routes other than routine commissioning is necessary.	Thank you for your comment. Section 1.5 of the guideline provides prescribing recommendations that would apply where specialist clinicians wished to prescribe CBMPs on an individual basis. Clinicians can also still make their own individual prescribing decisions in the best interest of their patients.
Epilepsy Action	Guideline	7	15 - 16	There is some evidence of potential for interaction of cannabis-based medicinal products with some antiepileptic drugs (AEDs) such as clobazam and phenytoin (https://www.sps.nhs.uk/wp-content/uploads/2018/11/Cannabis-based-medicinal-products-potential-drug-interactions-FINAL.docx). Recommend referencing this in this section.	Thank you for your comment. Because the committee did not make any recommendations, they did not provide further specific information about drug interactions. However, recommendation 1.5.5 states that prescribers should take into account the potential for interaction with other medicines.

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Epilepsy Action	Guideline	General	General	We are concerned that the current inability of NICE to produce clinical recommendations on the use of cannabis-based medicines for people with severe and treatment-resistant epilepsies has meant that no clinical guidance for these indications have been included in the draft document. In light of the draft guideline not recommending against the use of cannabis-based medicinal products for these indications, whilst also not recommending their use, specialist clinicians who may wish to explore these treatment options as a last line treatment where appropriate and after a full and frank discussion of the limited evidence base and potential adverse effects have been afforded no guidance around issues such as contraindications. The inclusion of limited clinical guidance addressing in line with the suggestion above and caveated with the inability of NICE to make a recommendation in light of the lack of available evidence would be beneficial to clinicians and patients.	Thank you for your comment. Section 1.5 of the guideline provides prescribing recommendations that would apply where specialist clinicians wished to prescribe CBMPs on an individual basis. Clinicians can also still make their own individual prescribing decisions in the best interest of their patients.
Epilepsy Society	Guideline	5	1.4	We support NICE's decision not to make a recommendation on the use of cannabis-based medicinal products for severe treatment-resistant epilepsy, but rather to recommend further research to inform future practice. There is a real need for new medications to treat epilepsy, and cannabis-based medicinal products may in the future provide a treatment option for some. But it is important that this is based on robust research that will give both the clinician and the person with epilepsy, or their families, the confidence that this is the best treatment option for them. As with all new medications, it is important that the therapeutic potential of CBMPs are robustly investigated and regulated. Anecdotal evidence suggests that some cannabis products containing both CBD and THC have anti-epileptic effects and there are reports of positive results for children with severe epilepsy. We endorse the view of the Association of British Neurologists (March 2019) that "anecdotal evidence should not determine treatment policy for the population as a whole, and products with higher concentrations of THC may cause significant damage to the developing brain."	Thank you for your comments and the support for this guideline.
Faculty of Pain Medicine of the Royal College of Anaesthetists	Evidence	General	General	The guidance is severely limited by the lack of quality evidence. For unlicensed products (e.g. CBD) this hopefully will act as a trigger for the basic clinical research that is needed. In products that have an old license (not necessarily for pain,) core safety information will exist. Occasional use for pain (prescribed by specialist pain services by clinicians on the Specialist Register with expertise in this area) currently exists. The onus of creating a large randomised controlled trial (RCT) or analogous research for a substance with a likely low Number Needed to Treat (NNT) risks causing individual harm without any real prospect of conducting trials to the rigour required for a new license. In this scenario (e.g. Nabilone), then a mandatory collection of data perhaps along the lines of databases for rare diseases would be a welcome consideration.	Thank you for your comment. The guideline has added a recommendation advising prescribers to record details of treatment, clinical outcomes and adverse effects for people prescribed cannabis-based medicinal products, using local or national registries. This will enable feedback from patients to feed into the evidence base.
Faculty of Pain Medicine of the Royal College of Anaesthetists	Guideline	4	12	Concerns over the recommendation to not offer nabilone. This has a role in chronic neuropathic pain management in carefully selected cases alongside other pharmacological management of chronic pain. Importantly, patients already stabilised, often for a long time after failure of other NICE recommended treatments, will likely have their effective medication withdrawn. Explicit consideration needs to be given to those already on treatment. It would be helpful to have advice on continuing prescribing or deprescribing for patients already prescribed cannabinoid products after this guidance has been published.	Thank you for your comment. The guideline recommends that all those receiving treatment before publication of this guidance can continue to receive treatment. Clinicians can also still make their own individual prescribing decisions in the best interest of their patients.
Faculty of Pain Medicine of the Royal College of Anaesthetists	Guideline	5	1	The guidance states that "CBD should not be offered to manage chronic pain in adults unless it is part of a clinical trial". This appears to be at variance with line 20-24 on page 14 which states 'Prescriptions of cannabis-based medicinal products for chronic pain are currently rare. GPs refer people with chronic pain to specialist pain services where clinicians on the Specialist Register with expertise in this area decide whether cannabis-based medicinal	Thank you for your comment. We have revised our recommendations for prescribing. The guideline recommends that all those receiving treatment before publication of this guidance can continue to receive treatment. Clinicians can also still make their own individual prescribing decisions in the best interest of their patients.

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				products should be prescribed. The new recommendation might reduce the number of these prescriptions.' The words "might reduce" seem inaccurate. As the guidance is written, the new recommendations "will stop" prescriptions. A clarification is needed as to whether Specialist Pain physicians can prescribe/continue/initiate licensed cannabinoid medicines in refractory cases or whether these have to be initiated in a clinical trial.	
Faculty of Pain Medicine of the Royal College of Anaesthetists	Guideline	General	General	In principle the Faculty agrees with the recommendations and supports the endorsement of proper research, for safety, efficacy and licencing. We would welcome advice on continuing prescribing or deprescribing for patients already prescribed cannabinoid products after this guidance has been published.	Thank you for your comment. The guideline recommends that all those receiving treatment before publication of this guidance can continue to receive treatment. Clinicians can also still make their own individual prescribing decisions in the best interest of their patients.
Guys and Saint Thomas' Hospitals Foundation NHS trust		20		Economic evidence and cost-utility analysis well balanced	Thank you for your comments and support.
Guys and Saint Thomas' Hospitals Foundation NHS trust		31	19	Important to state that there is a wide variation in outcome measures in 'spasticity'. Focus on adverse events particularly important in Paediatrics – safety as important as efficacy Patient related scales. Ashworth and tardieu scales are recognised as a very poor inter and intra observer reliant measure	Thank you for your comments. Different measures of spasticity, including issues associated with the Ashworth scale, are discussed in the quality of the evidence section of the evidence review.
Guys and Saint Thomas' Hospitals Foundation NHS trust		32-35	29	The committee pass no comment on Paediatric use, a comment about lack of sufficient grade of evidence to date would be useful. The committee have focussed on MS and lost Paediatric use altogether	Thank you for your comment. The committee did not make any recommendations for babies, children and young people as no evidence was found for paediatric spasticity. The committee did not feel they could comment further on this population group. The research recommendation includes both adults and children which should help to make evidence-based decisions in future guideline updates.
Guys and Saint Thomas' Hospitals Foundation NHS trust	General	General	General	Agree with position statement and lack of reasonable grade RCTs in child population – there are a number of case series in Paediatric Spasticity – either Cerebral Palsy or acquired. Initial comment is made that if less than 5 RCTs are found then cohort studies would be reviewed – there is no evidence of this. There was a good summative paper in Developmental Medicine and Child Neurology this year (Nielsen et al DMCN 61(6) 631-638) focussing on the cohort studies that have been reviewed. There is an abstract from an RCT which showed no benefit in Cerebral Palsy – publication of paper is pending (Fairhurst, Kumar, Turner) A greater discussion of the positive and negative factors of tone seen upper motor neurone syndrome – many clinicians are veering away from the term spasticity – what are we using the Cannabinoids for?	Thank you for your comments. Given the lack of RCTs for spasticity in children a search of observational studies was conducted. However, there were no studies that matched the inclusion criteria for this review. We do not include abstracts as part of our review process but any RCTs that results from this should form part of future updates. Thank you for highlighting terms being used in practice. The scope of this guideline focuses on people with spasticity. This term has been used in the evidence reviews and recommendations. The committee did not raise using an alternative term for spasticity in their discussions.
Guys and Saint Thomas' Hospitals Foundation NHS trust	General	General	General	In the absence of RCTs in Children we would ask for a research recommendation, also discussion about the ratios of CBD to THC for this use	Thank you for your comment. We have written a research recommendation for children who have persisting pain. Furthermore, in the case of intractable nausea and vomiting some evidence was identified in children. This evidence was predominantly on the use of nabilone which is currently not licenced in children. The committee noted that further research in children is required and therefore drafted a research recommendation. The committee did not make a research recommendation regarding the ratios of CBD: THC as improved evidence on effectiveness was considered a priority. Ratios of CBD to THC could then be examined further
GW Pharmaceuticals	Evidence Review C	23	42	Within the model, the treatment effects of THC:CBD spray were derived from the meta-analysis of four randomised controlled trials (RCTs) of THC:CBD spray in patients with MS spasticity (Collin *et al*., 2007, 2010; Novotna *et al*., 2011; Markova *et al*., 2019) by calculating odds ratios compared to placebo from the RCTs. We would question the inclusion of the two Collin *et al*. studies in this meta-analysis, given that the Novotna *et al.* and Markova *et al.* studies better reflect the use of Sativex in the real-world, and only include patients who are on the licensed dosing schedule. Novotna *et al.* has an enriched trial design which was both suggested, and deemed appropriate, by the Medicines and Healthcare products Regulatory Agency (MHRA). In	Thanks for your comments. No network meta-analysis (NMA) was conducted for this question; rather, RCTs comparing THC:CBD spray were combined in pairwise meta-analyses. The enriched enrolment trials were highlighted in the forest plots (see spasticity evidence review) and brought to the attention of the committee. This was not to dismiss the evidence but to generate discussion over the methods which are different to a traditional RCT. While there was discussion over the potential for these studies to overestimate the treatment effect, it was also argued, as you suggest, that this trial design better reflects clinical practice. As a result, these findings were still considered as a part of the evidence

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				correspondence with the MHRA, they stated that "it is acknowledged that enrichment designs can over-estimate the magnitude of the mean treatment effect and are therefore discouraged in most situations. However, in this case the enrichment design reflects proposed clinical practice, which is that only patients with an initial response to Sativex will receive treatment beyond the trial period." They also stated that "the difference between active and placebo should be a fair reflection of efficacy in the population that will be treated with Sativex in the medium- to long-term" (Correspondence from MHRA to GW Pharma Ltd, dated 15th August 2007, Ref: 090/THC + SCBD (Sativex)). This is in line with the Summary of Product Characteristics (SmPC) for Sativex, which specifically directs prescribers to cease treatment after 4 weeks in the event that the patient has not achieved clinically meaningful benefit (Sativex SmPC). The German sick funds were heavily involved in the design of Markova *et al.*, asking for the Novotna *et al*. design to be further refined via the inclusion of: 1. The possibility for standard of care (SoC) received to be titrated (to better reflect the effectiveness of SoC in the 'real world') 2. The inclusion of a washout period after the screening phase to avoid the effectiveness of SoC being overestimated through any remaining effect of Sativex. The Collin *et al.* 2007 and 2010 studies did not have these enrichments which were requested by external assessing institutions leading to the 'real-world' relative effectiveness of Sativex being underestimated. Furthermore, these studies did not use the licensed dosing schedule. Therefore, we suggest that Collin *et al.* 2007 and 2010 studies be removed from the analysis, since Novotna and Markova *et al.* are more appropriate studies to determine the effectiveness of Sativex for patients with MS-related spasticity in the NHS.	base and helped to form the committee's opinion that THC:CBD spray appears to have benefits for people with spasticity. It is notable that, despite some a priori grounds for suspecting heterogeneity of effect between trials of different design, there was no evidence that results were statistically different between enriched-enrolment and conventional RCTs for any outcome (see 'test for subgroup differences' in each forest plot – appendix F). The decision not to recommend THC:CBD spray was therefore made based on lack of cost-effectiveness rather than questions over clinical effectiveness or trial design. We acknowledged the limitations of the heterogeneity of the 4 RCTs. Hence, the economic analysis reported sensitivity analysis which tested different treatment effects (ORs), such as pooled OR from two enriched trials only and pooled OR from two non-enriched trials only. As explained in the 'model structure' section of appendix M, the initial cycle of the economic model simulates the 4-week run-in phase that is used in clinical practice. Patients enter the model before trying THC: CBD spray and then receive treatment for 4 weeks. Most non-responders are assumed to discontinue treatment; however, the model allows a small proportion of patients to continue treatment as the trials on which its estimate of response is based had more restrictive response criteria (30% improvement) than the 20% improvement criteria specified within SPC. The committee was also aware that Collin et al. 2007 and 2010 did not have a restrictive dose of a maximum of 12 THC: CBD sprays per day. As you pointed out, the mean daily dose of THC: CBD spray in Collin et al. 2007 and 2010 were lower than 12 sprays per day (9.4 and 8.5 respectively). Therefore, the committee agreed that the population from Collin et al. 2007 and 2010 are still relevant to the clinical and cost-effectiveness analyses. We acknowledged that there might be some patients used daily dose above 12 per day. Therefore, a sensitivity analysis was reported when excluding Collin et al. 2007 and 2010.
GW Pharmaceuticals	Evidence Review C	24	24	In its approach to estimate cost saving accrued by reducing spasticity symptoms, the NICE model assumes that only 25% of the resource use from Stevenson *et al*. 2015 could be attributed to spasticity alone, which we believe is a significant underestimation and an overly conservative assumption. The aim of the Stevenson *et al.* survey was "to quantify the impact of multiple sclerosis (MS) spasticity on healthcare resources and the associated costs at different levels of severity in people with multiple sclerosis". The questions in the survey (see questions Q2 to Q10 of Stevenson *et al*'s supplementary materials) were specifically focused on healthcare resource use for "primarily spasticity related problems". In addition, the results show an extremely strong relationship between spasticity severity and costs accrued. Given this extremely close relationship and the wording of the survey questions, it seems more appropriate to consider that up to 100% of the reported costs are related to spasticity. We understand that NICE might choose to take a more conservative assumption than 100%. However, we propose that, since the primary objective of the study was spasticity-related costs, the methods and the results would together indicate that ≥75% would be a more reasonable assumption for the base case. We consider that NICE's assumption of 25% undervalues the costs associated with spasticity in MS, and is an unreasonably conservative assumption in its value assessment of Sativex.	Thank you for your comments. Based on committee consensus, the committee agreed that the resource use estimated in Stevenson et al. 2015 cannot be said to be 100% attributable to spasticity alone. The committee felt that the vignette from the health care professional survey could be misleading as it explicitly stated that the disability described in the health states was caused by spasticity only. The committee agreed that some of the physical disability specified in the vignette, particularly in the most severe health states, would have involved multiple other features of the underlying MS. Based on published evidence and the committee's experience, the committee does not think treating spasticity would have a major impact on underlying disability associated with MS (measured by EDSS). Therefore, the committee concluded that Stevenson et al. 2015 overestimated the amount of resource use that is solely attributable to medically modifiable spasticity. However, the committee was sensitive to comments such as this, and did not want to underestimate the possible benefits of THC:CBD spray. Therefore, the committee made a consensus to change this parameter to 50%. The committee agreed that this parameter is highly uncertain, and it should be tested in the sensitivity analysis. This parameter has been modified in the model, tested extensively and reported in the spasticity evidence review chapter (Table 23). When doubling the background management costs (assuming 100% of costs from Stevenson et al. 2015 are attributable to spasticity alone), the cannabis strategy became dominant. When halving the background management costs (assuming 25% of costs are related to spasticity), the ICER is around £35,000.
GW Pharmaceuticals	Guideline	16	22-25	This section is mixing the research recommendations for Cannabis based medicines in refractory epilepsy with the published evidence from phase 3 trials that are currently being reviewed by NICE for cannabidiol in Dravet Syndome (ID1211) and Lennox Gastaut Syndrome (ID1308).	Thank you for your comments. Information on the RCTs for Dravet and Lennox Gastaut syndrome has been included in this section of the guideline because the findings from these studies formed part of the committee's discussion, albeit indirectly applicable to the research question. The recommendations section at the beginning of the guideline explains that CBD for Dravet syndrome and Lennox-Gastaut were excluded from the guideline.

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				We recommend deletion of the following sentence as this doesn't form part of the research recommendations; "Published randomised controlled trials have focused on the use of pure cannabidiol in people with Dravet and Lennox-Gastaut syndrome. People with these epilepsy syndromes also report a very high rate of adverse events." This section would then be confined to the research recommendation of the review as the section heading describes.	
Hanway Associates	Evidence Review B	33	17-21	**Hanway disagree with the committee's view that it is 'unlikely' that changes in CBMP efficacy and/or price will be forthcoming.** The evidence review included pricing for only a narrow range of the CBMPs available (or potentially available) in the UK. International production of CBMPs is rapidly increasing, with an anticipated significant reduction in costs of production and supply. In the near-term, EU production of various CBMPs is due to increase significantly. Given the expected significant changes to CBMP availability and pricing, Hanway suggest that NICE's modelling is frequently updated (on at least an annual basis) to take into account the actual cost of CBMP supply, as well as any additional study results relevant to NICE decision-making.	Thank you for your comments. The economic model is based on the best available evidence in chronic pain. NICE welcomes the upcoming CBMPs in the near future. However, until there is published clinical evidence to show the effectiveness these products, NICE cannot consider them in our analysis. All NICE guidelines update will be prompted by regular surveillance on new evidence or changes in clinical practice.
Hanway Associates	Evidence Review E	39	16-17	Given the Research Question and the clear need to compare international models of CBMP prescription and access, it is unclear as to why "*Guidelines… based on regulation from countries other than the UK were excluded at first sift."* **This appears only to limit relevant information available to the committee and reinforce the preconceived notion that only medical specialists should prescribe CBMPs.**	Thank you for your comment. In the UK, we have legislation that underpins who can prescribe and initiate cannabis-based medicinal products and so we would not need to look at legislation/regulation from other countries for this.
Hanway Associates	Evidence Review E	General	General	Hanway note that few of the studies included in the evidence review for 'Review Question 3' compare the different prescribing models of countries with medical cannabis access. Although the research questions given was "*Who should prescribe and monitor use of cannabis-based medicinal products in line with legislation?"* only studies from Australia and Ireland were included as part of an international comparison. **The broad exclusion criteria employed for this question means that the committee was not given information that accurately presents international systems of CBMP prescription.** Hanway would be pleased to provide NICE with details of prescription models in other developed healthcare systems if requested.	Thank you for your comment. Guidelines from developed countries with a similar healthcare system were included as part of the review. However, during the first sift of the evidence, guidelines from other international countries did not meet the inclusion criteria mainly because they did not report this data and it was in non-English language.
Hanway Associates	Evidence Reviews	General	General	**Hanway are concerned that NICE's economic models do not include a wide enough range of the CBMPs carried by (or which may be supplied by) UK distributors**. As a result, the incremental cost-effectiveness ratios generated may not accurately reflect the true cost of CBMP prescription. We therefore suggest that NICE calculations are amended to reflect CBMP pricing for products already available in the UK. While this may not return a favorable ICER at present, it will offer a more accurate understanding of the efficacy/cost gap to be addressed.	Thank you for your comments. The economic model is based on the best available evidence in chronic pain. NICE welcomes the upcoming CBMPs in the near future. However, until there is published clinical evidence to show the effectiveness these products, NICE cannot consider them in our analysis.
Hanway Associates	Evidence Reviews	General	General	The production of CBMPs (of various forms) is increasing rapidly at both an EU and international level. As a result, the cost of such products can be reasonably predicted to fall over the coming quarters and years. Likewise, the rate of good-quality research into medical cannabis is increasing. As a result, **we suggest that NICE update their guidance and economic modeling on a regular (e.g. a semi-annual) basis**, to account for new research and the true cost of CBMP treatment in the UK.	Thank you for your comments. The economic model is based on the best available evidence in chronic pain. NICE welcomes the upcoming CBMPs in the near future. However, until there is published clinical evidence to show the effectiveness these products, NICE cannot consider them in our analysis. All NICE guidelines update will be prompted by regular surveillance on new evidence or changes in clinical practice.
Hanway Associates	Evidence Reviews	General	General	The high current cost of UK CBMP treatment is in part a result of UK regulation and government policy. For example, import restrictions lead to tight supply and high costs, while the highly-restrictive Home Office licensing scheme for cultivation inhibits domestic supply**. We encourage NICE to identify regulatory and institutional roadblocks and their impact on the price and access of CBMPs.**	Thank you for your comments. NICE produce guidelines for NHS England. It is not within NICE's remit to comment on the policy of the Home Office licensing scheme or other regulatory bodies.
Hanway Associates	Evidence Reviews	General	General	Hanway is aware of a UK distributor with a supply of Bedrocan products and other CBMPs who could advise on pricing. Hanway is additionally aware of a UK producer of a pharmaceutical-grade generic CBD API who could advise on pricing. **We would be glad to facilitate an introduction** if this is helpful to NICE.	Thank you for your comments. We have reported the estimated costs of medicinal cannabis products, including products by Bedrocan (see Table 14 of the spasticity evidence review). These estimates are based on the publicly available sources but without importation.

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Hanway Associates	General	General	General	For simplicity, we have used the term 'CBMPs' in our consultation response to refer to all cannabis-based medical products as outlined on pages 8-9 of the draft guidelines.	Thank you for your comment.
Hanway Associates	Guideline	10	21	Hanway support the 'Other' Recommendations for Research given. However, we also urge NICE to consider alternative, non-RCT studies as an acceptable basis for prescribing recommendations.	Thank you for your comment. The committee reviewed your comment and noted that the 3 research recommendations drafted for intractable nausea and vomiting focus on the clinical and cost effectiveness of CBMPs. The committee agreed that these questions would be best answered using randomised controlled trials.
Hanway Associates	Guideline	12	3-5	Given that the committee were unable to make a recommendation for the treatment of intractable nausea and vomiting in children and young people due to the 'limited evidence' in the area, Hanway suggest that the guidelines are revised to be consistent with the draft advice offered for epilepsy. In this instance, the committee were similarly unable to issue a recommendation, yet greater discretion is afforded to specialists (Draft Guidelines, p.17, lines 5-10): "*until there is clear evidence, specialists, people with [epilepsy] and their carers should continue to make treatment decisions in the best interests of each person"*	Thank you for your comment. The committee reviewed your comment and agreed that a recommendation for the use of CBMPs in children could not be made. Due to limited evidence and ongoing technology appraisal guidance, the committee were unable to make a practice recommendation for the use of CBMPs for severe treatment resistant epilepsy. However, in the case of intractable nausea and vomiting some evidence was identified in children. This evidence was predominantly on the use of nabilone which is currently not licenced in children. Furthermore, the committee noted that further research in children is required and therefore drafted a research recommendation.
Hanway Associates	Guideline	13	17-18	**Although the evidence NICE actually included for evaluation "*did not show a reduction in opioid use in people prescribed medicinal cannabis"* there are numerous (non-RCT) studies and patient surveys that suggest otherwise.** Of these, a number do not appear in Appendix J - Excluded studies - of the chronic pain evidence review, suggesting that they were not considered for inclusion. Hanway would be happy to provide NICE with additional peer-reviewed literature regarding the opioid-sparing and substitution effect of cannabis. Some examples of this literature are detailed here: 'Medical cannabis access, use, and substitution for prescription opioids and other substances: A survey of authorized medical cannabis patients.' Lucas, P., Walsh, Z. *Int J Drug Policy*. 2017 Apr;42:30-35. DOI: 10.1016/j.drugpo.2017.01.011. 'Rationale for cannabis-based interventions in the opioid overdose crisis.' Lucas, P. *Harm Reduction Journal* (2017) 14:58 DOI: 10.1186/s12954-017-0183-9 'Patterns of medicinal cannabis use, strain analysis, and substitution effect among patients with migraine, headache, arthritis, and chronic pain in a medicinal cannabis cohort' Baron, E.P. et al. *The Journal of Headache and Pain* (2018) 19:37 DOI: 10.1186/s10194-018-0862-2.	Thank you for your comment. RCTs are the best studies for assessing medicinal cannabis. This is because all analgesia has a strong placebo effect. Therefore, studies should be double-blinded and randomised. Thank you for providing these references. We have considered them and they are outside the scope of our guideline. None of these references are studies examining the clinical effectiveness of CBMP using a trial design compared to a placebo.
Hanway Associates	Guideline	16- 17	5-10	**Hanway agrees with the proposal that specialists, patients and carers should be permitted to make treatment decisions in the best interests of the person with epilepsy until clear evidence is available.** This affords an element of flexibility and personalised care for those with epilepsy while acknowledging the existing research gap. As previously stated, Hanway would welcome similar wording for the other conditions covered by the guidance where research is still limited.	Thank you for your comment. The guideline recommends that all those receiving treatment for spasticity and chronic pain before publication of this guidance can continue to receive treatment.
Hanway Associates	Guideline	4	12-16	**Hanway is concerned that a recommendation against the use of CBMPs for the treatment of chronic pain will restrict research in this area**. The draft guidelines state that current evidence shows that CBMPs can cause a reduction in chronic pain, albeit on a modest scale, and the reason for a recommendation against prescribing is given as the 'high and ongoing costs' of CBMPs relative to their demonstrated efficacy. (Draft Guideline, p.13, lines 22-24). Hanway feel that increased research into the use of CBMPs may result in stronger and/or higher-quality evidence of efficacy, as well as the possible development of more cost-effective treatments. However, Hanway is concerned that NICE's recommendation against the use of CBMPs for chronic pain will negatively impact future research opportunities. Our reason for believing this is that within the context of CBMP treatment for epilepsy, it is stated that the NICE committee "*agreed that **they should not make a recommendation***	Thank you for your comment. With regards to adult studies, the economic analysis suggested that most types of chronic pain were not going to be cost-effective to manage using medicinal cannabis. However, if any types of chronic pain could be cost-effective to manage using medicinal cannabis, they are most likely to be fibromyalgia and treatment-resistant neuropathic pain. There is no RCT data for children with regards to medicinal cannabis.

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				against the use of cannabis-based medicinal products as this would restrict further research in this area *and would prevent people who are currently apparently benefiting from continuing with their treatment.*" (Draft Guideline, p.17, lines 2-5) If this is a legitimate concern of NICE regarding epilepsy research, it is reasonable to assume that the same will apply regarding research of CBMPs efficacy for treating chronic pain. Furthermore, by suggesting that (non-CBD) CBMPs should <u>not</u> be offered as part of a clinical trial for chronic pain, there is an implication that such clinical trials should not be approved within the UK. The Evidence Review cites "limited evidence of high quality" for the treatment of CBMPs for chronic pain (Evidence Review B, p.31, line 9). Until a greater amount of high-quality evidence is available, we believe that it would be harmful to restrict further research into this area. Hanway therefore suggest the following: i) NICE consider removing the recommendation against offering CBMPs in the treatment of chronic pain ii) If retained, that NICE stipulate that the recommendation should not impede future research into this area iii) If NICE do not believe that further research is required, to explain this position in the Chronic Pain Evidence Review iv) NICE permit other (non-CBD) CBMPs to be prescribed as part of a clinical trial for the treatment of chronic pain.	
Hanway Associates	Guideline	5	7-8	**Hanway is concerned that offering CBMPs to treat spasticity only when part of a clinical trial will deny access to those who may benefit from such treatment.** The draft guidelines (page 5, lines 25-31) state that evidence for the effectiveness and safety of non-THC/CBD spray products is *'much more limited'* (compared to the CBD/THC spray) and that there is also *'currently no evidence on the cost-effectiveness of products'.* This is not dissimilar to the evidence claimed regarding epilepsy (draft Guidelines, page 16, lines 21-22) that "*current research is limited and of low quality, making it difficult to assess just how effective these products are for people with epilepsy*". NICE also propose priority research recommendations regarding CBMP research for the treatment of both epilepsy and spasticity. Given the similarity between the two situations, Hanway suggest that NICE consider revising this recommendation so that it reflects the draft advice for epilepsy: "*until there is clear evidence, specialists, people with [epilepsy] and their carers should continue to make treatment decisions in the best interests of each person...people seeking treatment for [severe epilepsy] should be made aware that currently there is no clear evidence of the safety and effectiveness of cannabis-based medicinal products."* (Draft Guideline, p.17, lines 5-10).	Thank you for your comment. The guideline now recommends that all those receiving treatment before publication of this guidance can continue to receive treatment.
Hanway Associates	Guideline	5	11-15	Within context, **Hanway agree with NICE's proposal to withhold a recommendation for treatment-resistant epilepsy until greater research is available.** This is because withholding a recommendation allows treatment decisions to be made on a case-by-case basis and does not prevent specialists from offering CBMPs when they believe it is in the best interests of the patient. Hanway suggest that a similar approach is adopted **for all conditions** where there is not clear or good-quality evidence that CBMPs are i) ineffective or ii) cost-ineffective.	Thank you for your comment. The guideline now recommends that all those receiving treatment before publication of this guidance can continue to receive treatment.

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Hanway Associates	Guideline	6	4-8	**Hanway Associates do not agree that the initial prescription of CBMPs should be limited to a medical specialist, and argue that General Practitioners should be permitted to issue an initial prescription when they consider it to be in the best interest of the patient.** This requirement is not a reflection of standard international practice. Multiple jurisdictions allow the initial prescription of medical cannabis by a non-specialist healthcare practitioner, including Canada, Australia, Germany, the Netherlands, Italy and Denmark. Hanway do not believe that the committee have in this instance considered the full range of prescription models which could be used in the UK, largely due to the limited evidence included for review.	Thank you for your comment. The recommendation about who should prescribe is underpinned by UK legislation, The Misuse of Drugs (Amendments) (Cannabis and Licence Fees) (England, Wales and Scotland) Regulations 2018, regulation 16A
Hanway Associates	Guideline	6	10-13	Hanway argue that GPs should be permitted to make initial CBMP prescriptions. Given that this is not currently the case, **we support the subsequent prescriptions of CBMPs by non-specialist healthcare professionals as part of a shared care arrangement** and agree that such agreements may reduce tertiary healthcare costs. Hanway hope that these arrangements will pave the way for a greater role of non-specialist healthcare providers in CBMP access, such as dose adjustment, in the future.	Thank you for your comment. The recommendation about who should prescribe is underpinned by UK legislation, The Misuse of Drugs (Amendments) (Cannabis and Licence Fees) (England, Wales and Scotland) Regulations 2018, regulation 16A
Hanway Associates	Guideline	9	12	Hanway support the 'Key' Recommendations for Research given. However, we also urge NICE to consider alternative, non-RCT studies as an acceptable basis for prescribing recommendations.	Thank you for your comment. RCTs are the best studies for assessing medicinal cannabis. This is because all analgesia has a strong placebo effect. Therefore, studies should be double-blinded and randomised.
Hanway Associates	Guideline	General	General	**Hanway disagrees with the decision to exclude studies that examine the use of smoked cannabis-based products.** Thank youto cannabis' scheduling under international (and domestic) drug control conventions, research into the use of cannabis for therapeutic purposes has been curtailed. The exclusion of studies on the basis that the UK medical system does not permit smoked cannabis may therefore significantly lower the research base available to NICE. The number of studies automatically excluded from the Evidence Reviews on the basis of studying smoked cannabis certainly suggests this is the case. Secondly, smoked cannabis enters the bloodstream in a manner similar to vaporised cannabis, which is permitted for medical purposes in the UK. Research into smoked cannabis and its effects is therefore potentially relevant for UK prescribing guidelines. Given the limited number of studies included in each evidence review, Hanway suggest that studies should not be automatically excluded if they examine the use of smoked cannabis-based products.	Thank you for your comment. This guideline is underpinned by legislation in terms of which cannabis based medicinal products can be considered. Therefore we only considered the following: • cannabis-based medicinal products as defined by the UK Government in November 2018 • the licensed products nabiximols (Sativex) and nabilone. • plant-derived cannabinoids such as pure cannabidiol. • synthetic compounds which are identical in structure to naturally occurring cannabinoids such as delta-9-tetrahydrocannabinol (THC), for example dronabinol.
Hanway Associates	Guideline	General	General	**While Hanway supports the research recommendations offered, we believe they are (by themselves) insufficient to address the evidence gap that currently restricts NICE prescribing recommendations, and consequently UK patient access to CBMPs.** The 2018 CBMP regulations were introduced to provide access to medical cannabis for those patients who are most in need of it. That a mere handful of patients (at best) have achieved an NHS prescription in the following months demonstrates the significant failure of the policy to achieve this main objective. As admitted in the guideline, the proposed NICE recommendations will have little impact on the current level of access. As a result, UK patients will remain faced with the choice of either a private prescription and the high cost that that entails, or sourcing untested product from the illicit market, while around the world in increasing jurisdictions patients can receive CBMP treatment if it is believed to be in their best interest by healthcare professionals.	Thank you for your comment. NICE guideline recommendations are based on the best available evidence. A randomised controlled trial is often the most appropriate type of study to assess the efficacy or effectiveness (including cost effectiveness) of an intervention. The committee agreed that an additional recommendation on a national or local registry was needed. This will facilitate an improved evidence base for CBMPs.

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				The limitations to an RCT-led evidence framework for CBMPs have been described at length by various clinical, patient and industry groups and we will not repeat them here. Hanway believe that the UK's almost exclusive reliance on RCT-led evidence with respect to prescription of CBMPs is sub-optimal and that its consequences reflect poorly on both our healthcare system and the law. **We urge NICE to consider the acceptance and generation of alternative standards of evidence for CBMPs, which can then be used to inform future prescribing recommendations**. For example, the Danish medical cannabis pilot has allowed several thousand patients to receive CBMP treatment in little over 18 months, with the collection of observational data that will be used to inform further prescribing advice and policy decisions. A similar two-year pilot scheme is also due to commence in France in 2020. There is already a degree of institutional support for non-RCT approaches to evidence generation: The NHS England Review '*Barriers to accessing cannabis-based products for medicinal use on NHS prescription*' (published 8 August 2019) recommends an 'alternative study design' to be implemented 'as soon as possible' for those treated with CBMPs for paediatric epilepsy who are ineligible for enrollment in a RCT. We acknowledge that scientific and ethical questions regarding CBMP 'best evidence' goes beyond NICE's scope to develop prescribing guidelines. However, Hanway believe that NICE are acutely aware of the complexities surrounding CBMP research, and urge the body to join other official bodies that are engaging positively in this area.	
Hanway Associates	Guideline	General	General	**Hanway is concerned that the lack of CBMP access offered by the proposed guidelines will mean that a proportion of the UK population will continue to self-medicate with cannabis that has been illicitly obtained**, placing themselves at risk of exposure to harmful contaminants and unknown dosing of active substances. Indeed, the patient association End Our Pain estimate that as many as one million people in the UK use illicit cannabis for therapeutic purposes. We believe that the health and legal risks which members of the UK population are willing to expose themselves to for access to therapeutic cannabis should be taken into account when considering whether alternative forms of research (e.g. observational studies and those which examine smoked-cannabis products) or burdens of evidence for CBMPs may be admissible to increase access in a safe yet timely manner.	Thank you for your comment. The guideline recommends that all those receiving treatment before publication of this guidance can continue to receive treatment. Clinicians can also still make their own individual prescribing decisions in the best interest of their patients NICE guideline recommendations are based on the best available evidence. A randomised controlled trial is often the most appropriate type of study to assess the efficacy or effectiveness (including cost effectiveness) of an intervention. The committee agreed that an additional recommendation on a national or local registry was needed. This will facilitate an improved evidence base for CBMPs.
Health and Justice Clinical Reference Group NHS England and Improvement	Guideline	6 7 18 19	General 2-23 1-5 25-29 1-3	We are supportive of the use of shared care between specialists and GPs in principle where this is safe and where there are a high number of on long-term, stable patients requiring minimal monitoring between specialist visits. We disagree with the recommendation that prescribing of cannabis-based medicinal products can be via a shared care arrangement between a specialist and another prescriber. All prescribing should be restricted to specialists only. This is because: • The treatment is new and has been rarely used with little evidence for benefit as described in the previous recommendations. New specialist treatments with a poor evidence base are not appropriate for shared care with community GPs. • Given that there is only one indication recommended by this guidance and this is very specialist, there is no need for this to be under shared care. Specialists should prescribe and supply for this indication and for any clinical trial prescribing for the other indications. • There are commonly used and efficient access to medicines that are prescribed monthly and supplied by specialists for other specialist medicines which are needed long-term. Examples include HIV medicines (which are long-term medicines), erythropoetin and oral cancer therapy	Thank you for your comment. The committee considered your comment and agreed that recommendation 1.5.2 as is not a strong recommendation but one that uses the word 'may' to enable this to be an option if the GP feels confident to continue on prescribing and agrees with the shared care arrangement in place.The committee also considered the NHS England document 'Responsibility for prescribing between Primary & Secondary/Tertiary Care', that provides details about arrangements and considerations. The committee agreed to refer to this guidance to supplement recommendation 1.5.2.

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				• Hospital generated prescriptions are delivered directly to patients via arrangements made by the hospital using Homecare contracts. Alternatively, the hospital provides a prescription that the patient can access from a community pharmacy (FP10HP). This means the rationale for the recommendation for shared-care on the grounds of patient burden is not justified when considered against other risks of this approach. • There is a high risk of diversion of cannabis-based medicinal products (which are classified as controlled drugs). Restricting the supply chain (prescribing and delivery to the patient) via the specialist centre reduces the risk of inappropriate non-specialist prescribing or access via the diversion of the medicines from the legitimate supply chain. • Experience with shared care of other specialist medicines already results in diversion of dependence forming medication that are specialist initiated and then continued by another prescriber (e.g. the GP). Given the risks with cannabis-based medicinal products for illicit use or diversion of prescribed products, these outweigh the small benefits in having shared-care. • Experience and feedback from GPs and other non-specialist prescribers about shared care for highly specialised medicines especially those which have a high risk of illicit use, is that GPs are unwilling to prescribe under shared care arrangements. This means that if the shared care recommendation remains in this guideline, there is likely to be local variation in this arrangement being implemented as GPs will continue to refuse requests from specialists for shared care. In health and justice settings, where the challenge of managing people on high risk medicines is high both clinically and operationally, shared care arrangement with specialists for these medicines would not be supported. • Increased activity for GP appointments within prison establishment for prisoners that may exhibit drug-seeking behaviours. This may impact on waiting times and delays in treatment for prisoners with a genuine health concern. Some indicators for use e.g. chronic pain can easily be staged by prisoners therefore difficult for prescribers to assess genuine symptoms. Specialist assessment and monitoring including retaining prescribing responsibility will reduce this risk. • The concept of shared care and consistency of care is problematic due to transfers of prisoners between prisons. Specialist-led prescribing will minimise variation in how prescribing is continued for transferred and released prisoners • In addition, the prescribing of these medicines by HJ-based prescribers increases the potential for increase in challenging behaviours for those prisoners requesting this medication but that do not meet the criteria: ie bullying of prisoners that have a prescription; increase in violence and aggression towards health care professionals that do not support an individual's request for a prescription. • If prescribed, there will be a requirement for healthcare teams to work with prisons as this medication will impact on mandatory and random drug testing results. Medication could mask the use of illicit drug taking. • There is a likelihood that patients will access private specialists who will initiate medicinal cannabis for indications not supported by NICE. Enabling shared care for these medicines will a) encourage NHS care to be provided outside NICE guidance and b) create a two tier system of access to those patients who can afford to fund a private specialist. This is a particular risk for patients admitted to HJ settings. Retaining prescribing with specialists will prevent this issue from arising as patients will need to fund ongoing supplies of medicinal cannabis.	
Health and Justice Clinical Reference Group NHS	Guideline	4	15	We are concerned that these recommendations will limit the ability to further develop the evidence of the management of chronic pain with THC (delta-9-tetrahydrocannabidiol) as part of a clinical trial.	Thank you for your comment. With regards to adult studies, the economic analysis suggested that most types of chronic pain were not going to be cost-effective to manage using medicinal cannabis. However, if any types of chronic pain could be cost-effective to manage using medicinal cannabis, they are most likely to be fibromyalgia and treatment-resistant neuropathic pain. Therefore, we wrote research recommendations for these conditions. For

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England and Improvement				We believe that consideration should be given to amending the recommendation to read: "Do not offer THC (delta-9-tetrahydrocannabidiol) to manage chronic pain in adults unless as part of a clinical trial."	the adult research recommendation, the committee wanted to focus on CBD (either as a pure product or containing traces of THC). There is no RCT data for children with regards to medicinal cannabis. Therefore, the research recommendations for children are less specific.
Health and Justice Clinical Reference Group NHS England and Improvement	Guideline	4	16	We are concerned that these recommendations will limit the ability to further develop the evidence of the management of chronic pain with a combination of cannabidiol (CBD) and THC. We believe that consideration should be given to amending the recommendation to read: "Do not offer with a combination of cannabidiol (CBD) and THC to manage chronic pain in adults unless as part of a clinical trial."	Thank you for your comment. With regards to adult studies, the economic analysis suggested that most types of chronic pain were not going to be cost-effective to manage using medicinal cannabis. However, if any types of chronic pain could be cost-effective to manage using medicinal cannabis, they are most likely to be fibromyalgia and treatment-resistant neuropathic pain. Therefore, we wrote research recommendations for these conditions. For the adult research recommendation, the committee wanted to focus on CBD (either as a pure product or containing traces of THC). There is no RCT data for children with regards to medicinal cannabis. Therefore, the research recommendations for children are less specific.
Health and Justice Clinical Reference Group NHS England and Improvement	Guideline	7	11	We believe that the "history of substance misuse" should be changed to explicitly refer to a "…history of substance misuse **including the illicit use of cannabis**."	Thank you for your comment. The committee agreed illicit use of cannabis has been captured in recommendation 1.5.7
Health and Justice Clinical Reference Group NHS England and Improvement	Guideline	General	General	We support the NICE recommendations for the indications for which medicinal cannabis can be used. We would value the opportunity for people residing in HJ settings be included in clinical trials recommended for other indications in this consultation. Many individuals in health and justice services e.g. prisons have high levels of substance misuse. There is significant potential therefore for dependence, diversion and misuse in these environments. There are also high levels of mental health and medical history such as liver impairment, renal impairment and cardiovascular disease in health and justice. This potentially increases the risk of using cannabis based medicinal products in these settings.	Thank you for your comment.
Health and Social Care Board Northern Ireland	Guideline	1	7	The link to legislation is GB. The scope should include the corresponding Northern Ireland legislation: http://www.legislation.gov.uk/nisr/2018/173/made	Thank you for your comment. NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the Northern Ireland Executive.
Health and Social Care Board Northern Ireland	Guideline	18	20-21	There is acknowledgement of the BPNA advice in this section – therefore the recommendations around shared care are contradictory	Thank you for your comment. The cannabis-based products for medicinal use FAQs provided by NHS England state that it is possible for a GP to continue prescribing legally. In terms prescribing responsibilities, the NHS England document 'Responsibility for prescribing between Primary & Secondary/Tertiary Care' provides details of what the arrangements should consider, and this would be for local determination.
Health and Social Care Board Northern Ireland	Guideline	19	1	While there is an argument in relation to the potential service model to facilitate access, such a service model needs to be compliant with the law and good professional practice. As outlined previously, prescribing of an unlicensed CBPM by a generalist and/or a non-medical prescriber at this stage would not be appropriate.	Thank you for your comment. The committee discussed this further and agreed that shared care may be an option if the prescriber feels competent and agrees to the shared care arrangement.
Health and Social Care Board Northern Ireland	Guideline	5	14	Support the need for further clinical trials to assess the risks/benefits of cannabis based medicinal products	Thank you for your comment.
Health and Social Care Board Northern Ireland	Guideline	6	5	The legislation does not specify initial or continuing prescription of cannabis based medicinal products – it specifies supply through either prescribing or a direction: "**16A Orders, supply and use of cannabis-based products for administration** (1) Subject to paragraph (4), a person shall not order (whether by issuing a prescription or otherwise) a cannabis-based product for medicinal use in humans for administration, unless that product is—	Thank you for your comment. Although not specified in legislation, the cannabis-based products for medicinal use FAQs provided by NHS England advise that all prescriptions will need to be initiated and signed by a specialist doctor. In terms of continuation, this would depend on the patient's response and agreement with the specialist to continue treatment or not.

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				(a)a special medicinal product that— (i)is not also an investigational medicinal product, but (ii)is for use in accordance with a prescription or direction of a specialist medical practitioner; (2) Subject to paragraph (4), a person shall not supply a cannabis-based product for medicinal use in humans by way of or for the purpose of the administration of that product, unless the supply— (a)is pursuant to an order that complies with paragraph (1); and (b)is— (i)in the case of a product that is a special medicinal product but is not also an investigational medicinal product, for use in accordance with a prescription or direction of a specialist medical practitioner, The current draft guidance therefore interprets the legislation broadly in a way that it is unclear that the policy makers arranged. Please refer to MHRA guidance issued in October 2018: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/752796/Cannabis_Guidance__unlicensed_CBPMs__-_Final_311018.pdf	
Health and Social Care Board Northern Ireland	Guideline	6	10	There is a lack of specificity within the draft guidance around shared care Shared care can mean many different things – ultimately the principle of clinicians with various expertise and service accessibility sharing elements of care in the best interest of the patient is good. But clarity over what can and can't be shared is critical in the arrangements particularly from a patient safety perspective. The service model that may emerge for CBMPs will likely involve quaternary centres linking with tertiary and secondary care. For certain conditions this may be appropriate. However, to have a section within this document around shared care without a structured pathway having been developed is problematic. The draft guidance states that the ongoing prescription could be taken forward by another prescriber. While this may be possible within the same legal entity e.g. a consultant directing a prescription and the junior organising the supply this would be problematic in 'traditional' shared care arrangements which have developed between consultants in Trusts and GPs in primary care for three reasons: 1. The legislation – supply/administration is made either on the direction or prescription by a doctor on the specialist register 2. Professional standards – for example, GMC guidance - GP is required to act within his competency of practice as set out by the General Medical Council https://www.gmc-uk.org/-/media/documents/prescribing-guidance_pdf-59055247.pdf : ***37*** *If you prescribe at the recommendation of another doctor, nurse or other healthcare professional, you must satisfy yourself that the prescription is needed, appropriate for the patient and within the limits of your competence.*	Thank you for your comment. The committee considered your comment and agreed that recommendation 1.5.2 is not a strong recommendation but one that uses the word 'may' to enable this to be an option if the GP feels confident to continue prescribing under a shared care arrangement. The committee also considered the NHS England document 'Responsibility for prescribing between Primary & Secondary/Tertiary Care' that provides details about arrangements and considerations. The committee agreed to refer to this guidance to supplement recommendation 1.5.2.

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				38 *If you delegate assessment of a patients' suitability for a medicine, you must be satisfied that the person to whom you delegate has the qualifications, experience, knowledge and skills to make the assessment. You must give them enough information about the patient to carry out the assessment required. You must also make sure that they follow the guidance in paragraphs 21–29 on consent.* ***39*** *In both cases, you will be responsible for any prescription you sign.* 3. Professional guidance – for example the British Paediatric Neurology Association - (https://bpna.org.uk/userfiles/BPNA_CBPM_Guidance_Oct2018.pdf) "Guidance on the use of cannabis-based products for medicinal use in children and young people with epilepsy. At 5.1 of this guidance it states: *"In order to prescribe a cannabis-based product for medicinal use, you must be on the Specialist Register. It is further advised that clinicians should prescribe only within their relevant specialist registration. Consequently, for a child with intractable epilepsy, the prescription should be made by a Consultant Paediatric Neurologist."*	
Healthcare Improvement Scotland	Guideline	4	12	It would be useful to continue to clarify the age of adults as in Line 4 on Page 4 to ensure this is clear.	Thank you for your comment. NICE uses the legal definition of an adult, which is 18 years and older.
Healthcare Improvement Scotland	Guideline	5	4	This position in useful as promotes consistency across the UK as Sativex is not recommended for use in NHS Scotland - https://www.scottishmedicines.org.uk/medicines-advice/cannabinoid-sativex-nonsubmission-70311/	Thank you for your comment.
Healthcare Improvement Scotland	Guideline	5	16	We note that the NICE technology appraisals are expected in December 2019. We feel it may have been useful to have these technology appraisals published at the same time as the guideline to help address the use of CBD in the treatment of these conditions.	Thank you for your comment. This guideline is scheduled to publish before the results of the technology appraisals. However, if the results of the appraisals affect anything in the guideline then this information would be updated. A cross reference to the technology appraisals will be made when published.
Healthcare Improvement Scotland	Guideline	6	4	The prescribing of nabilone is excluded from this recommendation. For completeness and although not recommended should the position with Sativex also be mentioned in this sentence for clarity.	Thank you for your comment. The term cannabis-based medicinal products include Sativex as within its marketing authorisation it needs to be prescribed by a specialist only. Nabilone does not according to its marketing authorisation.
Healthcare Improvement Scotland	Guideline	6	1.5	This should reflect the current national guidance in relation to the prescribing of cannabis based medicinal products to ensure consistent messaging to clinicians.	Thank you for your comment. The guideline section 1.5 is underpinned by legislation and took into consideration available national advice from the MHRA, NHS England, GMC and the BPNA regarding cannabis-based medicinal products.
Healthcare Improvement Scotland	Guideline	7	9	This specifies over the counter or online supplied cannabis but there is likely to use of cannabis acquired elsewhere and this should be clear in the guidance e.g. or cannabis obtained from other sources/routes.	Thank you for your comment. This is not limited to just over-the-counter or online sources.
Healthcare Improvement Scotland	Guideline	7	23	Although mentioned later on page 20 line 8 it would be useful in this area to highlight the unknown long term effects of cannabis-based medicinal products in particular in babies, children and young people and the need for joint decision making with the parents/carer/ individual as appropriate and the recording of the decision made.	Thank you for your comment. The committee agreed that adding in the unknown effect of cannabis-based medicinal products to the recommendation was not helpful and also this would be known by the prescribers as most of these medicines would be unlicensed. Recommendation 1.5.10 takes into account shared decision making and has been amended to discuss the listed information with the patient, family members or carer.
Healthcare Improvement Scotland	Guideline	7	23	Definition of age group would be beneficial	Thank you for your comment. It would be difficult to define an age group here as these are generic prescribing recommendations which apply across population groups.
Healthcare Improvement Scotland	Guideline	9	14	There are numerous key recommendations for research highlighted in the guidance and the rationale and impact section describes why further research is required by clearly articulating	Thank you for your comment.

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				the potential areas of benefit of cannabis based medicinal products may deliver where evidence of clinical and cost effectiveness can be shown.	
Healthcare Improvement Scotland	Guideline	General	General	The guideline highlights the evidence gap in many areas related to the use of cannabis-based medicinal products. This is reflected throughout the guideline and it may be of use to those intending to use the guideline to include an explicit statement at the start of the guideline to highlight this position.	Thank you for your comment. The guideline has made a number of research recommendations to address the gaps in the evidence base.
Healthcare Improvement Scotland	Guideline	General	General	In most areas the guideline recommends that cannabis-based medicinal products are not provided to treat the condition unless as part of a clinical trial. This recommendation is not made in relation to intractable nausea and vomiting although this is a recommendation for research.	Thank you for your comment. Recommendations limiting the use of CBMPs to clinical trials were made based on the evidence for chronic pain. In the chronic pain evidence review, no evidence was identified for the use of CBD alone, therefore the committee restricted the use of this product to clinical trials. After publication of the consultation draft of the guideline, the manufacturer reduced the list price of THC:CBD spray, and this had an important impact on our assessment of its cost effectiveness. In light of stakeholder comments, the committee also reviewed their estimates of likely resource use associated with spasticity symptoms. The committee are now able to make a more positive recommendation. In the intractable nausea and vomiting review, evidence was identified for a number of different interventions. This evidence supported the use of nabilone to be considered as an add-on treatment for intractable nausea and vomiting. The committee noted that there was a rationale for further research into the use of CBMPs, including further research into the use of nabilone. Therefore, the committee did not restrict the use of these products to clinical trials only. For further information on the committee's decision please refer to rationale and impact section. For further information on research recommendations please refer to Appendix K in Evidence review A.
Helen and Douglas House	Guideline	10	4	In the interests of consistency, should this read 'infants, children, young people and adults'?	Thank you for your comment. NICE editorial policy now prefers to use babies, children and young people to promote clarity and understanding of our recommendations.
Helen and Douglas House	Guideline	10	11	In the interests of consistency, should this read 'infants, children, young people and adults'? (as above)	Thank you for your comment. NICE editorial policy now prefers to use babies, children and young people to promote clarity and understanding of our recommendations.
Helen and Douglas House	Guideline	10	15	What age groups / diagnosis would apply to a proposed research recommendation for spasticity? Adult MS population; Children with neurodisability, etc…?	Thank you for your comment. This inclusion criteria for this research question is 'adults and children with spasticity who haven't fully responded to optimal treatment'. For the full details of this research recommendation see Appendix K in the spasticity evidence review.
Helen and Douglas House	Guideline	11	1	'Babies, children and young people' rather than 'infants, children and young people'? (as above)	Thank you for your comment. NICE editorial policy now prefers to use babies, children and young people to promote clarity and understanding of our recommendations.
Helen and Douglas House	Guideline	11	6	For what age groups would this research be recommended? Clarity would help with any grant applications – in particular, knowing whether you feel children ought to be investigated….	Thank you for your comment. Rationale for each research recommendation has been provided in individual evidence reviews. For further information on the research recommendations for intractable nausea and vomiting please refer to Appendix K in evidence review A.
Helen and Douglas House	Guideline	20	9	'Babies, children and young people' (as above)	Thank you for your comment. NICE editorial policy now prefers to use babies, children and young people to promote clarity and understanding of our recommendations.
Helen and Douglas House	Guideline	4	4	Would it be worth directly stating that you are NOT recommending this for children <18?	Thank you for your comment. Some evidence was identified for the use of CBMPs in children however this evidence was limited and of low quality. Additionally, nabilone is not currently licensed in children as safety and efficacy has not been established. The committee did not think a 'do not use' recommendation was appropriate for this population as more evidence is

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					needed. Therefore, the committee drafted a research recommendation to further explore the clinical and cost effectiveness in this population. For further information on research recommendations please refer to Appendix K in Evidence review A.
Helen and Douglas House	Guideline	4	12	Why is this stated to be for adults only? Should it not also state that it should not be used for chronic pain in children?	Thank you for your comment. We have made research recommendations for babies, children and young people. If we advised that medicinal cannabis should not be used for children, research is likely to be inhibited. This would not be warranted because we have no RCT data on children and our aim is to promote further research to improve the evidence base.
Helen and Douglas House	Guideline	5	7	Should be clearly stated as applying to both adults and children? (The statement relating to MS can presumably be assumed to apply to adults?)	Thank you for your comment. The spasticity recommendations are for all ages and this is reflected in the recommendation by using 'people' as opposed to 'adults'.
Helen and Douglas House	Guideline	5	10	Would it be worth clarifying the age groups covered by the upcoming technology appraisal guidance on use in Lennox Gastaut and Dravets – presumably this will be largely for the paediatric population? Or at least inclusive of them?	Thank you for your comment. The details of the RCTs for Lennox Gastaut and Dravet syndromes, including the age groups, are discussing in more detail in the evidence review for epilepsy.
Helen and Douglas House	Guideline	7	18	Previous related NICE guidance has referred to 'infants, children and young people' rather than 'babies, children and young people' (NG61)	Thank you for your comment. NICE editorial policy now prefers to use babies, children and young people to promote clarity and understanding of our recommendations.
HSP Support Group	Guideline	10	16-18	We are pleased to see the research questions on assessing effectiveness and changes to quality of life from cannabis based medicinal products. There is a fair bit of anecdotal evidence around perceptions of benefits from cannabis based products in people with HSP. It would be good to see some research work assessing these benefits.	Thank you for your comments and support for this guideline.
HSP Support Group	Guideline	18	25-27	We are pleased that the guidelines acknowledge the potential burden from limited prescriptions, given that mobility problems are a key feature of HSP and journeys to pick up medications can be difficult.	Thank you for your comment.
HSP Support Group	Guideline	19	8-12	We are pleased to see the recommendation for a shared care agreement. Those with HSP often see multiple specialists and a written care agreement could help share important information between specialists.	Thank you for your comment.
HSP Support Group	Guideline	5	7-8	We are pleased to see that cannabis based medicinal products are recommended to be allowed to be prescribed as part of a clinical trial for all types of spasticity. We hope that this will lead to better evidence being gathered to make an informed decision in the future.	Thank you for your comments and support for this guideline.
International Association for the Study of Pain			Methods	IASP is concerned that the search strategy appears to exclude not only many published studies but also unpublished studies and that there is no estimation of the impact of publication bias. It has been previously shown that unpublished data for cannabinoid trials are identifiable and extractable for meta-analysis purposes and that the impact of publication bias can be estimated (Finnerup et al. The Lancet Neurology. 2015;14(2):162-73). The lack of attention to this point compromises the usefulness of the guidance.	Thank you for your comment. NICE considers a wide range of evidence to assess clinical effectiveness. It is not possible to assess publication bias adequately using a funnel plot with fewer than 10 studies that have the same intervention and condition. It is possible for the sift of abstracts to reveal many unpublished studies (RCTs) that have only been presented at conferences. However, this was not the case in this evidence review. Unpublished data is not considered by NICE as it has not undergone the quality assurance peer review process.
International Association for the Study of Pain			Methods	The review ignored risk of bias assessment specifically relating to pain clinical trials and used only the Cochrane Risk of Bias instrument, which is generic and inadequate. For example, there was no mention of initial pain intensity, imputation where appropriate, or size of study or sample when calculating outcome data.	Thank you for your comment. The Cochrane Risk of Bias tool 2.0 is a validated tool for interventions such as drugs. Medicinal cannabis is a drug intervention. Therefore, Cochrane RoB 2.0 is appropriate. Other tools would either be similar or less appropriate. For example, the CASP (Critical Appraisal Skills Programme) tool for RCTs is very similar to the Cochrane RoB 2.0 tool. EPOC (Effective Practice and Organisation of Care) is about non-drug interventions such as: forms of continuing education, quality assurance projects, financial, organisational or regulatory interventions that can affect the ability of healthcare professionals to deliver services more effectively and efficiently. Cochrane's RoB 2.0 tool does address the issues of concern raised in this comment: Initial pain intensity outcomes incorporated the mean initial pain intensities of both arms of the studies. In other words, we compared the mean changes of pain intensity of both arms. The size of the study or sample in this review was incorporated by including minimally important differences (MIDs): The larger the study, the narrower the 95% confidence interval of the outcome is likely to be. Therefore, the larger the study, the less likely the 95% confidence interval is to cross lines of minimally important difference. Therefore, larger studies are less likely to be downgraded.
International Association for			Methods	No attempt was made to distinguish between the potential analgesic effects of delta-9-tetrahydrocannabinol (delta-9-THC) and cannabidiol (CBD); therefore, the NICE recommendations conflate any putative effect of one versus the other compound. Further,	Thank you for your comment. We can only analyse the data that we have available and committee provided a steer on the common outcomes used. We acknowledge that some people with chronic pain feel that CBD helps them. Therefore, we have made a CBD

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the Study of Pain				any putative benefit of CBD could have been obscured by adverse effects of THC in the studies that used a combination of the two in approximately 1:1 ratio.	research recommendation for adults (either as a pure product or containing traces of THC) due to the lack of evidence for CBD alone.
International Association for the Study of Pain			Methods	The bioavailability of many cannabis-based products is known to be variable and uncertain, especially when the high lipophilicity of most cannabinoids is considered. To be credible, studies should report, at the very least, plasma levels of the test compounds or other target engagement data. In clinical trials of cannabinoids, it is essential to confirm adequate bioavailability in all study participants, particularly those ingesting cannabis products, unless the pharmacokinetic and pharmacodynamic profile for the intervention has been well-defined and published. This limitation should be explicitly and prominently stated in the NICE guidance.	Thank you for your comment. The bioavailability of cannabis-based products is outside the scope of this guideline. NICE uses common outcomes (based on advice from the committee) that matter most for patients and clinicians when deciding treatment in preference to indirect or surrogate measurements. We have published a list of outcomes for each research recommendation in the relevant evidence review.
International Association for the Study of Pain			Methods	Most cannabinoids are highly lipophilic and have lengthy and variable elimination times. In cross-over studies of cannabinoids, on what basis is a one-week washout period considered adequate? If a cross-over study is to be considered as robust evidence, IASP recommends that adequate drug washout should be confirmed by direct plasma measurement of active compounds at the start of the next crossover phase in all subjects. The NICE guidance should highlight this shortcoming as a limitation of the evidence base derived from crossover design studies, when this essential precaution was not reported.	Thank you for your comment. The washout period of 1 week or more was decided by the committee based on their knowledge and experience. This was also confirmed by expert testimony on cannabinoid psychopharmacology provided to the committee. If a study were conducted to ascertain a reasonable washout period, that would be useful for future updates. However, formulating a research recommendation for this would be out of scope for this evidence review.
International Association for the Study of Pain			Methods	Some included studies required a washout period for subjects who were prior cannabis users, then underdosed the study drug relative to the baseline dose self-administered by subjects prior to study enrolment. This could lead to symptoms of THC withdrawal, including heightened anxiety, which might obscure any potential analgesic effect of the study product. This limitation should be highlighted in the draft guidance.	Thank you for your comment. This limitation has been added to evidence review B.
International Association for the Study of Pain			Methods	There appears to be little or no attention given to whether the cannabis/cannabinoid-based products in the included studies were administered adjunctively to other analgesic drugs, or administered and assessed alone. When a study reported an investigation examining the analgesic effect of a cannabis product as an "add-on" to existing analgesic drugs, then the report must be scrutinised to ensure that adequate and appropriate measures were taken to mitigate against a confound. Any such confounds should be reported in the guidance and the evidence treated appropriately.	Thank you for your comment. We have checked the included studies in evidence review B and none administered adjunctively other analgesic drugs. All studies compared a CBMP versus a placebo. There was therefore no need to mitigate against a confounder drug. A research recommendation was made to investigate the effectiveness of CBMP as an add-on treatment.
International Association for the Study of Pain			Research recommendation 1	IASP recommends that opioids plus adjuvants should not be defined as "standard treatment" for fibromyalgia or neuropathic pain.	Thank you for your comment. We have changed the comparator to "usual care as defined by the researchers"
International Association for the Study of Pain		31	33	suggest change to phrase "high doses of analgesia"?	Thank you for your comment. Following further consideration, we have revised the wording in the guideline to 'pain relief'. .
International Association for the Study of Pain		31	28	The IASP experts are not familiar with the term "functional pain"? What is meant by this?	Thank you for your comment. The committee agreed that a 'functional pain measurement tool' is a tool that includes a measurement of functional limitations (such as disabilities) that are caused by the chronic pain. However, we acknowledge that opinion as to what the 'best' tool is changes. Furthermore, functional pain measurement tools can vary with regards to the extent to which functional limitations are measured. Therefore, in the research recommendations, we have changed this term to "a validated pain measurement tool". It would be useful if a validated pain measurement tool had a minimally important difference.
International Association for the Study of Pain		37	Methods	The McGill Pain Questionnaire is not a measure that is specific (as stated in the draft guidance) for neuropathic pain. Similarly, the Brief Pain Inventory is not specific for nociceptive pain. Furthermore, the McGill Pain Questionnaire is not a measure of function. IASP strongly recommends revising these recommendations on pages 37 and 257. If a measure of function that could be used across studies differing in types of pain is desired, a single measure of pain interference with activities (which is not the same as "functional impairment") such as the Brief Pain Inventory Interference Scale could be used. If a specific measure of function is desired, one could use a measure specific to the part of the body involved (for example, back/leg pain versus arm/shoulder pain).	Thank you for your comment. With regards to the research outcomes, we have now changed the wording to: "A validated pain measurement tool". This is because we acknowledge there is no consistency between studies with regards to using measurement tools for pain; favoured measurement tools frequently change. Furthermore, we have deleted the term 'functional' in the evidence review when used in conjunction with the McGill Questionnaire (with the exception of the wording in the protocol, which we should not change retrospectively).

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International Association for the Study of Pain		9	Methods	IASP is concerned by the inaccurate and misleading statement on page 9 that,*" The committee agreed that the clinical outcome that matters most is average pain intensity. This is widely used and easily understood. The next most important outcomes were the proportion of patients who experienced pain relief of 30% or 50% or more from baseline. These are also direct measurements of pain."* There are no direct measures of pain, as pain intensity ratings are patient self-reported. IASP recommends that this last sentence be removed, as should the reference to "direct measurements of pain" on line 40, page 9. Measures of pain-compromised function and quality of life are important and potentially more relevant than simple pain intensity measures when estimating overall effectiveness. Moreover, improvements in pain or functioning that may be due to effects of cannabinoids on associated variables (e.g., improvements in sleep or anxiety) need to be considered.	Thank you for your comment. The reason why average pain intensity and the proportion of patients who experienced pain relief of 30% or 50% or more from baseline can be considered direct measurements of pain is because the context is versus placebo in randomised double-blinded controlled trials; we realise that all analgesia has a strong placebo effect. We acknowledge that other outcomes, such as quality of life and improvements in functioning are important too. Therefore, outcomes included quality of life and Patient Global Rating of Change (PGRC), the McGill Pain Questionnaire and the Brief Pain Inventory.
International Association for the Study of Pain	General	General	General	The International Association for the Study of Pain (IASP) welcomes the draft NICE guidance on cannabis-based medicinal products. IASP will restrict its comments to the chronic pain aspects of the draft guidance. IASP has identified a number of shortcomings in the methods employed to formulate the draft guidance.	Thank you for your comment.
International Association for the Study of Pain	General	General	General	The general lack of a reasonable volume of high quality evidence is concerning. The current evidence base is inadequate for confidence in either refuting or confirming any putative analgesic effects of cannabis-based medical products in various distinct clinical pain conditions. IASP recommends that this limitation be given a higher prominence in the guidance and believes that NICE may not be justified in issuing such firm and generalized recommendations as stated in the draft guidance.	Thank you for your comment. The committee felt able to make recommendations on chronic pain based on the quality and quantity of evidence available. The findings of the health economics modelling also informed recommendations.
International Association for the Study of Pain	General	General	General	1. Scope: IASP notes that studies were excluded from the NICE analysis if they: a) Examined the use of synthetic cannabinoids in schedule 1 of the 2001 regulations. b) Examined the use of smoked cannabis-based products (although one study cited used inhaled vaporized cannabis). c) Did not clearly report the amount of cannabis-based constituents in the intervention. Whilst IASP understands the brief that NICE was given for this guidance, it is concerned that excluding items a & b means that that the guidance is not a complete or comprehensive summary of the evidence pertaining to putative analgesic effects of cannabis and cannabinoids in people living with chronic pain. There is considerable potential for some parties to report/interpret this guidance somewhat loosely without attention to these exclusions and limitations. Therefore, IASP recommends that the exclusions be emphasized in the title and dissemination materials. Exclusion c is also important but IASP is uncertain as to whether some of the included studies reported sufficient data that allow the amount of cannabis-based constituents to be rigorously ascertained.	Thank you for your comment. The exclusions applied in the evidence review is stated in the review protocol. Constituents of the CBMP in the studies was noted in evidence review B, however this information was often poorly reported in the studies.
International Brain Tumour Alliance	Guideline	General	General	The International Brain Tumour Alliance (IBTA) welcomes NICE's plans to issue a Guideline on cannabis-based products for medicinal use. We also welcome guidance from NICE in its current draft, that healthcare professionals should consider nabilone as an add-on treatment for adults with persistent chemotherapy-induced nausea and vomiting not successfully treated with conventional optimal use of antiemetics. But we are disappointed, now that the draft guidance has been published, that NICE has been unable to recommend cannabis-based products for wider use, especially for treating chronic pain. Equally, though, we understand that their decisions must be based on clinical evidence and to this end, NICE has included in its Guideline some recommendations for further research into cannabis-based medicinal products – specifically into the areas of fibromyalgia or persistent treatment-resistant neuropathic pain in adults; children and young people with cancer-associated chronic pain; severe-treatment resistant epilepsy and chemotherapy-induced intractable nausea and vomiting in adults. But we are also disappointed that neither an imperative nor	Thank you for your comment. It is not within NICE's remit to decide which research should be fast-tracked. The committee agreed that an additional recommendation on a national or local registry was needed. This will facilitate an improved evidence base for CBMPs.

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				suggested expedited timeline for fast-tracking clinical research into the use of cannabis-based medicinal products has been included in the draft guidelines. For patients suffering from cancer-associated chronic pain, severe-treatment resistant epilepsy and chemotherapy-induced intractable nausea, these devastating side effects of disease and/or treatment mean that their quality of life is severely affected. Therefore, it is crucial that the further research on cannabis-based products for medicinal use that NICE is recommending is instigated without delay and via trials which are robust but can also deliver the results of their studies rapidly. Time is absolutely of the essence for many of these patients and particularly those with extremely life-limiting prognoses. We strongly support the gathering of a robust evidence bank for the use of cannabis-based medicinal products, and also strongly support the statement in NHS England's paper on *"Barriers to accessing cannabis-based products for medicinal use on NHS prescription"* whereby there is a call for "the development of a national UK patient registry to collect a uniform data set, across all indications, for patients prescribed a cannabis-based product for medicinal use in the United Kingdom". Such a registry for cannabis-based medicinal products could house prescribing data, and clinical outcomes and patient reported outcomes data. Private sector data should also be collected. Clearly, and as mentioned in NICE's draft guidance, close monitoring of every patient taking cannabis-based medicines should be in place on an individual basis. But we believe that a national registry with outcomes data could greatly support future research into this treatment approach as well as providing a detailed assessment of patient outcomes which will assist with issues of patient safety and better understanding of the use of cannabis-based medicinal products.	
Manchester Health and Care Commissioning	General	General	General	British Paediatric Neurology Association advice for prescribers is to check if the insurance will cover prescribing unlicensed CBPM, this can potentially introduce barriers in prescribing cannabis based products.	Thank you for your comment. As part of our prescribing recommendations (rec 1.5.4) we have recommended that a shared care agreement should detail how treatment will be funded.
Manchester Health and Care Commissioning	General	General	General	Commissioning arrangements and its implication remaining unclear.	Thank you for your comment. The shared care agreement will be for local determination.
Manchester Health and Care Commissioning	General	General	General	It is unclear who would be funding the drug.	Thank you for your comment. This will be determined by local funding arrangements.
Manchester Health and Care Commissioning	General	General	General	In addition to your comments below on our guideline documents, we would like to hear your views on these questions: 1. Which areas will have the biggest impact on practice and be challenging to implement? Please say for whom and why. Due to lack of the recommendation on treatment of severe treatment resistance epilepsy, potentially we may see some requests for supply of cannabis based treatment going through IFR panel, this would be subject to commissioning arrangements. Treatment for chemotherapy induced nausea and vomiting (Nabilone) is currently likely to be prescribed by specialist centre. Due to lack of expertise and experience and limited evidence GPs may be resistance prescribe cannabis based treatment. 2. Would implementation of any of the draft recommendations have significant cost implications? Due to lack of data on numbers of patients potentially affected difficult to assess exact cost implication. 3. What would help users overcome any challenges? (For example, existing practical resources or national initiatives, or examples of good practice.) • More evidence on use of cannabis in severe treatment resistance epilepsy, • GM wide guidance and local RAG classification that would support decision making process,	Thank you for your comment.

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				• Development local shared care guidance, • Development of practical resource on prescribing of cannabis, • Ensuring that all clinical systems have appropriate updates to identify interactions with cannabis based products.	
Manchester Health and Care Commissioning	Guideline	4, 11,12,13	general	The evidence for use of nabilone is limited and outdated and there is no data long term safety data which is concerning especially if that to be prescribed in primary care.	Thank you for your comment. The committee agreed that nabilone may play a role in treating intractable chemotherapy-induced nausea and vomiting in people who have not had a full response to optimal antiemetic therapy. Based on the limited evidence, the committee were unable to make a strong recommendation for its use. Therefore, the committee only recommended that nabilone could be considered as an add-on treatment in adults with intractable chemotherapy-induced nausea and vomiting which persists despite the use of optimised conventional antiemetics.
Manchester Health and Care Commissioning	Guideline	General	General	This recommendation will be challenging in implementation due to lack of the expertise and experience in prescribing amongst GPs.	Thank you for your comment. Health Education England have developed a training package to support prescribers. The NHS England document 'Responsibility for prescribing between Primary & Secondary/Tertiary Care' provides details of what the arrangements should consider, and this would be for local determination.
Manchester Health and Care Commissioning	Guideline	General	General	There may be some confusion regarding prescribing responsibilities of cannabis based products and the role of the Specialist Registrars and GPs. Unsure if a GP would be legally able to prescribe under shared care guidance if they not a specialist within the area. Governance processes around prescribing cannabis based products are unclear.	Thank you for your comment. The cannabis-based products for medicinal use FAQs provided by NHS England state that it is possible for a GP to continue prescribing legally under the direction of the initiating specialist prescriber. In terms of prescribing responsibilities, the NHS England document 'Responsibility for prescribing between Primary & Secondary/Tertiary Care' provides details of what the arrangements should consider, and this would be for local determination.
Manchester Health and Care Commissioning	Guideline	General	General	The guideline mentioned shared care guidance; clarification is needed to establish between which organisations the shared care guidelines would be, secondary care and tertiary care or secondary care and primary care.	Thank you for your comment. The shared care agreement will be for local determination.
Manchester Health and Care Commissioning	Guideline	General	General	Potential difficulties in obtaining the drug from a community or hospital pharmacy should be taking in consideration when developing this guideline.	Thank you for your comment. The NHS England/Improvement document 'Barriers to accessing cannabis-based products for medicinal use on NHS prescription' addresses these issues and provides recommendations around access.
MS Society	EIA	General	General	Gender should be subject to explicit consideration. Specifically, prevalence within conditions covered in the guideline should be formally considered and published within equality impact assessment documents. For example, women are three times more likely to receive a diagnosis of MS than men. This should be noted in the equality impact assessment and the committee should consider how to mitigate adverse impacts on women as a result. Its considerations on these issues should be published.	Thank you for your comment. Your suggested gender consideration was added to the equality impact assessment for this guideline. The health economic model did incorporate gender difference in the estimate of background mortality and QALYs. It should also be noted that patients are only allowed Sativex when all other treatment options have been considered, before they undergo invasive intervention/ surgery. They are not eligible to receive Sativex at the point of initial diagnosis.
MS Society	Evidence Review C	189	General	**Background management costs** We agree that the estimated 25% of the resource use costs from Stevenson et al. (2015) could be attributed to spasticity alone is highly uncertain. Without detailed explanation as to why that figure was raised, this appears arbitrary and requires further discussion. This estimation has serious implications to the cost-effectiveness of Sativex and this (unexplained) figure risks treatment options for people with MS being denied.	Thank you for your comments. Based on committee consensus, the committee agreed that the resource use estimated in Stevenson et al. 2015 cannot be said to be 100% attributable to spasticity alone. The committee felt that the vignette from the health care professional survey could be misleading as it explicitly stated that the disability described in the health states was caused by spasticity only. The committee agreed that some of the physical disability specified in the vignette, particularly in the most severe health states, would have involved multiple other features of the underlying MS. Based on published evidence and the committee's experience, the committee does not think treating spasticity would have a major impact on underlying disability associated with MS (measured by EDSS). Therefore, the committee concluded that Stevenson et al. 2015 overestimated the amount of resource use that is solely attributable to medically modifiable spasticity. However, the committee was sensitive to comments such as this, and did not want to underestimate the possible benefits of THC:CBD spray. Therefore, the committee made a consensus to change this parameter to 50%. The committee agreed that this parameter is highly uncertain, and it should be tested in the sensitivity analysis. This parameter has been modified in the model, tested extensively and reported in the spasticity evidence review chapter (Table 23). When doubling the background management costs (assuming 100% of costs from Stevenson et al. 2015 are attributable to spasticity alone), the cannabis strategy

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					became dominant. When halving the background management costs (assuming 25% of costs are related to spasticity), the ICER is around £35,000. The modelling approach you propose would be attractive if any data were available for either the effectiveness of THC:CBD spray in influencing transit between spasticity health states or for the resource use independently associated with any such health states. As no such data are available, the model structure adopted made use of best-available evidence regarding the effectiveness of THC:CBD spray and the resource use associated with spasticity.
MS Society	Evidence Review C	189	10-12	We believe that there are other studies, involving primarily UK patients, that should be considered when assessing what average dosage should be applied in the economic model for Sativex. The Messina et. Al (2017) study, based on Italian data, assumes a dosage of 6.8 sprays daily. Evidence we've heard from patients being prescribed Sativex suggests that average dosage is lower than this. We recommend the inclusion of data from Etges et al. (2016), a peer—reviewed study which included a higher proportion of patients living in the UK (761). Daily dose information in this study was recorded for 798 patients; the mean and median doses were 5.4 and 4.4 sprays/day, respectively. Source: https://www.dovepress.com/an-observational-postmarketing-safety-registry-of-patients-in-the-uk-g-peer-reviewed-article-TCRM	Thank you for your comments. The committee reviewed different published doses of THC:CBD spray (Sativex). The mean THC:CBD spray dose from RCTs is around 7–9 sprays per day. The committee agreed that the initial dose would decrease over time and stabilise around 6 months. The committee also noted that the mean initial dose from a dataset of THC:CBD spray 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. The committee reviewed the post-marketing study by Etges et al. 2016. While the committee agreed that, all other things being equal, it would prefer to use UK-specific data, it chose to retain its reliance on Messina et al. (2017), for the following reasons: • Etges et al. (2016) reports spasticity of various types, whereas Messina et al. (2017) is solely concerned with confirmed MS-related spasticity. • Etges et al. (2016) relied on voluntary submission of data, whereas Messina et al. (2017) is based on a mandatory regulatory registry, meaning it reflects the whole population of interest, rather than a subset selected according to unknown criteria. • Messina et al. (2017) provide patient-level data on response and continuation rates that are used in the model, whereas Etges et al. (2016) provide no such data. Therefore, using Messina et al. (2017) gives the model the important strength that dosage data and effect data are kept together. • The dosage data reported by Messina et al. (2017) are closer to committee-members' own experience (including their knowledge of unpublished audit data from UK practice). On a balance of these considerations, the committee concluded that, despite comprising mostly UK participants, Etges et al. (2016) provides a less reliable estimate of dosage than Messina et al. (2017). However, the committee noted that the value from Messina et al. (2017) used in the consultation draft (6.8 sprays/day) had been taken from the first period of that study and, in common with other evidence, average dosage had reduced over time. Therefore, it agreed that it was inappropriate to use 6.8 sprays/day throughout the treatment phase of the model,

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					and revised its base case so that the dosage reduced to 6.3 sprays/day from 12 weeks onwards, in reflection of Messina et al.'s findings. The revised model assumes: • For the first 4 weeks, a mean THC: CBD spray dose of 8.55 sprays per day, based on a weighted average of doses observed in the 4 included RCTs. • The mean dose decreases to 6.5 per day by 12 weeks and to 6.3 by 24 weeks (Messina et al., 2017) • Beyond this point, a constant dose of 6.3 sprays/day is assumed. This was tested in the sensitivity analysis. With the new daily THC: CBD spray assumption (decrease over time), the ICER is lower than the scenario assuming a constant daily dose of 6.8 sprays (as shown in Table 23 scenario analyses of the spasticity evidence review). De Trane S, Buchanan K, Keenan L, Valentine C, Liddicut M, Stevenson V, Farrell R. 2016. P1292 Nabiximols has a beneficial effect on self report of MS related spasticity. Multiple Sclerosis Journal 22 (Supp 3), 684. De Trane S, Buchanan K, Keenan L, Simeoni S, O'Brien L, Stevenson V, Farrell R. 2017. P1898 THC: CBD (Nabiximols) has a beneficial effect on resistant MS related spasticity and reduces the need for Intrathecal baclofen. Multiple Sclerosis Journal 23 (Supp 3), 1012–1013. De Trane S, Buchanan K, Keenan L, Valentine C, Liddicut M, Stevenson V, Farrell R. 2017. PO123 THC: CBD (Nabiximols) has a beneficial effect on multiple sclerosis related spasticity and delays the need for intrathecal baclofen. Journal of Neurology, Neurosurgery & Psychiatry 88 (Supp 1), A44.
MS Society	Evidence Review C	32	20-22	We agree with the cited limitations of the Ashworth and Modified Ashworth scales. These scales have been criticized as only providing an "ordinal" level assessment of resistance to passive movement, which has limited inter-rater reliability and which does not distinguish well between muscle over activity (spasticity) and biomechanical causes of resistance to passive movement (often referred to as contracture).	Thank you for your comments.
MS Society	Evidence Review C	33	40-41	Agree with the limitation of the studies, which appear not to acknowledge the impact this recommendation will have on people with MS who have been prescribed Sativex and are benefiting now.	Thank you for your comment. After publication of the consultation draft of the guideline, the manufacturer reduced the list price of THC:CBD spray, and this had an important impact on our assessment of its cost effectiveness. In light of stakeholder comments, the committee also reviewed their estimates of likely resource use associated with spasticity symptoms. The committee are now able to make a more positive recommendation.
MS Society	Evidence Review C	35	7-9	During the MS Society's policy review in 2016, our expert medical advisers suggested that the group of patients most likely to benefit are people with severe treatment resistant spasticity and chronic pain. Our advisers estimate that this could be up to 10% of the UK MS population, which would mean approximately 10,000 people. Source: https://www.mssociety.org.uk/about-ms/treatments-and-therapies/cannabis/about-cannabis-and-ms.	Thank you for your comment. This guideline also considered the effects of spasticity on chronic pain. However, limited evidence for chronic pain meant it was not possible to make further recommendations for this population.
MS Society	Evidence Review C	35	26-27	We agree with the committee's recommendations that we need improved tools to assess outcomes for people with spasticity. We have outlined some of the outcomes on quality of life, such as sleep, which need to be taken into specific consideration.	Thank you for your comments. The research recommendation for spasticity includes quality of life and sleep as potential outcomes. The full list of outcomes for the research recommendation can be found in Appendix K of the spasticity evidence review.
MS Society	Evidence Review C	7	5-6	**Definition of spasticity** We believe that the definition of spasticity should be expanded, as it can often be mischaracterised. One clinician we spoke to has previously suggested the definition of spasticity cited has its limitations. Spasticity has been defined as "a specific form of increased muscle tone (hypertonia) associated with a number of neurological disorders".	Thank you for your comment. The definition of spasticity was decided on as part of the scoping process and agreed with the committee at the start of guideline development. Although this differs to your suggestion, this would not affect the studies that were included within the analysis or the recommendations made by the committee.

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				Suggest to amend reference and define spasticity as: "a velocity-dependent increase in tonic stretch reflexes that results from abnormal intra-spinal processing of primary afferent input".	
MS Society	Evidence Review C	7	6-9	**Spasticity prevalence** We believe the prevalence figure cited is an underestimate. Other sources that both the MS Society and the MS Trust use, suggest 60-90% of people living with MS in the UK are affected by spasticity at any one time. Cochrane review of non-pharmacological interventions for MS spasticity has a robust review of prevalence and cites two studies which cite higher prevalence figure. Source: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD009974.pub2/full#CD009974-sec1-0001 Rizzo 2004: Rizzo MA, Hadjimichael OC, Preiningerova J, Vollmer TL. Prevalence and treatment of spasticity reported by multiple sclerosis patients. *Multiple Sclerosis* 2004; 10:589-95. Source: https://journals.sagepub.com/doi/10.1191/1352458504ms1085oa Beard 2003: Beard S, Hunn A, Wight J. Treatments for spasticity and pain in multiple sclerosis: a systematic review. *Health Technology Assessment* 2003; 7:1-111. Source: https://www.journalslibrary.nihr.ac.uk/hta/hta7400/#/abstract There is another source which states prevalence of up to 80%: Pozzili C. Overview of MS Spasticity. European Neurology 2014; 71 (suppl 1):1-3. Source: https://www.karger.com/Article/FullText/357739	Thank you for your comments. These figures are based on a systematic review which we have made reference to in the introduction. We have based our estimates on this review because we are looking at spasticity in a range of conditions as well as MS. However, this has not affected the evidence included in the review or the recommendations made by the committee.
MS Society	Evidence Review C	7	35	**PICO Table** The comparators should specifically include: stretching; Botox (for severe focal spasticity); in-patient or intense physiotherapy and Baclofen pump.	Thank you for your comments. The comparators for this review were any relevant treatment and so would include any evidence on these specific treatments.
MS Society	Evidence Review C	9	8	We believe that studies involving people using synthetic cannabinoid cannabis-based products should be included in order to better understand real-world comparisons. We would not recommend including studies using smoked cannabis, as we know this to have a negative impact on MS prognosis.	Thank you for your comment, This guideline is underpinned by legislation in terms of which cannabis based medicinal products can be considered. Therefore we only considered the following: • cannabis-based medicinal products as defined by the UK Government in November 2018 • the licensed products nabiximols (Sativex) and nabilone. • plant-derived cannabinoids such as pure cannabidiol. • synthetic compounds which are identical in structure to naturally occurring cannabinoids such as delta-9-tetrahydrocannabinol (THC), for example dronabinol.
MS Society	Evidence Review C	General	General	The economic model needs to account for illegal street cannabis as part of its cost-effectiveness assessment. Cannabis based medicinal products should not be viewed in isolation to the significant and persistent evidence that people experiencing chronic pain and spasticity are using illicit sources in order to manage their symptoms, resulting in significant risk to patient safety and costs to public services. The evidence review into spasticity needs to adequately take into account the evidence cited in the submission to the All Wales Medicines Strategy Group in 2014. **Spasticity standard of care** We are not clear from the Appendix what definition of standard of care has been adopted to model the incremental cost-effectiveness ratio for Sativex. As outlined above, our research	Thank you for your comment. NICE can only consider medicinal cannabis that is legally available to patients. It is not within NICE's remit or in the guideline scope to comment on illegal street cannabis. As described in the economic model report, the target population is defined as people for whom all available standard spasticity treatments have failed (Appendix M of the spasticity evidence review). 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. We assume that the standard of care may also include all the supportive care included in the resource use estimate in Stevenson et al. 2015. Medicinal cannabis is only considered as the last treatment option as an add-on to the standard of care before the invasive or surgical interventions in the economic model. As such, medicinal cannabis cannot displace any other standard treatments. The model has considered potential cost saving from the resource use of spasticity management.

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				shows that many people do not benefit from other treatments – or experience very significant side effects from alternative treatments. Any overestimate of the standard of care available would significantly impact on the ICER calculations: we urge NICE to clarify the definition it has adopted and ensure that it reflects our findings	
MS Society	Evidence Review C	General	General	**Impact on caring** The current model also does not adequately account for the impact that effective treatment of spasticity has on the ability to work and the impact this had on carers. See comment 30 below for further details. Elaine, 58, living with MS told us that being able to access effective treatment for spasticity like Sativex would be really significant. "It would give me my life back because really I'm stuck in the house and my husband has had to drop his hours to two days a week so that he can be my carer. So unless my friends take me out or my husband I can't get out of the house"	Thank you for your comments. The costs in a guideline are calculated in line with the NHS and PSS perspective. As described in the economic model report, the model has included resource use associated with home care which was funded by NHS (Appendix M of the spasticity evidence review). The model did not include carer services that are self-funded or care by family members that are not funded by NHS.
MS Society	Guideline	10	15-18	**Research recommendations** We agree with this recommendation and suggest that a specific focus on quality of sleep is included.	Thank you for your comment. The committee discussed your comment and agreed that sleep problems as part of adverse events is more widely reported in studies. Research recommendations have been developed where the committee think evidence would currently be the most useful and are meant to be used as a guide for future research.
MS Society	Guideline	14	23-24	Over 160 people living with MS told us they were accessing cannabis-based medicinal products. 36 of these were people who told us they were prescribed cannabis-based medicinal products. This recommendation puts existing cannabis based product prescriptions for spasticity and at risk of being discontinued. We therefore we would like seek an exemption for existing prescriptions to ensure previous clinical decisions about treatment that have been made by clinicians are upheld. We also spoke to 74 people with MS who have told us that they have either considered taking criminal action or have done in order to receive relief from symptoms. One woman who didn't want to be named, aged 58 and living with MS spoke to us about how before Sativex, she was sourcing symptom relief illegally. She told us: "I've tried a number of anti-spasticity drugs, including baclofen, gabapentin and Pregabalin. I call these 'the zombie drugs', due to the effect they can have. After taking baclofen I also experienced worsening bladder problems, and I'm aware of how people can build up a tolerance to these drugs. With the pain I experienced being so awful, and my responsibility as a mother to four children, I resorted to getting relief from my symptoms by taking street cannabis." Now being prescribed Sativex on the NHS, she told us: "Right now I feel very lucky to have access to Sativex on the NHS. Sativex has improved my quality of life, and meant that this year I was able to enjoy a holiday with my family."	Thank you for your comment. The guideline has been amended to recommend that all those receiving treatment before publication of this guidance can continue to receive treatment. Clinicians can also still make their own individual prescribing decisions in the best interest of their patients
MS Society	Guideline	15	20-21	The explicit referral to the amount of price reduction (over 50%) required to achieve adequate cost-effectiveness criteria provides much needed clarity. However, the recommended cost per quality-adjusted life year does not recognise the benefit Sativex already provides people who are accessing it. It also adds to concerns that this guidance undermines the significant benefit to patients.	Thank you for your comments. The estimated price reduction required to achieve cost-effectiveness is based on the threshold analysis in the economic model, which we have updated to reflect revisions to the model agreed by the committee in response to stakeholder feedback. We acknowledge that there are other measures available to estimate health outcomes among patients. As per NICE guideline manual and NICE reference case, the health effect in

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				The secondary costs to the social and care system to deal with uncontrolled symptoms that medicinal cannabis can help with are also not adequately addressed. Similarly, there are significant benefits to carers of people with MS if the people they care for are able to access relief from painful and exhausting symptoms, even more so for partners if quality of sleep improves. An estimated 86% of people with MS receive caring support from friends and family members. Source: MS Society (2017) Social care and the MS community in England. Link:https://www.mssociety.org.uk/care-and-support/resources-and-publications/publications-search/social-care-and-the-ms-community We would expect this figure to be higher in the patient cohort for Sativex as having moderate or severe spasticity correlates to a higher EDSS score in general (as reflected in the economic model). The cost-effectiveness mode does not adequately address the costs to patients and carers or to society and the economy in general, particularly when it comes to employment and the impact of family and friends of people living with MS. **Impact on employment** We know that there is a significant gap in employment rates between people with MS (36 per cent) and the overall population (75 per cent) in the UK, which means that people with MS may lose a significant number of working years. The current average employment rate of people with a 'mild' form of MS is 37 per cent and for people with severe MS it is 4 per cent. Source : Kobelt et al (2017) 'New insights into the burden and costs of multiple sclerosis in Europe', Multiple Sclerosis Journal; Office for National Statistics, UK labour market July 2017 A report by the Work Foundation in 2016 found that up to 80 per cent of people with MS stop working within 15 years of the onset of diagnosis and 44 per cent retire early because of the condition. It also found that the "professional careers of 57 per cent of relatives are adversely affected by MS of a family member. Source: Bajorek, et al. (2016) The impact of long term conditions on employment and the wider UK economy Link:http://www.theworkfoundation.com/wp-content/uploads/2016/11/397_The-impact-of-long-term-conditions-on-the-economy.pdf This guideline should therefore take into account the potential impact of access Sativex on: • the ability of unpaid carers of people with MS to remain in the workforce and therefore secure tax revenue; and, • the independence and quality of life of unpaid carers.	the economic model should be expressed as QALYs so that an outcome can be compared between different populations and disease areas. As described in the economic model report, the model has included resource use associated with home care which was funded by NHS (Appendix M of the spasticity evidence review). The model did not include carer services that are self-funded or care by family members that are not funded by NHS. As per the manual for Developing NICE guidelines , the costs in a guideline are calculated in line with the NHS and PSS perspective but do not include the wider societal perspective such as loss of productivity. The reason for this is that productivity costs in our analyses would favour those interventions aimed at the working population. We would then discriminate against the elderly, children, unemployed people and people with disabilities. As regards the impact caring for someone with MS has on the quality of life of carers or family members, while such impacts are included in NICE's reference case, we found no evidence that THC:CBD spray leads to improvements in this domain.
MS Society	Guideline	15	8	**Quality of life** The current evidence review does not sufficiently measure the improvement in quality of life as described by patients. The most glaring area of omission comes when assessing the impact of significantly improved sleep. Dr Eli Silber, consultant neurologist, Kings College NHS Foundation Trust said: "Managing spasticity at night enables people to get to sleep. Lack of sleep exacerbates MS symptoms like low mood depression and 'MS fog'" MS fog is a common symptom for people with MS that describes a lack of concentration or slower cognitive function. Iain, living with relapsing-remitting MS who has been prescribed and using Sativex but is unsure whether he will be able to continue treatment in the future, told us: "The only side effect I get from Sativex is a fabulous night's sleep"	Thank you for your comments. Quality of life, sleep and adverse events were considered as part of this review but there was limited evidence on these outcomes to be able to make a recommendation.

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MS Society	Guideline	15	12- 17	**Model and data for Sativex** The economic model suggests that the mean average use of Sativex is 6.8 sprays a day, which runs contrary to the patient reported evidence we have received. A number of patients we spoke to about their Sativex use referred to taking less than 6.8 sprays per day. This also reflects the lower per-day spray model that was used in the 2014 appraisal undertaken by the All Wales Medicines Strategy Group (AWMSG). The precise number of sprays is subject to commercial confidence but we recommend that the committee review the evidence and number of sprays per day recommendation within the AWMSG appraisal. Link: http://www.awmsg.org/awmsgonline/app/appraisalinfo/644 David, living with primary progressive MS, told us: "I'm prescribed 6 sprays a day, but I actually take about 3" F Iain told us: "I use the spray when I need to, for when I get the MS hug, it depends on how bad I am feeling. It is as I need it. I take 3 sprays and within 10-15 minutes, the symptoms are gone." The cost effectiveness analysis should account for and integrate the dosing that is used by patients in practice, which is often lower than the licensed dose. The model used for the appraisal undertaken by the All Wales Medicines Strategy group was lower, making a significant impact on its cost-effectiveness. One neuro-rehab consultant we spoke to told us: "I've got several patients who are on 1, 2, 3 sprays [Sativex] a day. And for the ones who are on more sprays, they tend to wean off other anti-spasticity drugs like baclofen".	Thank you for your comments. NICE produce guidelines for NHS England. It is not within NICE's remit to comment on the AWMSG decisions. Thank you for providing the information on THC:CBD spray dose cases. However, we cannot comment on the individual cases. The committee reviewed different published doses of THC: CBD spray (Sativex). The mean THC:CBD spray dose from RCTs is around 7–9 sprays per day. The committee agreed that the initial dose would decrease over time and stabilise around 6 months. The committee also noted that the mean initial dose from a dataset of THC:CBD spray 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. The committee reviewed the post-marketing study by Etges et al. 2016. While the committee agreed that, all other things being equal, it would prefer to use UK-specific data, it chose to retain its reliance on Messina et al. (2017), for the following reasons: • Etges et al. (2016) reports spasticity of various types, whereas Messina et al. (2017) is solely concerned with confirmed MS-related spasticity. • Etges et al. (2016) relied on voluntary submission of data, whereas Messina et al. (2017) is based on a mandatory regulatory registry, meaning it reflects the whole population of interest, rather than a subset selected according to unknown criteria. • Messina et al. (2017) provide patient-level data on response and continuation rates that are used in the model, whereas Etges et al. (2016) provide no such data. Therefore, using Messina et al. (2017) gives the model the important strength that dosage data and effect data are kept together. • The dosage data reported by Messina et al. (2017) are closer to committee-members' own experience (including their knowledge of unpublished audit data from UK practice). On a balance of these considerations, the committee concluded that, despite comprising mostly UK participants, Etges et al. (2016) provides a less reliable estimate of dosage than Messina et al. (2017). However, the committee noted that the value from Messina et al. (2017) used in the consultation draft (6.8 sprays/day) had been taken from the first period of that study and, in common with other evidence, average dosage had reduced over time. Therefore, it agreed that it was inappropriate to use 6.8 sprays/day throughout the treatment phase of the model, and revised its base case so that the dosage reduced to 6.3 sprays/day from 12 weeks onwards, in reflection of Messina et al.'s findings. The revised model assumes: • For the first 4 weeks, a mean THC: CBD spray dose of 8.55 sprays per day, based on a weighted average of doses observed in the 4 included RCTs. • The mean dose decreases to 6.5 per day by 12 weeks and to 6.3 by 24 weeks (Messina et al., 2017) • Beyond this point, a constant dose of 6.3 sprays/day is assumed. This was tested in the sensitivity analysis. With the new daily THC: CBD spray assumption (decrease over time), the ICER is lower than the scenario assuming a constant daily dose of 6.8 sprays (as shown in Table 23 scenario analyses of the spasticity evidence review). De Trane S, Buchanan K, Keenan L, Valentine C, Liddicut M, Stevenson V, Farrell R. 2016. P1292 Nabiximols has a beneficial effect on self report of MS related spasticity. Multiple Sclerosis Journal 22 (Supp 3), 684. De Trane S, Buchanan K, Keenan L, Simeoni S, O'Brien L, Stevenson V, Farrell R. 2017. P1898 THC: CBD (Nabiximols) has a beneficial effect on resistant MS related spasticity and

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					reduces the need for Intrathecal baclofen. Multiple Sclerosis Journal 23 (Supp 3), 1012–1013. De Trane S, Buchanan K, Keenan L, Valentine C, Liddicut M, Stevenson V, Farrell R. 2017. PO123 THC: CBD (Nabiximols) has a beneficial effect on multiple sclerosis related spasticity and delays the need for intrathecal baclofen. Journal of Neurology, Neurosurgery & Psychiatry 88 (Supp 1), A44.
MS Society	Guideline	15	12-17	**On Sativex trials** queried economic or clinical comparisons made solely on cheaper treatments such as Baclofen, Tizanidine, gabapentin or clonazepam. More adequate comparisons would be second/ third line therapies e.g. botox injections, inpatient / intensive rehab. Other clinicians we spoke to suggested treatment options for spasticity are as follows: • physical treatments, • oral medications that have a systemic effect on spasticity (such as baclofen, Tizanidine and Sativex), • focal treatments for spasticity in a small number of muscle groups (such as phenol peripheral nerve blocks and botulinum toxin) • intra-thecal baclofen • palliative, destructive intra-thecal treatments for lower limb spasticity: intra-thecal phenol and radio-frequency rhizotomy	Thank you for your comments. As described in the economic model report, the target population is defined as people for whom all available standard spasticity treatments have failed (Appendix M of the spasticity evidence review). Medicinal cannabis is only considered as the last treatment option as an add-on to the standard of care before the invasive or surgical interventions in the economic model. As such, medicinal cannabis cannot displace any other standard treatments. The model has considered potential cost saving from the resource use of spasticity management.
MS Society	Guideline	16	7-11	We disagree with this assessment. Our testimonies outline a fragmented and increasingly confused picture of prescribing that is consolidating profound inequity of access across the UK to important symptom relieving therapies like Sativex. Underlining this confusion, Yvonne living with secondary progressive MS, described a distressing, disjointed and unclear clinical pathway to accessing Saitvex that the draft guideline will do little to change. "I was prescribed Sativex by a neurologist in Norfolk. I had been using this for 7 months then CCG stopped it saying it was not cost effective. The hospital then said it was only prescribed by Pain Management department who refused my prescription saying I was a new patient. I have written to the head of Waveney CCG which was a total waste of time. My local MP also wrote to him with the same negative results […] I am still waiting for his help but am not feeling confident that the outcome will be good." One neuro-specialist pharmacist we spoke to told us: "Despite the consistent approach, it actually makes it more confusing not being focused on individual symptoms. This may mean that the timelines are much longer as actually 4 or 5 guidelines are needed rather than one."	Thank you for your comments. We do not expect the recommendation to impact on current practice because this is the same as the recommendation that is currently in the guideline for MS.
MS Society	Guideline	4	12-16	We spoke to over 300 people living with MS within the consultation period and 160 told us they were using medicinal cannabis to manage their symptoms. Symptoms included chronic pain such as the "MS hug" [strong pain in the chest], fatigue and muscle spasms. Of the remaining 140 people, 130 told us that they were or would like to use cannabis-based medicinal products to manage pain specifically. This guidance ignores the patient-reported evidence that cannabis-based medicinal cannabis can help relieve painful symptoms. One of these people, Iain, living with progressive MS told us "I get the "MS hug" quite aggressively and the only thing that helps is Sativex"	Thank you for your comment. This guideline reviewed evidence for chronic pain as well as spasticity. However, current evidence that was within the scope of this review was not sufficient to lead to a recommendation in favour of prescribing Sativex to people with pain from MS.
MS Society	Guideline	4	12	This recommendation does not reflect the unmet meet of people living with progressive neurological conditions like MS that do not respond to licensed treatments for pain.	Thank you for your comment. After publication of the consultation draft of the guideline, the manufacturer reduced the list price of THC:CBD spray, and this had an important impact on our assessment of its cost effectiveness. In light of stakeholder comments, the committee

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				In June 2019, the Neurological Alliance, consisting of over 80 member organisations representing millions of people in England living with neurological conditions, published the results of a survey of 10,339 neurological patients Source: Neurological Alliance, Neuro Patience, July 2019. Link: https://www.neural.org.uk/resource_library/neuro-patience/ 1,195 respondents had MS and the results demonstrate the impact of pain on the lives of many with the condition. A quarter (24%) of respondents with MS said that MS caused pain and discomfort "to a great extent", while almost two thirds (69%) said that they experienced pain and discomfort to a moderate or small extent. In total, 93% percent of respondents with MS experience pain and discomfort, compared to 88% of people living with other neurological conditions. There is a significant unmet need for people with MS experiencing chronic pain. The survey also found that one quarter (26%) of respondents with MS were not receiving any prescribed treatment to help manage their MS, whilst being significantly more likely to be taking non-prescribed medicine to help manage their condition (41%) compared to people living with other neurological conditions (27%).	also reviewed their estimates of likely resource use associated with spasticity symptoms. The committee are now able to make a more positive recommendation.
MS Society	Guideline	5	General	**Chronic pain** One consultant neurologist that we spoke to, , commented that the draft guideline when referring to pain does not distinguish between neuropathic and other pain types in making recommendations. They also omit some results from clinical trials. told us: "In the Sativex clinical trials, in addition to the primary end point which was spasticity there were additional secondary endpoints on pain, bladder and sleep. This is not reflected in the recommendation." Of the over 300 people who contacted us, we also found that significant numbers (61) were accessing CBD oil over the counter, some at great expense, to get relief from painful symptoms in the absence of licenced treatments. This is an intolerable situation which is exacerbated by this recommendation, with a further 69 people (approximately 20% of the total we consulted) telling us that their current treatment for pain or spasticity is not working. To place in context, in 2019, 8,369 people with MS living in the UK responded to the MS Society's My MS My Needs survey between 1st March and 14th June (results to be published later this year). We asked respondents whether they had a conversation with their GP about cannabis for medicinal use. Of the 4430 people who had such a conversation, 21 said that they had received a prescription for medicinal cannabis.	Thank you for your comment. The chronic pain recommendations reflect the quality and quantity of evidence. Outcome such as pain, bladder and sleep were considered in evidence review B but there was insufficient evidence to make a recommendation.
MS Society	Guideline	5	3-8	**Spasticity** We have since spoken to a number of people who are fortunate enough to be accessing Sativex on an NHS prescription and receiving significant relief from pain as well as spasticity. David living with secondary progressive MS: spoke to us about the effect that Sativex has had on him:. "It has been a game changer, it completely got rid of my night cramps. I used to get it occasionally. I don't get any spasticity now. It's been unbelievable. If someone would have said that it would have helped me that quickly, I would not have believed them." John, sole carer for his wife Janice, who lives with secondary progressive MS, spoke to us about Janice's experience of using Sativex. "Janice's spasms and cramps have gone. Pain relief has been significant. Before she couldn't talk or eat without significant pain. Since she	Thank you for your comment. After publication of the consultation draft of the guideline, the manufacturer reduced the list price of THC:CBD spray, and this had an important impact on our assessment of its cost effectiveness. In light of stakeholder comments, the committee also reviewed their estimates of likely resource use associated with spasticity symptoms. The committee are now able to make a more positive recommendation.

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				has been on Sativex she can talk. It's not a whole cure, she still does get some pain, but it is significantly better. It takes about 20 - 30 minutes to take effect." John summed up what many people have told us about their experience of using Sativex: "It puts her back to normal". The 'do not do' recommendation could create greater barriers to the relief that people like Janice experience using Sativex and further barriers to access should not be permitted. We need to see clarity on the face of the final guideline, that ongoing prescriptions for Sativex should not be affected directly by this guideline, and that these decisions should be taken by a specialist consultant alongside people with MS.	
MS Society	Guideline	5	1-2	**Chronic pain in clinical trials** We disagree with this recommendation. The decision to allow the prescriptions of CBD to manage chronic pain within a clinical trial, but not Sativex, does not appear to reflect the patient-reported evidence that Sativex can for some people, bring relief for painful MS symptoms such as the 'MS hug'. We have important patient reported evidence that products such as unlicensed CBD products and Sativex can help people get relief from pain. We believe this should be amended to include the recommendation that Sativex should be assessed and used for its treatment of pain within a clinical trial.	Thank you for your comment. We did consider the clinical evidence on use of Sativex but did not make a recommendation due to a lack of evidence.
MS Society	Guideline	5	4-6	We disagree with this recommendation. This recommendation puts existing NHS cannabis based product prescriptions for Sativex and any other cannabis-based medicinal products at risk of being discontinued. We would like to seek assurances that existing prescriptions about treatment that have been made by clinicians are upheld. Suspending treatment could have serious consequences for the people we have spoken to that are currently accessing life-changing relief from debilitating symptoms, and could be subject to legal challenge. This recommendation also puts people with treatment-resistant symptoms at further risk of considering illegal means for managing their symptoms. 58 people out of the over 300 people who came forward to speak to the MS Society about their experiences in August 2019 told us they have felt driven to source illegal forms of cannabinoids for symptom relief. A further 16 had considered illegal activity to source symptom relief but had not done so for fear of prosecution. This supports previous evidence gathered by the MS Society in 2014. In an anonymised survey, 22% of people with MS told us that they have tried illegal forms of cannabis. Cannabis and MS report in 2017. Link: https://www.mssociety.org.uk/get-involved/campaign-with-us/treat-me-right/cannabis-and-ms A number of people who could benefit from Sativex, but cannot access it, feel their only option is to obtain cannabis illegally. Other people may have tried licensed treatments for pain and spasticity, and found that they do not work for them, and so turn to illicit forms of cannabis instead. In either of such cases they cannot be sure of its quality or dosage and cannot access medical advice on the most safe and effective way of taking it. One person we spoke to, who didn't not want to be identified, aged 40 and living with primary progressive MS, reflected the frustration of many in the MS community who don't have any effective treatment options.	Thank you for your comment. The guideline has been amended to recommend that all those receiving treatment before publication of this guidance can continue to do so. Clinicians can also still make their own individual prescribing decisions in the best interest of their patients

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				"The NHS constitution says that it's there or those who need, not those who can afford. So why when you have a doctor saying that it would work on a prescription can you not get it on the NHS? It blows my mind and is so unfair." She went on to talk about her use of illicit cannabis, saying: "I am at the age of 40 doing something that I never in a million years thought I'd do. And I feel bad about it. And I have had to sit my children down to tell them why I am smoking cannabis – all this because the NHS won't make Sativex available. There is not many options out there for people with primary progressive MS. […] We don't have any more options!" This recommendation should not be viewed in isolation as this type of activity has wide-reaching societal impacts. We know illicit cannabis to be dangerous and smoking cannabis in particular to worsen the prognosis of people living with MS. Source: Briefing on smoking in the UK and specifically in people with MS. Link: https://www.mssociety.org.uk/what-we-do/our-work/our-evidence/risk-factors-and-prevention Debbie, 54, living with secondary progressive MS, highlighted the lack of treatment options available: "I will never or have ever taken drugs […] So please let us have cannabis that our consultants can prescribe and manage" Julie, 45, living with MS who is currently accessing Sativex on the NHS said: "If I wasn't able to access Sativex via the NHS, I'd be faced with paying hundreds of pounds a month for a private prescription – which I could never afford! No wonder so many people choose to buy other forms of cannabis, when it's so much cheaper". People should not be put in a position where they feel the need to take their treatment into their own hands for lack of alternatives, particularly when they feel they need to break the law. The NICE guideline does not consider the very serious patient safety risk that a negative recommendation on Sativex will push people into an unregulated black market for similar treatments – a black market that is much more developed than for other treatments NICE would usually consider. One frequent NHS prescriber of Sativex told us: "Sativex does enable people to get off street cannabis. One person who stands out in my memory, is a young man who had muscle spasms, whose wife was about to have a baby. He told me 'I don't want cannabis in the house', and Sativex offered a much safer and legal option for him and his new family". Sativex being only routinely available on the NHS for people who live in Wales means that the draft guideline consolidates an unacceptable inequality in current treatment options across the UK. Elaine, 58, living with MS, highlighted this starkly: "As I live on the Wirral it seems totally unfair that the consultant working from the Countess of Chester Hospital […] tells me he can prescribe Cannabis for his patients coming from North Wales but not England." We urge the pharmaceutical companies that manufacture and market Sativex, along with NICE and NHS England and NHS Improvement, to open discussions immediately as a means of making Sativex available on the NHS for people with MS as soon as possible. This may include manufacturers accepting a lower price for the medicine.	
MS Society	Guideline	5	7	**Managed access scheme**	Thank you for your comment. The consideration of a managed access scheme is beyond the scope of this guideline.

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				We advocate for a managed access scheme to be implemented alongside any further research into cannabis-based medicinal products. We believe that any further research into cannabis-based products that is undertaken should be undertaken with the purpose to provide immediate access to the estimated 10,000 people living with MS in the UK that we believe could benefit from symptom relief. We believe the best way to do this is via a managed access scheme that may include observational trials of participants linked to prescribing on the NHS. It is important that MS patients, who will be managing painful and treatment-resistant symptoms, are not required to pay to be involved in any access scheme. Source: Cannabis and MS report in 201. Link: https://www.mssociety.org.uk/get-involved/campaign-with-us/treat-me-right/cannabis-and-ms This would be in addition to any randomised, double-blind phase 3 clinical trials into cannabinoids for treating MS. A managed access scheme alongside an observational trial has been cited as a practical solution to balancing the difficult issues of timely access with proving long-term clinical efficacy. The manufacturer already has an agreement in place with the NHS to make Sativex available free of charge for four weeks so a clinician and patient can understand if they respond to the treatment, which could form a strong basis for a wider access scheme. Link: http://sativex.co.uk/doctors/pay-for-responders-scheme/ A spokesperson from the Danish MS Society said that there are currently 6 products that are being accessed through the Danish Medicinal Cannabis Pilot Programme. Link: https://laegemiddelstyrelsen.dk/en/special/medicinal-cannabis/companies/pilot-programme/list-of-admitted-cannabis-products/ We would like any managed access scheme to include trials on chronic pain, in line with recommendations the MS Society made to the Health and Social Care Select Committees inquiry into medicinal cannabis. Link: http://data.parliament.uk/writtenevidence/committeeevidence.svc/evidencedocument/health-and-social-care-committee/drugs-policy-medicinal-cannabis/written/96327.html While it is encouraging that the Danish Medicines Agency has set up an access scheme, it is not without its limitations, with one barrier cited being prescriber confidence to refer patients into the scheme and that patients have to pay in order to take part. Any scheme undertaken in the UK would need to be implemented with this in mind and ensure that relevant professional bodies are consulted on the design.	
MS Society	Guideline	5	10	**Shared care** We agree with this recommendation. However, clinicians we spoke to during the consultation period highlighted the huge challenges incumbent on them to achieve the principles of shared care within current capacity constraints. Whilst we support the recommendation, some clinicians we spoke to warned of unintended consequences. Joela Matthews, neuro-specialist pharmacist, Barts Health NHS Trust said: "It is very difficult to get it [shared care arrangements] approved for a licensed therapy. It is not practical for CBMPs as shared care agreements suit medication that require blood monitoring and the GP will often take over the supply of medication and prescribing but hospital specialists will monitor the bloods and give advice on adjusting the dose if necessary.	Thank you for your comment. The committee considered your comment and agreed that recommendation 1.5.2 as not a strong recommendation but one that uses the word 'may' to enable this to be an option if the GP feels confident to continue prescribing and agrees with the shared care arrangement. The committee also considered the NHS England document 'Responsibility for prescribing between Primary & Secondary/Tertiary Care' that provides details about arrangements and considerations. The committee agreed to refer to this guidance to supplement recommendations 1.5.2 and 1.5.4.
MS Society	Guideline	6	4	**Prescribing**	Thank you for your comment. The recommendation about who should prescribe is mainly based on legislation. Due to the limited evidence base and their unlicensed nature, the

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				We believe this is a sensible recommendation, but it should be stressed that a variety of specialist health professionals should be encouraged to prescribe. During our consultation, we received a number of testimonies from patients who have been receiving repeat prescriptions of Sativex from a variety of specialists, including GPs that have adequately managed their care and treatment. One patient, David aged 60 and living with primary progressive MS, told us: "I consider myself extremely lucky. When Sativex was licensed, I went to my GP. Within a few weeks they had a prescription for me, I continued to get it every three months." This is in stark contrast to the experience of Lorraine living with relapsing-remitting MS who said: "When I have discussed controlling symptoms, the consultants and doctors don't want to go near it [medicinal cannabis] and goes instantly for gabapentin which I won't take because of the side-effects" Lisa, living with primary progressive MS spoke about being prescribed baclofen and Pregabalin: "The medications I've been prescribed have always had a more negative side effect with little result" The current situation reflected in the draft guideline means people like Lorraine and Lisa will continue to not have effective treatment for painful symptoms.	Government has chosen to restrict the decision to prescribe cannabis-based products for medicinal use to only those clinicians listed on the Specialist Register of the General Medical Council. This restriction has been set out in regulations.
MS Society	Guideline	9	14	We would like to see a research recommendation that advocates further research into unlicensed CBD products, such as CBD oil, to treat chronic pain. Sally, living with relapsing-remitting MS told us about her experience trying to obtain effective pain relief and how using CBD oil alongside licensed treatments has helped her feel more herself and reduced the impact of her symptoms. "I wouldn't say my pain has gone completely, but I can now rest and relax a lot better. Which in turn gives me more energy in the day that I wouldn't have had otherwise. I've since come completely off of Pregabalin and take half the Baclofen I used to. I think the combination of Baclofen and Pregabalin side effects not being there makes you more energetic and sociable. I'm more myself now and my active time is a lot more active. When I was on them, I'd often have to have a little nap when I was out. I haven't had to do that in the last year." A consultant neurologist we spoke to said [on prescribing Sativex for pain]: "It demonstrably has a useful role in the management of treatment-resistant spasticity. And by the balance of probability, it will have the same risk/benefit ratio of other drugs that the use for other MS symptom management".	Thank you for your comments. The guideline considered the clinical effectiveness of CBMPs and not over-the-counter products like cannabis oil sold as food supplements. The research recommendation refers to a number of cannabis-based medicinal products that could be investigated. A more detailed list of the products that are included within the research recommendation can be found in Appendix J of the evidence reviews for spasticity and chronic pain.
MS Society	Guideline	General	General	There was unanimity amongst people living with MS and MS professionals that we engaged with over the consultation period that this guideline was extremely disappointing. Over 300 people living with MS responded to the call for evidence we ran during the consultation, the largest response we've ever received on any NICE consultation to date. Lorraine, 50, diagnosed with relapsing-remitting MS in 2009 summed up the overwhelming feedback from people with MS when she said: "We've seen a legal change, but not a change for people managing symptoms." This experience reflects many stories we heard from people with MS who all want a secure and safe means to receive effective relief from painful and relentless symptoms. We spoke with three consultant neurologists, one neuro-rehab specialist and a neuro-specialist pharmacist. Based on feedback from the professional community, the guideline does not adequately address the current issues being described by clinicians; neither	Thank you for your comment. After publication of the consultation draft of the guideline, the manufacturer reduced the list price of THC:CBD spray, and this had an important impact on our assessment of its cost effectiveness. In light of stakeholder comments, the committee also reviewed their estimates of likely resource use associated with spasticity symptoms. The committee are now able to make a more positive recommendation.

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				supporting prescriber confidence, improving uptake, or enabling clinicians to have well-informed conversations with their patients. This guideline doesn't adequately account for clinical expertise and scientific evidence, and would put in highly restrictive guidance for prescribers. One clinician highlighted the inconsistency in approach to this issue, especially when compared to other treatments, citing the case of opioids for chronic pain which are widely available but can be significantly more harmful than cannabis-based medicinal products. It was also commented by professionals that the guideline does not adequately reflect the unique position of medicinal cannabis as a third-line treatment option where there are very few licensed medicinal products for a limited range of symptoms, but a large range of unlicensed products used by patients for a variety of reasons (e.g. CBD oil, health food products). The guideline does not provide patients and clinicians with adequate information on this wide range of products. In addition to MS specialist health care professionals and people with MS, during the consultation period we have engaged wider MS stakeholders such as the MS Trust and the company responsible for marketing Sativex in the UK, Bayer plc.	
MS Society	Guideline	General	General	To answer the questions posed to consultees specifically: 1. "Which areas will have the biggest impact on practice and be challenging to implement?" The area that will have the biggest impact on practice is the recommendation to not recommend the routine use of Sativex for spasticity. This means many people with MS who experience moderate to severe spasticity will be denied an effective treatment option. It also risks terminating treatment for people already being prescribed on the NHS and responding well, in addition to exacerbating the inequality of provision between patients living in Wales and the rest of the UK. 2. "Would implementation of any of the draft recommendations have significant cost implications?" The draft recommendations could have significant cost implications for those people with MS who are receiving treatment for spasticity through Sativex and will face paying up to £450 a month for treatment if required to pay for it privately. The draft recommendations also do not account for the cost impact that managing painful symptoms such as chronic pain and spasticity has on people with caring responsibilities (see comment 29) 3. "What would help users overcome any challenges? (For example, existing practical resources or national initiatives, or examples of good practice.)" A managed access scheme, in line with the MS Society's proposals (see comment 9) would help overcome significant short and medium-term challenges that the draft recommendations could create.	Thank you for your comment. After publication of the consultation draft of the guideline, the manufacturer reduced the list price of THC:CBD spray, and this had an important impact on our assessment of its cost effectiveness. In light of stakeholder comments, the committee also reviewed their estimates of likely resource use associated with spasticity symptoms. The committee are now able to make a more positive recommendation.

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Multiple Sclerosis Trust	Evidence Review C	185	10	**Mean spray dose** The economic model assumes a mean Sativex spray dose of 6.8 sprays per day based on an observational study which recorded this dose level after 4 weeks of treatment (3). We believe that this dose is higher than the dose taken in long term clinical use. In an observational, post marketing safety registry of patients in the UK, Germany and Switzerland (4), the daily dose information was recorded for 798 patients (85%); the mean spray dose was 5.4 sprays/day. The registry includes data from 941 patients, of whom 761 (80%) were UK patients. As 80% of the patients represented by this registry are from the UK, we believe this mean spray dose more accurately reflects the use of Sativex in the UK and should be incorporated into the economic model. It is more appropriate to use data from this registry rather than data from the Messina study. Other studies confirm that in clinical practice, people often require fewer sprays of Sativex per day over the long term. In one registry study (5), a mean dose of 4 sprays/day was recorded, over a mean follow-up of 9 months. (3) Messina S et al. **Sativex in resistant multiple sclerosis spasticity: Discontinuation study in a large population of Italian patients (SA.FE. study).** PLoS One. 2017 Aug 1;12(8):e0180651. https://www.ncbi.nlm.nih.gov/pubmed/8763462 (4) Etges T, et al. **An observational postmarketing safety registry of patients in the UK, Germany, and Switzerland, who have been prescribed Sativex® (THC:CBD, nabiximols) oromucosal spray.** Ther Clin Risk Manag 2016 Nov 11;12:1667-1675. https://www.ncbi.nlm.nih.gov/pubmed/27956834 (5) Koehler J, et al. **Clinical experience with THC:CBD oromucosal spray in patients with multiple sclerosis-related spasticity.** Int J Neurosci. 2014 Sep;124(9):652-6. https://www.ncbi.nlm.nih.gov/pubmed/24392812	Thank you for your comments. The committee reviewed different published doses of THC: CBD spray (Sativex). The mean THC:CBD spray dose from RCTs is around 7–9 sprays per day. The committee agreed that the initial dose would decrease over time and stabilise around 6 months. The committee also noted that the mean initial dose from a dataset of THC:CBD spray 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. The committee reviewed the post-marketing study by Etges et al. 2016. While the committee agreed that, all other things being equal, it would prefer to use UK-specific data, it chose to retain its reliance on Messina et al. (2017), for the following reasons: • Etges et al. (2016) reports spasticity of various types, whereas Messina et al. (2017) is solely concerned with confirmed MS-related spasticity. • Etges et al. (2016) relied on voluntary submission of data, whereas Messina et al. (2017) is based on a mandatory regulatory registry, meaning it reflects the whole population of interest, rather than a subset selected according to unknown criteria. • Messina et al. (2017) provide patient-level data on response and continuation rates that are used in the model, whereas Etges et al. (2016) provide no such data. Therefore, using Messina et al. (2017) gives the model the important strength that dosage data and effect data are kept together. • The dosage data reported by Messina et al. (2017) are closer to committee-members' own experience (including their knowledge of unpublished audit data from UK practice). On a balance of these considerations, the committee concluded that, despite comprising mostly UK participants, Etges et al. (2016) provides a less reliable estimate of dosage than Messina et al. (2017). However, the committee noted that the value from Messina et al. (2017) used in the consultation draft (6.8 sprays/day) had been taken from the first period of that study and, in common with other evidence, average dosage had reduced over time. Therefore, it agreed that it was inappropriate to use 6.8 sprays/day throughout the treatment phase of the model, and revised its base case so that the dosage reduced to 6.3 sprays/day from 12 weeks onwards, in reflection of Messina et al.'s findings. The revised model assumes: • For the first 4 weeks, a mean THC: CBD spray dose of 8.55 sprays per day, based on a weighted average of doses observed in the 4 included RCTs. • The mean dose decreases to 6.5 per day by 12 weeks and to 6.3 by 24 weeks (Messina et al., 2017) • Beyond this point, a constant dose of 6.3 sprays/day is assumed. This was tested in the sensitivity analysis. With the new daily THC: CBD spray assumption (decrease over time), the ICER is lower than the scenario assuming a constant daily dose of 6.8 sprays (as shown in Table 23 scenario analyses of the spasticity evidence review). De Trane S, Buchanan K, Keenan L, Valentine C, Liddicut M, Stevenson V, Farrell R. 2016. P1292 Nabiximols has a beneficial effect on self report of MS related spasticity. Multiple Sclerosis Journal 22 (Supp 3), 684. De Trane S, Buchanan K, Keenan L, Simeoni S, O'Brien L, Stevenson V, Farrell R. 2017. P1898 THC: CBD (Nabiximols) has a beneficial effect on resistant MS related spasticity and reduces the need for Intrathecal baclofen. Multiple Sclerosis Journal 23 (Supp 3), 1012–1013. De Trane S, Buchanan K, Keenan L, Valentine C, Liddicut M, Stevenson V, Farrell R. 2017. PO123 THC: CBD (Nabiximols) has a beneficial effect on multiple sclerosis related spasticity and delays the need for intrathecal baclofen. Journal of Neurology, Neurosurgery & Psychiatry 88 (Supp 1), A44.

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Multiple Sclerosis Trust	Evidence Review C	24 189 215	28 27	**Resource use cost** The economic model assumes that only 25% of the resource use costs from Stevenson et al (2) were attributed to spasticity alone, based on a suggestion from the committee. No evidence-base is provided for this assertion. Data for the cost of spasticity were taken from a study conducted by Dr Stevenson, a leading expert in the treatment of MS-related spasticity, drawing on the expertise of 221 healthcare specialists and published in a highly respected, peer-reviewed journal. There is no justification given for the arbitrary cut-off of 25%. We would maintain that resource use costs for people with moderate to severe spasticity (those covered by the Sativex indication) are likely to be significant and likely to include costly treatments such as intensive in-patient neurorehabilitation, intrathecal baclofen, phenol and botulinum toxin, as well as the cost of health and care for people with very disabling spasticity, such as provision of costly equipment such as hospital beds and hoists and treatment of complications such as contractures and bed sores. A detailed reading of the published study demonstrates that, in fact, all costs increased with higher disease states. (2) Stevenson VL, et al. **The high cost of spasticity in multiple sclerosis to individuals and society**. Mult Scler. 2015 Oct;21(12):1583-92. https://www.ncbi.nlm.nih.gov/pubmed/25623252	Thank you for your comments. Based on committee consensus, the committee agreed that the resource use estimated in Stevenson et al. 2015 cannot be said to be 100% attributable to spasticity alone. The committee felt that the vignette from the health care professional survey could be misleading as it explicitly stated that the disability described in the health states was caused by spasticity only. The committee agreed that some of the physical disability specified in the vignette, particularly in the most severe health states, would have involved multiple other features of the underlying MS. Based on published evidence and the committee's experience, the committee does not think treating spasticity would have a major impact on underlying disability associated with MS (measured by EDSS). Therefore, the committee concluded that Stevenson et al. 2015 overestimated the amount of resource use that is solely attributable to medically modifiable spasticity. However, the committee was sensitive to comments such as this, and did not want to underestimate the possible benefits of THC:CBD spray. Therefore, the committee made a consensus to change this parameter to 50%. The committee agreed that this parameter is highly uncertain, and it should be tested in the sensitivity analysis. This parameter has been modified in the model, tested extensively and reported in the spasticity evidence review chapter (Table 23). When doubling the background management costs (assuming 100% of costs from Stevenson et al. 2015 are attributable to spasticity alone), the cannabis strategy became dominant. When halving the background management costs (assuming 25% of costs are related to spasticity), the ICER is around £35,000. The modelling approach you propose would be attractive if any data were available for either the effectiveness of THC:CBD spray in influencing transit between spasticity health states or for the resource use independently associated with any such health states. As no such data are available, the model structure adopted made use of best-available evidence regarding the effectiveness of THC:CBD spray and the resource use associated with spasticity.
Multiple Sclerosis Trust	Evidence Review C	31	21	**Clinically significant improvement in spasticity** Committee decided that outcomes of 30% or greater improvement in spasticity were key outcomes for assessing effectiveness. This is in contrast to 20% improvement in spasticity related symptoms on a 0-10 patient reported numeric rating scale which were considered clinically significant in the pivotal clinical trials referenced in the Sativex Summary of Product Characteristics (1) and now recommended to identify responders. Sativex Oromucosal Spray. https://www.medicines.org.uk/emc/product/602/smpc	Thank you for your comments. The choice of 30% or greater improvements in spasticity was based on committee expertise and is an outcome that was more commonly reported in the literature. In addition to the 30% responder analysis we also considered 'change in spasticity using any validated scale' which also included the effects for people who did not reach the 30% threshold.
Multiple Sclerosis Trust	Evidence Review C	31 32	37 1	**Enriched enrolment design** The committee was critical of the design of two of the RCT studies which employed an initial phase to identify responders to Sativex. As noted by some members of the committee, this approach reflects clinical practice and is entirely appropriate to select those patients covered by the Sativex indication. This is analogous to subgroup analyses routinely used in NICE technology appraisals. However, the other members of the committee chose to downgrade these studies for risk of bias. We entirely agree with those members of the committee who considered that an enriched study design reflects clinical practice; it specifically identifies those people with MS covered by the Sativex indication and therefore gives the most accurate measure of clinical efficacy for the eligible subgroup. Evidence from the two studies which have used enriched enrolment should certainly not be downgraded.	Thank you for your comments. Although the studies were classified as high risk of bias, they were still considered part of the evidence base and helped to form the committee's opinion that Sativex appears to have benefits for people with spasticity. The committee's final decision on recommendations was made on the basis of lack of cost-effectiveness rather than questions over clinical effectiveness or trial design.
Multiple Sclerosis Trust	Evidence Review C	33 35	46 26	**Impact of Sativex on quality of life** People with MS-related spasticity report gaining benefit from Sativex in small advances, such as remaining mobile enough to self-toilet, for example, or being able to transfer with less pain from wheelchair to bed and vice versa.	Thank you for your comments. There was limited evidence on the effects on quality of life for people with spasticity. However, the committee discussed that this is an important outcome that is not well reflected in existing outcomes. For this reason the committee made a research recommendation aimed at investigating the effects of cannabis-based medicinal products on

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				The way that Sativex is used (self-dosing by oral spray) means it can be taken before activity, (for example, transferring) as this is when spasm can be a problem. This may mean that the person with MS can take a minimum dose and keep control of managing their own symptoms. The addition of Sativex means that it may be possible to decrease the dose of other anti-spasticity medication and so decrease troublesome side effects. Patient carers have also reported that taking Sativex before activity results in easier handling and moving of someone with spasticity. These are subtle but significant therapeutic gains which improve quality of life and reduce the burden of care but are not reflected in crude measures such as EQ-5D.	quality of life. More detailed information on the research recommendation can be found in Appendix K of the evidence review for spasticity.
Multiple Sclerosis Trust	Guideline	4 9	11 15	**Chronic pain** Neuropathic pain is a very common and debilitating symptom of MS. Current treatments may not be effective and have significant side effects. There is evidence that a number of cannabis based medicinal products (CBMP) may improve neuropathic pain in MS; we would like to see the committee extend their recommendations for research to include a broader range of CBMP (rather than just CBD) for persistent treatment-resistant neuropathic pain.	Thank you for your comment. With regards to adult studies, the economic analysis suggested that most types of chronic pain were not going to be cost-effective to manage using medicinal cannabis. However, if any types of chronic pain could be cost-effective to manage using medicinal cannabis, they are most likely to be fibromyalgia and treatment-resistant neuropathic pain. Therefore, the committee wrote research recommendations for these conditions. There is no RCT data for children with regards to medicinal cannabis. Therefore, the research recommendations for children are less specific.
Multiple Sclerosis Trust	Guideline	5	3	**Spasticity** The MS Trust is disappointed that the committee have been unable to recommend Sativex for spasticity in people with multiple sclerosis (MS) despite acknowledging that the evidence demonstrates clinical benefits. The committee's decision is based on an economic model developed for this guideline. We entirely recognise the importance of establishing cost effectiveness for a treatment but we feel that the committee decision has been dominated by a very technical analysis of the economic model. This gives little opportunity for stakeholders with limited expertise in health economics to be able to participate and challenge assumptions. There is a danger of the decision process being consumed by a mathematical model and disconnected from the reality of clinical practice. Although cost effectiveness estimates take account of comparative costs of treatment and monitoring, they do not take account of supply of limited resources. In particular, cost effectiveness estimates do not reflect the real-world impact of limited access to NHS services such as physiotherapy, wheelchair services and even GP appointments or the effect that efforts to access these services can have on the lives of people with MS and their families and carers. Sativex is licensed as a treatment for symptom improvement in adult patients with moderate to severe spasticity due to multiple sclerosis (MS) who have not responded adequately to other anti-spasticity medication and who demonstrate clinically significant improvement in spasticity related symptoms during an initial trial of therapy. This is a specific subgroup of people with intractable spasticity, identified by three criteria: • Moderate to severe spasticity • Not responded to other anti-spasticity medication • Show clinically significant improvement after an initial trial (free one month trial, funded by Bayer's Pay by Responder Scheme) We do not believe that the committee's discussions have adequately reflected the small number of people identified by this very specific subgroup for whom Sativex could offer significant benefits.	Thank you for your comment. We have responded to your comments separately.

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				While it is possible to be prescribed Sativex privately, in practice the cost of the treatment makes this option impossible for the vast majority of people with MS, particularly those on limited income or who are unable to work. We hear from people who are facing real economic hardship in order to fund the cost of Sativex for themselves or a member of their family. These are the issues that people are facing in order to access a licenced CBMP. However, our understanding is that the economic model does not adequately represent several critical factors which we address in our comments 4, 5, 6 and 7 below.	
Multiple Sclerosis Trust	Guideline	General	General	The Multiple Sclerosis Trust welcomes the development of this guideline. Access to cannabis-based medicinal products (CBMP) is a frequent subject of enquiries taken by the information team at the MS Trust; anecdotally many people with multiple sclerosis (MS) report benefits from cannabis and cannabis-based medicinal products. Feedback from MS specialist nurses and neurologists confirms that access to cannabis-based medicines is a regular topic of discussion in clinics. We congratulate the committee on developing these guidelines in a very short timescale. However, it is very disappointing that the only positive recommendation made in this guideline is for nabilone to treat intractable nausea and vomiting. In contrast to almost every other medicine, those people who are unable to access licenced cannabis-based medicinal products can resort to sourcing illicit cannabis, with all the associated risks and costs to society. Recent changes to the legal status of medicinal cannabis and the recommendations of this guideline take us nowhere nearer to resolving these issues.	Thank you for your comments. The recommendations for this guideline were based on current available evidence. The committee acknowledged that more, high quality, evidence was needed. A number of research recommendations were therefore developed which are aimed at improving the quality of evidence so that future committees will be able to make more evidence-based decisions on the use of cannabis-based medicinal products.
National Institute of Medical Herbalists	Guideline	General	General	The National Institute of Medical Herbalists is the UK's leading professional body of herbal practitioners. The Institute sets standards of education and of professional conduct for its members. We promote the benefits, efficacy and safe use of herbal medicine and believe that this can only be assured when administered by appropriately-qualified practitioners. Although herbal practitioners tend to focus on whole-plant preparations, the Institute welcomes the development of national practice Guidelines to support the use of cannabis-based medicinal products and other plant-based medicines. Herbal practitioners are not empowered to prescribe cannabis-based medicinal products but our patients may be users of such products. The Guideline will be helpful in this regard. Last year, the Institute adopted the following position on the therapeutic use of cannabis. Although certain aspects of the position clearly fall beyond the scope of the Guideline, we hope that other aspects, such as the call for evidence from practice-based research might, for example, inform the recommendations for research. We have included also the background to the position that pre-empts to some extent the development of the Guideline. ***Position*** *NIMH believes that:* • *the current legal status of cannabis in the UK (and the current proposed changes)* *limits opportunities for herbal practitioners a) to support their clients in the therapeutic* *use of cannabis and b) to conduct related practice-based research;*	Thank you for your comments.

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				• *evidence from practice-based research in itself would serve to better quantify benefits and mitigate risks associated with the therapeutic use of cannabis;* • *in order to protect their clients from known risks, as well as to explore the benefits of cannabis, herbal practitioners need to be well-informed on the therapeutic use of cannabis, irrespective of current legal status, including but not limited to forms and dosage (including modes of administration), therapeutics (actions and indications) and contraindications.* ***Background*** *The National Institute of Medical Herbalists (NIMH) recognises that:* • *there is robust scientific evidence to support the beneficial therapeutic use of cannabis for a range of conditions;* • *scientific evidence has revealed a degree of risk associated with the therapeutic use of cannabis;* • *much, although not all, of the evidence around the therapeutic use of cannabis has resulted from relatively-narrow empirical studies involving botanically-derived products;* • *recent challenges to the legal status of cannabis in the UK may result in changes that may make certain botanically-derived products available for prescription by approved medical practitioners;* • *a substantial number of current and prospective clients of herbal practitioners are using cannabis for "self-treatment" in a number of therapeutic settings.*	
Neonatal and Paediatric Pharmacists Group	Guideline	1		States guideline covers 'people…'. We would suggest that this guideline covers, children, young people and adults.	Thank you for your comment. People is used as a catch all term to include babies, children, young people and adults. Specific recommendations for populations are made based on the quality and quantity of the evidence.
Neonatal and Paediatric Pharmacists Group	Guideline	4	4	Only adults have been considered here. Is there any recommendations for chemotherapy induced nausea and vomiting in patients <18 years of age. We are aware the nabilone is used in some centres and part of some local guidelines. We note that use is also within the Children's Cancer and Leukaemia Group guidelines https://www.piernetwork.org/uploads/4/7/8/1/47810883/cclg_cinv_guideline_march_2018.pdf which covers adolescent patients.	Thank you for your comment. In the intractable nausea and vomiting review, evidence was identified for a number of different interventions. This evidence supported the use of nabilone to be considered as an add-on treatment for intractable nausea and vomiting in adults. Some evidence was identified for the use of CBMPs in children however this evidence was limited and of low quality. Additionally, nabilone is not currently licensed in children as safety

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				I note there is a comment on page 12 lines 3-5 indicating that the group could not make any recommendations for children and young people – but this statement was not included on page 4.	and efficacy has not been established. The committee did not think a 'do not use' recommendation was appropriate for this population as more evidence is needed. Therefore, the committee drafted research recommendations for the use of CBMPs in this population.
Neonatal and Paediatric Pharmacists Group	Guideline	4	12	Recommendation not to use for chronic pain in adults. Presume this is the same for children, but we would suggest recommendation covers children, young people and adults. We welcome the research recommendation on page 9 line 22-27 and page 14 – line 17/18	Thank you for your comment. We have not made a recommendation for children. This is due to a lack of robust, high quality evidence. Instead, we have made research recommendations for babies, children and young people. If we advised that medicinal cannabis should not be used for children, research is likely to be inhibited. This would not be warranted because we have no RCT data on children and our aim is to promote further research to improve the evidence base.
Neonatal and Paediatric Pharmacists Group	Guideline	5	4-6	Only multiple sclerosis is covered in the statement – does this statement need to also cover the wider range of spasticity conditions discussed on page 15/16 i.e. Cerebral palsy, motor neurone disease and spinal cord injury,	Thank you for your comments. The committee felt unable to broaden their recommendations to other conditions because limited evidence was available for conditions other than MS.
NHS Ealing CCG	Evidence Review B	147	1	Is there an editorial decision to only produce forest plots when there is a meta-analysis i.e. more than one trial? It is helpful to have the forest plots to see the visual effects of all treatments covered in the summary of evidence tables. (As per most previous NICE guidelines)	Thank you for your comment. Forest plots are only produced when there is a meta-analysis.
NHS Ealing CCG	Evidence Review B	147	1	Please paste all forest plots into Word using a vector graphic format (.emf, .svg) so that the plots are not pixelated (aids reading), and text can be searched once converted to PDF. Some of the text is unreadable when magnified, and the text cannot be searched (e.g. for trial author)	Thank you for your comment. We will follow your suggested formatting advice.
NHS Ealing CCG	Evidence Review B	15	Table	Malik 2017: population. Please check if this is a chronic primary pain population as the description 'functional' implies primary not secondary pain. The exclusions for the study also seem to imply that secondary disorders were excluded.	Thank you for your comment. The inclusion criteria for pain for Malik 2017 was: "Patients aged 18–75 years were included if they fulfilled diagnostic criteria of at least two weekly episodes of chest pain for the last 3 months." This fulfilled our protocol's definition of chronic pain because the pain persisted for 3 months or longer. We did not discriminate against studies on the basis of whether the pain was primary or secondary. This is because, according to the ICD-11 classification of chronic pain, if we only included secondary causes of chronic pain, we would have to exclude conditions such as chronic widespread pain (including fibromyalgia). If we only included primary causes of chronic pain, we would have to exclude conditions such as cancer, diabetic neuropathy and rheumatoid arthritis.
NHS Ealing CCG	Evidence Review B	185	(Johnson 2010) Parallel RCT 96 MD -4.07 (-8.05, -0.09)	"Functional impairment caused by pain: Brief Pain Inventory - Short Form for cancer pain (values greater than 0 favour placebo)" Johnson 2010 MD -4.07 (-8.05, -0.09). Please check the MIDs for this metric. The mean difference here is less than 10% of subscale for pain interference (7 Qs each score 0-10, so scale is 0-70). There is likely to be imprecision. If there is imprecision, please change GRADE and see comment 9 p31 ln 20 above, which relies on this.	Thank you for your comment. For this evidence review, the default MID was crossing the line of no effect rather than an MID of 10%. With regards to outcomes, a notable exception was mean pain intensity that had an MID of 20%, which is a value that is commonly used for mean pain intensity, for example in Cochrane reviews. Therefore in this review, Brief Pain Inventory – Short Form was be downgraded once for imprecision if the 95% confidence interval for the effect size crossed the line of no effect, 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 (<40 participants).
NHS Ealing CCG	Evidence Review B	213	11	The model assumes that a 30% reduction in pain is plausible. Yet the only input to the model from the clinical review for the chronic pain population is Van de Donk 2018. This was a study of Fibromyalgia in 20 patients and looked at pain reduction 3 hours after single dose. The decision to model a 30% pain reduction in the chronic pain population therefore lacks external validity. Can you make it clear that the committee's assumption here is not based on any evidence from the clinical review, and is simply a modelling construct? This should also be noted as a limitation of the model.	Thank you for your comments. The 30% improvement threshold is based on the expert opinion at the committee. This parameter is only used to determine the continuation of treatment. The treatment response is based on the absolute NRS changes in the model. We have added further information in the relevant section in Appendix I of chronic pain evidence review to clarify.
NHS Ealing CCG	Evidence Review B	215	10-11	The Langford 2013 paper describes treatment for central neuropathic pain due to multiple sclerosis. Is there any evidence to confirm that this pain mechanism is typical and can be applied to the broader population of chronic pain patients in England? There are about 100,000 patients with multiple sclerosis in England, most of whom do not have neuropathic pain. The Portnoy 2012 paper describes treatment of cancer pain, with a 4 week follow up. Are either of these papers describing the 28 million people in UK with chronic disabling pain? (Fayaz 2016). **Given the indirectness of the populations in the inputs to the model, do you think that you should downrate the applicability of the model from 'minor limitations'?**	Thank you for your comments. We acknowledge that there is heterogeneity in chronic pain populations. As per the guideline scope, the analysis should be inclusive and does not specify types of pain. The model is based on the best available clinical evidence. Subgroup analyses were conducted for specific treatments and for specific types of chronic pain where data were available. We recognise the limitations that some of the subgroup analysis conclusions may not be generalisable to the overall chronic pain population. We have validated the model data with the committee as well as submitted the report for peer-review

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					with additional clinical experts during the consultation. As such, we consider the model estimate to reflect best-available clinical evidence and experience. The de novo model is critically appraised using the economic evaluation checklist from NICE guideline manual 2018 Appendix H. 'Minor limitations' means that the study is unlikely to change the conclusions about cost effectiveness. 'Potentially serious limitations' indicates that the limitations could change the conclusions about cost effectiveness. As described in Appendix I of the chronic pain evidence review, albeit the limitations, the conclusion of the chronic pain model is unlikely to change. Therefore, the chronic pain model has minor limitations, rather than potentially serious limitations.
NHS Ealing CCG	Evidence Review B	217	23	The model assumes that "pain score does not change over time". However, the Langford study shows that pain scores converge with placebo, and no significant difference beyond 10 weeks. In a chronic pain (fibromyalgia) population, it is more likely that the pain scores will return to pre-treatment levels over a longer period of time. Therefore, the most likely scenario for people with chronic primary pain (fibromyalgia) lies somewhere between your current base case and the sensitivity analysis No10 p239 (ICER £1.3m). Why was a more conservative base case not chosen? How have you reflected this in the committee discussion of the model?	Thank you for your comments. We acknowledge that there is heterogeneity in chronic pain populations. As per the guideline scope, the analysis should be inclusive and does not specify types of pain. The model is based on the best available clinical evidence and the committee consensus. As you highlighted in your other comments, there is a lack of evidence in chronic pain. We relied on the committee consensus for several model assumptions. We have validated the model data with the committee as well as submitted the report for peer-review with additional clinical experts during the consultation. As such, we consider the model estimate to reflect best-available clinical evidence and experience.
NHS Ealing CCG	Evidence Review B	222	7	The estimate of 10% is vastly over-estimated. There are 16 million people in England with chronic LBP. There is pain clinic capacity to perform RFD in less than 1% of these pts per year. If the proportion of people with LBP in your model is small, you can probably ignore this poor estimate.	Thank you for your comments. We acknowledge that there are other potential downstream treatment options in chronic pain. Radiofrequency denervation (RFD) was considered as a common downstream treatment for people with chronic low back pain. This is only relevant when considering the population with low back pain in the model.
NHS Ealing CCG	Evidence Review B	230	3	For the chronic pain population (fibromyalgia), there are two studies reporting EQ-5D, neither of which show clinically important differences. The strongest evidence in the clinical review for fibromyalgia pts relates to Skrabek 2008, which use the Fibromyalgia Impact Questionnaire in 40pts, assessed at 1 week follow up. To consider the utility, you have to make two assumptions: 1: the FIQ maps to pain (which it doesn't) and 2: that the pain score can be mapped to utility. In addition, there is no long-term utility data in the clinical review, and it is difficult to see how the modelled long-term utility data has external validity. See comment 19 p217 ln23 above. In the light of this, **do you think that you should downrate the applicability of the model from 'minor limitations'?**	Thank you for your comments. We acknowledge that there are other measures available to estimate health outcomes among patients. As per NICE guideline manual and NICE reference case, the health effect in the economic model should be expressed as QALYs so that an outcome can be compared between different populations and disease areas. FIQ (Fibromyalgia Impact Questionnaire) is only applicable for fibromyalgia. EQ-5D is the preferred measure of health-related quality of life. The model applied data from a regression model based on an EQ-5D survey of 2,719 neuropathic pain patients, which is in line with the NICE reference case. The de novo model is critically appraised using the economic evaluation checklist from NICE guideline manual 2018 Appendix H. 'Minor limitations' means that the study is unlikely to change the conclusions about cost-effectiveness. 'Potentially serious limitations' indicates that the limitations could change the conclusions about cost-effectiveness. As described in Appendix I of the chronic pain evidence review, albeit the limitations you have highlighted, the conclusion of the chronic pain model is unlikely to change. Therefore, the chronic pain model has minor limitations, rather than potentially serious limitations.
NHS Ealing CCG	Evidence Review B	233	7	The problem with this assumption "then the model settles into a steady state where about 43% and 37% of patients remain as responders respectively (see Figure 4)" is that it is amplifying a non-clinically and non-statistically important difference between the groups beyond the end of the trial data at 14 weeks, represented by the area between the two curves. This lacks external validity and overestimates treatment effects, although this is partially addressed by the sensitivity analysis No10 p239 (ICER £1.3m). In the light of this, **do you think that you should downrate the applicability of the model from 'minor limitations'?**	Thank you for your comments. We acknowledged the uncertainty of long-term treatment effect in CBMPs in chronic pain. We have tested relevant parameters in sensitivity analyses: different treatment effects in pain subgroups, declining treatment effect over time, declining placebo effect (Table 12 in the chronic pain evidence review). The ICER results of the sensitivity analyses showed that CBMPs are not cost-effective in all scenarios. The de novo model is critically appraised using the economic evaluation checklist from NICE guideline manual 2018 Appendix H. 'Minor limitations' means that the study is unlikely to change the conclusions about cost effectiveness. 'Potentially serious limitations' indicates that the limitations could change the conclusions about cost effectiveness. As described in Appendix I of the chronic pain evidence review, albeit the limitations, the conclusion of the chronic pain model is unlikely to change. Therefore, the chronic pain model has minor limitations, rather than potentially serious limitations.
NHS Ealing CCG	Evidence Review B	240	13	See comment 12 p33 ln18 (duplicated here): Please consider rewording or removing this sentence. As currently drafted, patients and clinicians may seize on this to prescribe privately or purchase over-the-counter. Whilst the sentence is technically correct when considering the numerator and denominator of the ICER, it lacks external validity. I am concerned that a person with chronic pain or their clinician might conclude that if the person bought their own cannabis, that this would mean that the scenario now falls within the NICE usual ICER for a recommendation. However, this ignores the lack of clinical evidence for a long-term effect	Thank you for your comments. This statement is based on a threshold analysis. We have revised the statement based on the new list price of THC: CBD spray, which concluded to become cost-effective, the cannabis treatment needs to be around 6 times less expensive, or the cannabis strategy needs to accrue 1.22 QALYs compared to 0.162 QALY in the base case. This statement is intended to highlight the unlikelihood of cannabis being cost-effective for treating chronic pain. Therefore, the model could only be based on RCT data. The economic model already included the costs of managing the side effects.

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				and ignores the risk of harm. Also, even if the provision cost to the NHS of the drug is zero, there are still the costs of consultation and management of side-effects, which would fall to the NHS. Also, if you consider scenario 10 in the sensitivity analysis on p239, with an ICER of £1.3m, you would need implausible reductions in cost and improvements in clinical effectiveness.	
NHS Ealing CCG	Evidence Review B	25	10	The choice to create a de novo economic model seems odd given the lack of long-term data for the chronic pain population and the number of assumptions and indirect methods used to calculate utility. (see also comment 11 p33 ln16) Perhaps you would consider: 1. A threshold analysis: how much QALY gain or pain improvement would need to be seen, or how much the drug acquisition costs would need to be for this to be considered cost effective. It is highly unlikely that the committee would conclude that this could be cost effective. 2. A resource impact analysis could be provided based on current list prices for varying percentages of the UK chronic pain population. Again, it will be seen that this is rapidly unaffordable, particularly as there was no evidence of opioid reduction in the clinical review. Please consider adding these two analyses.	Thank you for your comments. This statement has been based on a threshold analysis, which concluded that the cannabis strategy needs to accrue 1.22 QALYs to be cost-effective, compared to 0.162 QALY in the base case. We have revised the statement in the chronic pain evidence review accordingly. The guideline doesn't recommend the use of medicinal cannabis for chronic pain or any subgroups of chronic pain. Hence, it is not feasible to estimate the resource impact.
NHS Ealing CCG	Evidence Review B	31	18	Please redraft the opening statement in view of the limited evidence – see comment 9 p31 ln20 below. "There is very limited evidence to suggest…"	Thank you for your comment. There was enough evidence to suggest that most types of chronic pain were not cost-effective to manage using medicinal cannabis. However, if any types of chronic pain could be cost-effective to manage using medicinal cannabis, they are most likely to be fibromyalgia and treatment-resistant neuropathic pain. Therefore, we wrote research recommendations for these conditions. For the adult research recommendation, the committee wanted to focus on CBD (either as a pure product or containing traces of THC). There is no RCT data for children with regards to medicinal cannabis. Therefore, the research recommendations for children are less specific.
NHS Ealing CCG	Evidence Review B	31	20	Please consider rewording this sentence: "THC reduced mean functional impairment caused by pain in a population of 96 participants who had cancer" because there may be inconsistencies in the reporting of Johnson 2010 in the review: p29 line 5 states favours placebo. Forest plot on p151 favours active. Also, please check comment on p185; GRADE score may need to be revised as very likely to be imprecision. (The MD is much less than 10% of the scale 0-70, and the CI almost reach point of no effect -zero). Therefore, less reliance should be placed on this study. (see comment 16 p185 Johnson 2010 below)	Thank you for your comment. We have presented the relevant data published in Johnson 2010. The RCT data that we reviewed favours some types of medicinal cannabis for managing chronic pain compared to placebo. However, although this reaches statistical significance, the effect size is so small that individual people are unlikely to notice any difference. We have changed our minimally important difference for chronic pain intensity from 10% to 20% so that it is consistent with Cochrane and similar to a 2018 systematic review of MIDs for chronic pain intensity (median 23%). Furthermore, we have updated the GRADE table.
NHS Ealing CCG	Evidence Review B	31	22	Please break into two sentences because there are two separate issues relating to the clinical evidence and limitations of the economic evidence. Firstly, there is no clinical evidence presented that cannabis-based medicine products provide pain relief or reduce functional impairment in the longer term, and there is a high uncertainty about the effects in the shorter term, complicated by high drop-out rates in the active treatment groups. Secondly, the economic evidence needs to be seen in the context of highly uncertain short-term clinical effects and lack of evidence of clinical effects in the longer term. As a result of the input assumptions and lack of long-term data, the economic model is amplifying a small and highly uncertain clinical effect.	Thank you for your comment. We can only analyse the data we have available and the quality and quantity of evidence is limited. However, if an effect of medicinal cannabis on chronic pain cannot be detected at 14 weeks (for example) it is unlikely to be detectable at 6 months.
NHS Ealing CCG	Evidence Review B	33	16	Please explain why the economic model is considered to only have minor limitations. There are three problems: lack of long-term data, lack of data representing the breadth of pain conditions and lack of utility data. 1. The lack of long-term clinical efficacy data for the chronic pain population and the number of assumptions and indirect methods used to calculate utility suggest that the model has moderate or severe limitations. Specifically, with respect to the model inputs, the Langford 2010 study shows that pain scores converge with placebo, and no significant difference beyond 10 weeks.	Thank you for your comments. The de novo model is critically appraised using the economic evaluation checklist from NICE guideline manual 2018 Appendix H. 'Minor limitations' means that the study is unlikely to change the conclusions about cost-effectiveness. 'Potentially serious limitations' indicates that the limitations could change the conclusions about cost-effectiveness. As described in Appendix I of the chronic pain evidence review, in spite of the limitations you have highlighted, the conclusion of the chronic pain model is unlikely to change. Therefore, the chronic pain model has minor limitations, rather than potentially serious limitations. We acknowledge that there are other measures available to estimate health outcomes among patients. As per NICE guideline manual and NICE reference case, the health effect in

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				2. In addition, Langford 2013 describes treatment for central neuropathic pain due to multiple sclerosis. Is there any evidence to confirm that this pain mechanism is typical and can be applied to the broader population of chronic pain patients in England? There are about 100,000 patients with multiple sclerosis in England, most of whom do not have neuropathic pain. Portnoy 2012 describes treatment of cancer pain, with a 4 week follow up. Are either of these papers describing the 28 million people in UK with chronic disabling pain? (Fayaz 2016). 3. To consider the utility, you have had to make two assumptions: a) the FIQ score maps to pain (which it doesn't because it measures functional impairment not pain) and b) that the pain score can be mapped to utility and There is no long-term utility data in the clinical review, and it is difficult to see how the modelled long-term utility data has any external validity. **Please consider revising the committee's view of the economic model.**	the economic model should be expressed as QALYs so that an outcome can be compared between different populations and disease areas. FIQ (Fibromyalgia Impact Questionnaire) is only applicable for fibromyalgia. EQ-5D is the preferred measure of health-related quality of life. The model applied data from a regression model based on an EQ-5D survey of 2,719 neuropathic pain patients, which is in line with the NICE reference case.
NHS Ealing CCG	Evidence Review B	33	18	Please consider rewording or removing this sentence. As currently drafted, patients and clinicians may seize on this to prescribe privately or purchase over-the-counter. Whilst the sentence is technically correct when considering the numerator and denominator of the ICER, it lacks external validity. I am concerned that a person with chronic pain or their clinician might conclude that if the person bought their own cannabis, that this would mean that the scenario now falls within the NICE usual ICER for a recommendation. However, this ignores the lack of clinical evidence for a long-term effect and ignores the risk of harm. Also, even if the provision cost to the NHS of the drug is zero, there are still the costs of consultation and management of side-effects, which would fall to the NHS. Also, if you consider scenario 10 in the sensitivity analysis on p239, with an ICER of £1.3m, you would need implausible reductions in cost and improvements in clinical effectiveness.	Thank you for your comments. This statement is based on a threshold analysis. We have revised the statement based on the new list price of THC: CBD spray, which concluded to become cost-effective, the cannabis treatment needs to be around 6 times less expensive, or the cannabis strategy needs to accrue 1.22 QALYs compared to 0.162 QALY in the base case. This statement is intended to highlight the unlikelihood of cannabis being cost-effective for treating chronic pain.
NHS Ealing CCG	Evidence Review B	33	18	As drafted, this sentence does not reflect the implementation costs (impact assessment) given the large population who might benefit. So simply reducing the cost does not mean that the drug would necessarily be recommended without an impact assessment. (see request for impact assessment comment 8 p25 ln 10 – due to the large number of people with chronic pain in the population). Please redraft to acknowledge that a financial impact assessment would need to be carried if the intervention met the usual ICER threshold for recommendation.	Thank you for your comments. The guideline doesn't recommend the use of medicinal cannabis for chronic pain or any subgroups of chronic pain. Hence, it is not feasible to estimate the resource impact.
NHS Ealing CCG	Guideline	14	8	What is the reference for the statement that 15% of people with chronic pain have high-dose analgesic side-effects? (i.e. how has this figure been estimated). Please add the reference as a footnote or add this to the introduction in the full evidence review.	Thank you for your comment. This figure was provided by our expert committee based on their clinical experience of managing pain.
NHS Ealing CCG	Guideline	14	9	What is the reference for the statement that CBMP might improve safety? Is this committee opinion or based on research? Please add the reference as a footnote or add this to the introduction in the full evidence review.	Thank you for your comment. This was provided by our expert committee based on their clinical experience of managing pain. The guideline has been amended accordingly.
NHS Ealing CCG	Guideline	4	12	Given the lack of clinical and cost-effectiveness evidence (rather than evidence of no benefit), would you consider an 'only in a clinical trial' recommendation for THC for managing chronic pain in adults? (See comments 17 p213 ln11, 18 p215 ln10-11, 21 p230 ln3, 22 p233 ln7) below.	Thank you for your comment. There was no evidence for the use of CBD alone (either as a pure product or containing traces of THC). Therefore, the committee recommended that CBD should not be offered unless as part of a clinical trial. A research recommendation was also made accordingly. THC was not included in the research recommendation as evidence was found for THC alone and in combination with CBD.
NHS Ealing CCG	Guideline	9	15	Given the lack of clinical and cost-effectiveness evidence (rather than evidence of no benefit), would you consider a broader research recommendation covering all cannabinoid products and common painful conditions. For instance "What is the clinical and cost effectiveness of cannabinoids, singly or in combination, in individual chronic painful conditions including both chronic primary pain conditions (e.g. fibromyalgia), and chronic secondary pain conditions (e.g. low back pain, osteoarthritis)	Thank you for your comment. With regards to adult studies, the economic analysis suggested that most types of chronic pain were not going to be cost-effective to manage using medicinal cannabis. However, if any types of chronic pain could be cost-effective to manage using medicinal cannabis, they are most likely to be fibromyalgia and treatment-resistant neuropathic pain. Therefore, we made research recommendations for these conditions. For the adult research recommendation, the committee wanted to focus on CBD (either as a pure product or containing traces of THC). There is no RCT data for children with regards to medicinal cannabis. Therefore, the research recommendations for children are less specific.

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NHS Ealing CCG	Guideline	9	18	The sentence "What is the effectiveness of CBD as an add-on treatment compared to standard treatment alone?" appears to be a repetition of the previous sentence. Should this be removed? Should it be reworded to also recommend research into the clinical and cost-effectiveness of CBD compared to standard treatment or placebo (i.e. not as an add-on)?	Thank you for your comment. We have now removed the second sentence. The comparator is now usual care as defined by the researcher.
NHS England/Improvement	Guideline			- *Which areas will have the biggest impact on practice and be challenging to implement? Please say for whom and why.* The recommendations are mainly related to specialist services, however, impact on primary care will be at the time of transfer of shared care to primary care services. Monitoring of side effects, titration of treatment and most importantly identification of dependence, misappropriation or inappropriate use might pose most challenges for general practitioners. Initial assessment at the time of initiating treatment may prove to be challenging due to lack of continuity and transfer of information between services. Risk of lack of knowledge and expertise for monitoring in primary care - *Would implementation of any of the draft recommendations have significant cost implications?* Shared care arrangements between primary and secondary care services may require additional resources to fully implement recommendations in the guidelines – coordination of care between multidisciplinary team may require additional staff/manpower to maintain continuity of care. - *What would help users overcome any challenges? (For example, existing practical resources or national initiatives, or examples of good practice.)* Access to practical information, availability of specialist services for general practitioners to approach when needed, ease of communication between services such as secure emails and advice and guidance pathways as part of e-referral system. Access to information on clinical decision support softwares such as DXS, map of medicine and CKS would help confirm understanding of knowledge and recommendations of the guidelines.	Thank you for your comment. The guideline has recommendations on shared care, supporting shared decision making, the use of national or local registry and transition of care which are all of relevance and acknowledge the importance of primary care.
NHS England/Improvement	Guideline			- *Which areas will have the biggest impact on practice and be challenging to implement? Please say for whom and why.* The recommendations are mainly related to specialist services, however, impact on primary care will be at the time of transfer of shared care to primary care services. Monitoring of side effects, titration of treatment and most importantly identification of dependence, misappropriation or inappropriate use might pose most challenges for general practitioners. Initial assessment at the time of initiating treatment may prove to be challenging due to lack of continuity and transfer of information between services. Risk of lack of knowledge and expertise for monitoring in primary care - *Would implementation of any of the draft recommendations have significant cost implications?* Shared care arrangements between primary and secondary care services may require additional resources to fully implement recommendations in the guidelines – coordination of care between multidisciplinary team may require additional staff/manpower to maintain continuity of care. - *What would help users overcome any challenges? (For example, existing practical resources or national initiatives, or examples of good practice.)* Access to practical information, availability of specialist services for general practitioners to approach when needed, ease of communication between services such as secure emails and advice and guidance pathways as part of e-referral system.	Thank you for your comment.

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				Access to information on clinical decision support softwares such as DXS, map of medicine and CKS would help confirm understanding of knowledge and recommendations of the guidelines	
NHS England/Improvement	Guideline			Overall for the management of the epilepsies the guidance appears clear.	Thank you for your comment.
NHS England/Improvement	Guideline	6 7 18 19	General for the following lines lines 2-23 lines 1-5 lines 25-29 lines 1-3	We are supportive of the use of shared care between specialists and GPs in principle where this is safe and where there are a high number of on long-term, stable patients requiring minimal monitoring between specialist visits. We disagree with the recommendation that prescribing of cannabis-based medicinal products can be via a shared care arrangement between a specialist and another prescriber. All prescribing should be restricted to specialists only. This is because: • The treatment is new and has been rarely used with little evidence for benefit as described in the previous recommendations. New specialist treatments with a poor evidence base are not appropriate for shared care with community GPs. • Given that there is only one indication recommended by this guidance and this is very specialist, there is no need for this to be under shared care. Specialists should prescribe and supply for this indication and for any clinical trial prescribing for the other indications. • There are commonly used and efficient access to medicines that are prescribed monthly and supplied by specialists for other specialist medicines which are needed long-term. Examples include HIV medicines (which are long-term medicines), erythropoetin and oral cancer therapy • Hospital generated prescriptions are delivered directly to patients via arrangements made by the hospital using Homecare contracts. Alternatively, the hospital provides a prescription that the patient can access from a community pharmacy (FP10HP). This means the rationale for the recommendation for shared-care on the grounds of patient burden is not justified when considered against other risks of this approach. • There is a high risk of diversion of cannabis-based medicinal products (which are classified as controlled drugs). Restricting the supply chain (prescribing and delivery to the patient) via the specialist centre reduces the risk of inappropriate non-specialist prescribing or access via the diversion of the medicines from the legitimate supply chain. • Experience with shared care of other specialist medicines already results in diversion of dependence forming medication that are specialist initiated and then continued by another prescriber (e.g. the GP). Given the risks with cannabis-based medicinal products for illicit use or diversion of prescribed products, these outweigh the small benefits in having shared-care. • Experience and feedback from GPs and other non-specialist prescribers about shared care for highly specialised medicines especially those which have a high risk of illicit use, is that GPs are unwilling to prescribe under shared care arrangements. This means that if the shared care recommendation remains in this guideline, there is likely to be local variation in this arrangement being implemented as GPs will continue to refuse requests from specialists for shared care. In health and justice settings, where the challenge of managing people on high risk medicines is high both clinically and operationally, shared care arrangement with specialists for these medicines would not be supported. • Increased activity for GP appointments within prison establishment for prisoners that may exhibit drug-seeking behaviours. This may impact on waiting times and delays in treatment for prisoners with a genuine health concern. Some indicators for use e.g. chronic pain can easily be staged by prisoners therefore difficult for prescribers to	Thank you for your comment. The committee considered your comment and agreed that recommendation 1.5.2 as is not a strong recommendation but one that uses the word 'may' to enable this to be an option if the GP feels confident to continue on prescribing and agrees with the shared care arrangement in place. The committee also considered the NHS England document 'Responsibility for prescribing between Primary & Secondary/Tertiary Care', that provides details about arrangements and considerations. The committee agreed to refer to this guidance to supplement recommendation 1.5.2.

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				assess genuine symptoms. Specialist assessment and monitoring including retaining prescribing responsibility will reduce this risk. • The concept of shared care and consistency of care is problematic due to transfers of prisoners between prisons. Specialist-led prescribing will minimise variation in how prescribing is continued for transferred and released prisoners • In addition, the prescribing of these medicines by HJ-based prescribers increases the potential for increase in challenging behaviours for those prisoners requesting this medication but that do not meet the criteria: ie bullying of prisoners that have a prescription; increase in violence and aggression towards health care professionals that do not support an individual's request for a prescription. • If prescribed, there will be a requirement for healthcare teams to work with prisons as this medication will impact on mandatory and random drug testing results. Medication could mask the use of illicit drug taking. There is a likelihood that patients will access private specialists who will initiate medicinal cannabis for indications not supported by NICE. Enabling shared care for these medicines will a) encourage NHS care to be provided outside NICE guidance and b) create a two tier system of access to those patients who can afford to fund a private specialist. This is a particular risk for patients admitted to HJ settings. Retaining prescribing with specialists will prevent this issue from arising as patients will need to fund ongoing supplies of medicinal cannabis.	
NHS England/Improvement	Guideline	1	Table – bullet 4	We believe that there should be a footnote for "dronabinol" referencing the definition in the Misuse of Drugs Regulations 2001 (SI 2001/3998 Regulation 2) as amended.	Thank you for your comment. This information is included in the guideline.
NHS England/Improvement	Guideline	17	1-10	This is very confusing and could be open to misinterpretation. It does not recommend either for or against CBD in adult epilepsy syndromes. The ABN guidelines suggest CBD should only be prescribed to adults with Dravet syndrome and Lennox-Gaustat syndrome. However, these draft NICE guidelines state 'The committee agreed that they should not make a recommendation against CBD based medicinal products as this would restrict further research… and prevent people who are apparently benefiting from continuing with their treatment…' At the very least, this paragraph could perhaps be worded better, perhaps to reflect that those already apparently benefitting from CBD should continue on their treatment but that there is currently no clear evidence that CBD is effective in adult epilepsy syndromes, and caution should be taken when prescribing this medication until further research regarding safety and effectiveness is available.	Thank you for your comment. The rationale and impact section of the guideline states: 'The committee discussed the limited evidence and agreed that it did not warrant a practice recommendation. However, they also agreed that they should not make a recommendation against the use of cannabis-based medicinal products as this would restrict further research in this area and would prevent people who are currently apparently benefiting from continuing with their treatment. Until there is clear evidence, specialists, people with epilepsy and their carers should continue to make treatment decisions in the best interests of each person with epilepsy in line with the GMC information for doctors.'
NHS England/Improvement	Guideline	17	13-14	"…[the committee] discussed that some individual funding request are denied because of lack of evidence of effectiveness." NHS England assumes this relates to CCG IFRs as the only specific IFRs considered by NHS England (Spec Comm) are for the paediatric epilepsies – these have been declined on the basis of the patient belonging to a cohort for which a policy is required. As such no commentary has been made about clinical effectiveness.	Thank you for your comments. This was highlighted based on local decision-making rather than reference to NHS England specifically.
NHS England/Improvement	Guideline	20		Economic evidence and cost-utility analysis well balanced (JC)	Thank you for your comments and support.

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NHS England/Improvement	Guideline	31	19	Important to state that there is a wide variation in outcome measures in 'spasticity'. Focus on adverse events particularly important in Paediatrics – safety as important as efficacy Patient related scales. Ashworth and tardieu scales are recognised as a very poor inter and intra observer reliant measure (JC)	Thank you for your comments. Different measures of spasticity, including issues associated with the Ashworth scale, are discussed in the quality of the evidence section of the evidence review.
NHS England/Improvement	Guideline	32-35	29	The committee pass no comment on Paediatric use, a comment about lack of sufficient grade of evidence to date would be useful. The committee have focussed on MS and lost Paediatric use altogether (JC)	Thank you for your comments. As there was no evidence available for paediatric spasticity the committee felt that they could only comment on CBMPs in relation to adults. However, the research recommendation in Appendix K of the evidence review is aimed at both adults and children.
NHS England/Improvement	Guideline	4	15	We are concerned that these recommendations will limit the ability to further develop the evidence of the management of chronic pain with THC (delta-9-tetrahydrocannabidiol) as part of a clinical trial. We believe that consideration should be given to amending the recommendation to read: "Do not offer THC (delta-9-tetrahydrocannabidiol) to manage chronic pain in adults unless as part of a clinical trial."	Thank you for your comment. There was no evidence for the use of CBD alone (either as a pure product or containing traces of THC). Evidence was found for CBD in combination with THC, THC alone, dronabinol and nabilone. Therefore, the committee recommended that CBD should not be offered unless as part of a clinical trial. The committee also made a research recommendation for CBD in adults with fibromyalgia or treatment-resistant neuropathic pain. THC was not included in the research recommendation as evidence was found for THC alone and in combination with CBD. .
NHS England/Improvement	Guideline	4	16	We are concerned that these recommendations will limit the ability to further develop the evidence of the management of chronic pain with a combination of cannabidiol (CBD) and THC. We believe that consideration should be given to amending the recommendation to read: "Do not offer with a combination of cannabidiol (CBD) and THC to manage chronic pain in adults unless as part of a clinical trial."	Thank you for your comment. There was no evidence for the use of CBD alone (either as a pure product or containing traces of THC). Evidence was found for CBD in combination with THC, THC alone, dronabinol and nabilone. Therefore, the committee recommended that CBD should not be offered unless as part of a clinical trial. The committee also made a research recommendation for CBD in adults with fibromyalgia or treatment-resistant neuropathic pain. THC was not included in the research recommendation as evidence was found for THC alone and in combination with CBD.
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NHS England/Improvement	Guideline	5	16	It appears appropriate to make no recommendation on the basis that the HTA of CBD in Dravet and Lennox Gastaut syndromes is separate, although it would be useful for both sets of guidance to be announced at the same time	Thank you for your comment. This guideline is scheduled to publish before the results of the technology appraisal. However, if the results of the appraisal affect anything in the guideline then this information would be updated. A cross reference to the technology appraisal will be made when published.
NHS England/Improvement	Guideline	6	1	Research recommendations for severe treatment-resistant epilepsy only cover CBD and THC in combination with CBD, but recommendations on 5 line 11 covers use of all cannabis-based medicinal products for severe treatment-resistant epilepsy.	Thank you for your comment. The protocol for this review meant that we looked for evidence of the effectiveness of a range of cannabis-based medicinal products. Once the committee were aware of the limited evidence base for the treatment of severe treatment-resistant epilepsy they decided to make the research recommendations specific to CBD and CBD:THC to try and promote more high quality research towards the medications investigated in the observational studies.
NHS England/Improvement	Guideline	6	10	Recommendation for specialist to provide initial prescription could be expanded by inclusion of point covered on line 15 so that it is clear that titration and adjustment of the dose will remain responsibility of the specialist initiating the treatment. It will help make clear that	Thank you for your comment. The committee agreed that recommendation 1.5.3 makes it clear that dose adjustment will be made by specialist initiating treatment. This would be

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				recommendation will not lead to additional workload for primary care physicians to consider adjustments for future treatment.	captured as part of the shared care agreement which would be an agreement between the specialist and the GP.
NHS England/Improvement	Guideline	6	1	Research recommendations for severe treatment-resistant epilepsy only cover CBD and THC in combination with CBD, but recommendations on 5 line 11 covers use of all cannabis-based medicinal products for severe treatment-resistant epilepsy.	Thank you for your comment. The prescribing recommendations cover all of the conditions included in the review and so cover more than just those included for severe treatment-resistant epilepsy.
NHS England/Improvement	Guideline	6	10	Recommendation for specialist to provide initial prescription could be expanded by inclusion of point covered on line 15 so that it is clear that titration and adjustment of the dose will remain responsibility of the specialist initiating the treatment. It will help make clear that recommendation will not lead to additional workload for primary care physicians to consider adjustments for future treatment.	Thank you for your comment. The committee agreed that recommendation 1.5.3 makes it clear that dose adjustment will be made by specialist initiating treatment. This would be captured as part of the shared care agreement which would be an agreement between the specialist and the GP.
NHS England/Improvement	Guideline	6	4	Prescribing – further definition of a 'specialist' with criteria for 'interest' in the condition would be preferable. What expertise would be counted as an 'interest'. As it is stated, the interpretation will be difficult in practice	Thank you for your comment. The committee agreed that it would be difficult to define specialist with an interest because the accreditation and actual term 'specialist' and 'interest' varies amongst the Royal colleges for specific disease areas.
NHS England/Improvement	Guideline	6		There is an incongruence in that these prescribing guidelines are highlighted, although there is no recommendation for epilepsy. Would it be useful to highlight at the beginning of this section, for those where cannabinoid products can be utilised?	Thank you for your comment. The committee agreed the prescribing recommendations support prescribers with safe and effective prescribing of CBMPs when they are considered for treatment in patients when all treatments options have been exhausted and benefits of treatment outweighs the harm. These prescribing recommendations will be useful when there is more evidence around the use of cannabis-based medicinal products.
NHS England/Improvement	Guideline	7	4-5	This recommendation may result in challenging situation for primary care physician should initiating prescriber move location without information.	Thank you for your comment. This could be part of the shared care agreement and would need to be agreed locally. Recommendation1.5.4 also outlines that share care arrangements should make provision for when the patient, initiating specialist prescriber or other prescriber moves location (including transition to adult services).
NHS England/Improvement	Guideline	7	11-12	The recommendation may prove to be difficult to implement given lack of continuity of information across services such as secondary care, substance misuse, mental health and primary care services.	Thank you for your comment. The committee agreed that a multidisciplinary team discussion may help when thinking about the factors to consider and may be addressed as part of the treatment history of the patient.
NHS England/Improvement	Guideline	7	15	Whilst including advice on line 24, this recommendation does not take into account substances that can be purchased over the counter or from herbal shops.	Thank you for your comment. This issue has been addressed in recommendation 1.5.5 - When prescribing and monitoring cannabis-based medicinal products, take into account: current and past use of cannabis (including any over-the-counter and online products).
NHS England/Improvement	Guideline	7	4-5	This recommendation may result in challenging situation for primary care physician should initiating prescriber move location without information.	Thank you for your comment. This could be part of the shared care agreement and would need to be agreed locally.
NHS England/Improvement	Guideline	7	11-12	The recommendation may prove to be difficult to implement given lack of continuity of information across services such as secondary care, substance misuse, mental health and primary care services.	Thank you for your comment. The committee agreed that a multidisciplinary team discussion may help when thinking about the factors to consider.
NHS England/Improvement	Guideline	7	15	Whilst including advice on line 24, this recommendation does not take into account substances that can be purchased over the counter or from herbal shops.)	Thank you for your comment. The recommendation states including over the counter and the committee agreed that this would capture those purchased from herbal shops.
NHS England/Improvement	Guideline	7	11	We believe that the "history of substance misuse" should be changed to explicitly refer to a "…history of substance misuse **including the illicit use of cannabis**."	Thank you for your comment. The recommendation has been amended in line with your feedback.
NHS England/Improvement	Guideline	General	General	Agree with position statement and lack of reasonable grade RCTs in child population – there are a number of case series in Paediatric Spasticity – either Cerebral Palsy or acquired. Initial comment is made that if less than 5 RCTs are found then cohort studies would be reviewed – there is no evidence of this. There was a good summative paper in Developmental Medicine and Child Neurology this year (Nielsen et al DMCN 61(6) 631-638) focussing on the cohort studies that have been reviewed.	Thank you for your comments. Given the lack of RCTs for spasticity in children a search of observational studies was conducted. However, there were no studies that matched the inclusion criteria for this review. We do not include abstracts as part of our review process but any RCTs that results from this should form part of future updates.

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				There is an abstract from a large multicentre blinded RCT in the use of Sativex in children age 8-18, which showed no benefit in Cerebral Palsy – publication of paper is pending (Fairhurst, Kumar, Turner) A greater discussion of the positive and negative factors of tone seen in upper motor neurone syndrome – many clinicians are veering away from the term spasticity – what are we using the Cannabinoids for? No discussion about dystonia is made at any point – either positive or negative	There was limited evidence for upper motor neurone syndrome. The committee therefore did not feel they could discuss the effects in detail until more evidence becomes available. Dystonia was out of scope for this guideline.
NHS England/Improvement	Guideline	General	General	In the absence of RCTs in Children we would ask for a research recommendation, also discussion about the ratios of CBD to THC for this use. More comment should be made about age limitation and risk in children	Thank you for your comments. Two research recommendations were made for CBMPs for people with epilepsy. More detail on these can be found in Appendix K of the evidence review. The committee did not make a research recommendation regarding the ratios of CBD: THC as improved evidence on effectiveness was considered a priority. Ratios of CBD to THC could then be examined further
NHS England/Improvement	Guideline	General	General	We support the NICE recommendations for the indications for which medicinal cannabis can be used. We would value the opportunity for people residing in HJ settings be included in clinical trials recommended for other indications in this consultation. Many individuals in health and justice services e.g. prisons have high levels of substance misuse. There is significant potential therefore for dependence, diversion and misuse in these environments. There are also high levels of mental health and medical history such as liver impairment, renal impairment and cardiovascular disease in health and justice. This potentially increases the risk of using cannabis based medicinal products in these settings	Thank you for your comment.
NHS Greater Glasgow & Clyde	Guideline	6	6	Consider adding in "Though not recommended in children and young people under the age of 18 if prescribed the initiating prescriber should be a tertiary paediatric specialist"	Thank you for your comment. These recommendations are intended to be general and apply in all circumstances where clinicians are considering prescribing CMBPs.
NHS Greater Glasgow & Clyde	Guideline	6	22	When considering reasons to stop treatment could ethical considerations such as "patient, family carer responsibilities" not being met be included?	Thank you for your comment. This could be part of the shared care agreement and would need to be agreed locally.
NHS Greater Glasgow & Clyde	Guideline	7	9	Include "illicit use" as it does later in text	Thank you for your comment. Following further discussion by the committee, it agreed that this is already covered in recommendation 1.5.5 and 1.5.7 and is an important issue to consider.
NHS Greater Glasgow & Clyde	Guideline	7	15	Include "antipsychotics"	Thank you for your comment. The list in this recommendation is not exhaustive but includes some examples.
NHS Greater Glasgow & Clyde	Guideline	8	7-8	Signs of dependence should be discussed at initiation	Thank you for your comment. The committee agreed that this is covered in recommendation 1.5.5.
NHS Greater Glasgow & Clyde	Guideline	8	7	Remove word "any"	Thank you for your comment. The recommendation has been amended to reflect your comment.
NHS Greater Glasgow & Clyde	Guideline	8	16	Add in that is it "illegal" to pass these medicines on	Thank you for your comment. The committee agreed that this is an important issue and is addressed further in the controlled drugs guideline which is cross-referenced in recommendation 1.5.9.
NICE Chronic Pain Guideline Committee	Evidence Review B	33	18	We would suggest that the wording explaining the ICER should be modified so it doesn't imply that these products aren't being funded just because they are too expensive. As written it could suggest that if it was cheaper the NHS would fund it, but this would not be the case if the clinical effectiveness evidence is still lacking.	Thank you for your comments. We have revised the statement in the chronic pain evidence review accordingly.

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NICE Chronic Pain Guideline Committee	Guideline	4	11 +	We don't share the committee's confidence in extending the available evidence to all types of chronic pain, especially as much of the evidence is from studies in people with multiple sclerosis, a very distinct condition that is not translatable to all other chronic pain conditions. (Relates to recommendation 1.2 and evidence in Evidence review B). Furthermore, we are concerned that a 'do not use' recommendation may restrict the likelihood of research funding. As the reason for this 'do not use' recommendation was a lack of evidence of sufficient quality, it would seem perverse if this recommendation led to a low priority being attached to research into the use of cannabis-based medicinal products to treat other chronic pain conditions.	Thank you for your comment. The committee felt able to make recommendations on chronic pain based on the quality and quantity of evidence available. The findings of the health economics modelling also informed recommendations. Furthermore the committee made research recommendations for chronic pain to promote the evidence base in this area.
NICE Chronic Pain Guideline Committee	Guideline	9 and 14	15-21 and 3-18	Given the paucity of evidence available for most chronic pain conditions / categories, the range of cannabis-based medicinal products within them, and the overall low quality of the evidence they found, a more general research recommendation covering all cannabis- based medicinal products and all chronic pain conditions in adults might have been expected. The first research recommendation for people with chronic pain only considers CBD in fibromyalgia and persistent treatment-resistant neuropathic pain. However, there is no good justification given for why other cannabis-based products were excluded or why it is restricted to fibromyalgia and persistent treatment-resistant neuropathic pain. If the committee's only research recommendation in adult chronic pain is to be so specific, an evidence based rationale for this specificity is essential. There is growing interest in cannabis, and cannabis-derived substances as medicines, leading to potential wider use in the UK. In addition there is widespread marketing and availability of CBD oil, without prescription, for chronic pain and anxiety symptoms. We recognise that this is a matter of concern and welcome the inclusion of the research recommendation for cannabidiol (CBD) for fibromyalgia. However we think that the recommendation should go further. We would suggest a rewording of the research recommendation to broaden to other chronic pain conditions, and to other cannabis-based medicinal products, for example: "*What is the clinical and cost effectiveness of cannabis-based medicinal products, singly or in combination, in individual chronic painful conditions including both chronic primary pain conditions (e.g. fibromyalgia), and chronic secondary pain conditions (e.g. osteoarthritis).*"	Thank you for your comment. With regards to adult studies, the economic analysis suggested that most types of chronic pain were not going to be cost-effective to manage using medicinal cannabis. However, if any types of chronic pain could be cost-effective to manage using medicinal cannabis, they are most likely to be fibromyalgia and treatment-resistant neuropathic pain. Therefore, the committee wrote research recommendations for these conditions. For the adult research recommendation, the committee wanted to focus on CBD (either as a pure product or containing traces of THC) as there was no evidence for the use of CBD alone. There is no RCT data for children with regards to medicinal cannabis. Therefore, the research recommendations for children are less specific.
Parkinson's UK	Guideline	6	10-13	We endorse recommendation 1.5.2 and would argue that should effective cannabis-based products for Parkinson's be identified in the future Parkinson's nurse prescribers would be able to participate in the shared care arrangements. Parkinson's nurse prescribers work with consultants to initiate, monitor and optimise medications for people with Parkinson's and there should be no issues with adding cannabis-based products to this with the relevant guidance and training.	Thank you for your comment. This would be down to local determination on who could share the prescribing with the specialist doctor.
Parkinson's UK	Guideline	6	14-16	Respondents to our survey who have used cannabis-derived products in the past said they didn't experience side effects, and that these products didn't interact with their Parkinson's medication. This was backed by professionals. However, people who haven't used cannabis-based products are worried about potential side effects and interactions with Parkinson's medication. (Parkinson's UK. Cannabis and Parkinson's: the views of people with Parkinson's and health and care professionals, July 2019 - https://bit.ly/2ksvzXA accessed 4 September 2019). Therefore, we agree with recommendation 1.5.3 as it is important there is ongoing monitoring to ensure the safety and efficacy of the product and that there are no contraindications with other medications the person may be taking for their condition(s). We believe it is important that effective communications are developed to ensure that the professionals involved in the shared care agreement are fully engaged in this monitoring and evaluation too.	Thank you for your comment.
Parkinson's UK	Guideline	7	12	We endorse recommendation 1.5.5 and the need for prescribers to take the potential for dependence into account. We would recommend that there is an addition of regular	Thank you for your comment. This has been amended to reflect your comment.

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				monitoring and explaining the side effects to both the patient and carer as there is in the Parkinson's guideline NG71 regarding dopamine agonists, recommendation 1.4.3.	
Parkinson's UK	Guideline	7	3	We would recommend that there is an addition so if any cannabis-based products are approved and funded by the NHS professionals outline the prescription pre-payment certificate to ensure that people can take advantage of it.	Thank you for your comment. The use of a prescription prepayment certificate varies among individuals and is not within the scope of this guideline.
Parkinson's UK	Guideline	9	16	We endorse the NHS England review process and the NICE recommendation that there must be more research about cannabis-based products to understand their effect and what symptoms they can ease for people with long-term conditions. People with Parkinson's experience over 40 non-motor symptoms and our recent survey shows the desperation of people living with the condition for better treatments to control their symptoms. We were disappointed that studies on symptoms that impact Parkinson's were not included in the search criteria as outlined in comment 1.	Thank you for your comments. Parkinson's disease was out of scope for this review.
Parkinson's UK	Guideline	General	General	We are disappointed that the guideline didn't reference other symptoms that cannabis-based products could help alleviate as we suggested in the scope, like depression or pain in Parkinson's. There is evidence that cannabis-based products can assist people with their Parkinson's symptoms (bradykinesia, dyskinesia and pain) and even be a neuroprotector (Sandeep Vasant More and Dong-Kug Choi: Promising cannabinoid-based therapies for Parkinson's disease: motor symptoms to neuroprotection. *Molecular Neurodegeneration* (2015) 10:17 DOI 10.1186/s13024-015-0012-0) and (A.G. Beiske, J.H. Loge, A. Rønningen, E. Svensson: Pain in Parkinson's disease: Prevalence and characteristics. PAIN 141 (2009) 173–177). However, we were encouraged by the recommendations for research as we agree there is not enough evidence about the impact cannabis-based products could have on long term conditions.	Thank you for your comment. Other conditions were beyond the scope of this review.
Parkinson's UK	Guideline	General	General	We recently undertook a survey with the Parkinson's community about their use and experience of cannabis-based products. A quarter of the 1,660 people that responded have either used or are using a cannabis-based product to ease their Parkinson's symptoms and 59% who haven't used a cannabis-based product are interested in trialling it to control their Parkinson's symptoms. People currently using, and those who have used cannabis-based products in the past, said that they are most effective at easing anxiety. Professionals surveyed said that they seem to be most effective at easing stiffness, intense or vivid dreams, difficulties concentrating, slowness and constipation. Professionals also reported that they are regularly asked about using cannabis-based products by their patients. 70% of professional respondents offer advice. 86% of respondents are not confident about prescribing a cannabis-based medicinal product for their patients, and many are not sure if the current prescribing guidance is fit for purpose, as no guidelines currently mention Parkinson's. (Parkinson's UK. Cannabis and Parkinson's: the views of people with Parkinson's and health and care professionals, July 2019 - https://bit.ly/2ksvzXA accessed 4 September 2019) We would therefore recommend that NICE recognise the results of this survey and the views of people living with Parkinson's who are eager to have better treatments available to them.	Thank you for your comments. The conditions to be included within this review were agreed at the scoping phase. Parkinson's disease was not included within this and was therefore out of scope for this review.
Peer Reviewer 1	Guideline	6	39	The PICO seizure outcomes section is unclear. The seizure outcomes could be more usefully categorised as seizure freedom, >50% reduction or reduction of seizures from baseline. In other words, seizure freedom should not be conflated with >50% reduction, commonly used in epilepsy clinical trials.	Thank you for your peer review comment. The committee defined seizure freedom as 50% or greater reduction in seizures. The PICO table and review protocol have been amended to provide further clarification of the outcomes.
Peer Reviewer 1	Guideline	6	7	The guideline states that "For children and young people under 18 years, the initiating prescriber should be a tertiary paediatric specialist". • Firstly, the term "tertiary paediatric specialist" is broader than the current UK Departments of Health recommendations that CBPMs should be prescribed by a clinician on the GMC Specialist Register prescribing in the usual area of their practice. Was that the committee's specific intention? • Secondly, the practicalities of a tertiary paediatric specialist initiating a CBPM prescription for a young person between 16 and 18 years may need to be considered	Thank you for your peer review comment. The wording of the recommendation takes into account all conditions specified in the guideline. It was the committee's intention to specify 'tertiary paediatric specialist' in the recommendation. This was to ensure expert management of the conditions covered in the guideline with cannabis-based medicinal products (CBMPs). Most CBMPs are unlicensed and will require specialist input for treating children with these medicines. The practicalities of transition to adult services has been covered in the last bullet of recommendation 1.5.4

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				further. Many young people with severe epilepsy will have had epilepsy from childhood and by that stage will already have transitioned to adult neurology or adult learning disability care. Moving that young person's care back to a paediatric neurologist in order to initiate a CBPM prescription is unlikely to be feasible.	
Peer Reviewer 1	Guideline	General		I am commenting specifically on the children and young people's epilepsy part of this guideline. It is clearly written and gives helpful recommendations for future research. I have no suggestions to make regarding its general content.	Thank you for your peer review comment.
Peer Reviewer 1	Guideline	General		I am not aware of other relevant evidence and the analysis and interpretation of the evidence seem to me to be entirely reasonable	Thank you for your peer review comment.
Peer Reviewer 2	Evidence Review C	13	19	Important to state that there is a wide variation in outcome measures in 'spasticity'. Focus on adverse events particularly important in Paediatrics – safety as important as efficacy Patient related scales. Ashworth and tardieu scales are recognised as a very poor inter and intra observer reliant measure	Thank you for your peer review comment. The committee shared similar concerns and raised that the scales used in the studies are not often used in clinical practice. This is discussed in the committee's discussion of the evidence, quality of the evidence section.
Peer Reviewer 2	Evidence Review C	20		Economic evidence and cost-utility analysis well balanced	Thank you for your comments and support.
Peer Reviewer 2	Evidence Review C	32-35	29	The committee pass no comment on Paediatric use, a comment about lack of sufficient grade of evidence to date would be useful. The committee have focussed on MS and lost Paediatric use altogether	Thank you for your pe review comment. We have clarified the lack of paediatric evidence in the committee's discussion of the evidence section. Additionally, the populations specified in the recommendation for research are both adults and children.
Peer Reviewer 2	General	General	General	Agree with position statement and lack of reasonable grade RCTs in child population – there are a number of case series in Paediatric Spasticity – either Cerebral Palsy or acquired. Initial comment is made that if less than 5 RCTs are found then cohort studies would be reviewed – there is no evidence of this. There was a good summative paper in Developmental Medicine and Child Neurology this year (Nielsen et al DMCN 61(6) 631-638) focussing on the cohort studies that have been reviewed. There is an abstract from an RCT which showed no benefit in Cerebral Palsy – publication of paper is pending (Fairhurst, Kumar, Turner) A greater discussion of the positive and negative factors of tone seen upper motor neurone syndrome – many clinicians are veering away from the term spasticity – what are we using the Cannabinoids for?	Thank you for your pee review comment. Observational studies were also incorporated into the literature search. No paediatric studies were identified. The summary of the clinical evidence section has been amended to clarify this. Thank you for your comments. Given the lack of RCTs for spasticity in children a search of observational studies was conducted. However, there were no studies that matched the inclusion criteria for this review. We do not include abstracts as part of our review process but any studies that results from this should form part of future updates. The summary of the clinical evidence section has been amended to clarify this. Thank you for highlighting terms being used in practice. The scope of this guideline focuses on people with spasticity. This term has been used in the evidence reviews and recommendations. The committee did not raise using an alternative term for spasticity in their discussions.
Peer Reviewer 2	General	General	General	In the absence of RCTs in Children we would ask for a research recommendation, also discussion about the ratios of CBD to THC for this use	Thank you. The issues that you've raised have been included in the research recommendations.
Peer Reviewer 3	Evidence Review B	104-107		Cochrane Risk of Bias Tool missing	Thank you for your peer review comment. The Cochrane risk of bias tool has now been added for Rog 2005
Peer Reviewer 3	Evidence Review B	121		Conflicting information Published in Multiple Sclerosis 2204 Aug 10(3) 434-41 but in study details reportedly submitted for publication in 2014	Thank you for your comment. We have corrected the typo.

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Peer Reviewer 3	Evidence Review B	133		Typo Svendsen 2004 appears within Cochrane risk of bias Tool referring to Lynch 2014 study	Thank you for your comment. We have corrected the typo.
Peer Reviewer 3	Evidence Review B	256		Cannabis based product is given both CBD and CBP abbreviation but are given the same defining criteria. This confusing and needs clarification. CBP is a broader term than CBD.	Thank you. We have clarified this inconsistency in terms and have amended appendix K in the evidence review accordingly.
Peer Reviewer 3	Evidence Review B	32	1	The suggested inclusion criteria for future research for people with fibromyalgia or persistent treatment resistant neuropathic pain defining standard treatment as WHO pain ladder step 3 (opioids plus adjuvants) is immediately prejudicial. Although a significant proportion of individuals living with these conditions continue to use these medications a number have stopped using them as they did not improve their quality of life, There is a danger that setting such inclusion criteria may either exclude these individuals or push them back on to medication in order to be included in studies.	Thank you for your peer review comment. For the adult research recommendation, we have changed the comparator to "usual care as defined by the researchers".
Peer Reviewer 3	Evidence Review B	32	1	Entirely agree that at least a 6 month follow up required	Thank you for your comment.
Peer Reviewer 3	Evidence Review B	7	11	The term persistent pain is increasingly the preferred term in clinical practice with adults living in pain not just children and young people in the UK partly as a result of the negative association with chronic pain. It is incorrect to imply that persistent has a non-temporal status. This is reflected in recent Welsh Government Published Guidance on Living with Persistent pain in Wales (May 2019) and by numerous other organisations including British Pain Society and various patient support groups. The inclusion of Chronic Pain for the first time in WHO ICD 11 clinical classification system will influence UK recording systems and may result in a further change in preferred terminology. This should be acknowledged.	Thank you for your peer review comment. We used the term 'chronic pain' for adults because this is a common phrase in the adult literature. It normally means a period of 3 months. We accepted that the term 'persistent pain' is better for children. This is because for some children, 3 months might be too long to wait for further treatments to be considered.
Peer Reviewer 3	Evidence Review B	9	28	The committee statement that the clinical outcome that matters most is average pain intensity is a challenge in clinical practice as we aim to improve functional performance not pain intensity scores or percentage pain relief. These factors are more readily measured and therefore reported in clinical trials as is recorded in the text but this should be stated clearly as being used as a proxy measure.	Thank you for your peer review comment. The committee agreed that the most important outcome was pain intensity. This is because it is ubiquitous and therefore allows comparison using a meta-analysis. We did include functional pain measurement tools: the McGill pain questionnaire and Brief Pain Inventory. However, they were not frequently reported. For the research recommendations, the committee acknowledged that favoured functional pain measurement tools change all the time. Therefore, we have included the outcome: "A validated functional pain measurement tool".
Peer Reviewer 4	Appendix 1			It could be worth explicitly stating reasons why NNTs were not able to be generated.	Thank you for your comments. We acknowledge that there are other measures such as NNT available. As per NICE guideline manual and NICE reference case, the results of economic models should be expressed as cost per QALYs so that an outcome can be compared between different populations and disease areas.
Peer Reviewer 4	Appendix 1	212	3	Health Economic analysis: Health economic modelling is always difficult, largely because of the lack of data to populate the models requires a myriad of assumptions to be made, that despite sensitivity analysis are often open to criticism. However, there are several examples of assumptions and using data from other studies (i.e. not the included 20) that are perhaps more open to censure (vide infra). For example the categorising all the pain aetiologies into only 3 different groups (neuropathic pain, cancer pain and MSK pain) could be questioned.	Thank you for your comments. We acknowledge that there is heterogeneity in chronic pain populations. As per the guideline scope, the analysis should be inclusive and does not specify types of pain. The model is based on the best available clinical evidence. Subgroup analyses were conducted for specific treatments and for specific types of chronic pain where data were available. We recognise the limitations that some of the subgroup analysis conclusions may not be generalisable to the overall chronic pain population. We have validated the model data with the committee as well as submitted the report for peer-review with additional clinical experts during the consultation. As such, we consider the model estimate to reflect the existing clinical evidence and experience correctly.
Peer Reviewer 4	Appendix 1	217	21	Using data from the Farrar paper is potentially questionable since none of the pain groups in the 10 papers included MS pain or cancer pain (or indeed RA, pancreatitis or abdo pain) which accounts for 15 of the 20 papers included in NICE review.	Thank you for your comments. Farrar et al. 2001, a large epidemiological study in chronic pain, only provided baseline characteristics in the model: age, gender, pain NRS. Data from Farrar et al. 2001 are similar to the patient characteristics in the included RCTs. The

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					committee has validated these assumptions and made a consensus that patients from Farrar et al. 2001 represented the chronic pain population in the current clinical practice.
Peer Reviewer 4	Appendix 1	221	5	It is unclear and upon what evidence the decision was made to introduce radiofrequency denervation in the modelling. The contention that the 'only invasive treatment that was common enough to potentially influence the model's results' is controversial and no supporting evidence is given. The review does not include any data on cannabinoids for patients with chronic low back pain. None of the causes of pain from the 20 papers included in the review would usually be considered for radiofrequency denervation. Again this is unlikely to affect the modelling results and indeed one of the sensitivity analyses was done without this with no great change in ICER.	Thank you for your comments. The decision to include radiofrequency denervation was based on the committee expert consensus. We acknowledged that there are other potential downstream treatment options in chronic pain. Radiofrequency denervation was considered as a common downstream treatment for people with chronic low back pain. This is only relevant when considering the population with low back pain in the model.
Peer Reviewer 4	Appendix 1	223	3	Why was the side effect data taken from a separate systematic review (Wang 2008) rather from the adverse effect data from the 20 included papers? Given that 11 of the 20 papers were not published before the Wang review, can one assume the characteristics of the adverse effects in Wang reflect those from the efficacy data? Indeed, one could argue that the Johnson et al (2013) paper [J Pain Symptom Manage. 2013 Aug;46(2):207-18. doi: 10.1016/j.jpainsymman.2012.07.014. An open-label extension study to investigate the long-term safety and tolerability of THC/CBD oromucosal spray and oromucosal THC spray in patients with terminal cancer-related pain refractory to strong opioid analgesics. Johnson JR, Lossignol D, Burnell-Nugent M, Fallon MT] could have been a better 'fit' to use for the economical modelling. This paper is not mentioned at all but conceivably could have added to the adverse effect data.	Thank you for your comments. We had conducted a targeted review to identify incidence data for AEs and serious AEs across of medicinal cannabis versus placebo/ standard of care across all indications. Wang et al. 2008 is the only study that provided the appropriate data for the model. A more recent meta-analysis by Whiting et al. 2015 did not report incidence data. Observational studies of medicinal cannabis only reported AEs of medicinal cannabis, rather than comparison against standard treatments. We have validated the safety data with the committee as well as submitted the report for peer-review with additional clinical experts during the consultation. As such, we consider Wang et al. is still the most appropriate source for safety data in the model. Whiting PF, Wolff RF, Deshpande S, Di Nisio M, Duffy S, Hernandez AV, Keurentjes JC, Lang S, Misso K, Ryder S, Schmidlkofer S, Westwood M, Kleijnen J. Cannabinoids for Medical Use: A Systematic Review and Meta-analysis. JAMA. 2015 Jun 23-30;313(24):2456-73.
Peer Reviewer 4	Appendix 1	231	4	Also why was adverse event disutility extrapolated from patients with breast cancer? Apart from the gender difference, is this simply too different a population to use?	Thank you for your comments. We conducted a targeted review to identify disutility data associated with adverse events. However, there is no relevant data available in the chronic pain population. The AE disutility is only looking at the difference between with and without the specific event, not related to the background disease. The underlying assumptions are we expected to the relative effect of each AE to be consistent across any disease. The AE disutility was estimated as a utility decrement and was applied using the validated additive approach (Ara and Wailoo, 2012). Ara, R. & Wailoo, A., 2012. Using health state utility values in models exploring the cost-effectiveness of health technologies. Value in health: the journal of the International Society for Pharmacoeconomics and Outcomes Research, 15(6), pp. 971-974.
Peer Reviewer 4	Appendix 1	236	10	Table 11 Even with modest efficacy data the result of only 0.162 incremental QALY is surprising. In my experience such 'unexpected' results need to be carefully and categorically explained or people with question the veracity of the model (even if there is no cause). Incidentally, the labelling of cannabinoid treatment as 'Cannabis' is this table is incorrect.	Thank you for your comments. We acknowledged the limitations of the model and conducted several sensitivity analyses. The terms 'cannabis' was used to align with the terms within the guideline scope, where we referred to the treatments as cannabis-based medicinal products.
Peer Reviewer 4	Appendix 1	240	15	What is meant by 10x more effective? For example, a 10x reduction in NRS would not make sense. I think this way of presenting the findings is liable to misunderstanding.	Thank you for your comments. This statement has been based on a threshold analysis: 10 time more effective means accruing 1.54 QALYs compared to 0.162 QALY in the base case. We have revised the statement in the chronic pain evidence review accordingly.
Peer Reviewer 4	General	General	General	Given the recommendations of the draft guidance, the three questions stated at the top of this form are not applicable.	Thank you for your comment. We acknowledge that where there is a lack of positive recommendations, questions about resource impact and implementation do not apply. However where positive recommendations are made, it was felt appropriate to include these questions.

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Peer Reviewer 4	General	General	General	I think that the main comments about the draft guidelines from stakeholders will be that it does not recognise that although the evidence of efficacy is modest and limited, there are some patients for whom cannabinoids 'work' (achieve the desired outcome). As Moore stated, 'Expect analgesic failure; pursue analgesic success' (Expect analgesic failure; pursue analgesic success. Moore A, Derry S, Eccleston C, Kalso E. BMJ. 2013 May 3;346:f2690.) The challenge (as with most other analgesics with modest NNTs) is finding those patients.	Thank you for your comment. We agree that the evidence of efficacy is modest, limited and all analgesia has a strong placebo effect. RCTs are the best studies for assessing medicinal cannabis. This is because all analgesia has a strong placebo effect. Therefore, studies should be double-blinded and randomised. You are correct that the data favours some types of medicinal cannabis for managing chronic pain compared to placebo. However, although this reaches statistical significance, the effect size is so small that individual people are unlikely to notice any difference. For example, pain intensity is measured on a scale of 0 to 10, 0 being no pain and 10 being maximum pain. In order for a person to notice any difference, analgesia should reduce pain intensity by at least 2 or even 3 points. Most pain intensity effect sizes were either statistically insignificant (oral delta-9-THC, oromucosal THC, vaporised THC (minimal CBD), vaporised THC:CBD, vaporised CBD (minimal THC)), or they caused less than a 2 point pain intensity drop (oromucosal CBD:THC) or the 95% confidence interval crossed the 2 point pain intensity drop threshold (oral nabilone). The cost of medicinal cannabis for chronic pain is 10 times greater than the NHS is willing to pay for such a small effect.
Peer Reviewer 4	Guideline	137		Why is the van de Donk paper stated as being both 2018 and 2019?	Thank you for your comment. When this study was first published on the internet, it was cited as 2018. Now, this date has changed on the internet to 2019. We have updated the evidence review accordingly.
Peer Reviewer 4	Guideline	31	12	It is stated that the 6 week study duration was 'unrealistic'. There very few studies in chronic pain that are longer and it is probably 'unrealistic' to expect studies of longer duration. What is then even more puzzling is why the van de Donk (2018) paper was included at all since the only outcomes were measured at 3 hours.	Thank you for your comment. When the review's protocol was written, the committee did not include a follow-up duration because it was not entirely known what studies were available. The finding that there was an RCT with a short follow-up period was useful information because this further endorsed the need for research recommendations that had a longer follow-up period. Thank you for your comment. The committee agreed that the follow-up period for chronic pain studies should be 6 months or longer. With the benefit of hindsight, we probably should have included a minimum duration of follow-up in the exclusion criteria of the protocol. However, including van de Donk 2018 did not change a recommendation.
Peer Reviewer 4	Guideline	69	2	The Fallon et al (2017) paper appears to be incompletely documented. Only one of the 2 RCTs contained in the paper is described. The study described in the NICE document has 399 subjects (at the start) and 294 completed (200 intervention and 199 placebo) which corresponds to 'Study 1'. 'Study 2' has not been mentioned in the draft guideline. 'Study 2' included another 204 patients making in total (study 1 and 2) 303 who received treatment and 302 placebo. Although this 'study 2' used enriched enrolment methodology, is was still an RCT. If this 'study 2' was considered and rejected for a methodological (or other) reason, then that should be disclosed. If there is no reason for rejection then surely the data should be included. It is, however, unlikely to impact majorly on the overall recommendations.	Thank you for your comment. Study 2 of Fallon 2007 was not included because it was a withdrawal study. Therefore, it did not meet our inclusion criteria. However, you should probably be aware that enriched enrolment studies are difficult to interpret. Therefore, they can easily be abused or manipulated by unscrupulous investigators. This is especially so when the treatment of interest is adjunctive rather than an active maintenance treatment.
Peer Reviewer 4	Guideline	General		Inconsistencies in outcome measures: 'Average pain intensity' noted as being the major outcome measure (page 9 line 28), yet in the economic model 'mean change in pain intensity' is used (P214 line8). The inconsistency of what the committee decided was the most important outcome is further highlighted by the Review Protocol (P37) that lists the outcomes in a different order with >30% reduction and >50% reduction in pain above 'change in pain intensity' 4th in line. 'Mean pain intensity' is not stated in the outcomes despite being a 'clinical outcome that matters most (Page 9 Line 28). In addition, in the Minimal clinically important differences (MIDs) part (Page 45 Line 35) it states, 'a key outcome is participant reported pain relief of 30% or greater'.	Thank you for your comment. The phrase "average pain intensity" has been changed to "mean change in pain intensity" for consistency. Mean pain intensity was the main outcome used to assess how clinically effective medicinal cannabis is. However, it is common for economic analyses to use >30% reduction and >50% reduction in pain. For your interest, we have changed the minimally important difference of mean pain intensity from 10% to 20%, which is the same minimally important difference that Cochrane use for this outcome.
Peer Reviewer 4	Guideline	General	General	The conversion of VAS scores to NRS makes assumptions that can be open to criticism. J Spinal Cord Med. 2010 Jun; 33(3): 232–242. Comparing Quantification of Pain Severity by Verbal Rating and Numeric Rating Scale. Marcel Dijkers.	Thank you for your comment. The committee agreed that scoring pain intensity on a 0 to 10 scale was similar enough to comparing pain intensity on a 0 to 100 scale, providing one uses a conversion factor of 10.

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Peer Reviewer 5		20	11	What evidence is there that individuals with Dravet and Lennox Gastaut Syndrome experience more adverse events than other individuals with, or without epilepsy? They have more comorbidities than the general population and many other epilepsies	Thank you for your comment. The wording of this paragraph has been amended.
Peer Reviewer 5		Table 2	10	'Partly applicable – cannabidiol for Dravet syndrome was not the focus of this review' and same comment for LGS. This could imply that cannabidiol was not the drug under investigation – which I'm sure is not intended. Could the limitations be clarified	Thank you for your comment. This limitation was previously highlighted under the section 'clinical evidence' (page 8, line 35) and discussed further in section 'the committee's discussion of the evidence'.
Peer Reviewer 5	Guideline	19	19	Whilst I agree that results from Dravet syndrome RCT and LGS RCT cannot inform treatment of all epilepsies the criteria for LGS was very broad in these RCTs – and the results could be applicable to a range of drug-resistant epilepsies	Thank you for your comment. The committee discussed the generalisability of the evidence included and agreed that whilst different epilepsies can have some common mechanisms, there are differences in underlying pathologies. Therefore, the committee could not generalise this evidence. With the limited evidence available, the committee made a research recommendation to inform further practice.
Peer Reviewer 5	Guideline	19	42	I am unclear why the RCTs, which are discussed in some detail, are then excluded from the review as they are part of the technology appraisal. Surely if they are discussed in the review then they should contribute towards the recommendations – or they should be completely excluded from the review	Thank you for your comment. These RCTs were included however the committee were unable to make recommendations as they are currently being assessed by our technology appraisals team. This appraisal will be published after the publication of this guideline.
Peer Reviewer 5	Guideline	20	45	The statement 'had the potential to generate significant gains in quality of life and reduction in resource use in those patients who respond very well to treatment' does not appear to be backed up by evidence in this review. It is a strong statement and should be supported by evidence if it is to remain in the review	Thank you for your comment. The section 'the committee's discussion of the evidence' not only highlights the clinical and cost effectiveness evidence, but also captures the committee's discussion which is intended to capture their knowledge and insights into the topic. While there was no economic evidence, there was a view among the committee members that there were potential gains in quality of life and reduction in resource use in those who responded well to treatment.
Peer Reviewer 5	Guideline	21		Can't find recommendation 1.4.1 so not sure what this refers to	Thank you for your comment. This has been amended.
Peer Reviewer 5	Guideline	7	1	Seizure freedom and > 50% seizure freedom are not the same outcomes. Were these outcomes considered separately? If so should be stated more clearly	Thank you for your comment. All outcomes were intended to be looked at separately. Once the review was conducted, evidence was only found on 50% seizure reduction.
Peer Reviewer 5	Guideline	9	16	States Error – presumably needs to be clarified	Thank you for your comment. This has been amended.
Primary Care Rheumatology Society	Evidence Review A, B, C, D and E	General	General	The evidence reviews only mention plant-derived cannabinoids such as pure cannabidiol (CBD). There is no mention of plant-derived delta-9-tetrahydrocannibinol and cannabidiol (THC:CBD) products. This is a significant omission and is likely lead to people believing that the medicinal cannabis products do not apply to plant-derived THC:CBD products	'Thank you for your comment. The text you refer to is an example and is not meant to be an exhaustive list of all plant-derived cannabinoids. The guideline does not exclude natural THC as this is included in the 2018 regulations and so products that meet the requirements of this regulation were included. Canabidiol on the other hand is not a controlled drug and so this would not be captured by the 2018 regulations which is why it was specifically mentioned under plant-derived and was also included. As a result any product that had a combination of THC:CBD was included in this guideline as part of the evidence review.
Primary Care Rheumatology Society	Evidence Review B	22	General	Corticosteroid injections are common and frequent forms of invasive therapy for people with chronic low back pain as is low back pain surgery. The health economic model only appears to consider radiofrequency denervation as able to influence the model's costs, evidence of the North of England Low Back Pain Project (published by the Health Foundation) and the NICE low back pain guidelines (2017) indicate that injections and spinal surgery are also valid and costly invasive therapies that should be included in the economic model.	Thank you for your comment. The RCT data that we reviewed favours some types of medicinal cannabis for managing chronic pain compared to placebo. However, although this reaches statistical significance, the effect size is so small that individual people are unlikely to notice any difference. For example, pain intensity is measured on a scale of 0 to 10, 0 being no pain and 10 being maximum pain. In order for a person to notice any difference, analgesia should reduce pain intensity by at least 2 or even 3 points. Most pain intensity effect sizes were either statistically insignificant (oral delta-9-THC, oromucosal THC, vaporised THC (minimal CBD), vaporised THC:CBD, vaporised CBD (minimal THC)), or they caused less than a 2 point pain intensity drop (oromucosal CBD:THC) or the 95% confidence interval crossed the 2 point pain intensity drop threshold (oral nabilone). We acknowledge that there

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					are other potential downstream treatment options in chronic pain. Radiofrequency denervation (RFD) was considered as a common downstream treatment for people with chronic low back pain. This is only relevant when considering the population with low back pain in the model.
Primary Care Rheumatology Society	Evidence Review B	General	General	The Society agrees that studies requiring a minimum of 6 months follow-up is required for chronic pain studies.	Thank you for your comment.
Primary Care Rheumatology Society	Evidence Review B	General	General	The Society believes that 30% pain reduction is clinically important to chronic pain patients and what should be considered (rather than a 50% reduction).	Thank you for your comment. Both the 30% and the 50% pain reduction outcomes were data extracted and analysed. The reason why we do not have much data for these is that they were rarely reported.
Primary Care Rheumatology Society	Evidence Review B and Guideline	General	General	Functional impairment is important for both chronic pain patients and their clinicians. However, experience suggests that determining this will require very large patient cohorts. It may be prohibitively expensive to do RCTs and prospective observational datasets may be more appropriate. The Society requests NICE considers this point especially given that NICE is currently undertaking a review on how to use more 'real world' data collection as pragmatic alternatives to traditional RCTs.	Thank you for your comment. RCTs are the best studies for assessing medicinal cannabis. This is because all analgesia has a strong placebo effect. Therefore, studies should be double-blinded and randomised. The guideline has added a recommendation advising prescribers to record details of treatment, clinical outcomes and adverse effects for people prescribed cannabis-based medicinal products, using local or national registry. This will enable feedback from patients to feed into the evidence base.
Primary Care Rheumatology Society	Evidence Review B and Guideline	General	General	There are different pharmacokinetic properties between different formulations of medicinal cannabis products, as such it may not be appropriate to combine all of the medicinal cannabis products together for analysis of chronic pain:- the results may be biased. The Society whilst highlighting this believes that this underlines the requirement for more, formalised data collection on safety, tolerability and clinical effectiveness (or lack thereof). The Society believes that this data collection should be both through further RCTs and through a national dataset or national dataset collection standards for prospective observational data collection (in the latter case as discussed in point 9 above).	Thank you for your comment. RCTs are the best studies for assessing medicinal cannabis. This is because all analgesia has a strong placebo effect. Therefore, studies should be double-blinded and randomised. The guideline has added a recommendation advising prescribers to record details of treatment, clinical outcomes and adverse effects for people prescribed cannabis-based medicinal products, using local or national registry. This will enable feedback from patients to feed into the evidence base.
Primary Care Rheumatology Society	Evidence Review B and Evidence Review E	General	General	The Society believes that because medicinal cannabis appears to be excreted mainly via the bowels rather than kidney, medicinal cannabis products might be considered as investigative targets for chronic renal failure patients. At the same time the Society urges caution in the use of medicinal cannabis products in patients with bowel cancer and other forms of bowel disease. Analysis of these 2 subsets of patients should be a key area of analysis of any medicinal cannabis safety and effectiveness dataset.	Thank you for your comment. Chronic renal failure was beyond the scope of this review.
Primary Care Rheumatology Society	Evidence Review B and Evidence Review E	General	General	The Society believes that Network Meta-analysis may provide useful and valid answers to some of the queries raised about the safety and clinical efficacy of medicinal cannabis and which it is difficult to answer using traditional meta-analysis. The Society suggests that consideration should be given to Network Meta-analysis in the review of the clinical evidence on chronic pain.	Thank you for your comment. There is not enough RCT data for a network meta-analysis to be conducted. Furthermore, a network meta-analysis would be relevant if we were ranking treatments which was not the case in this review. Therefore, the notion of using a network meta-analysis is outside the scope of this review.
Primary Care Rheumatology Society	Guideline	General	General	The Society believes that until further credible, peer-reviewed evidence is published, medicinal cannabis should only be prescribed by tertiary specialists. The Society believes that it is highly unlikely at this stage that GPs will feel confident or willing to take the clinical risks of entering into shared-care agreements for patients prescribed unlicensed medicinal cannabis products without a significant improvement in the medicinal cannabis evidence base.	Thank you for your comment. The committee agreed that the initial prescription must be by a specialist medical practitioner who has a special interest in the condition being treated but they wanted to facilitate prescribing through shared care when appropriate.
Primary Care Rheumatology Society	Guideline	General	General	The Society believes that medicinal cannabis provides an exciting area for research into a new, important and previously unexplored important neuro-endocrinological aspect of the body which may lead to important new and important therapeutic options for chronic pain. The Society believes that these therapeutic options must be evidence-based and the manufacturers of medicinal cannabis products encouraged to apply for registration and licensing of their products through the standard MHRA/EMA licensing regime.	Thank you for your comment.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Primary Care Rheumatology Society	Guideline	General	General	The draft guidelines only mention plant-derived cannabinoids such as pure cannabidiol (CBD). There is no mention of plant-derived delta-9-tetrahydrocannibinol and cannabidiol (THC:CBD) products. This is a significant omission and is likely lead to people believing that the medicinal cannabis products do not apply to plant-derived THC:CBD products.	Thank you for your comment. The text you refer to is an example and is not meant to be an exhaustive list of all plant-derived cannabinoids. The guideline does not exclude natural THC as this is included in the 2018 regulations and so products that meet the requirements of this regulation were included. Canabidiol on the other hand is not a controlled drug and so this would not be captured by the 2018 regulations which is why it was specifically mentioned under plant-derived and was also included. As a result any product that had a combination of THC:CBD was included in this guideline as part of the evidence review.
Primary Care Rheumatology Society	Guideline	General	General	The Society agrees with the draft guidelines that medicinal cannabinoid products require further clinical trials before they can be considered for general use for chronic pain.	Thank you for your comment.
Primary Care Rheumatology Society	Guideline	General	General	The Society does not believe that medicinal cannabis products should be used for chronic low back pain and until further evidence, the NICE low back pain guidelines remain the appropriate, evidence-based summary of best clinical practice.	Thank you for your comment.
Primary Care Rheumatology Society	Guideline and Evidence Review B and Evidence Review E	General	General	The Society believes that experience has proven the benefits of the current licensing regimen and whilst medicinal cannabis products offer potentially exciting options there is no valid reason why exceptions should be made to them not having to ultimately apply for a product license and to go through the required attainment of standards and production of evidence of clinical safety and efficacy. This is especially important in musculoskeletal and rheumatological conditions given how wide-spread chronic pain is and how many patients could potentially be injured by widespread use of unlicensed products if appropriate regulations are not in place.	Thank you for your comment.
Primary Care Rheumatology Society	Guideline and Evidence Review E	6	General	The draft guidelines do not appear to advocate a national data registry for collection of safety and clinical effectiveness data. This is in contrast to what the Government suggested in November 2018 and was advocated by DHSC ministers and Dame Sally Davies, CMO, during the 2019 Health Select Committee medicinal cannabis inquiry. The draft guidelines also do not reflect the current thinking advised by NHS England and NHS Improvement in their report on barriers to accessing medicinal cannabis published on 8th August 2019: https://www.england.nhs.uk/wp-content/uploads/2019/08/barriers-accessing-cannabis-based-products-nhs-prescription.pdf . The current guidelines risk poorly designed datasets with disparate designs and quality of data collection being created for medicinal cannabis. The Society is concerned that these resulting datasets would lack both sufficient statistical power preventing meaningful analysis and lack of common design features risking an inability to combine the datasets to allow for valid statistical assessments from analysis and interrogation of the combined data. Ultimately the current advice for data collection risks adversely affecting patient safety through lack of detailed advice on data collection. The Society believes that as numerous private clinics are springing up across the UK, it is crucial that NICE advise on either a national dataset covering both NHS and private healthcare prescribing of medicinal cannabis for collection of safety and clinical effectiveness data or alternatively minimum requirements for a dataset design that must be followed in collecting this data. The Society suggests that NICE engage with NHS Digital and NHSX for advice re data collection and intra-operability standards.	Thank you for your comment. The committee agreed that an additional recommendation on a national or local registry was needed. This will facilitate an improved evidence base for CBMPs.
Primary Care Rheumatology Society	Guideline and Evidence Review E	7	General	Factors to think about when prescribing also should include driving and use of machinery.	Thank you for your comment. The effect of cannabis-based medicinal products on driving is already included in the recommendation. Best practice states that caution about the use of machinery would be stated on the product packaging of both licensed and unlicensed products if there was an impact, therefore the committee agreed to not make this addition.
Primary Care Rheumatology Society	Guideline and Evidence Review E	7	General	Factors to think about when prescribing should also include advice re foreign travel and international laws re medicinal cannabis products (e.g. Japan where it is illegal).	Thank you for your comment. The recommendation has been amended to reflect your comment.

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Primary Care Rheumatology Society	Guideline and Evidence Review E	General	General	The Society is concerned that it is currently unclear who are safe and appropriate manufacturers providing medicinal cannabis products in the UK. This is especially the case for the unlicensed medicinal cannabis manufacturers. The Society believes that NICE should clearly indicate that Good Manufacturing Practice (GMP) certification is the minimum international standard to indicate quality. The Society is aware that medicinal cannabis products are currently being offered in the UK by manufacturers who do not hold this GMP certification. This needs to be stopped as a matter of priority in the interests of patient safety. The Society believes that NICE and the MHRA need to work together to achieve this. To overcome the information asymmetries the Society suggests that NICE should consider advising that the MHRA publish list of 'acceptable' medicinal cannabis manufacturers who are attaining minimum international standards of quality and safety and that this list should be updated regularly.	Thank you for your comment. This issue is outside the scope of this guideline.
Primary Care Rheumatology Society	Guideline and Evidence Review E	General	General	The Society notes that there appears to be some discord in thoughts between the draft guidelines and NHS England's and NHS Improvement's published report on 8th August 2019: https://www.england.nhs.uk/wp-content/uploads/2019/08/barriers-accessing-cannabis-based-products-nhs-prescription.pdf . This is the case despite it appearing that publication of the NICE draft guidelines and the above report appear to have been co-ordinated. These differences risk perseverating barriers to access to medicinal cannabis by UK patients. The concerns raised in the report about the quality and difficulty expressed by pharmacists in determining pharmaceutical grade quality in medicinal cannabis products available in the UK appear to be very concerning and these concerns do not appear to have been sufficiently identified and addressed in the NICE draft guidelines. The Society suggests that NICE reviews the above report and considers whether there are additional points from the report that should be aligned with the draft guidelines.	Thank you for your comment. The two reports were produced separately, used different methodology and considered different evidence. The difficulty in determining pharmaceutical grade quality in medicinal cannabis products available in the UK is beyond the scope of this review.
Royal College of General Practitioners	General	General	General	If shared care agreements are considered as part of this guideline the committee must consider the NHSE document on shared care agreements agreed by the BMA, NHS clinical commissioners, the RCN and RCGP "Responsibility for prescribing between primary and secondary care/tertiary care" which can be found at https://www.england.nhs.uk/publication/responsibility-for-prescribing-between-primary-and-secondary-tertiary-care/. Particular attention should be paid to section 4.4 and annex 1 quotes from which include: ○ Where possible shared care will be disease specific rather than medicine specific ○ Transfer of clinical responsibility to primary care should only be considered once the patients clinical condition is stable ○ Referral to the GP should only take place once the GP has agreed this in each individual case Table 2 in Annex 1 details the times that shared care may not be appropriate. Statement which relate to the current state of cannabis based medicines include: ○ Medicines requiring on-going specialist monitoring ○ Medicines that are unlicensed and /or being used outside of product license ○ The GP does not feel competent in taking on clinical responsibility for the prescribing of a specialist medicine.	Thank you for your comment. The committee considered the NHS England document 'Responsibility for prescribing between Primary & Secondary/Tertiary Care' and have referred to it in the recommendation.
Royal College of General Practitioners	Guideline	6	4	Can the committee consider rephrasing the sentence "Initial prescription of cannabis-based medicinal products *must* be made by a clinician on the General Medical Council's Specialist Register who *should* have a special interest in the condition being treated" to "Initial prescription of cannabis-based medicinal products *must* be made by a clinician on the General Medical Council's Specialist Register who ***must*** have a special interest in the condition being treated" as per NHSE advice https://www.england.nhs.uk/wp-content/uploads/2018/10/letter-guidance-on-cannabis-based-products-for-medicinal-use..pdfhttps:/www.england.nhs.uk/wp-content/uploads/2018/10/letter-guidance-on-cannabis-based-products-for-medicinal-use..pdf.	Thank you for your comment. The term 'must' is used when underpinned by legislation. Regulation 16A of The Misuse of Drugs (Amendments) (Cannabis and Licence Fees) (England, Wales and Scotland) Regulations 2018 does not specify that a clinician on the General Medical Council's Specialist Register must have a special interest in the condition being treated. As you point out in your comment, this is stated in the NHS England guidance which the committee took into consideration and therefore used the term 'should' in line with NICE style.

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Royal College of General Practitioners	Guideline	6	4 & 10	The committee should consider limiting the prescribing of cannabis-based products in adults to secondary and tertiary care as per NHSE advice and the governmental legislation until further evidence is available. ○ In paediatrics the NICE draft guidance agrees the on-going repeat prescriptions should be tertiary referral paediatrician led which is in line with the guidance and legislation. No shared care agreements are suggested. ○ In adults however, the NICE draft guideline states that this prescribing could be devolved to primary care via shared care agreements after the *first* prescription. (Pg 19, line 17-22). Whilst we understand the cost implications for keeping the prescribing in secondary or tertiary care, and that a patient requiring monthly prescriptions may be inconvenienced by having to attend secondary care on a monthly basis, (although this could be mitigated by secondary care issuing FP10 prescriptions by post), by devolving the prescribing of cannabis based medication to general practitioners after "1 prescription" in tertiary care, the unintended consequences on GPs will be significant. This includes, but is not limited to, workload (monthly prescribing of the drugs and regular monitoring of side effects), and professional development (the requirement for additional education and training in cannabinoid products). The cost implications of this must be considered. The current RCGP position on this from the desk top guide https://www.rcgp.org.uk/-/media/Files/CIRC/Desktop-guides/Cannabis-based-medication-desk-guide-nov-2018.ashx?la=en is as follows "In England Cannabis based medicines can be prescribed by a specialist doctor for unmet clinical need on named patient basis provided approval is granted by the Trust Drug and Therapeutic Committee Chair or Trust Medical Director. *This must be supplied by a specialist doctor and there are no shared care arrangements*. GPs should not prescribe these products but record them in their clinical systems as hospital supplied drugs". "In Scotland, Wales, and Northern Ireland, the hospital specialist will decide whether an application to the home office is appropriate. Once an application has been submitted to the expert panel through the formal procedure set out by the Home office. The expert panel will assess and then make a finding which will be shared with the Home Office or the Department for Health in Northern Ireland" Government guidance is clear (https://www.england.nhs.uk/wp-content/uploads/2018/10/letter-guidance-on-cannabis-based-products-for-medicinal-use..pdfhttps:/www.england.nhs.uk/wp-content/uploads/2018/10/letter-guidance-on-cannabis-based-products-for-medicinal-use..pdf.) "Due to the limited evidence base and their unlicensed nature, the Government has chosen to restrict the decision to prescribe cannabis-based products for medicinal use to only those clinicians listed on the Specialist Register of the General Medical Council. This restriction has been set out in regulations". Devolving the prescribing to GPs is difficult to justify until further evidence is available. Instead, the committee should consider the initial shared care agreements between tertiary and secondary care (possibly the chronic pain services as detailed on page 14, line 20), who can then issue the FP10 prescription to the patient by post if monthly prescriptions are required. Once more evidence is available and legislation agrees that primary care can prescribe these medications then: ○ The committee should consider the shared care agreement to be "once the patient is stabilised on the medication and side effects have been monitored by secondary/ tertiary care and only if agreed by the GP" and not "after the first prescription" as currently stated.(Pg 6, line 10 and Pg 19, line 19) ○ The committee should consider the cost and time implications of moving the prescribing to primary care, including the costs and time for providing training and	Thank you for your comment. The committee considered your comment and agreed that recommendation 1.5.2 is not a strong recommendation but one that uses the word 'may' to enable this to be an option if the GP feels confident to continue prescribing under a shared care arrangement. The committee also considered the NHS England document 'Responsibility for prescribing between Primary & Secondary/Tertiary Care' that provides details about arrangements and considerations. The committee agreed to refer to this guidance to supplement recommendation 1.5.2.

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				information for GPs to enable them to prescribe cannabis based medicines safely, whilst evidence is still emerging, and to cover the cost and time implications for monthly prescribing and close monitoring of side effects.	
Royal College of General Practitioners	Guideline	7	17	There is only 1 mention is made in regard to consideration of pregnancy and breastfeeding in the guidance. Can the committee make it clearer what the safety of these medications are in pregnancy and when breast feeding, or recommend thy are "best avoided" until definitive evidence is available? There is currently discussion of using these products for pregnancy related vomiting and clear direction from the guidance regarding its use and safety profile in pregnancy and with breastfeeding would be beneficial.	Thank you for your comment. Pregnancy and breastfeeding advice on licensed products has been added as a footnote. The evidence for unlicensed CBMPs is too limited to give clearer advice.
Royal College of General Practitioners	Guideline	8	5	Can the committee consider using 'discuss with patients' rather than 'advise' to emphasise two-way communication in shared decision making	Thank you for your comment. The recommendation has been amended to reflect your comment.
Royal College of General Practitioners	Guideline	General	General	The RCGP has produced a desktop guide about cannabis-based medicines giving advice to GPs and is the current RCGP stance on these products. https://www.rcgp.org.uk/-/media/Files/CIRC/Desktop-guides/Cannabis-based-medication-desk-guide-nov-2018.ashx?la=en	Thank you for your comment.
Royal College of Nursing	Evidence	10	20	'*Quality assessment of clinical studies included in the evidence review.* *a. 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.'* It is stated that the quality of evidence was 'initially high' but in the guideline it stated it the quality of evidence was low. Our reviewers could not find out why the evidence was downgraded?	Thank you for your comments. Reasons why the quality of the evidence was downgraded are included in the tables in Appendix E of the evidence review.
Royal College of Nursing	Evidence	General	General	It is noted that some of the studies weakness is used as an adverse effect – however this may mean the product is having an impact on the person by removing spasticity and exposing weakness.	Thank you for your comment and the additional information about weakness. Weakness was reported because it was one of the most commonly reported adverse events across studies but did not form a major part of the committee discussion when considering potential harms of cannabis-based medicinal products.
Royal College of Nursing	General	General	General	The Royal College of Nursing (RCN) welcomes proposals to develop NICE guidance for the use of cannabis-based medicinal products. The RCN invited members who care for people who may be have to use cannabis-based medicinal products to review and comment on the draft NICE guidance. The comments below reflect the views of our reviewers.	Thank you for your comments.
Royal College of Nursing	Guideline	1	1	As the guideline is for 'People taking cannabis-based medicinal products, their families and carers.' It is considered that clarification is needed between a drug that is licensed, non-licensed drugs and/ or drugs that have a marketing authority and what this means in reality with regard to whether a drug can be prescribed or not.	Thank you for your comment. The term cannabis-based medicinal product is defined in the 'terms used in this guideline' section and is further explained in the evidence review for prescribing . The guideline has a footnote when medicines that are unlicensed or off-label are recommended.
Royal College of Nursing	Guideline	4 - 7	General	The guideline is confusing in that it seems not to recommend cannabis-based medicinal products for the different symptoms listed and then it has a section on 'Prescribing' – Section 1.5, and the criteria for who can prescribe? In reality, in the recommendations in this guideline, healthcare professionals are restricted from prescribing cannabis-based medicinal products	Thank you for your comment. The committee agreed the prescribing recommendations support prescribers with safe and effective prescribing of CBMPs when they are considered for treatment in patients when all treatments options have been exhausted and benefits of treatment outweighs the harm. These prescribing recommendations will be useful when there is more evidence around the use of cannabis-based medicinal products. Furthermore, clinicians can still make their own individual prescribing decisions in the best interest of their patients.
Royal College of Nursing	Guideline	6	4-8	Restricting prescribing by a clinician who is on the GMC Specialist Register may affect the patient journey as the specialist might be non-medical such as a consultant nurse. It would be more inclusive and future proof if stated – a prescribing clinician with specialist competence.	Thank you for your comment. Due to the limited evidence base and their unlicensed nature, the Government has chosen to restrict the decision to prescribe cannabis-based products for medicinal use to only those clinicians listed on the Specialist Register of the General Medical Council. This restriction has been set out in legislation.
Royal College of Nursing	Guideline	General	General	Our members have expressed disappointment that this guidance has remained very limited in its recommendations and scope despite previous recommendations to review this.	Thank you for your comments.

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Royal College of Nursing	Guideline	General	General	Quality-adjusted Life Year (QALY) data is only a part of the outcomes that healthcare professionals need to consider. Perhaps the guidelines would consider allowing prescription of cannabis-based medicinal products and with a caveat for people participating in both short-term and long-term trial.	Thank you for your comments. We acknowledge that there are other measures available to estimate health outcomes among patients. As per NICE guideline manual and NICE reference case, the health effect in the economic model should be expressed as QALYs so that an outcome can be compared between different populations and disease areas.
Royal College of Nursing	Guideline	General	General	The economic impact of spasticity and chronic pain is huge. a. Several aspects include keeping persons with Multiple Sclerosis (MS) at work whether full time or part time. b. There is also the cost of the ever-increasing poly pharmacy to manage these symptoms. Most current drugs have a massive impact of cognitive and physical function c. Most patients will require several GP, MS Nurse, MS consultant appointments to help manage the above symptoms. These services are already under strain	Thank you for your comments. As per the manual for Developing NICE guidelines, the costs in a guideline are calculated in line with the NHS and PSS perspective but do not include the wider societal perspective such as productivity benefit of keeping MS patients at work. The reason for this is that productivity costs in our analyses would favour those interventions aimed at the working population. We would then discriminate against the elderly, children, unemployed people and people with disabilities. As described in the model report in both spasticity and chronic pain evidence reviews, the economic models included resource use, such as cost of GP, nurse, and consultant appointments to manage spasticity and chronic pain. Both economic models compared the economic impact of strategies with and without medicinal cannabis.
Royal College of Nursing	Guideline	General	General	Persons with MS currently are left with no choice but to either buy cannabis-based medicinal products illegally which in itself has ethical and legal consequences. These have unknown drug interactions and potentially harmful due to the lack of regulation and unknown dosages. This puts clinicians who are prescribing other medications to individuals at risk. Our reviewers, therefore, consider that the only safe practice is to allow wide prescribing.	Thank you for your comment. After publication of the consultation draft of the guideline, the manufacturer reduced the list price of THC:CBD spray, and this had an important impact on our assessment of its cost effectiveness. In light of stakeholder comments, the committee also reviewed their estimates of likely resource use associated with spasticity symptoms. The committee are now able to make a more positive recommendation.
Royal College of Nursing	Guideline	General	General	There needs to be more clarification regarding the difference between medicinal and over the counter preparations.	Thank you for your comment. In the guideline we have referred to the term 'medicinal' when referring to cannabis-based medicinal products and this is defined in the 'terms used in this guideline' section. Over-the-counter preparations are those that can be purchased from a retail outlet such as a pharmacy. The guideline considered the clinical effectiveness of CBMPs and not over-the-counter products like cannabis oil sold as food supplements.
Royal College of Paediatrics and Child Health	General	General	General	It is implied in the first few indications that the recommendations don't apply to children because it only talks about adults, it would be better to say this explicitly, and also to include why this is so i.e. there is no/not enough evidence for children.	Thank you for your comment. Specific recommendations for adults and children are made based on the quality and quantity of evidence. Further justification is provided in the rationale and impact section of the guideline. NICE editorial policy now prefers to use babies, children and young people to promote clarity and understanding of our recommendations.
Royal College of Paediatrics and Child Health	General	General	General	It should be reflected in the guideline that there is a licensed cannabidiol product; Epidyolex received positive opinion from EMA (CHMP) in July 2019. https://www.ema.europa.eu/en/medicines/human/summaries-opinion/epidyolex	Thank you for your comments. The use of Epidiolex for Lennox Gastaut and Dravet syndromes is currently being assessed by our technology appraisal team, due to be published later this year. This is referred to in the evidence review for epilepsy.
Royal College of Paediatrics and Child Health	General	General	General	Overall this Is a sensible, measured document. It seems to fit well with the Health select committee report released last month (https://irp-cdn.multiscreensite.com/51b75a3b/files/uploaded/Report%20%7C%20CBD%20in%20the%20UK%20-%20Exec%20Summary.pdf).	Thank you for your comment.
Royal College of Paediatrics and Child Health	General	General	General	It can be a bit limited in the definitions of cannabis-based medicines – there are only a few that are made to GMP quality and could be used in childhood epilepsy – Epidiolex, Bedrocan, and Tillray. For Lennox gastaut and Dravets, the only evidence is for Epidiolex (currently unlicensed) – these are not mentioned by name although sativex and others are. For Epidioliex, even if UK paediatric neurologists wish to prescribe, the company manages access via a scheme, so it is not only parent and patient wish – there is an extra hurdle to cross. There are plenty of other products – but the quality of these is highly variable (see https://publications.parliament.uk/pa/cm201719/cmselect/cmhealth/1821/182102.htm)	Thank you for your comment. This guideline is underpinned by legislation in terms of what cannabis based medicinal products can be considered. Therefore we only considered the following: • cannabis-based medicinal products as defined by the UK Government in November 2018 • the licensed products nabiximols (Sativex) and nabilone. • plant-derived cannabinoids such as pure cannabidiol. • synthetic compounds which are identical in structure to naturally occurring cannabinoids such as delta-9-tetrahydrocannabinol (THC), for example dronabinol.
Royal College of Paediatrics and Child Health	General	General	General	Despite the inclusion in the panel of a Psychologist and Psychiatrist, mental health conditions seem to have been omitted from consideration. Was this deliberate? If so, will they be the subject of a subsequent guideline? In particular, there is anecdotal evidence that it may help anxiety: to my knowledge, no RCTs have been done. This is of relevance to RCPCH, since many young people use cannabis to self-medicate their anxiety, often with sufficient success and insufficient side-effects for there	Thank you for your comment. Psychiatric disorders were out of scope for this guideline. The current research recommendations in the guideline will take into account safety of CBMPs which may include psychotic symptoms.

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				to be any logic in dissuading them. It may be possible to persuade them to stop if they are getting psychotic symptoms, or even depressive symptoms, but since their subjective experience is that anxiety improves, even despite some paranoid ideas, they are obviously likely to continue. It would be safer if they did so without having to take the concomitant THC. Would it be so awful for NICE to consider CBD as a third-line treatment for anxiety? CBD oil is, after all, legally available over-the-counter, albeit at great expense.	
Royal College of Paediatrics and Child Health	General	General	General	MHRA has issued guidance in respect of unlicensed CBPMs - in case a cross reference in the NICE guideline is considered useful. (https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/752796/Cannabis_Guidance__unlicensed_CBPMs__-_Final_311018.pdf)	Thank you.
Royal College of Paediatrics and Child Health	General	General	General	The reviewer agrees with the recommendations laid out in this guideline	Thank you.
Royal College of Paediatrics and Child Health	Guideline	20	10-12	The concerns about effects on brain development are fair, but in the case of poorly treated intractable epilepsy, this also has effects on normal brain development and this overall need is a balance between the two sets of risks and benefits – the text as it currently reads seems to focus on the harms of prescription only.	Thank you for your comment. The wording of the rationale has been amended to reflect your comment.
Royal College of Paediatrics and Child Health	Guideline	4-5		There are no recommendations for "intractable nausea and vomiting", "chronic pain" and "spasticity" specifically for children and young people (there are however research questions). It would be better to distinguish what applies for the paediatric population for each condition, i.e. is it a "Do not offer…" statement or "there is limited evidence to make recommendation…"? For example, for spasticity Sativex is not recommended in the paediatric population according to the SmPC (following an RCT in children that did not meet its primary endpoint, assessed in 2018 https://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/Paediatric_Regulation/Assessment_Reports/Article_46_work-sharing/Sativex_2018_09.pdf)	Thank you for your comment. Specific recommendations for adults and children are made based on the quality and quantity of evidence. Research recommendations have been made to fill gaps in the evidence base for children.
Royal College of Paediatrics and Child Health	Guideline	5	10	The section should be split into two sections – the Lennox-gastaut and Dravet first (where there is evidence, and it is being appraised separately) and then "other treatment resistant epilepsies second. There should be some comments on ongoing clinical trials in these areas (e.g. Retts syndrome) – otherwise it looks like the area where there actually is evidence is being ignored as it is tucked away at the end.	Thank you for your comment. The evidence review considered evidence on treatment-resistant epilepsies such as Lennox-Gastaut and Dravet syndromes, however they were unable to make recommendations as this will be covered by the technology appraisal guidance. Furthermore, the committee considered whether it would be possible to extrapolate the findings from the Lennox-Gastaut and Dravet populations but felt that this wouldn't be appropriate given the differences between different types of epilepsy.
Royal College of Paediatrics and Child Health	Guideline	6-7		Review by the specialist should not be only at initiation of treatment but should be recommended also at regular intervals (to decide continuation or not, review adverse effects, etc) determined based on the disease treated/population, for such severe cases this should be at least annually or every 6 months.	Thank you for your comment. Recommendation 1.5.3 states that the efficacy and safety should be monitored and evaluated by the specialist as part of the shared care agreement. The frequency of review would be patient, medicine and condition specific.
Royal College of Paediatrics and Child Health	Guideline	7	15-16	"potential for interaction with other medicines, for example…": antiepileptics should be added in "other medicines" list.	Thank you for your comment. This has been added to reflect your comment.
Royal College of Paediatrics and Child Health	Introduction	1		It should be stated that the guideline covers: "children, young people and adults" rather than "people".	Thank you for your comment. Specific recommendations for adults and children are made based on the quality and quantity of evidence. NICE editorial policy now prefers to use babies, children and young people to promote clarity and understanding of our recommendations.
Royal College of Paediatrics and Child Health	Prescribing	6	7-8	Could amend final sentence to "For Children and Young people under 18 years, the initiating prescriber should be a tertiary paediatric neurologist (or epilepsy specialist)". Suggest amend from just "specialist" as all paediatric consultants in tertiary hospitals will fit this description. This is clarified on page 18, line 21, but it should be in the main section as well.	Thank you for your comment. The recommendation you refer to takes into account more than one condition and does not only just apply to epilepsy.
Royal College of Physicians	General	General	General	The RCP is grateful for the opportunity to respond to the above consultation. We have liaised with our experts in Palliative Medicine and would like to make the following comments.	Thank you for your comments.

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Royal College of Physicians	Guideline	19	10-12	If via s specialist could this include arrangements for remote monitoring or in conjunction with another professional such as GP, rather than always face to face?	Thank you for your comment. This may be part of the shared care agreement and would need to be agreed locally.
Royal College of Physicians	Guideline	4	4	Suggest 'add on or switch to' given other agents ineffective; also specify duration of use (eg 24 hours prior and for max 5 days after administration of chemotherapy)	Thank you for your comment. Nabilone is currently licensed in adults who have failed to respond adequately to conventional antiemetic treatments. Recommendation 1.1.1 states 'Consider nabilone as an **add-on** treatment for adults'. Duration of use is not included in the recommendation but is outlined in the BNF and SPC.
Royal College of Physicians	Guideline	5	1.4	This is a difficult position given the government amendment to regulations in response to high profile cases with intractable epilepsy and raised expectations that this would be now permissible through a specialist. This NICE recommendation appears to contradict that, and also, use of licensed drugs for other than licensed indications is recognised for specific situations. Our experts question whether the recommendation could (1) define exceptional circumstances assessed by a paediatric neuro-specialist where in absence of any other option, a short term trial of a cannabis based medicinal product is reasonable in the specialist's opinion, and b) this should be through a research study where available but c) in the meantime, and in anticipation of research studies, these cases should be registered and a basic clinical data set completed. Our experts note the importance of considering the position of a distressed parent with such a child and the position reached (even inadvisably) with the amended regulations.	Thank you for your comments. The committee did not feel that current evidence was sufficient to confidently recommend the use of cannabis-based medicinal products for severe treatment-resistant epilepsy. However, they appreciated that some people have shown benefits from the use of these products and so they chose not to make a recommendation against their use. The guideline does not provide a specific recommendation for exceptional circumstances because the committee did not feel there was sufficient evidence to guide these decisions. However, by not including a recommendation against the use of cannabis-based medicinal products, specialists are still able to prescribe them in circumstances where they think it may be beneficial. Clinicians can also still make their own individual prescribing decisions in the best interest of their patients
Royal College of Physicians	Guideline	6	1.5.1	Our experts question which specialist for chemotherapy induced n&v? There could be several, i.e. oncologist, haematologist, palliative medicine physician based in cancer centres.	Thank you for your comment. The committee agree that this could be a physician from a number of different specialities and will vary in different clinical teams depending on local responsibilities and areas of specialist interest. The wording has been agreed to reflect this.
Royal College of Physicians	Guideline	6	1.5.3	Our experts suggest be explicit that this means G, not just other prescribers in the specialist team. Our experts suggest that responsibility for ongoing monitoring then be part of shared care agreement otherwise the patient always has to attend for direct review at hospital.	Thank you for your comment. The arrangements for monitoring would be agreed locally between the specialist and the prescriber.
Royal College of Physicians	Guideline	7	5	Our experts suggest be explicit that in the event of the patient or initiating prescriber moving , it is the responsibility of the latter to hand over to a different specialist- when the patient has moved away this needs to be assisted by their new GP	Thank you for your comment. This could be part of the shared care agreement and would need to be agreed locally.
Royal College of Physicians	Guideline	7	11	Need to bear in mind such previous illicit use might have been in attempt to alleviate symptoms rather than 'recreational'.	Thank you for your comment. This would be captured by the first bullet point in recommendation 1.5.5.
Royal College of Physicians	Guideline	8	23	Easier (and more sensible) to simply say do not drive if using cannabis based products	Thank you for your comment. The committee considered your suggestion and felt that as the effect of cannabis-based medicinal products on driving may vary, it is important to discuss this with the person rather than to say not to drive.
Royal College of Physicians and Surgeons of Glasgow	Guideline	7	11	Both "history of" and "current" substance misuse are of relevance to prescribing in this context and this should be explicit.	Thank you for your comment. The committee discussed this and agreed that the current wording captures 'current use'.
Royal College of Physicians and Surgeons of Glasgow	Guideline	7	24	Given the possibility of multiple drug misuse, and the inherent uncertainty over active moieties in illicit drugs, there should be explicit guidance to desist from ingestion of all illicit drugs rather than just those which (may) contain cannabis.	Thank you for your comment. The recommendation you refer to included illicit products as well as non-prescribed cannabis
Royal College of Physicians and Surgeons of Glasgow	Guideline	General	General	The Royal College of Physicians and Surgeons of Glasgow was founded in 1599 to improve quality and practice of Medicine. The College although based in Glasgow represents Fellows and Members throughout the United Kingdom. While NICE has a remit for England, many of the recommendations are applicable to all devolved nations including Scotland. They should be considered by the relevant Ministers of the devolved governments	Thank you for your comments.

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				The College welcomes this document in area where hitherto there has been little expert guidance. It notes that this topic has received publicity for various quarters in the public domain. This document sets out very sensible, pragmatic and evidence-based guidance for practitioners in an area where such guidance is needed. It is well structured, clear and authoritative. Areas which will be addressed separately and hence fall outside the scope of this document are clearly defined.	
Royal Pharmaceutical Society	Guideline	10	3	We support more research into CBD for severe treatment resistant epilepsy, including post marketing clinical trials for Epidiolex which now has approval in other countries.	Thank you for your comments and support for this guideline. The evidence review considered evidence on treatment-resistant epilepsies such as Lennox-Gastaut and Dravet syndromes, however they were unable to make recommendations as this will be covered by the technology appraisal guidance.
Royal Pharmaceutical Society	Guideline	10	8	Research into the possible combinations of CBD and THC and the synergistic effect of this combination is required. Clinical trials for products already licensed in other countries would increase patient access to treatment and facilitate prescribing in a structured way. Until the long term effects are established this approach should always be after standard treatments have been tried without success. This may help stop families attempting to import products individually and reduce people resorting to internet sales where quality cannot be assured.	Thank you for your comments. Research into the effects of CBD in combination with THC for severe treatment-resistant epilepsy has been recommended as part of the guideline (recommendation 4).
Royal Pharmaceutical Society	Guideline	10	15	We support further research on spasticity. It is our understanding that most evidence is qualitative from patient reporting and without more robust evidence some patients may not be receiving a treatment which would improve their quality of life. We have concerns that the rigid criteria being used to model cost effectiveness is not a person-centred approach which will facilitate prescribing and accommodate the small numbers of people who have said they are already benefiting from CBMPs.	Thank you for your comments. The model is based on the best available clinical evidence. We have validated the model data with the committee as well as submitted the report for peer-review with additional clinical experts during the consultation. As such, we consider the model estimate to reflect best-available clinical evidence and experience. We have revised the guideline to ensure patients who started CBMPs in the NHS before this guidance was published should be able to continue treatment until they and their NHS clinician think it appropriate to stop.
Royal Pharmaceutical Society	Guideline	10	23	We support further research into the clinical effectiveness of chemotherapy induced intractable nausea and vomiting. Prescribing in this area could be for a larger patient group and cost effectiveness is important but the short-term nature of chemotherapy treatment and the longer-term benefits if people are still able to work and carry on normal life must be considered when evaluating overall cost.	Thank you for your comment.
Royal Pharmaceutical Society	Guideline	14	19	We would welcome more clinical trials to evaluate the benefits in chronic pain. CBMPs have been used in other countries as an alternative to opioids or to reduce opioid use and more research is required to fully assess this.	Thank you for your comment. Our systematic review of RCTs found that the outcomes for opioid usage were not statistically significant.
Royal Pharmaceutical Society	Guideline	18	22	We agree that there are challenges for ongoing monitoring and prescribing for patients, but person centred solutions must be sought to facilitate this which include robust clinical governance. Signing of any prescription assumes responsibility. Is this an option for GPs at the moment with unlicensed products and a clear recommendation for consultant prescribing of all CBMPs? The guideline has made detailed recommendations for shared care, but this aspect still needs further consideration. New models for clinical trials might be required using outreach into community and other health care professionals including pharmacists working in GP practice and in community. An integrated approach is required. With protocols in place and innovative IT solutions, including remote consultations hospital visits could be minimised.	Thank you for your comment. The committee took into consideration the NHS England document 'Responsibility for prescribing between Primary & Secondary/Tertiary Care' that provides details of what the arrangement should consider. The committee agreed that shared care for cannabis-based medicinal products would be for local agreement between the GP and specialist and, in line with the NHS England guidance the GP could accept or decline shared care.
Royal Pharmaceutical Society	Guideline	4	4	We agree that looking at the currently available evidence on long term side effects, nabilone should only be an option when other conventional antiemetics have failed. It should be short term, unless used for palliative care and should not be used in young people. More research into interactions with other medicines and the development of psychological disorders is required.	Thank you for your comment.
Royal Pharmaceutical Society	Guideline	4	16	We agree that there is limited high-quality evidence for cannabidiol (CBD) and tetrahydrocannabinol (THC), or combinations of both, in chronic pain and these products should not be prescribed for chronic pain unless part of a clinical trial. However, we question the criteria used to measure quality-adjusted life years (QALYs) in this area as products are not expected to extend life or be fundamentally disease modifying and so pain products appear to be scored unfairly.	Thank you for your comments. We acknowledge that there are other measures available to estimate health outcomes among patients. As per NICE guideline manual and NICE reference case, the health effect in the economic model should be expressed as QALYs so that an outcome can be compared between different populations and disease areas. EQ-5D is the preferred measure of health-related quality of life.

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Royal Pharmaceutical Society	Guideline	5	1	We agree CBD should not be used for chronic pain unless part of a clinical trial. More research is required in areas such as fibromyalgia where Cannabis-based medicinal products (CBMPs) have the potential to improve safety by replacing or reducing doses of standard treatments.	Thank you for your comment.
Royal Pharmaceutical Society	Guideline	5	4	Sativex is a licensed product and patients using it have reported improvements in spasticity. Prescribing Sativex should be a clinical decision between a consultant and a patient and only used in an individual in whom other treatments have failed. The product should be trialled on short term basis to assess outcomes. This treatment should not be withheld to patients already finding improvement purely on the basis of cost. As with other products we advocate for more research and prescribing to be part of a clinical trial.	Thank you for your comment. After publication of the consultation draft of the guideline, the manufacturer reduced the list price of THC:CBD spray, and this had an important impact on our assessment of its cost effectiveness. In light of stakeholder comments, the committee also reviewed their estimates of likely resource use associated with spasticity symptoms. The committee are now able to make a more positive recommendation. A research recommendation was also made to encourage more research for the treatment of spasticity. This can be found in Appendix K of the evidence review.
Royal Pharmaceutical Society	Guideline	5	7	There is limited evidence for other CBMPs so they should only be prescribed within a clinical trial. More research is required to build an evidence base.	Thank you for your comments.
Royal Pharmaceutical Society	Guideline	5	10	We agree that further research is required to ascertain the potential of CBMPs in severe treatment resistant epilepsy. We called for the rescheduling of Cannabis to encourage and enable more research projects and trials. Since the rescheduling of Cannabis, it should be easier to access products licensed in other countries. Making no recommendation on the use of CBMPs will detract from consultants considering prescribing for patients who have already shown improvement in severe epilepsy. These products are usually only used as a last resort when traditional treatments have failed and there are concerns that the severity and frequency of the epilepsy seizures could be life threatening. The decision to prescribe should be a clinical one between patient/guardians and the prescriber with usual best practice around discussion of the unlicensed nature of the product and the lack of long term data on developmental complications.	Thank you for your comments. The committee discussed that the lack of evidence and decided that although they could not make a recommendation in favour of CBMPs for people with severe treatment-resistant epilepsy, they did not want to recommend specifically against it either. This means that people can still be prescribed CBMPs if their clinician thinks they will benefit. This is described in more detail in the 'committee's discussion of the evidence' section of the epilepsy evidence review.
Royal Pharmaceutical Society	Guideline	6	4	We agree that prescribing should be the remit of specialists and for under 18s then a tertiary specialist as appropriate.	Thank you for your comment.
Royal Pharmaceutical Society	Guideline	6	10	While every effort should be made to minimise visits to hospital for patients and their families and to support care closer to home to reduce the need for travel, there are many complexities around having shared care agreements. We can understand if General Practitioners are reluctant to sign prescriptions for CBMPs while these are unlicensed and there is still a lack of evidence and educational support available, or for potential new treatments. Arrangements for shared care would have to be very tightly controlled and this could be difficult. A more pragmatic approach would be to have prescribing from the appropriate consultants and supply to be made through community pharmacies where an agreed supply arrangement/procedure has been established - good communication and a formal process agreed between these two healthcare professionals will be essential. This would give convenience to patients and negate the need for extra hospital visits.	Thank you for your comment. This may be an option based on available resources and local agreement.
Royal Pharmaceutical Society	Guideline	7	7	NICE has considered a comprehensive list of factors to support prescribers in their decision making.	Thank you for your comment.
Royal Pharmaceutical Society	Guideline	8	4	The information on shared decision making is essential to ensure patients and their families fully understand the unlicensed nature of the products and the potential consequences of this.	Thank you for your comment.
Royal Pharmaceutical Society	Guideline	9	15	We agree with recommendations for more research into fibromyalgia. CBMPs might "improve safety" in patients with treatment resistant neuropathic pain (fibromyalgia) by either replacing or reducing doses of medicines used in standard care.	Thank you for your comment.

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Royal Pharmaceutical Society	Guideline	9	22	We would like to see more research into the clinical effectiveness for CBMPs in both adults and children. A validated model must be used to estimate this. Criteria for this model might have to be revised from standard QALYs to give realistic results until a more robust evidence base is available. It is not clear from the rationale presented why higher levels of response have been used in the cost analysis than in the clinical effectiveness review and why there should be any difference?	Thank you for your comments. The committee made research recommendations for both adults and children. As per NICE guideline manual and NICE reference case, the health effect in the economic model should be expressed as QALYs so that an outcome can be compared between different populations and disease areas. The economic models estimated the treatment response based on some of the included RCTs from the clinical review, which provided relevant data. Further details are described in the economic model sections in the evidence review. We have validated the model data with the committee as well as submitted the report for peer-review with additional clinical experts during the consultation. As such, we consider the model estimate to reflect best-available clinical evidence and experience.
Royal Pharmaceutical Society	Guideline	General	General	The review is a comprehensive assessment of the available randomised controlled trials (RCTs) (and observational studies where included) and we broadly support the findings of clinical effectiveness based on the evidence assessed by NICE. We agree with NICE that we need high quality evidence for CBMPs as the evidence currently available is generally of poor quality. We need to encourage more clinical trials of CBMPs to enable more products to become licensed in the UK thus ensuring consistent quality, safety and efficacy. including products that are licensed for medicinal use in other countries. We should currently consider CBMPs as a treatment of last resort for patients when all other treatment options have failed. Ideally, they should only be used in those conditions where there is some evidence that they are clinically effective. We are disappointed that only one product (Nabilone) is recommended by NICE for use in specific situations in intractable nausea and vomiting. We are pleased to see the prescribing issues well outlined in the guideline but think some aspects of shared care still need to be considered.	Thank you for your comments. We have amended our prescribing recommendations following stakeholder feedback.
Royal Pharmaceutical Society	Guideline	General	General	There is nothing in the guideline to guide prescribers if they have patient demand for conditions not mentioned. Intractable vomiting can be due to conditions other than a reaction to chemotherapy. A general principle should now be that all new prescribing is part of clinical trials. It is not clear why Sativex and other cannabinoids are excluded from the guidelines despite the fact they may have a role in the conditions discussed in the scope.	Thank you for your comment. The guideline is unable to make recommendations for conditions not investigated in the scope. In the intractable nausea and vomiting review, 28 studies were included, 27 of which focused on chemotherapy induced nausea and vomiting and 1 study focused on radiotherapy induced nausea and vomiting. The committee noted that there was a lack of evidence for other causes of intractable nausea and vomiting and drafted a research recommendation to support further research. The scope of this guideline included the following cannabis-based medicinal products: • cannabis-based products for medicinal use as set out by the UK Government in the 2018 Regulations • the licensed products delta-9-tetrahydrocannibinol and cannabidiol (Sativex) and nabilone • plant-derived cannabinoids such as pure cannabidiol (CBD) • synthetic compounds which are identical in structure to naturally occurring cannabinoids such as delta-9-tetrahydrocannabinol (THC), for example, dronabinol. Evidence on the use of following products for intractable nausea and vomiting was found: • Tetrahydrocannabinol (THC) • Tetrahydrocannabinol (THC) plus prochlorperazine • Dronabinol • Dronabinol plus prochlorperazine • Nabilone For further information on evidence reviewed please refer to Evidence review A. For further information on the research recommendations drafted, please refer to Appendix K in evidence review A.
Royal Pharmaceutical Society	Guideline	General	General	RCTs are relied heavily on by NICE in the analysis. While this has been recognised as the gold standard in terms of evidence, other data are available that could help inform decisions. CBMPs are an emerging treatment option and we should look at all the evidence. At this	Thank you for your comment. NICE guideline recommendations are based on the best available evidence. Review questions guide the search for evidence, and the type of evidence used depends on the type of question. For example, a randomised controlled trial is

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				stage we should use real-world data/observational data/patient case studies and experiences to inform our position on clinical efficacy until data from RCTs become available. It is interesting to note that Drugs Science have recently announced they will carry out 'real-world data' research into the prescription of cannabis-based medicinal products, using data on the health, lives and experiences of 20,000 patients. This study is due to begin in September 2019 and it will be interesting to see the impact of the outcomes of this research. There needs to be the ability to prescribe for patients in a compassionate way until more detailed data become available. The guideline as written does not allow flexibility for this.	often the most appropriate type of study to assess the efficacy or effectiveness (including cost effectiveness) of an intervention. The guideline has added a recommendation advising prescribers to record details of treatment, clinical outcomes and adverse effects for people prescribed cannabis-based medicinal products, using local or national registry. This will enable feedback from patients to feed into the evidence base.
Royal Pharmaceutical Society	Guideline	General	General	It is disappointing that NICE have placed such a huge reliance on the economic analysis (often modelled rather than based on published data) to base decisions on efficacy/suitability. This could underestimate the potential benefits of treatments and their place in therapy.	Thank you for your comments. The economic models are based on the best available clinical evidence. We have validated the model data with the committee as well as submitted the report for peer-review with additional clinical experts during the consultation. As such, we consider the economic analyses to reflect best-available clinical evidence and experience.
Royal Pharmaceutical Society	Guideline	General	General	In spasticity, the committee considered the evidence from two published economic evaluations but noted that they were contradictory and subject to potentially serious limitations. A new economic model was developed specifically for the Cannabis guideline. It is unclear, how the published economic evaluations were contradictory. It is also not clear whether the new evaluation was consistent with one of the published ones.	Thank you for your comment. After publication of the consultation draft of the guideline, the manufacturer reduced the list price of THC:CBD spray, and this had an important impact on our assessment of its cost effectiveness. In light of stakeholder comments, the committee also reviewed their estimates of likely resource use associated with spasticity symptoms. The committee are now able to make a more positive recommendation.
Sapphire Medical Clinics	Guideline	13	17-20	We feel that the conclusion that there was no reduction in opioid use is not supported by the evidence that was reviewed. No RCTs were powered to determine this as a primary or co-primary endpoint, there was significant heterogeneity in recording this outcome and further bias due to generalisation of multiple different CBMPs preparations and doses. The conclusion should be that there is insufficient evidence to determine if there is a significant reduction in opioid use, and further data which were not based on RCTs may have been useful to review.	Thank you for your comment. Our systematic review of RCTs found that the outcomes for opioid usage were not statistically significant. Following draft guideline consultation, the evidence review has been amended stating that 'the data could not differentiate whether there was an opioid sparing effect for THC:CBD'. With regards to adult studies, the economic analysis also suggested that most types of chronic pain were not going to be cost-effective to manage using CBMPs.
Sapphire Medical Clinics	Guideline	4	16	Whilst we acknowledge the scientific rigour applied to summarising the evidence and have no concerns regarding the methodology of the analysis or economic model we feel that the inherent limitations of the evidence are not well presented in the guideline document which is what is scrutinised by patients, clinicians and other stakeholders. For instance, the guideline on chronic pain is based on trials mostly investigating Sativex. Whilst the rationale for this is obvious (lack of RCTs evaluating other medicines) the recommendation should specify precisely that based on the evidence relating to Sativex the cost-effectiveness analysis is not favourable for recommendation on NHS. There has been no evaluation of CBMPs that are more commonly prescribed in Canada, North America, Germany or Italy, which may have a different efficacy profile due to differences in THC:CBD concentrations, method of administration and whether it is an extract or isolate. This review can therefore simply conclude that there is a lack of evidence to determine cost-effectiveness of THC:CBD products (as a group) in chronic pain.	Thank you for your comment. After publication of the consultation draft of the guideline, the manufacturer reduced the list price of THC:CBD spray, and this had an important impact on our assessment of its cost effectiveness. In light of stakeholder comments, the committee also reviewed their estimates of likely resource use associated with spasticity symptoms. The committee are now able to make a more positive recommendation.
Sativa Group PLC	Evidence Review	General	General	A number of statements in the guidelines regarding the use of CBMPs in chronic pain contradict other published (and accepted) data and are not referenced– for example on page 13 of the draft guidelines, it is stated that the evidence did not show a reduction in opioid use in people prescribed medicinal cannabis, a finding not mirrored in data emerging from the United States.	Thank you for your comment. RCTs are the best studies for assessing medicinal cannabis. This is because all analgesia has a strong placebo effect. Therefore, studies should be double-blinded and randomised. Our systematic review of RCTs found that the outcomes for opioid usage were not statistically significant.
Sativa Group PLC	Evidence Review B	222	2-6	The economic modelling is in parts based on the advice of the NICE committee (regarding pain interventions for example). There appears to only be one pain consultant on the committee and so in effect the advice regarding pain management approaches is based on the opinion of a single pain specialist – this approach is flawed and likely to lead to oversights with respect to current pain treatments. For example it appears that the economic modelling in some parts was based on the concept that only RF denervation of medial branches is common enough to influence the guidelines, negating other high-cost interventional treatments for localised neuropathic pain which are commissioned by the NHS such as 8% capsaicin patches or spinal cord stimulators.	Thank you for your comments. The model is based on the best available clinical evidence. We have validated the model data with the committee as well as submitted the report for peer-review with additional clinical experts during the consultation. As such, we consider the model estimate to reflect best-available clinical evidence and experience. We acknowledged that there are other potential downstream treatment options in chronic pain. Radiofrequency denervation (RFD) was considered as a common downstream treatment for people with chronic low back pain. This is only relevant when considering the population with low back pain in the model.

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Sativa Group PLC	Evidence review B	General	General	Cost of CBMPs – as the draft document states, NICE believes there are currently no publicly available UK prices for dronabinol or for the various Bedrocan products, but the overall cost per patient is expected to be higher than that for the THC:CBD spray. Therefore they have made a number of assumptions; namely that the cost of CBMPs will be high and that Bedrocan is the only supplier of CBMPs that may potentially be used in the UK. The current prices of most CBMPs can be ascertained by contacting the relevant companies – there is no discussion as to whether this was attempted.	Thank you for your comments. We have reported the estimated costs of medicinal cannabis products, including products by Bedrocan (see Table 14 of the spasticity evidence review). These estimates are based on the publicly available sources but without importation. It is not part of the guideline process to contact companies for confidential prices.
Sativa Group PLC	General	General	General	In general, throughout the document there appears to be an overarching lack of understanding of CBMPs – there is no mention of differing constituent phytochemicals (many hundreds) and an apparent fixation on THC/CBD preparations. This approach is counter to the current discussion in the medicinal cannabis community regarding the relative merits of constituent phytochemicals.	Thank you for your comment. This review focussed on medicinal cannabis. The constituents of CBMPs were reported in the evidence review if available in the included studies. Other types of cannabis were beyond the scope of this review.
Sativa Group PLC	General	General	General	The authors also appear to have ignored research published by financial institutions such as Cenkos Securities plc, amongst others, who's June 2019 research note details the expected "commoditised extract pricing in the near term" of medical grade GMP products. We believe that if government agencies collaborated to establish a more effective regulatory and licencing framework for the production of CBMPs, including domestic extraction in the UK, this would facilitate an effective competitive market place for the emerging UK medicinal cannabis sector, in conjunction with larger international players, resulting in rapid price reductions, The domestic medicinal cannabis sector would appreciate more engagement - either directly with individual companies, or via respected trade bodies such as the Centre for Medicinal Cannabis (CMC) – with regards to sustainable pricing of CBMPs for patients.	Thank you for your comments. NICE produce guidelines for NHS England. It is not within NICE's remit to comment on the policy, licensing or pricing negotiation of the other regulatory bodies. Furthermore, it is not part of the guideline process to contact companies for confidential prices. We have reported the estimated costs of medicinal cannabis products, including products currently unavailable in the UK (see Table 14 of the spasticity evidence review). These estimates are based on the publicly available sources but without importation.
Sativa Group PLC	Methodology – chronic pain section	General	General	Discussions and assessment regarding pain outcomes were limited to pain only being assessed on simple 11 point numerical rating scale - CBMP have multisystem effects and may improve overall feelings of wellbeing, there is no discussion of this in the text of the draft guidelines. Chronic pain is a bio-psycho-social construct and so psychological morbidity, functional levels and general wellbeing are of equal importance when assessing the effectiveness of CBMP in pain patients.	Thank you for your comment. The committee agreed that the most important outcome was pain intensity. This is because it is ubiquitous and therefore allows comparison using a meta-analysis. We did include other outcomes such as quality of life and functional measurements of pain. However, studies did not often include them.
SEEK	Guideline	4	16	Whilst it is unusual to make a strong "do not offer" recommendation on the basis of an economic model, we generally welcome 1.2.1. We have some concern about the final bullet point. Because it is technically very difficult to isolate other cannabis products to the complete exclusion of THC and CBD, we are concerned that, as currently worded, this final bullet point might have a chilling effect on research where THC and CBD are unavoidable secondary constituents of a complex extract cannabis-based medicinal product albeit at lower levels than would otherwise be the case in THC/CBD focussed product or in plant products for recreational purposes.	Thank you for your comment. The recommendation wording is based on the evidence of clinical and cost effectiveness. The recommendation is referring to products where CBD and THC are the primary constituents.
SEEK	Guideline	5	1	On recommendation 1.2.2, we welcome the restriction on CBD prescribing for pain to a clinical trial context.	Thank you for your comment.
SEEK	Guideline	9	15	On research recommendation 1, we note that this is restricted to CBD only. Given that the *in vivo* evidence base is similar for other non-psychoactive cannabinoids and there is *in vitro* evidence of beneficial activity in some other compounds (for example the anti-inflammatory effect of cannflavinoids), we wonder whether it would be more appropriate to extend this to non-psychoactive cannabinoids as a whole.	Thank you for your comment. For the adult research recommendation, the committee wanted to focus on CBD (either as a pure product or containing traces of THC) due to a lack of evidence.
SEEK	Guideline	General	General	We are a clinical research organisation and one of our research projects regards the use of cannabis based medicinal products in the management of chronic pain. Our view of the (limited) evidence base is that neither CBD nor THC alone or in combination are particularly effective in pain management. We are primarily interested in the substances that occur in cannabis other than CBD or THC and how these may interact. Some of these have demonstrated significant *in vitro* pain and anti-inflammatory activity but *in vivo* trials are limited. Extraction processes today are not effective in capturing all these, so it is our view	Thank you for your comment.

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				that a complex plant extract is the best solution to this phase of research. We therefore welcome the thrust of this draft guidance.	
Spectrum Therapeutics UK				**Uncertainty and sensitivity.** A key requirement of economic evaluations for decision-making is to indicate how uncertainty in the available evidence relating to a given policy problem translates into decision uncertainty. The Committee were clear that the evidence for the effectiveness of CBMPs in chronic pain is very uncertain. However, the review document does not make clear the uncertainties in clinical evidence that made the modelling process very uncertain, nor the implication that its economic analysis was also full of uncertainties around the decision-making process. The lack of proper identification and discussion of the evidence, modelling and decision uncertainties associated with this work is a major limitation. Whilst sensitivity analysis can deal with some parameter uncertainties due to variability, the modellers have not adequately dealt with the structural uncertainties in their work. **Guideline change.** As the Markov model is clearly misspecified, the review document should discuss the problems associated with making recommendations about NHS decision-making with a model that has a high degree of structural uncertainty. In response, we request a fuller discussion of parameter and structural uncertainty in any subsequent draft of the chronic pain guideline.	Thank you for your comments. We presented to the committee different proposed model structures to the committee, based on the best available clinical evidence. After careful consideration of the limitations of different model structures, the committee agreed that the Markov model is the most appropriate approach for our decision problem and allow us to make the most use of robust evidence. The model has addressed parameter uncertainties and limitations in extensive sensitivity and scenario analyses, as described in Appendix I of the chronic pain evidence review. The committee is aware that there are limitations of the model, primarily due to lack of long-term evidence for CBMPs in general. We have validated the model data with the committee as well as submitted the report for peer-review with additional clinical experts during the consultation. As such, we consider the model estimate to reflect best-available clinical evidence and experience.
Spectrum Therapeutics UK	Evidence Review B			**Evidence.** In 2017, the US National Academies of Sciences, Engineering, and Medicine reviewed evidence and provided recommendations on the health effects of cannabis and cannabinoids and concluded that there is conclusive or substantial evidence that cannabis or cannabinoids are effective for the treatment of chronic pain in adults. We are concerned that the NICE guidance does not reflect this level of certainty over the benefits of CBMPs. **Guidelines that support use**. In Canada, it has been suggested that medical cannabinoids be considered when other standard therapies have failed: For refractory neuropathic pain, refractory pain in palliative care, chemotherapy-induced nausea and vomiting, spasticity in multiple sclerosis, and spinal cord injury. The Canadian Pain Society recommends using cannabinoids as third-line analgesic agents in the treatment of neuropathic pain. The European Pain Federation position paper suggest that CBMPs can be considered as third-line therapy for chronic neuropathic pain, and that CBMPs should be regarded as an individual therapeutic trial, when established treatments have failed, for all other chronic pain conditions (cancer, non-neuropathic non-cancer pain). Also, cannabinoids are recommended by the European Federation of Neurological Societies as second or third-line agents for refractory cases of central neuropathic pain in multiple sclerosis. **NICE recommendations.** We believe that the NICE guidance should reflect the world-wide growth in support for the CBMP treatment of chronic pain. Therefore, the final guidance should be amended to reflect emerging practice in other developed health systems.	Thank you for your comment. The RCT data that we reviewed favours some types of medicinal cannabis for managing chronic pain compared to placebo. However, although this reaches statistical significance, the effect size is so small that individual people are unlikely to notice any difference. For example, pain intensity is measured on a scale of 0 to 10, 0 being no pain and 10 being maximum pain. In order for a person to notice any difference, analgesia should reduce pain intensity by at least 2 or even 3 points. Most pain intensity effect sizes were either statistically insignificant (oral delta-9-THC, oromucosal THC, vaporised THC (minimal CBD), vaporised THC:CBD, vaporised CBD (minimal THC)), or they caused less than a 2 point pain intensity drop (oromucosal CBD:THC) or the 95% confidence interval crossed the 2 point pain intensity drop threshold (oral nabilone). This review focussed on medicinal cannabis. Other types of cannabis were beyond the scope of this review.
Spectrum Therapeutics UK	Evidence Review B			**Our main concerns.** We are concerned with the scientific quality of the evidence review for chronic pain. From an analytical point-of-view, the main issues are: 1. Not outlining a clear clinical pathway that can be used to perform the decision analysis necessary to construct a robust and scientific economic analysis of the cost-effectiveness of using CBMPs in treating chronic pain in NHS patients; 2. Treating CBMPs as a homogeneous class of drugs regardless of their active ingredient, delivery method, target condition, or patient group; 3. Building a generic economic model for all CBMPs when the economics of different conditions and products actually differ, which included the inappropriate step of creating an aggregated group of patients who use CBMPs for their chronic pain.	Thank you for your comment. The cost of medicinal cannabis for chronic pain is around 6 times greater than the NHS would normally deem an efficient use of resources. We did not treat medicinal cannabis products as a homogenous class of drugs: We had a separate meta-analysis for each individual drug.

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				Inappropriate conclusions. In response to these problems, we believe that the negative conclusions of the economic modelling are not valid on scientific grounds, and that the limitations of the economic model constructed cannot be addressed with sensitivity analysis alone. Given the problems of the modelling performed, we believe that the conclusion that CBMPs are not cost-effective is, in part, due to the inappropriate specification of the decision problem, and subsequent problems with the modelling process.	
Spectrum Therapeutics UK	Evidence Review B	33 212	6-17 14-15	**Our analysis.** We read all the studies included in the evidence review for chronic pain and thoroughly reviewed the economic model constructed. Following our analysis, we are concerned about the quality and the design of the economic modelling presented in the Evidence Review for Chronic Pain. In the document, the Committee acknowledges the limitations of the economic model, particularly due to the lack of good quality clinical and economic data. However, we strongly disagree with its conclusion that "Overall, the committee considered the economic model to be directly applicable with minor limitations for decision-making". We believe this conclusion is incorrect because of the lack of a clearly specified clinical pathway, and the absence of the data required to build a robust economic model. These problems have forced NICE analysts to make some invalid assumptions, and to adopt an approach to modelling that does not truly reflect NHS and clinical decision-making processes.	Thank you for your comments. The model is based on the best available clinical evidence. We have validated the model data with the committee as well as submitted the report for peer-review with additional clinical experts during the consultation. As such, we consider the model estimate to reflect best-available clinical evidence and experience.
Spectrum Therapeutics UK	Evidence Review B	25	10-13	**Modelling NHS decision-making.** Economic analysis is concerned with decision-making under conditions of uncertainty. To perform a robust economic evaluation, the clinical decision-making process must be accurately described and modelled. Due to the lack of an agreed clinical pathway for CBMPs as a generic group of interventions, the NICE analysts were unable to construct a well-executed decision model. The problem is as follows: **No clinical pathway.** First, the clinical guidance that NICE has followed is either: (i) general guidance on chronic pain, or (ii) NICE guidance for chronic pain in specific conditions. There is currently no agreed clinical pathway for use of CBMPs in this area. As a result, the standard step of building a decision tree to model the choices offered by the clinical pathway was not followed. **Inappropriate model.** In the absence of an available clinical pathway, the Committee commissioned a *de novo* economic model that considers CBMPs + Standard of Care (SoC) versus SoC alone. This logic reflects the RCT literature reviewed by NICE, but this simple head-to-head comparison does not reflect the complexities of NHS treatment, where CBMPs may be used as: (i) replacement treatments, (ii) adjunct interventions, (iii) treatments that promote opioid sparing, (iv) post-operative pain relief, and (v) "third line" agents. To perform the modelling correctly, the Committee must decide when and how CBMPs will be used within the NHS, and this complex issue was avoided by the simplification of the decision problem to reflect the "intervention versus placebo" structure of the clinical trials performed in this area. This is inappropriate because the RCTs undertaken were pilot studies and therefore were not designed to capture the complexities of real world decision-making. **No decision tree.** Due to the fact that the Committee avoided the complexities of the real world decision-making processes, the usual step of building a decision tree was missed in the analysis. This is a severe limitation because economics is the science of analysing choices amongst viable alternatives. Given this problem, the Committee has oversimplified the decision problem. The comparison of CBMPs+SoC versus SoC is not economically meaningful because it does not reflect the complex clinical decisions involved in CBMP treatment choices. **Economic conclusions.** As the complexities of CBMP care have been ignored, the simple head-to-head comparison modelled for this guidance does not reflect the realities of NHS decision-making. Therefore, the conclusions and recommendations of the guidelines are invalid and will prevent patient access.	Thank you for your comments. NICE is currently developing a Chronic Pain guideline to provide general guidance on chronic pain management. As mentioned below, this guideline is only addressing a small part of the clinical pathway. As described in the economic model report, the target population is defined as people for whom all available standard chronic pain treatments have failed (Appendix I of the chronic pain evidence review). Medicinal cannabis is only considered as the last treatment option as an add-on to the standard of care before the invasive or surgical interventions in the economic model. As such, medicinal cannabis cannot displace any other standard treatments. The included RCTs did not show any benefit of CBMPs in reducing dosage of other medical analgesia. The treatment options you have suggested are not considered as appropriate comparisons in the model, or they have already formed part of the standard of care strategy in the model. We presented to the committee different proposed model structures to the committee, based on the best available clinical evidence. After careful consideration of the limitations of different model structures, the committee agreed that the Markov model is the most appropriate approach for our decision problem and allow us to make the most use of robust evidence. While decision trees can often form part or all of an economic model, they are not an essential component of such analyses. In this case, the decision tree was not considered as an appropriate model structure due to its limitations and inflexibility. In particular, a decision tree is too simplistic to estimate lifetime benefits, harms and costs using continuous effectiveness data. The model that the committee agreed on is based on the best available clinical evidence. We have validated the model data with the committee as well as submitted the report for peer-review with additional clinical experts during the consultation. As such, we consider the model estimate to reflect best-available clinical evidence and experience.

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Spectrum Therapeutics UK	Evidence Review B	8 249 242-250 255 249 39 249 253 17/19	1 Appendix J Appendix J Appendix J Appendix J Appendix A and J Appendix J	We believe that the review team made the following errors or did not identify available data, which are damaging to the credibility of the review's evidence selection and modelling procedures: **Active placebo.** The PICO table states that de Vries (2016) is a placebo and this is an inclusion criteria for study inclusion. However, this paper reports a study that uses diazepam as an "active placebo" to mimic the sedative effects of delta-9-tetrahydrocannabinol. Diazepam has been shown to produce significant pain relief (Singh, 1981) and to affect the emotional component of the pain experience (Chapman, 1978). Therefore, diazepam is not suitable as a placebo in this review and should be removed from the analysis. **Should be included.** 2 conference abstracts by Riva (2016a and 2016b) were excluded by NICE. However, a paper based upon them was published in the Lancet (Riva, 2019). The Lancet paper should be included in the NICE review. **Wash-out period.** 8 studies (252 patients) were excluded because they had wash-out periods of less than 7 days. Four studies have wash out periods of a minimum of 3 days and four have no wash out period. The 7 day wash-out period is not universal and the 8 excluded trails were all considered valid by their authors. The following papers support wash-out periods of less than 7 days: Berman (2004), Wilsey (2016) and Wilsey (2013). With the current absence of available data, we suggest that studies with wash-out periods of less than 7 days be considered. **Data available.** Selvarajah (2010) was excluded because the reviewers could not find patient numbers in the paper. When we checked, this data was available in the text of the paper. **Symptoms included.** Zajicek (2003) was excluded because the reviewers could not find the relevant symptoms. We believe that they were included. **Was a placebo.** Rintala (2010) was excluded because placebo was not the comparator. However, the control drug was not active but was acting as a placebo. **Headaches.** The review excluded headaches and/or orofacial pain, but included cancer related headaches. No reason is provided why this distinction was made. This problem was caused by the exclusion of Pini (2012). **Graph data.** Dana (2015) was excluded for inadequate reporting of data. We believe that the required data can be extracted from the graphs in the paper. **Single dose trials.** We are also concerned about the inclusion of de Vries (2016) and van de Donk (2018) as both were single dose trials and this is not a realistic way of assessing chronic pain treatment	Thank you for your comment. The committee considered the best quality RCT data which met the review protocol inclusion criteria. The de Vries (2016) study is included in the evidence review however it states that the placebo was not specified. We do not include abstracts as part of our review process but any RCTs that results from this should form part of future updates. Unpublished data is not considered by NICE as it has not undergone the quality assurance peer review process. The washout period of 1 week or more was decided by the committee based on their knowledge and experience. This was also confirmed by expert testimony on cannabinoid psychopharmacology provided to the committee. We have checked these suggested references: Selvarajah (2010) was excluded due to a lack of relevant reported data. [No details as to how many of the 30 patients were randomised to each arm. Six patients withdrew from the study. However, there is no information as to which arms they withdrew from.] Zajicek et al (2013) was excluded as the paper was on multiple sclerosis and the relevant symptoms were not included. Rintala (2010) was considered by the committee however this paper did not meet the inclusion criteria. This was a crossover study and the active placebo (diphenhydramine – an antihistamine with active properties that causes adverse events) wasn't considered adequate. The committee discussed headaches and cancers that cause headaches. The protocol excluded headaches and orofacial pain but included headaches caused by cancer. This was because the committee felt that there is no definitive test to establish the cause of headaches and orofacial pain. NICE evidence review methodology does not recommend extracting data from charts as this can introduce imprecision. When the review's protocol was developed, the committee did not include a follow-up duration because stipulate a follow up period as it not entirely known what studies were available. The finding that there were some RCTs with a short follow-up period was useful information because this further endorsed the need for research recommendations that had a longer follow-up period.

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Spectrum Therapeutics UK	Evidence Review B	13	17-18	**Opioid sparing.** The review of the evidence did not show a reduction in opioid use with prescribed medicinal cannabis. The three studies reviewed by the Committee - Lichtman (2018), Johnson (2018) and Fallon (2017) - all state that the design of their studies make it difficult to draw clear cut conclusions. For instance, Lichtman states that the study required that maintenance opioid doses be kept stable across the treatment periods, so the likelihood of finding an opioid-sparing effect was very low. Moreover, in this study of advanced cancer patients with unstable conditions, the ability to observe any form of opioid sparing would be very difficult. Similar problems are evident in the other two trials used in the evidence review. Fallon (2017) states that "The tendency, but lack of significance, of a slight opioid-sparing effect of Sativex in the trials may have been attributable to the advanced stage of disease and the small incremental pain control given by Sativex administration. It is also important to note that, per protocol, all other medications prescribed for pain were to be continued during the study period at a stable dose." **Review evidence.** We recommend that the Committee revisit the opioid-sparing papers they reviewed because restrictions in the trial design and the severity of patient illnesses suggest they were not designed to fully-capture the effects of opioid-sparing. Therefore, they are an unreliable basis for pragmatic modelling.	Thank you for your comment. The chronic pain evidence review has undergone a peer review process where experts in this field were broadly content with the review methodology and findings. The review will therefore remain as it is.
Spectrum Therapeutics UK	Evidence Review B	212 217	12-13 7-8	**Misleading statement.** The claims that CBMPs are "expensive, costing several thousand pounds per year" and that the "positive resource impact of a positive recommendation could be very high" are very emotive, value-laden statements, which could prejudice common understanding of the economic issues involved. The issue examined by the Committee was not pricing or NHS spending, but cost-effectiveness. A product with a higher than average price or higher than average spending can still be cost-effective. Therefore, we request that this value-laden wording is amended.	Thank you for your comments. The statement is based on the estimated CBMP costs alone. We have reported the estimated costs of medicinal cannabis products, including products currently unavailable in the UK (see Table 14 of the spasticity evidence review). These estimates are based on the publicly available sources but without importation. We have revised the statement to reflect this.
Spectrum Therapeutics UK	Evidence Review B	213	14-21	**Markov model.** The economic modellers for the review constructed a Markov model. This is state-transition approach which differs from the usual procedure of constructing a decision tree because it simulates patient flows between clinical states rather than modelling the choices faced by clinicians. Usually, economics studies would start with a decision tree because they wish to be clear about the choices being made by NHS decision-makers. In contrast, Markov models focus solely on automatic transitions between health states. As economics is concerned with decision-making regarding viable options under conditions of uncertainty, Markov models alone cannot fully describe the economic choices facing clinicians. The absence of a decision tree from the evidence review for chronic pain is, therefore, a major limitation. In response, we request that NICE produce an appropriate decision tree before publishing its final guidance and recommendations. **Assumptions.** As simulations, all Markov models are based upon assumptions, which determine model structure and results. We believe that the following assumptions are inappropriate: (i) patients start in a homogenous "aggregated group" that does not reflect their treatment history, and (ii) patients who do not continue treatment drop back to baseline in both arms of the model. Regarding the first assumption, we believe that the model has not captured the complexities of available treatment choices because it does not differentiate between CBMPs being used as replacement treatments, adjunct interventions, treatments that promote opioid sparing, post-operative pain relief, and as "third line" agents. This is a major limitation because the Markov model is currently unable to answer the primary question of whether CBMPs are effective in managing chronic pain, particularly when conventional treatment options have failed or not been tolerated. Regarding the second assumption, we suggest that patients who have tried CBMPs and been unresponsive should then go into a second loop in the Markov model where they do not try CBMPs again. Therefore, it is a major problem that the Markov model does not include secondary, post-intervention states. Secondary states are usually included in most Markov models constructed within health economics.	Thank you for your comments. We presented to the committee different proposed model structures to the committee, based on the best available clinical evidence. After careful consideration of the limitations of different model structures, the committee agreed that the Markov model is the most appropriate approach for our decision problem and allow us to make the most use of robust evidence. While decision trees can often form part or all of an economic model, they are not an essential component of such analyses. In this case, the decision tree was not considered as an appropriate model structure due to its limitations and inflexibility. In particular, a decision tree is too simplistic to estimate lifetime benefits, harms and costs using continuous effectiveness data. As described in the economic model report, the target population is defined as people for whom all available standard chronic pain treatments have failed (Appendix I of the chronic pain evidence review). Medicinal cannabis is only considered as the last treatment option as an add-on to the standard of care before the invasive or surgical interventions in the economic model. As such, medicinal cannabis cannot displace any other standard treatments. The included RCTs did not show any benefit of CBMPs in reducing dosage of other medical analgesia. The model is based on the best available clinical evidence. We have validated the model data with the committee as well as submitted the report for peer-review with additional clinical experts during the consultation. As such, we consider the model estimate to reflect best-available clinical evidence and experience. We acknowledged the uncertainty of treatment effect in CBMPs in different chronic pain subgroups. Where data is available, we have tested the different treatment effects in pain subgroups in the sensitivity analyses. The ICER results of the sensitivity analyses showed that CBMPs are not cost-effective in all scenarios.

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				Misspecification. Given its simplicity, it is clear that the Markov model created for the evidence review for chronic pain is misspecified. To follow good practice in health economics, the model should be preceded by a well-designed decision tree, and be constructed in a way that reflects actual clinical choices. As CBMP patients are not a generic group, constructing one Markov model for an aggregated group of patients is clearly inappropriate. Therefore, we recommend that decision trees and accompanying Markov models are constructed at the sub-group level. For instance, separate decision trees and Markov models may be needed for cancer, post-surgical, post-traumatic, neuropathic, visceral and musculoskeletal pain.	
Spectrum Therapeutics UK	Evidence Review B	213 33	1-8 6-15	**Patient aggregation**. The modelling decision to consider all people with chronic pain as an aggregate group (which was broken down into pain aetiological subgroups) was inappropriate. This was done because there are not enough studies or evidence to build six individual models. As a compromise, patients were merged into one population. This aggregated approach produces a general model that reflects a non-existent totality of patients. There is no generic patient for CBMPs. Trying to build a model for this aggregate population is inappropriate because it does not reflect clinical reality. **Sub-group models.** The general model contains operational assumptions and structural choices that do not reflect the clinical decisions or economic realities evident at the sub-group levels. The sub-group models are therefore built on an inappropriate analytical base. The decision to use a general model to create various sub-models for different CBMPs (CBD spray, oral dronabinol, oral nabilone and oromucosal THC) means that the resulting analysis: (i) is not based upon comprehensive, real-world or trial data for the products being analysed, and (ii) carries the inappropriate structure and modelling assumption from the main model into the individual sub-group models. As a result, the product-level modelling is unrealistic and not useful for informing NHS policies. Sensitivity analysis cannot solve the structural problems inherent in the Markov model built for chronic pain.	Thank you for your comments. We acknowledge that there is heterogeneity in chronic pain populations. As per the guideline scope, the analysis should be inclusive and does not specify types of pain. The model is based on the best available clinical evidence. Subgroup analyses were conducted for specific treatments and for specific types of chronic pain where data were available. We recognise the limitations that some of the subgroup analysis conclusions may not be generalisable to the overall chronic pain population. We have validated the model data with the committee as well as submitted the report for peer-review with additional clinical experts during the consultation. As such, we consider the model estimate to reflect best-available clinical evidence and experience.
Spectrum Therapeutics UK	Evidence Review B	213 217	10-12 1-5	**30% pain reduction.** We question the validity of the Committee's indication that CBMPs would be trialled for one month, then discontinued if patients did not achieve a 30% reduction in pain on the basis that this is a "well accepted" Minimally Clinically Important Difference (MCID) in this population that has been reported by several reviews. We agree that 30% reduction is an outcome measure in 4 key studies, but we believe it has no validity as a benchmark for guiding clinical practice. We are concerned that the 30% success criteria will be adopted as "stop criteria" for patient treatment without any clinical justification. Using percentages alone is highly misleading. Any percentage change in pain will depend upon the baseline level for both its magnitude and meaning. 30% is an arbitrary figure not intended to be the basis for assigning health outcomes and costs in economic models. The use of this benchmark is a censoring of the data, and this categorisation should not be used because it reduces the information available in the analysis. **20% reduction**. If the Committee wish to use a MCID in its work, evidence from the literature suggests that 20% is a better cut-off. However, this figure still suffers from many of the problems described above.	Thank you for your comments. The 30% improvement threshold is based on the expert opinion at the committee. This parameter is only used to determine the continuation of treatment. The treatment response is based on the absolute NRS changes in the model. We acknowledge your concerns. We have validated the model data with the committee as well as submitted the report for peer-review with additional clinical experts during the consultation. As such, we consider the model estimate to reflect best-available clinical evidence and experience.
Spectrum Therapeutics UK	Evidence Review B	217	18-22	**Out-of-date study.** We question the validity of using Farrar (2001) as a source of modelling assumptions because the paper is now out-of-date.	Thank you for your comments. Farrar et al. 2001, a large epidemiological study in chronic pain, only provided baseline characteristics in the model: age, gender, pain NRS. Data from Farrar et al. 2001 are similar to the patient characteristics in the included RCTs. The committee has validated these assumptions and made a consensus that patients from Farrar et al. 2001 represented the chronic pain population in the current clinical practice. We have also submitted the report for peer-review with additional clinical experts during the consultation. As such, we consider the model estimate to reflect best-available clinical evidence and experience.
Spectrum Therapeutics UK	Evidence Review B	223	2-7	**Adverse events.** The modellers have chosen different rates of adverse events between the two arms. This is only valid if the model is misspecified in the way we describe above. If the comparator was an alternative intervention rather than a placebo, then adverse event rates	Thank you for your comments. As described in the economic model report, the target population is defined as people for whom all available standard chronic pain treatments have failed (Appendix I of the chronic pain evidence review). Medicinal cannabis is only considered

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				may be nearer in the two groups, or even lower in the CBMP arm. Better data on relative rates of adverse event data would probably be forthcoming if the model was better specified.	as the last treatment option as an add-on to the standard of care before the invasive or surgical interventions in the economic model. We conducted a targeted review to identify incidence data for AEs and serious AEs across of medicinal cannabis versus placebo/ standard of care across all indications. Wang et al. 2008 is the only study that provided the appropriate data for the model. A more recent meta-analysis by Whiting et al. 2015 did not report incidence data. Observational studies of medicinal cannabis only reported AEs of medicinal cannabis, rather than comparison against standard treatments. We have validated the safety data with the committee as well as submitted the report for peer-review with additional clinical experts during the consultation. As such, we consider Wang et al. is still the most appropriate source for safety data in the model. Whiting PF, Wolff RF, Deshpande S, Di Nisio M, Duffy S, Hernandez AV, Keurentjes JC, Lang S, Misso K, Ryder S, Schmidlkofer S, Westwood M, Kleijnen J. Cannabinoids for Medical Use: A Systematic Review and Meta-analysis. JAMA. 2015 Jun 23-30;313(24):2456-73.
Spectrum Therapeutics UK	Evidence Review B	225	Table	**Secondary care costs.** The non-drug treatment costs presented for CBMP patients seem high for secondary care interventions. This is because the modellers did not collect evidence on actual secondary use, so the costs used are an assumption. This assumption seems highly unrealistic and needs to be reviewed.	Thank you for your comments. Due to a lack of relevant evidence, the resource use assumption is based on the committee consensus, as described in Appendix I of the chronic pain evidence review. We acknowledge there are limitations on these assumptions and have tested them in the sensitivity analysis. We have validated the model data with the committee as well as submitted the report for peer-review with additional clinical experts during the consultation. As such, we consider the model estimate to reflect best-available clinical evidence and experience.
Spectrum Therapeutics UK	Evidence Review B	227 228	7 1-3	**Monitoring costs.** The Committee assume a range of costs for CBMP patients including monitoring costs. Because of comparison with placebo, these seem relatively high. If an adequate control was found, then CBMP costs would have a different comparator, which may partially change the economic results. For instance, the model assumed that patients treated with CBMPs might be expected to receive four extra outpatient visits within the first year and 2 in subsequent years to monitor their medication. Outpatient costs were costed at £147 (non-admitted face-to-face consultant-led attendance, follow-up pain management). This seems very costly. However, if the control arm were opioid-sparing (for instance) rather than placebo, CBMP patients may have fewer monitoring visits, thus improving the incremental cost-effectiveness of their care. In response, we ask the Committee to review its assumptions about monitoring costs.	Thank you for your comments. As described in the economic model report, the target population is defined as people for whom all available standard chronic pain treatments have failed (Appendix I of the chronic pain evidence review). Medicinal cannabis is only considered as the last treatment option as an add-on to the standard of care before the invasive or surgical interventions in the economic model. As such, medicinal cannabis cannot displace any other standard treatments. The included RCTs did not show any benefit of CBMPs in reducing dosage of other medical analgesia. The clinical evidence review did not identify evidence supporting opioid use reduction in the included RCTs. Therefore, we cannot consider the benefit in the opioid use reduction or preventing opioid dependence or mortality.
Spectrum Therapeutics UK	Evidence Review B	227	7	**Cost assumptions.** The NICE report has listed treatment prices based on approved and marketed products in the UK. Based upon international prices, other CBMPs that enter the market may have significantly lower prices because they contain higher concentrations of active ingredients than currently licensed cannabinoid-based medicines. In response, we suggest that NICE seeks expert opinion about accurate costs of treatment because they be significantly lower than existing regimes. As NICE's economic recommendations are based upon deterministic analysis, we suggest that actual figures are included in the model rather than dealing with this issue using sensitivity analysis. We are willing to help with seeking expert opinion for product prices. **Other points.** In reviewing it's modelling, we would also like the Committee to consider the following influences on costs and benefits which we feel are not properly captured. First, we believe that there are significant cost savings from preventing addiction to opioids, as well as major economic savings linked to rehabilitation. As cannabis is assumed to be an "adjunct" treatment in the guideline and its modelling, we believe that the opportunity has been missed to include cost savings from other drugs that could be reduced or replaced. For instance, analgesics, narcotics, anxiolytics, antiemetics, antiepileptics.	Thank you for your comments. NICE acknowledges the upcoming CBMPs in the near future. However, until there is published clinical evidence to show the effectiveness these products, NICE cannot consider them in our analysis. Additionally, we have reported the estimated costs of medicinal cannabis products, including products currently unavailable in the UK (see Table 14 of the spasticity evidence review). These estimates are based on the publicly available sources but without importation. The clinical evidence review did not identify evidence supporting opioid use reduction in the included RCTs. Therefore, we cannot consider the benefit in the opioid use reduction or preventing opioid dependence or mortality. As described in the economic model report, the target population is defined as people for whom all available standard chronic pain treatments have failed (Appendix I of the chronic pain evidence review). Medicinal cannabis is only considered as the last treatment option as an add-on to the standard of care before the invasive or surgical interventions in the economic model. As such, medicinal cannabis cannot displace any other standard treatments. The included RCTs did not show any benefit of CBMPs in reducing dosage of other medical analgesia. The treatment options you have suggested are not considered as appropriate comparisons in the model, or they have already formed part of the standard of care strategy in the model.

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Spectrum Therapeutics UK	Evidence Review B	228	4-12	**Pain costs.** The modellers assigned resource use to the 5 levels of pain NRS. The Committee confirmed that this was reasonable. The NHS activity was estimated from clinical experience. The Committee acknowledged that calculating costs in this way is extremely uncertain and they were tested using extreme sensitivity analysis. We believe that this generic approach to costing is not realistic enough to reflect current NHS practice, with the result that the associated analysis is misleading. This approach is flawed that its limitations cannot be addressed with sensitivity analysis. We ask the Committee to review and replace its cost model.	Thank you for your comments. The model is based on the best available clinical evidence. We have tested two extreme scenario analyses when doubling the pain management costs and halving the pain management costs, which led to an ICER of £133,797 and £160,248 per QALY, respectively (Table 12 of the chronic pain evidence review). Both scenarios came to the same conclusion that it's unlikely that CBMPs would be cost-effective for treating chronic pain. We have validated the model data with the committee as well as submitted the report for peer-review with additional clinical experts during the consultation. As such, we consider the model estimate to reflect best-available clinical evidence and experience.
Spectrum Therapeutics UK	Evidence Review B	40	Appendix A Appendix J	**English language only.** The review stated that non-English language studies would be excluded from its analysis. Given the relatively small number of studies published in English, we believe that further evidence could be generated by including studies in German and Chinese. The following could be included: Pinsger (2006); Wissel (2004); Wu (1992).	Thank you for your comments. As per NICE guideline manual, the clinical evidence review is limited to studies in English language only as we don't have the resource to translate papers. We acknowledge there is evidence published in the non-English language.
Spectrum Therapeutics UK	Guideline Evidence Review B	General 13 14 General 7 25 9	General 12-25 1-18 General 20-22 10-13 3-5	**Proposed guidelines need reworking before publication.** Spectrum Therapeutics UK request that NICE review its guidance on prescribing Cannabis Based Medicinal Products (CBMPs) because the proposed guideline does not correctly represent the clinical pathway recommended for use by the NHS. In particular, the recommendations for chronic pain should not be followed because they are based upon an inaccurate specification of the decision problem, which does not reflect the precise realities of NHS clinical practice. **The analysis lacks precision.** After performing a detailed review of the Committee's work, we conclude that the analysis underpinning the guideline is too vague when it states that "the aim of this review was to find out how effective cannabis-based medical products are in managing chronic pain, particularly when conventional treatment options have failed or not been tolerated". This statement is too general, and covers too wide a patient group, to be a clear basis for robust decision analytical modelling. This lack of precision on the exact clinical pathway for CBMPs has meant that the evidence review has not included a decision tree (which is a standard step in economic evaluation) and has misspecified its Markov model. The consequence of these errors is that the resulting guidance is unreliable and should be reconsidered as a basis for NHS policy. **Reconsider conclusions.** Given the weaknesses of the economic analysis, we request that the Committee reconsiders its position on whether CBMPs should be prescribed on the NHS because the *de novo* economic modelling presented in the evidence review is not underpinned by a robust health economic evaluation, as requested by the Committee. **Recommendation.** We recommend that the NHS, NICE and relevant clinical bodies work together to produce an agreed clinical pathway for CBMP treatments in chronic pain so that future economic analysis can be based upon a robust description of clinical practice. This would help reduce the current issues with the economic model. **Inaccuracies and errors.** As well as not correctly representing the clinical pathways used within the NHS, the Evidence Review for Chronic Pain suffers from key methodological problems, as well as major inaccuracies and errors, that make the Committee's recommendations unreliable as a guide to NHS decision-making. **RCT evidence.** Limiting the data search to published RCTs has skewed the evidence available for analysis. Many of the published RCTs are proof of concept or small sample pilot studies, which were not performed as efficacy studies. To date, much of the evidence for the effectiveness of CBMPs comes from longitudinal, real-world or open label studies. The exclusion of these sources of evidence has meant that the modelling performed for this guideline underestimates the efficacy of CBMPs.	Thank you for this summary of your detailed comments. We have responded to your comments separately, within each specific section of the guideline. .

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				Reason. In this document, we outline our reasons for questioning the validity of the CBMP guidance and explain why we believe that the proposed recommendations should be reconsidered. **Support.** Spectrum Therapeutics UK is willing to work with the NICE Committee and NICE staff to improve the modelling of the clinical pathway and to create an improved approach to the economic analysis of CBMPs. Soon, , Medical Director of Spectrum Therapeutics UK, will write directly to the Committee's chair, Steve Pilling, to offer our support and mutual cooperation with NICE in order to revisit the clinical assumptions and economic modelling presented in the evidence review document.	
St Luke's Hospice	Guideline	5	4-8	The decision to not offer cannabis in spasticity in MS is a concern, especially as it seems to be an economic decision rather than based solely on the research evidence which suggest benefits outweigh harms. We think this will cause a challenge in supporting these patients. We feel that since some people do benefit that it would make sense for this to be made available on the basis of local commissioning through an individual funding request.	Thank you for your comment. After publication of the consultation draft of the guideline, the manufacturer reduced the list price of THC:CBD spray, and this had an important impact on our assessment of its cost effectiveness. In light of stakeholder comments, the committee also reviewed their estimates of likely resource use associated with spasticity symptoms. The committee are now able to make a more positive recommendation.
St Luke's Hospice	Guideline	6	10-13	We agree that having shared care arrangements will ensure safe prescribing and monitoring of patients with added convenience of seeing a different prescriber within the multi-disciplinary team. This could include nurse or pharmacist independent prescribers or GPs.	Thank you for your comment.
St Luke's Hospice	Guideline	9	15-19	We agree that the research recommendation is important to ensure these drugs are not prescribed without sufficient evidence. Minimising polypharmacy and harm in fibromyalgia and chronic pain is really important.	Thank you for your comment.
St Luke's Hospice	Guideline	9	22-27	We note that the research recommendation in children includes medical cannabis as an add-on treatment for symptom management in intractable cancer-related pain and chronic pain associated with other illnesses however such a recommendation has not been included for adults. This omission is a concern.	Thank you for your comment. With regards to adult studies, the economic analysis suggested that most types of chronic pain were not going to be cost-effective to manage using medicinal cannabis. However, if any types of chronic pain could be cost-effective to manage using medicinal cannabis, they are most likely to be fibromyalgia and treatment-resistant neuropathic pain. Therefore, we wrote research recommendations for these conditions. For the adult research recommendation, the committee wanted to focus on CBD (either as a pure product or containing traces of THC). There is no RCT data for children with regards to medicinal cannabis. Therefore, the research recommendations for children are less specific.
St Luke's Hospice	Guideline	General	General	The guideline seems clear-cut and fits with experience of side-effects being an issue.	Thank you for your comment
SUDEP Action	Guideline	10	6-7	Cost and clinical impact are certainly factors which must be considered with new medications, however the impact on quality of life for the person with epilepsy (& their families), as well as the potential to reduce epilepsy mortality risks and potentially avoid some of the 21 epilepsy deaths weekly in the UK must also be factors considered in decision making. The cost of epilepsy deaths on communities and the bereaved after a death are often costs not considered or quantified in decision making processes, but which have long-lasting and significant impact on services such as the NHS, Health and Social Care, and Welfare systems.	Thank you for your comments. NICE decisions are based on evidence of clinical and cost effectiveness, quality of life is also considered. The decision of the committee was made based on the current lack of high-quality evidence. However, the committee made research recommendations for the use of CBMPs for severe treatment-resistant epilepsy. This should help increase the understanding of the effects of CBMP on outcomes such as quality of life and mortality for future guideline updates.
SUDEP Action	Guideline	5 16/17	10-20 and 17-26	We welcome the view of the guideline that further research is required into cannabis-based medicinal products as it is vital that any new medicines for people with epilepsy follow the same rigorous approval processes as other anti-epilepsy medications to ensure they are safe for use among those with epilepsy. It is important that any deaths which occur during future research/trials however are reported to the Epilepsy Deaths Register so lessons can be learnt to save future lives. It is incredibly important to also consider the potential opportunity for Cannabis-based medicinal products to reduce seizures among those with severe, currently uncontrolled epilepsy. Available research suggests for rarer forms of the condition it could assist in reducing seizures, therefore improving quality of life. Added to this, people with epilepsy for whom this medication could be another treatment option are likely to be at an increased risk of premature mortality due to their epilepsy (SUDEP), risks which could be reduced with safe access to this medication.	Thank you for your comments. The committee discussed the need for national register and recommended that prescribers should record details of treatment, clinical outcomes and adverse events for people prescribed cannabis-based medicinal products in a local or national registry. The committee discussed the lack of evidence and decided that although they could not make a recommendation in favour of CBMPs for people with severe treatment-resistant epilepsy, they did not want to recommend specifically against it either. This means that people can still be prescribed CBMPs if their clinician thinks they will benefit. This is described in more detail in the 'committee's discussion of the evidence' section of the epilepsy evidence review.

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				We are concerned because of the high profile this issue has publicly, where lots of information and products out there claim to help people better manage their conditions, on top of significant media attention, that the current stance in the guideline for epilepsy could cause concern among people with epilepsy and their families and could cause uninformed decisions regarding using cannabis to be made. Many families are desperate to gain control over their loved ones' seizures, it can seem like 'the only option' is the widely available, 'cannabis based' products as a solution. But this comes with significant dangers, especially if families and clinicians aren't working together on managing seizures, or openly discussing epilepsy risks and the pros and cons of new treatment options. We have had increased contact from people with epilepsy considering or already using alternative cannabis products, many in the context of not being aware of their wider epilepsy mortality risks. This is incredibly concerning and may lead to preventable epilepsy deaths, if information on cannabis derived medicinal products are not shared publicly and shared in a balanced way with messages about the importance of also managing epilepsy risks to reduce risk of death. We would welcome future public communications on the development of these guidelines to provide clear balanced information on these issues to help mitigate these risks	
SUDEP Action	Guideline	General	General	There are elements throughout the guideline that would need adapting if in future cannabis-based medicinal products do become recommended for people with epilepsy. For example, sections 1.5.5 and 1.5.9would need to include a point to ensure prescribing clinicians take into consideration epilepsy mortality and the associated risks.	Thank you for your comments. Any updates of this guideline would take into account information on prescribing if they include updates to the recommendations of the use of cannabis-based medicinal products for people with epilepsy.
Surterra Wellness	Guideline	1	General	We are concerned that the draft guideline does not include the full range of conditions for which medicinal cannabis products are undergoing clinical investigation. Surterra Wellness is planning clinical trials to investigate generalised anxiety disorder and neuropathic pain, conducted to international standards of good clinical practice.	Thank you for your comments. The guideline was based on some of the most common conditions which could be treated with CBMP. Surveillance for future updates will help to identify areas which have been investigated after this guideline has been published.
Surterra Wellness	Guideline	1	General	The guideline should have a review period of 12 to 18 months, after first publication. Much of the data for the effectiveness of medicinal cannabis medicines is in the process of being generated. It is estimated that evidence will become available at an increasing rate. Therefore the guideline should be regularly reviewed and updated, at a frequency of every 12 to 18 months, to keep pace with and improve patient access as evidence of effectiveness accumulates.	Thank you for your comments. Our surveillance team keeps track of updates and new research and this is used to determine when an update of a topic is needed.
Surterra Wellness	Guideline	1	General	We are very concerned that the experience of using medicinal cannabis products in other countries has been almost entirely overlooked. More than 350,000 patients have been treated to date with Surterra Wellness products in the United States in Texas, Nevada, and Florida. There is also research and experience to consider from the use of medicinal cannabis products in Canada, Israel, Australia and Germany.	Thank you for your comment. The NICE guideline considered relevant studies from all counties and included international guidelines as part of the evidence review. This included the Canadian guideline. However, the recommendation about who should prescribe is set out in UK legislation, The Misuse of Drugs (Amendments) (Cannabis and Licence Fees) (England, Wales and Scotland) Regulations 2018, regulation 16A which differs from that in Canada.
Surterra Wellness	Guideline	13	17	There is published evidence from US (references available) that prescribing medicinal cannabis does reduce opioid use. Studies report a 42% reduction in patients opioid use after 3 months of medicinal cannabis treatment.	Thank you for your comment. Our systematic review of RCTs found that the outcomes for opioid usage were not statistically significant. We cannot comment on the US studies without further details.
Surterra Wellness	Guideline	17	21	The medicinal cannabis formulations developed by Surterra Wellness contain different concentrations and ratios of CBD:THC, which enable patients to select products that will optimize the effect on the patient's condition. This approach by Surterra Wellness helps ensure that each patient receives the optimum dose only.	Thank you for your comments.
Surterra Wellness	Guideline	6	3	We are concerned that limiting prescribing to physicians on the Specialist register in unduly restrictive.	Thank you for your comment. Due to the limited evidence base and their unlicensed nature, the Government has chosen to restrict the decision to prescribe cannabis-based products for medicinal use to only those

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				A model based on accredited prescribers who have completed specialist training (perhaps overseen by the Royal Colleges) is used successfully in US and could also be applied in UK.	clinicians listed on the Specialist Register of the General Medical Council. This restriction has been set out in legislation.
Surterra Wellness	Guideline	9	12	Research should not be limited to conventional clinical trials. In US, Registries have been set up by state regulators to ensure that access to medicinal cannabis products is controlled, patients monitored and outcome data generated. Large scale data from the US registries is expected to be available in 2020/21 which is a main reason why NICE guidance should be frequently reviewed and updated. The Florida state Registry has been collecting data since July 2018. Therefore a significant amount of outcome data will be available in 2020 onwards. The data set is expected to provide information relevant to UK health policy and NICE guidance development covering a wide range of important considerations including; the condition treated, formulation type, patient outcomes and potential adverse effects. These data will be an important contribution to developing the framework for the use of medicinal cannabis in UK.	Thank you for your comment. The guideline has added a recommendation advising prescribers to record details of treatment, clinical outcomes and adverse effects for people prescribed cannabis-based medicinal products, using local or national registry. This will enable feedback from patients to feed into the evidence base
The Association of UK Cannabis Clubs	General	General	General	We thank NICE for the opportunity to comment on these draft guidelines and look forward to working on future projects with you	Thank you
The Association of UK Cannabis Clubs	Guideline	General	General	In General, we agree with the Draft guidelines that have been proposed. It is our view that the push for medical access to cannabis is a smoke screen for the wider legalisation of Cannabis and would argue this is the view currently held by the majority of Government Ministers. We support the legalisation of Cannabis through licencing. There is clear evidence that the use of Cannabis can have a therapeutic effect that increases the standard of living for many people. By rescheduling Cannabis for medical use, a regulatory framework has been applied to the production and supply of Cannabis which we commend. This can only benefit the consumer as it ensures quality and consistency of product. We do not support "Medical Home Growing" for the reason it would further burden the authorities who would be required to enforce regulations whilst also making it harder to ensure quality and consistency of product. We favour and are campaigning for access to 'Medical Cannabis' by licencing. We feel that every adult has the right to choose and if choosing cannabis improves their quality of life then they should have access to Medical Cannabis. Given the wide media attention that medical Cannabis has received, it is likely there will be many people who will want to know if they can get Cannabis on prescription. NICE should take note that in most cases where people are already using Cannabis illicitly it is highly likely they will continue to do so even if advised not to. We would therefore recommend that the guidelines include licencing as an alternative route to access where patients have been denied a prescription. The greatest risk fast by people using Cannabis is the quality and consistency of illicit products. Even if a healthcare professional cannot prescribe a course of treatment they should be able to endorse the decision of a patient to seek it elsewhere when there is clear evidence it improves their standard of living. Healthcare professionals should not be dismissing a patients choices because of an outdated view that illicit Cannabis has no medical value.	Thank you for your comment. This guideline is underpinned by legislation in terms of what cannabis based medicinal products can be considered. We cannot comment on licensing or the use of illicit products.
The Association of UK Cannabis Clubs	Guideline	General	General	We feel that there is much confusion in the Public about medical cannabis as it is not clearly defined. 'CBD' is commonly referred to in the press as 'Medical Cannabis' and this is something we feel the guidelines needs to address. Our understanding is that most 'CBD' products that are on general sale and being classed as 'legal' cannabis are in fact manufactured with Cannabis resin that is high in CBD and low in THC. The definition of Cannabis resin under the MDA1971 is clear and does not mention cannabinoid content. It is therefore our view that most if not all 'CBD' products on general sale as food supplements or vaporiser products wouuld require MHRA and Home Office licencing and would only be available on prescription. There are many references made in guidelines to CBD without clearly distinguishing whether they refer to CBD as a single molecule or to 'CBD' high cannabis resin; please can there be more clarity on this.	Thank you for your comment. This guideline is underpinned by legislation in terms of what cannabis based medicinal products can be considered. We cannot comment on the definition of CBMPs.

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The Association of UK Cannabis Clubs	Guideline	General	General	In conclusion, it is our understanding that the UK Government is looking for a way to legalise Cannabis. We believe the best way to achieve this is by imposing pharmaceutical standard to the production and supply of this products. It would be our opinion that if NICE were to recommend wider access to cannabis on prescription it would open the flood gates for people wanting cheap access to cannabis with the result being the NHS picking up the bill for millions of consumers cannabis habits – this is something we do not want to see.	Thank you for your comment.
The Brain Tumour Charity	Guideline	4	General	The Brain Tumour Charity welcomes the guideline recommendation that Nabilone should be 'considered' as an add-on treatment for adults (18 years and over) with chemotherapy-induced nausea and vomiting. We are however concerned that this will not significantly increase the availability of Nabilone despite recent studies showing the positive effect it has in treating chemotherapy-induced nausea and vomiting. In her 2018 report, *Cannabis Scheduling Review: Part 1,* The Chief Medical Officer to England, Professor Sally Davies, found conclusive or substantial evidence that cannabis or cannabinoids are effective for the treatment of chemotherapy-induced nausea and vomiting. Our report, Finding Myself in Your Hands, found that 76% of high-grade brain tumour patients received chemotherapy as a treatment, with 10% of low-grade patients also receiving the treatment. Chemotherapy is a treatment considered to be very aggressive and may result in serious side effects. Within this report, chemotherapy was commonly reported to cause sickness, as well as other symptoms such as memory problems, hair loss, agitation and anger, and chronic tiredness. A research paper, Cannabinoids for Medical Use: A Systematic Review and Meta-analysis, again published via the National Centre for Biotechnology Information, reviewed a series of studies on the effect of cannabis on chemotherapy-induced nausea and vomiting. All studies suggested a greater benefit of cannabinoids than placebo, with on average 47% of patients showing a complete nausea and vomiting response with cannabinoids compared with just 20% with placebo. Though this recommendation for the use of Nabilone as an add-on treatment for adults (18 years and over) with chemotherapy-induced nausea and vomiting is welcome we believe that this recommendation does not go far enough based on recent evidence reviews. The scoping exercise and The Chief Medical Officer for England Review's findings, as well as those from patients, health professionals and charities, do not appear to have been adequately considered in the formulation of this guidance.	Thank you for your comment. While a number of studies were identified which examined the effectiveness of nabilone for chemotherapy-induced nausea and vomiting, majority of these studies presented methodological limitations and were considered to be outdated and not reflective of current practice. Based on these limitations the evidence was assessed as low quality. Based on the quality and the lack of data on long term adverse events the committee were unable to make a strong recommendation for the use of nabilone for chemotherapy induced nausea and vomiting. However, the committee noted that nabilone could be considered as an add-on treatment in adults. For further information on why the committee made the recommendations, please refer to rationale and impact section, in the guideline. We recognise that the CMO identified sufficient evidence to reschedule CBMPs. NICE considers cost-effectiveness evidence as well as clinical effectiveness when determining which treatments to recommend on a population-wide basis. For the chronic pain population, the evidence showed that CBMPs were not clinically and cost effective. For the epilepsy population, the committee did not feel that there was sufficient evidence available to make a positive or negative recommendation. Clinicians can still make their own individual prescribing decisions in the best interest of their patients.
The Brain Tumour Charity	Guideline	4	General	The Brain Tumour Charity is very disappointed that the guidelines do not recommend the use of medicinal cannabinoids for the treatment of chronic pain. We believe that there is enough evidence to show that cannabis-based medicinal products reduce chronic pain and whilst in some people the treatment effect was modest we believe the existing evidence is enough for this guideline to recommend medicinal cannabinoids to be considered as at least an add-on treatment for chronic pain. In her report, *Cannabis Scheduling Review: Part 1*, The Chief Medical Officer to England, Professor Sally Davies, found conclusive or substantial evidence that cannabis or cannabinoids are also effective for the treatment of chronic pain in adults. Pain is a significant feature of life with a brain tumour for many, with 43% of our community saying they currently endure headaches, and 21% experiencing other pain. The degree of pain and incapacity endured as a result of chronic headaches, migraines and accompanying nausea can be completely debilitating, confining people to bed to 'sleep it off' or to recover from drowsiness caused by strong pain relief. One member of our community	Thank you for your comments. We recognise that the CMO identified sufficient evidence to reschedule CBMPs. NICE considers cost-effectiveness evidence as well as clinical effectiveness when determining which treatments to recommend on a population-wide basis. For the chronic pain population, the evidence showed that CBMPs were not clinically and cost effective. For the epilepsy population, the committee did not feel that there was sufficient evidence available to make a positive or negative recommendation. Clinicians can still make their own individual prescribing decisions in the best interest of their patients. RCTs are the best studies for assessing medicinal cannabis. This is because all analgesia has a strong placebo effect. Therefore, studies should be double-blinded and randomised. Our systematic review of RCTs found that the outcomes for opioid usage were not statistically significant. The RCT data that we reviewed favours some types of medicinal cannabis for managing chronic pain compared to placebo. However, although this reaches statistical significance, the effect size is so small that individual people are unlikely to notice any difference. For example, pain intensity is measured on a scale of 0 to 10, 0 being no pain and 10 being

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				described constant head pain: 'I go to bed with a headache and wake with one'; with another reporting having migraines '24/7'. A research paper, Chronic pain patients' perspectives of medical cannabis, published via the National Centre for Biotechnology Information, found medicinal cannabis improved cancers patients' experience of chronic pain, with 75% of patients reporting the treatment as effective. As part of this consultation exercise we reached out to members of our community about their views on using medicinal cannabis to control chronic pain. Some of our community responded very positively about wanting to use medicinal cannabis to control pain but have found insurmountable barriers to accessing products on prescription and are being forced to live in constant pain as a result. The scoping exercise and The Chief Medical Officer for England Review's findings, as well as those from patients, health professionals and charities, do not appear to have been adequately considered in the formulation of this guidance. The committee making the recommendation felt there was not enough evidence to recommend medicinal cannabis for the treatment of chronic pain but The Brain Tumour Charity believes the committee should have at least recommended nabilone, dronabinol, THC and a combination of cannabidiol (CBD) with THC to be available as part of a clinical trial like they have with CBD. There should have also been explicit research recommendations to promote further research and inform future practice for the use of medicinal cannabis to treat chronic pain. The Brain Tumour Charity will continue to fund high-quality research into brain tumours and their treatments and is welcoming applications from researchers keen to investigate the potential benefits of medicinal cannabis to treat chronic pain. The Brain Tumour Charity would also suggest a recommendation for a form of managed access scheme for cannabis-based medicinal products to treat chronic pain in order to further gather evidence of the benefits and effectiveness of these products. We are concerned that NICE's failure to recommend medicinal cannabis for the treatment of chronic pain will result in people who would benefit from accessing cannabis facing even greater barriers and could lead to people putting themselves at risk by illegally self-medicating.	maximum pain. In order for a person to notice any difference, analgesia should reduce pain intensity by at least 2 or even 3 points. Most pain intensity effect sizes were either statistically insignificant (oral delta-9-THC, oromucosal THC, vaporised THC (minimal CBD), vaporised THC:CBD, vaporised CBD (minimal THC)), or they caused less than a 2 point pain intensity drop (oromucosal CBD:THC) or the 95% confidence interval crossed the 2 point pain intensity drop threshold (oral nabilone). The cost of medicinal cannabis for chronic pain is around 6 times greater than the NHS would normally deem an efficient use of resources. With regards to adult studies, the economic analysis suggested that most types of chronic pain were not going to be cost-effective to manage using medicinal cannabis. However, if any types of chronic pain could be cost-effective to manage using medicinal cannabis, they are most likely to be fibromyalgia and treatment-resistant neuropathic pain. Therefore, we wrote research recommendations for these conditions. For the adult research recommendation, the committee wanted to focus on CBD (either as a pure product or containing traces of THC). There is no RCT data for children with regards to medicinal cannabis. Therefore, the research recommendations for children are less specific. With regards to people putting themselves at risk by illegally self-medicating, that was out of the scope for this review.
The Brain Tumour Charity	Guideline	5	General	The Brain Tumour Charity is disappointed that the guidelines do not recommend the use of medicinal cannabinoids for the treatment of spasticity unless as part of a clinical trial. We do not agree with this recommendation. There is strong evidence of the benefits from the use of THC:CBD spray for treating spasticity for people with Multiple Sclerosis (MS) and spasticity is relevant to the brain tumour community and new therapeutics like medicinal cannabis could be highly beneficial.	Thank you for your comment. After publication of the consultation draft of the guideline, the manufacturer reduced the list price of THC:CBD spray, and this had an important impact on our assessment of its cost effectiveness. In light of stakeholder comments, the committee also reviewed their estimates of likely resource use associated with spasticity symptoms. The committee are now able to make a more positive recommendation.
The Brain Tumour Charity	Guideline	5	General	The Brain Tumour Charity is also disappointed that the guidelines do not recommend the use of medicinal cannabinoids for the treatment of severe treatment-resistant epilepsy. This is very relevant for the brain tumour community as 60% of brain tumour patients experience at least one seizure and 20-45% of patients will go on to develop epilepsy during the course of their illness. The recommendation to not recommend any cannabis medication to treat this is disappointing. As part of the charity's report 'Losing Myself' around 25% of participants reporting having seizures. The report also highlighted how this has impacted their quality of life, both mentally and physically. At the very least we believe that there should have been explicit research recommendations included in the NICE guidance to promote	Thank you for your comments. The committee did not feel that current evidence was sufficient to confidently recommend the use of cannabis-based medicinal products for people with severe treatment-resistant epilepsy. However, they appreciated that some people have shown benefits from the use of cannabis-based medicinal products and so they did not make a recommendation against their use either. This means that cannabis-based medicinal products can still be considered where a specialist thinks they may be beneficial. There are two research recommendations in the guideline for the use of cannabis-based medicinal products for people with treatment-resistant epilepsy (recommendation 3 and 4). These research recommendations are aimed at improving the quality of evidence so that

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				further research and inform future practice for the use of medicinal cannabis to treat severe treatment-resistant epilepsy.	future committees will be able to make more evidence-based decisions on the use of cannabis-based medicinal products.
The British Pain Society	Evidence Review B	General	General	BPS view is that the guideline committee has taken an unduly strict view of the evidence base underpinning cannabis based medicine. Whilst supporting the need for strong evidence of high quality and reliability, we feel that the public may be inadvertently harmed by being denied some potentially useful new therapeutic approaches because of this strictness in interpreting the research. This is particularly important for pain types like fibromyalgia or persistent neuropathic pains, for which there are currently few robustly informed medical treatments. The review protocol shows that the committees chose not to consider prospective cohort studies if there were fewer than five RCTs. Whilst the intention is understandable, it means that a larger body of evidence has been excluded. Most of the RCTs have relatively few participants (maximum 150) and it so it is our view that it may been better to consider cohorts if the total number of patients in the RCTs had not exceeded a reasonable number, rather than the number of RTCs themselves. Furthermore, we were surprised by some of the inclusion/exclusion criteria for studies that had been considered by the guideline committee, e.g. a study was excluded if the washout period was <1 week, but another study was included that was over just 24 hours. Although the guideline is based on detailed analyses of single RCTs, there appeared to be no attempt to undertake a quantitative analysis for a specific pain type, eg neuropathic pain; or to pool data across studies using a network analysis approach. It appears to us that some relevant systematic reviews have been overlooked or their conclusions underestimated, e.g. the Mücke et al 2018 Cochrane review; and the Wallit et al 2016 review in fibromyalgia.	Thank you for your comment. RCTs are the best studies for assessing medicinal cannabis. This is because all analgesia has a strong placebo effect. Therefore, studies should be double-blinded and randomised. Neuropathic pain was analysed separately as a subgroup in the meta-analyses. However, outcomes including pain intensity were no different compared to other types of pain. There is not enough RCT data for a network meta-analysis. Furthermore, a network meta-analysis would be relevant if we were ranking treatments. Therefore, the notion of using a network meta-analysis is outside the scope of this review. We did look at Mücke et al 2018 and Wallit et al 2016. Those systematic reviews did not meet our inclusion criteria. Furthermore, we have to take into consideration the findings of a health economic analysis: The cost of medicinal cannabis for chronic pain is around 6 times greater than the NHS would normally deem an efficient use of resources.
The British Pain Society	Guideline		Research recommendation 2	BPS welcomes the research recommendation for further studies in children for pain associated with cancer and other conditions. However, the research recommendation for chronic pain in children and young people inexplicably uses the phrase 'cannabis-based medicinal product', so this could be interpreted as including THC. This would appear to be inconsistent with the recommendation and research recommendation for persistent pain in adults, and we are not aware of the research which underpins this different view between adults and children. However, BPS was disappointed that there was not a specific clinical or research recommendation for the use of cannabis-based medicines in pain associated with cancer in adults. This is surprising in view of the clear positive clinical recommendation for the use of nabilone "an add-on treatment for adults (18 years and over) with chemotherapy-induced nausea and vomiting which persists with optimised conventional anti-emetics". In addition, the committee made no less than 2 additional recommendations for further research in the context of cannabis products to reduce intractable chemotherapy-associated nausea and vomiting, and one for nausea and vomiting not caused by chemotherapy. In doing so, the guideline committee seems unaware that international guidelines such as issued by MASCC and ASCO for several years have stipulated very specific sets of doublet or triplet targeted anti-emetic drug regimens, which can yield anti-emetic rates of up to 90%. In contrast, the latest international systematic review by van de Beuken-van Everdingen et al (2016) showed that pain is still present in >50% of cases at all stages of disease. Indeed, these authors had showed that that since their previous review of 2007, the proportion of patients with advanced cancer experiencing had actually increased from 64% to 67%. BPS would contend that the scale of the problem of under-treated pain associated with cancer is numerically and societally, far greater than that of nausea and vomiting arising from	Thank you for your comment. There is no RCT data for children with regards to medicinal cannabis. Therefore, the research recommendations for children are less specific (covering CBMPs) compared to the adult research recommendations (CBD) The committee were unable to make recommendations for the use of cannabis based medicinal products for cancer pain due to only a small number of studies identified. The benefit was found to be small and economic analysis shows that this compares poorly with the high costs of the intervention. THC reduced mean functional impairment caused by pain in a population of 96 participants who had cancer. Therefore, a research recommendation was made. The committee defined 'intractable cancer-related pain' as cancer-related pain that does not respond to multiple interventions including non- pharmacological and drug therapies sufficiently to enable a reasonable quality of life.

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				cancer chemotherapy. Thus BPS views the lack of a specific clinical and /or research recommendation for pain associated with cancer to be a serious omission.	
The British Pain Society	Guideline	Page 13	Rationale – Chronic pain	The Rationale for these Recommendations appears to be based on the lack of opioid reduction observed in people with persistent pain who had additional medical cannabis. Although patients may be prescribed opioids for fibromyalgia and neuropathic pain, BPS would respectfully point out that they are not regarded as first or second-line treatments in national or international guidelines. The guideline committee considered the WHO ladder should be used to guide treatment decisions and standard treatment for fibromyalgia and neuropathic pain is step 3 opioids and adjuvants, which is also not agreement with published recommendations. Indeed, the use of the WHO ladder to guide persistent non-cancer pain itself has been discredited, as it may have contributed to the 'opioid epidemic' occurring in the USA and other western countries (Ballatyne, Kalso, Stannard 2016). The BPS takes the view that these current recommendations do not take into account the medical, epidemiological and societal concerns about opioid prescribing for persistent pain in general, and the move away from this class of drug to other forms of pain management. Thus the way the clinical and research Recs are worded would seem to go against the grain of research moves to find alternatives to opioids, and not just ways of reducing their dose.	Thank you for your comment. With regards to the adult research recommendations, we have changed the comparator to "usual care as defined by the researchers". The rationale for these recommendations was not based on the lack of opioid reduction. The rationale for the recommendations is as follows: The RCT data that we reviewed favours some types of medicinal cannabis for managing chronic pain compared to placebo. However, although this reaches statistical significance, the effect size is so small that individual people are unlikely to notice any difference. For example, pain intensity is measured on a scale of 0 to 10, 0 being no pain and 10 being maximum pain. In order for a person to notice any difference, analgesia should reduce pain intensity by at least 2 or even 3 points. Most pain intensity effect sizes were either statistically insignificant (oral delta-9-THC, oromucosal THC, vaporised THC (minimal CBD), vaporised THC:CBD, vaporised CBD (minimal THC)), or they caused less than a 2 point pain intensity drop (oromucosal CBD:THC) or the 95% confidence interval crossed the 2 point pain intensity drop threshold (oral nabilone). Furthermore, the cost of medicinal cannabis is around 6 times greater than the NHS would normally deem an efficient use of resources.
The British Pain Society	Guideline	Page 4,	Rec 1.2	1. BPS prefers the term 'Persistent pain' over 'Chronic pain', in response to patient feedback.	Thank you for your comment. We used the term 'chronic pain' for adults because this is a common phrase in the adult literature. It normally means a period of 3 months. We accepted that the term 'persistent pain' is better for children. This is because for some children, 3 months might be too long to wait for further treatments to be considered.
The British Pain Society	Guideline	Page 4-5	Recs 1.2.1 and 1.2.2	We would question why Rec 1.2.1 is so clear that nabilone, dronabinol, THC, and combination of CBD with THC should not be offered, while Rec 1.2.2 states that CBD can be offered in the context of a clinical trial. This would unfairly restrict the opportunities for new clinical trials of the former cannabis-based medicines, with or without CBD. We are unaware of the weight of evidence that states no further trials of nabilone, dronabinol and THC, alone or in combination with CBD, are needed.	Thank you for your comment. While some clinical evidence was identified that showed cannabis-based medicinal products reduced chronic pain, the potential benefits of these products were small compared with the high and ongoing costs. Therefore, the committee recommended that nabilone, dronabinol, THC and a combination of CBD and THC should not be offered. In the chronic pain evidence review, no evidence was identified for the use of CBD alone, therefore the committee restricted the use of this product to clinical trials. For further information on why committee made the recommendations, please refer to rationale and impact section within the guideline.
The British Pain Society	Guideline	Page 9	Research Rec 1	Research Rec 1 is specifically for studies on the clinical and cost-effectiveness of CBD on 'adults with fibromyalgia or persistent treatment-resistant neuropathic pain'; but no recommendation is made for other cannabis-based medicines to conduct further research. While we acknowledge the deficiencies of previous cannabis-based trials in persistent pain, this would preclude further clinical studies with different designs (such as larger longterm cohorts and n=1 trials), which might potentially show clinical and other kinds of benefits and endpoints (including social and emotional functioning) of cannabis products other than CBD alone.	Thank you for your comment. For the adult research recommendation, the committee wanted to focus on CBD (either as a pure product or containing traces of THC). This is due to a lack of RCT evidence. There was no evidence for the use of CBD alone (either as a pure product or containing traces of THC). Therefore, the committee recommended that CBD should not be offered unless as part of a clinical trial. RCTs are the best studies for assessing medicinal cannabis. This is because all analgesia has a strong placebo effect. Therefore, studies should be double-blinded and randomised. The research recommendations include details of recommended outcomes in the evidence review document.
The Ehlers-Danlos Support UK	Guideline	9	15 and 16	We would like to see Ehlers-Danlos syndromes and hypermobility spectrum disorders added to the research recommendations. Chronic (or persistent treatment-resistant) pain is common in these conditions and has a variety of underlying mechanisms (Chopra et al, 2017). In addition, hypermobile EDS (hEDS) can be misdiagnosed as fibromyalgia due to diffuse pain with a strong myofascial component and other overlapping features (Chopra et al, 2017; Wolfe et al, 2010). The review by Chopra et al (2017) highlighted the need for specific studies looking at pain management in EDS. These could provide additional evidence leading to a different position on the prescription of cannabis derived medicinal products in EDS patients. Anecdotal information from our members indicates a high proportion of UK EDS patients self-medicate with CBD products to manage their pain. Chopra P., Tinkle B., Hamonet, C., Brock I., Gompel A., Bulbena A., Francomano C. 2017. Pain Management in the Ehlers-Danlos syndromes. *Am J Med Genet* 175 (1C): 212-219.	Thank you for your comment. These conditions are in the inclusion criteria for the research recommendation for children because we included "pain associated with specific diseases" in this research recommendation. Thank you for the suggested references. We have considered these, and they are outside the scope of this guideline. These studies do not investigate the clinical effectiveness of CBMPs compared to a placebo using a trial study design.

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				Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DJ, Katz RS, Mease P, Russell A, Russell IJ, Winfield J,Yunus M. 2010. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. *Arthritis Care Res* **62**: 600– 610.	
The Neurological Alliance	Guideline	1	General	If the guideline is for people taking CBMPs, there needs to be an appendix with explanations of terms like "delta-9-tetrahydrocannabinol and cannabidiol (Sativex) and nabilone", etc. It cannot be taken for granted that people taking cannabis-based medicinal products, their families and carers, would understand these terms. As above, a full, plain English, explanation of these terms is needed.	Thank you for your comment. The guideline has a terms used in the guideline section which provides an explanation of relevant terms.
The Neurological Alliance	Guideline	14	20-24	SEE COMMENT ON GUIDELINE PAGE 17 LINES 2-5.	Thank you for your comment. This comment has been addressed.
The Neurological Alliance	Guideline	17	2-5	This contradicts page 14 lines 20-26 about use with pain / how the recommendation against it might restrict use by those who correctly access it via specialist pain centres. Moreover, this contradicts the research recommendations made in relation to a 'do not recommend' for spasticity and pain. This paragraph ought to apply to the whole of the document – it is inconsistent to apply in one section only.	Thank you for your comment. The recommendations on prescribing cannabis have been revised.
The Neurological Alliance	Guideline	18	10-16	Question 2: Surely the use of international evidence is normal? Is this consistent with NICE's assessment of international evidence in other guidelines?	Thank you for your comment. The NICE guideline considered and included international guidelines as part of the evidence review. This included the Canadian guideline.
The Neurological Alliance	Guideline	19	13-15	Question 3: This is important, if rather specific. It is equally important to ensure continuity of care should the person be hospitalised as an inpatient (and more likely to occur)). Therefore suggest this should be added in.	Thank you for your comment. Recommendation1.5.4 outlines that share care arrangements should make provision for when the patient, initiating specialist prescriber or other prescriber moves location (including transition to adult services).
The Neurological Alliance	Guideline	4	12	This guideline overgeneralises pain, failing to separate neuropathic pain from non-neuropathic pain, and specific pain syndromes. This section applies in general for the kind of pain characteristic of fibromyalgia, but not other forms of pain (e.g. chronic pain associated with Multiple Sclerosis).	Thank you for your comment. We included a sub-analysis of the different pain types within each meta-analysis. This includes separate subgroups for neuropathic pain, cancer pain, musculoskeletal pain, visceral pain and widespread pain (fibromyalgia). Unfortunately, the effect size for reduction in pain intensity was not great enough in any subgroup to enable a recommendation to prescribe medicinal cannabis for any type of chronic pain.
The Neurological Alliance	Guideline	5	4-6	We disagree with this decision. Sativex in particular has been proven to be clinically effective. Sativex is available in other countries, and it offers considerable benefits to people with MS, for whom it works, including an improvement in their quality of life. The reason given for not recommending its use is cost-related. Yet the economic modelling underlying this is inadequate. The comparative use for Sativex is not other cheaply available drugs. For some people, it is: a) physiotherapy (for which there are access issues, including 6 month waiting lists), or Botox, or inpatient care, and b) illegal and unsafe forms of cannabis. A proportion of respondents to the National Neurology Patient Experience Survey who have MS said they use unprescribed cannabis based substances and products. This is concerning because of the safety issues involved. Sativex is unlike any other drugs NICE assesses – in that there is a readily available, illegal, unsafe alternative that people will turn to if Sativex is unavailable to them. True economic modelling would need to incorporate an estimate of the numbers of people turning to illegal forms of cannabis, and the costs to society of them doing so.	Thank you for your comments. As described in the economic model report, the target population is defined as people for whom all available standard spasticity treatments have failed (Appendix M of the spasticity evidence review). Medicinal cannabis is only considered as the last treatment option as an add-on to the standard of care before the invasive or surgical interventions in the economic model. As such, medicinal cannabis cannot displace any other standard treatments. The model has considered potential cost saving from the resource use of spasticity management. The treatment options you have suggested are not considered as appropriate comparisons in the model, or they have already formed part of the standard of care strategy in the model. NICE can only consider medicinal cannabis that is legally available to patients. It is not within NICE's remit or in the guideline scope to comment on illegal street cannabis.
The Neurological Alliance	Guideline	5	7-8	It is good to offer cannabis-based medicinal products (CBMPs) as part of trials, but people will resort to using illegal forms. There is a need for either significant increase in availability of clinical trials, or other methods to ensure increased access. We want to see CBMPs available to all who may benefit.	Thank you for your comments. The recommendation that other products should only be used as part of a clinical trial is designed to increase the evidence base for these products. This can then be used to help make more evidence-based decisions on these other products in future updates of this guideline.
The Neurological Alliance	Guideline	5	10-15	There is a huge need for high quality evidence in this area, and we hope to see managed access agreements in future to expedite access and evidence gathering.	Thank you for your comment.
The Neurological Alliance	Guideline	5	10-22	We agree with the research recommendation, but people with epilepsy and their families will be very disappointed that this guideline does not widen access to CBMPs on the NHS. They will continue to use non-pharmaceutical grade forms as a result, potentially putting themselves in danger, though ongoing seizures also puts them in danger, leaving them in a catch-22 situation. We know from our National Neurology Patient Experience Survey that a	Thank you for your comment. The rationale and impact section of the guideline states: 'The committee discussed the limited evidence and agreed that it did not warrant a practice recommendation. However, they also agreed that they should not make a recommendation against the use of cannabis-based medicinal products as this would restrict further research in this area and would prevent people who are currently apparently benefiting from continuing with their treatment. Until there is clear evidence, specialists, people with epilepsy and their

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				proportion of people with epilepsy are using unprescribed cannabis based substances and products.	carers should continue to make treatment decisions in the best interests of each person with epilepsy in line with the GMC information for doctors.'
The Neurological Alliance	Guideline	6	2	Given the media reporting in relation to cannabis, more and more people have been asking their clinicians about getting access – anecdotal evidence suggests a massive upsurge in interest in cannabis-based medicinal products. We do not recommend guidance forces people to illicit cannabis or CBD type products.	Thank you for your comment.
The Neurological Alliance	Guideline	6	4-8	The wording is unclear. We agree that specialists should initiate prescriptions, but when treatment is ongoing thereafter, there ought not be a need for specialists to always have to continue issuing prescriptions. After the initial prescription is made, there ought to be a review at some stage, perhaps after the patient's condition has become stable. So, perhaps this section should say that treatment should be initiated by specialists and reviewed as part of an annual review, but that ongoing prescribing could take place with GPs under shared care arrangements. There are other examples of this working well for specialised medicines, though issues may arise as to who is to bear the financial costs of this. Nevertheless, if GPs are happily prescribing at present already, they should be able to continue, again through shared care arrangements.	Thank you for your comment. The specifics of the shared care arrangement will be for local determination. The shared care recommendation (1.5.2) has been revised to reflect the NHSE guidance.
The Neurological Alliance	Guideline	6	16	This should be done in consultation with the patient and their family, and the guideline note should say so (i.e. "…as part of the shared care agreement**, in consultation with the patient and their family**").	Thank you for your comment. The committee agreed that this would be implicit, as with all treatments.
The Neurological Alliance	Guideline	6	21	We think this is good, but the shared care agreement should also include how shared decision making principles will be employed, especially when treatment may be stopped. The guideline should be amended to specify this.	Thank you for your comment. This could be part of the shared care agreement and would need to be agreed locally. Recommendation 1.5.2 has been amended to take into account the NHS England document 'Responsibility for prescribing between Primary & Secondary/Tertiary Care' that provides details about arrangements and considerations.
The Neurological Alliance	Guideline	7	1	This should include what will happen if communication breaks down or where disagreements arise.	Thank you for your comment. The list is not meant to be exhaustive. Details of a shared care arrangement would be for local determination as would be the case for all medicines prescribed as part of shared care.
The Neurological Alliance	Guideline	7	21	A balance of risks must be considered in relation to potential impacts on development of the ongoing seizures in children with epilepsy (seizures are known to cause brain damage and sometimes death).	Thank you for your comment. This has been captured in the rationale section to reflect your comment.
The Neurological Alliance	Guideline	7	26	This should be advised whether or not they have said they are using them because people may not be honest about illegal use.	Thank you for your comment.
The Neurological Alliance	Guideline	8	6	What the medicine is used to treat (e.g. specific symptoms). how to take the medicine should be added to the list.	Thank you for your comment. Recommendation 1.5.9 takes into account what the treatment has been prescribed for. The recommendation has been amended to reflect your comment about how to take it.
The Neurological Alliance	Guideline	8	10	"…are expected to…" is a poor choice of wording as it comes off too authoritative. Patients should be at the centre of their care. Suggest 'How long it is currently anticipated they will use the medicine for'	Thank you for your comment. The wording has been amended to reflect your comment.
The Neurological Alliance	Guideline	8	5-19	They should also be advised as to how to store the product, common side effects, and how to report adverse side effects.	Thank you for your comment. The committee agreed that the list was not exhaustive. Additional information can be provided during consultation with the patient. Adverse effects are covered in the recommendation.
The Neurological Alliance	Guideline	8	20	It is no good to include a terms section if the terms are not explained. All these terms need explanation.	Thank you for your comment. The terms that are included in this section have been explained.
The Neurological Alliance	Guideline	General	General	This guideline is not written in a way which suggests it is for "people taking cannabis-based medicinal products, their families and carers".In order for the guideline to be suitable for this audience it would need to provide greater explanation of a number of technical terms used - and it would need to be put in plain English. Short of doing this, they should be identified as being a secondary audience.	Thank you for your comment. All NICE guidelines are written in plain English with the use of technical terms kept to a minimum. The guideline is written for healthcare professionals, commissioners and providers of services and people taking CBMPs, their families and carers.
The Neurological Alliance	Guideline	General	General	This guideline appears to have been developed according to NICE's normal methods. However, cannabis-based medicinal products are not typical medicines – there are alternatives which are unsafe and illegal. Therefore, economic costing models need to consider the societal effects of people defaulting to illegal forms of cannabis – using data available via the Home Office/similar in relation to this. In our recent survey of people with	Thank you for your comment. As per the manual for Developing NICE guidelines, the costs in a guideline are calculated in line with the NHS and PSS perspective but do not include the wider societal perspective. We acknowledged that there are other forms of cannabis such as over-the-counter products. Due to lack of evidence, NICE can only consider medicinal cannabis that is legally available to

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				neurological conditions, we found that at least 5% of respondents with all neurological conditions use non-prescribed forms of cannabis. For individual conditions such as MS or epilepsy this figure will be much higher. Yet given people with some neurological conditions are less likely to use cannabis, for individual conditions, this number is likely to be much higher.	patients and those with high quality evidence. It is not within NICE's remit or in the guideline scope to comment on illegal forms of cannabis.
The Neurological Alliance	Guideline	General	General	This guideline does not state that is to be reviewed when additional evidence becomes available (especially in relation to the treatment of spasticity with Sativex). This should be amended.	Thank you for your comment. It is NICE policy to update a guideline when sufficient new information becomes available and this is something that our surveillance team will monitor.
The Neurological Alliance	Guideline	General	General	Disappointed that in response to the scoping consultation, the list of indications was not extended beyond Intractable nausea and vomiting, chronic pain, spasticity, and severe treatment-resistant epilepsy. There are additional symptoms that cannabis-based products could help alleviate, and for which there is some published evidence available, as well as patient reported evidence. There is some concern in the neurological community that the guideline is too narrow in scope, and not encompassing enough into what CBMPs can be, and are already being, used for.	Thank you for your comment. We had to concentrate efforts on a number of conditions where it was felt there was likely to be the most evidence available and greater potential benefit.
Tilray	Evidence Review A	11	General	Tilray is involved in an Australian federally funded study on CINV with a combination THC:CBD products. The available data to date are promising. Please see Tilray's associated submission (also included as an Appendix at the end of this document) for further information and thoughts on this point.	Thank you for your comment and for providing the additional data but we can only assess the effectiveness of a product based on the consideration of the balance between benefits and harms and relative cost-effectiveness. The report you have provided doesn't contain robust efficacy data (collected by RCT) or cost-effectiveness data and so we are unable to consider the findings.
Tilray	Evidence Review A	17	General	The table is incorrect regarding its view on the McCabe 1998 (USA) study and use of prochlorperazine. Prochlorperazine is currently standard of care, including first-line use for nausea and vomiting in pregnancy in the UK. See NICE guidelines and NICE CKS guidance for more information.	Thank you for your comment. During discussions, it was identified that optimal antiemetic treatment may involve the combined use of antiemetics such as serotonin receptor antagonist (5-HT3), dexamethasone, neurokinin receptor antagonists or dopamine receptor antagonists. Majority of the studies did not use a combination of antiemetics, and this was identified as a limitation, which was highlighted in the table.
Tilray	Evidence Review A	202	General	Chan, H. S.; MacLeod, S. M.; Correia, J. A. (1984) Nabilone vs. prochlorperazine for control of cancer chemotherapy-induced emesis in children. Proceedings of the American society of clinical oncology 3: 108, Abstract C-421 This abstract appears to have been published as a full paper in 1987: https://pediatrics.aappublications.org/content/79/6/946 It should be analysed and considered for inclusion in the NICE analysis as it appears to be highly relevant.	Thank you for your comment. Chan 1987 has been included in the evidence review for intractable nausea and vomiting. For further information please refer to Appendix E in Evidence review A.
Tilray	Evidence Review A	7	5 – 8	This should include radiotherapy-induced nausea and vomiting (RINV) as well. RINV is the most common form of nausea and vomiting after CINV and pregnancy.	Thank you for your comment. This has been added.
Tilray	Evidence Review B	General	General	Tilray acknowledges that a 30% pain reduction is clinically important to chronic pain patients rather than a 50% reduction.	Thank you for your comment. We looked at both 30% and 50% pain reduction outcomes. However, they are not often reported. This might give the false impression that we did not look for them.
Tilray	Evidence Review B and Guideline	General	General	Functional impairment is important for both chronic pain patients and their clinicians. This will require very large patient cohorts. It is very expensive to do RCTs; therefore, prospective observational studies may be more appropriate. Tilray believes that NICE should consider 'real world' data collection as pragmatic alternatives to traditional RCTs. Please see Tilray's associated submission (also included as an Appendix at the end of this document) for further information and thoughts on this point.	Thank you for your comment. RCTs are the best studies for assessing medicinal cannabis. This is because all analgesia has a strong placebo effect. Therefore, studies should be double-blinded and randomised. Your submitted data cannot be considered as it does not meet the inclusion criteria for our evidence review.
Tilray	Evidence Review B and Guideline	General	General	There are different toxicology characteristics between different formulations of cannabis-based medicinal products. This means it may not be clinically appropriate to combine all of the cannabis-based medicinal products together for analysis of chronic pain; the results may be biased. Please see Tilray's associated submission (also included as an Appendix at the end of this document) for further information and thoughts on this point.	Thank you for your comment. We did not combine all medicinal cannabis products together: Each cannabis product had its own separate meta-analysis.

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Tilray	Evidence Review C	23	34 – 45	The non-responder observation is an unrealistic observation and against best clinical practice. Non-responders should be stopped, only those clinically benefiting from the treatment should be continued on it. As such the Markov model likely over-estimates the cost of the treatment and underestimates its' cost-effectiveness.	Thank you for your comments. The model included the publicly available discount scheme offered by the manufacturer of THC: CBD spray (Sativex) to the NHS. The treatment is free for the first three vials, but the NHS pays for responders after that. The indication for responders is 20% improvement in NRS spasticity rather than the 30% improvement criteria used in the clinical trials. The committee advised that, in practice, THC: CBD spray 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. It is unclear whether the 10% adjustment produces an under or over-estimate of the true cost-effectiveness of THC: CBD spray. We have tested this parameter in the sensitivity analysis and reported in Appendix M of the spasticity evidence review.
Tilray	Evidence Review C	32	General	Consider using common clinically used tools for spasticity rather than the Ashworth 5-point to 6-point Modified scales. See discussion points for clinical rationale.	Thank you for your comments. The review protocol included any assessment for spasticity that was measured using any validated scale. However, while there was some data from the MSSS-88 scale or using NRS/VAS scales, the majority of trials reported using the Ashworth and Modified Ashworth scales as measures of spasticity.
Tilray	Evidence Review C	32	46 – 52	Tilray has done an in-house equivalence study comparing Tilray's T10:C10 against Sativex. Please see Tilray's associated submission (also included as an Appendix at the end of this document) for further information and thoughts on this point. The results are relevant and important and Tilray would be interested in discussing with NICE whether Tilray could provide their product for MS related spasticity at a cost-effective price.	Thank you for your comment. NICE acknowledges the upcoming CBMPs, such as Tilray products, in the near future. However, until there is published clinical evidence to show the effectiveness of these products, NICE cannot consider them in our analysis. As Tilray products are not currently licensed or available for the patients with spasticity in the UK, we could not include them in our clinical or economic analyses. Please liaise with MHRA directly for the licensing process. It is not within NICE's remit to comment on the MHRA process and decisions.
Tilray	Evidence Review E	10	General and Table 1, Line 8	Pregnant ladies are not specifically mentioned, is this an oversight?	Thank you for your comment. Pregnant women have been considered in this guideline. Concerns have been raised in recommendation 1.5.5 for prescribing cannabis based medical products to this population due to limited evidence on the safety of cannabis-based medicinal products during pregnancy and breastfeeding.
Tilray	Evidence Review E	49	General	The review does not appear to have considered the Royal College of Physicians' Guidelines for cannabis-based medicinal products, nor have the guidelines by the British Neurology Association Guidelines for adult prescribing been considered. Tilray believes that both these guidelines are highly relevant, designed for the UK market and conducted within the last 12 months and as such should be considered.	Thank you for your comment. NICE has carried out a separate evidence review on the efficacy and safety of cannabis-based medicinal products. The recommendations have been based on our evidence review and not the guideline issued by Royal College of Physicians' Guideline nor the ABN interim guideline. The Royal College of Physicians' Guideline and the ABN interim guideline referred to both the forthcoming NICE guidance, and the BPNA guidance, and provided a brief summary of the evidence that was reviewed in detail in the NICE evidence review.
Tilray	Evidence Review E	General	General	Barriers to access and data collection are real and significant issues. Tilray believes that the evidence does not look at these issues sufficiently and NICE needs to re-look at these before final publication of the guidelines in November. Please see Tilray's associated submission (also included as an Appendix at the end of this document) for further information and thoughts on these points.	Thank you for your comment and for providing the additional data. Barriers to access were outside the scope of the guideline. We can only assess the effectiveness of a product based on the consideration of the balance between benefits and harms and relative cost-effectiveness. The report you have provided doesn't contain robust efficacy data (collected by RCT) or cost-effectiveness data and so we are unable to consider the findings. The committee agreed that a national or local registry of prescribing practices of CBMPs was also needed to promote the evidence base.
Tilray	Evidence review for Epilepsy	21	19-26	To the best of our knowledge Tilray is the only company with proven GMP certification providing unlicensed cannabis-based medicinal products, and which can verify that we manufacture to consistent standards of production and concentrations of THC and CBD (ie accurate, reliable, reproducible labelling of potency and impurities). Please see Tilray's associated submission (also included as an Appendix at the end of this document) for further information and thoughts on this point. Tilray believes that NICE's guidelines should discern between companies who can deliver this certification and verified manufacturing quality and those who cannot. As per international standards for medicinal products those companies who cannot provide this standard should not be considered as eligible for providing cannabis-based medicinal products. Analysis of their products should be discounted from the NICE review and the companies should be	Thank you for your comment and for providing the additional data but we can only assess the effectiveness of a product based on the consideration of the balance between benefits and harms and relative cost-effectiveness. The report you have provided doesn't contain robust efficacy data (collected by RCT) or cost-effectiveness data and so we are unable to consider the findings.

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				banned from being allowed to import or wholesale their products into the UK market until they can prove that they meet the required standards. Tilray believes that this is a patient safety issue and that NICE and the MHRA have a duty to act on it as a matter with urgency.	
Tilray	Guideline	4	3	We are concerned that NICE suggest only nabilone may be used for treating CINV. Nabilone is a synthetic compound, rather than a cannabis-based medicinal product, and should therefore not be considered in this guideline. Cannabis-based medicinal products have been shown to be superior to placebo in controlling CINV. (Cancer 1981;47:1746-51). A published small pilot double-blind randomised trial of a buccal form of THC/CBD for CINV for the secondary prevention of CINV found substantial efficacy, high patient acceptability, and manageable side effects. (Duran et al. British journal of clinical pharmacology 2010;70:656-63). Dronabinol (THC) has been approved by the US Food and Drug Administration for refractory CINV. We strongly urge NICE to reconsider its guidelines to include the use of cannabis-based medicinal products for CINV.	Thank you for your comment. The scope of this guideline included the following cannabis-based medicinal products: • cannabis-based products for medicinal use as set out by the UK Government in the 2018 Regulations • the licensed products delta-9-tetrahydrocannibinol and cannabidiol (Sativex) and nabilone • plant-derived cannabinoids such as pure cannabidiol (CBD) • synthetic compounds which are identical in structure to naturally occurring cannabinoids such as delta-9-tetrahydrocannabinol (THC), for example, dronabinol. Evidence on the use of following products for intractable nausea and vomiting was found: • Tetrahydrocannabinol (THC) • Tetrahydrocannabinol (THC) plus prochlorperazine • Dronabinol • Dronabinol plus prochlorperazine • Nabilone Duran 2010 was identified in the literature search however following full text review this study was excluded. Based on the available evidence and their clinical experience, the committee recommended for nabilone to be considered as an add-on treatment if nausea and vomiting persists after optimised antiemetic therapy. For further information on why the committee made the recommendations, please refer to rationale and impact section within the guideline. For further information on excluded studies please refer to evidence review A.
Tilray	Guideline and Evidence Review A	203	General	It is important for the NICE guidelines to re-state that the UK's position is that cannabis-based medicinal products cannot be smoked products for patient safety concerns as stated by Prof Sally Davies, UK CMO. Tilray is concerned that with recent dried flower imports by other companies there is a significant risk that this may lead to prescriptions being issued either in the NHS or privately for 'smoked' medicinal cannabis.	Thank you for your comment. This guideline considered cannabis-based products for medicinal use as defined by the UK government in November 2018, licensed products (Sativex and nabilone), synthetic compounds which are identical in structure to naturally occurring cannabinoids and plant-derived cannabinoids. Additionally, synthetic cannabinoids in schedule 1 for the 2001 regulations and smoked cannabis-based products were excluded from this review. For further information on the exclusion and exclusion criteria, please refer to the scope.
Tilray	Guideline and Evidence Review B	General	General	The economic model focuses on two studies identified looking at the effectiveness of Sativex. We understand the limited evidence base for randomised clinical trials that are designed to demonstrate the effectiveness of cannabinoid products. We agree that the first study is a short term 14-week randomised study of "failure" patients and the second is an add on using Sativex in opioid refractory pain. Evidence for the use of medicinal cannabis is currently limited in terms of RCT, we believe that the modelling team should consider other types of evidence to gain an understanding of the potential that using medicinal cannabis for opioid "holidays" which are now being broadly recommended for patients that have been prescribed long term opioid therapy either in cancer or chronic pain. We believe that committee should consider a broader evidence base in their review, specifically the recent Tilray patient survey undertaken in Canada (Lucas et al 2019). The potential for reductions in the use of prescription drugs reported in the patient survey should be considered in this review and is outlined in the comprehensive Tilray submission of evidence to the guidelines committee. We have outlined that the potential impact of using medicinal cannabis could be approximately 143 million pounds per year at 2018 prescribing rates based on the NHS prescription costs data. The model developed to support the evidence review based on the Sativex studies has been well constructed and thus has produced a set of economic analysis results which reflect the data from these studies. Tilray would like to suggest the committee do consider the broader evidence base in this circumstance. The reality is that patients need an alternative to long-	Thank you for your comments. The economic model is based on the best available evidence on chronic pain. NICE acknowledges the upcoming CBMPs in the near future. However, until there is published clinical evidence to show the effectiveness of these products, NICE cannot consider them in our analysis. RCTs are the best for assessing medicinal cannabis as they are the gold standard study design for evaluating clinical effectiveness. Therefore, studies should be double-blinded and randomised. The clinical evidence review did not identify evidence supporting opioid use reduction in the included RCTs. Therefore, we cannot consider the benefit in opioid use reduction, preventing opioid dependence or mortality.

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				term opioid therapies. The Lucas et al. (2019) patient survey clearly suggests that cannabis-based medicinal products can be an option to replace or reduce other prescription medicines. Tilray would like to work with the UK regulatory bodies to enable an appropriate data collection program that will give the answers to the key questions being raised by the NICE Guidelines Committee. We suggest that there should be a period where we can examine the use of a quality-controlled product to provide data on patient reported outcomes in an appropriately designed study in chronic pain patients in the UK. This would provide validated data to consider in the context of the Canadian Patients Survey and inform policy changes in the use of opioids in the long-term management of chronic pain.	
Tilray	Guideline and Evidence Review D	General	General	There are different toxicology characteristics and pharmacokinetic characteristics between different compounds making it difficult to bucket trials using different cannabis-based medicinal products. Tilray's research in this area shows potential benefits of a THC:CBD combination drug product for childhood epilepsy. While we acknowledge the robust clinical trial data on CBD in treating seizures, there is also significant published data on combination THC:CBD products in treating seizures. Given the severity of this disease burden and the significant and dire clinical consequences of uncontrolled seizures, we urge NICE to consider cannabis-based medicinal products for the treatment of epilepsy from a risk/benefit context for the individual patient. Please see Tilray's associated submission (also included as an Appendix at the end of this document) for further information and thoughts on this point. Tilray respectively request NICE to review their analysis for this indication.	Thank you for your comments. Only products which met the inclusion criteria stated in the protocol in Appendix A of the evidence review could be included within this review. The protocol also states specific study types that could be included within the review. Other products are out of scope for this review. Thank you for providing the additional data but we can only assess the effectiveness of a product based on the consideration of the balance between benefits and harms and relative cost-effectiveness. The report you have provided doesn't contain robust efficacy data (collected by RCT) or cost-effectiveness data and so we are unable to consider the findings.
Tilray	Guideline and Evidence Review D	General	General	30% reduction in seizure frequency is certainly clinically important to patients and should be considered as well as the 50% reduction currently considered.	Thank you for your comment. After discussion with the committee it was agreed that clinicians often consider 50% seizure reduction an important outcome. 30% seizure reduction was reported in a small number of papers but most included a 50% reduction as part of the outcomes.
Tilray	Guideline and Evidence Review E	General	General	Tilray is aware that cannabis-based medicinal products are currently being offered in the UK by manufacturers who do not hold this Good Manufacturing Practice (GMP) certification. This needs to be stopped as a matter of priority in the interests of patient safety. Tilray believes that NICE and the MHRA need to work together to achieve this. Tilray believes that NICE should consider advising that the MHRA publish a list of 'acceptable' medicinal cannabis manufacturers who can prove that they are attaining minimum international standards of quality and safety and that this list should be updated regularly. Tilray holds GMP certification.	Thank you for your comments. It is not within NICE's remit to comment on the MHRA process and decisions.
Tilray	Guideline and Evidence Review E	General	General	The current guidelines risk poorly designed datasets with disparate designs and quality of data collection being created for cannabis-based medicinal products. Tilray is concerned that these resulting datasets lack sufficient statistical power. Please see Tilray's associated submission (also included as an Appendix at the end of this document) for descriptions of lessons Tilray has learned from working in other countries and their various data collection regimes.	Thank you for your comment. NICE guideline recommendations are based on the best available evidence. Review questions guide the search for evidence, and the type of evidence used depends on the type of question. For example, a randomised controlled trial is often the most appropriate type of study to assess the efficacy or effectiveness (including cost effectiveness) of an intervention.
Tilray	Guideline and Evidence Review E	General	General	Tilray is aware of NHS England's and NHS Improvement's published report on 8th August 2019: https://www.england.nhs.uk/wp-content/uploads/2019/08/barriers-accessing-cannabis-based-products-nhs-prescription.pdf . There appears to be differing advice proposed by the draft guidelines compared to this NHS report despite that publication of the NICE draft guidelines and the above report appear to have been co-ordinated. These differences risk exacerbating the barriers to access to cannabis-based medicinal products by UK patients. The concerns raised in the report about the quality and difficulty expressed by pharmacists in determining pharmaceutical grade quality in cannabis-based medicinal products available in the UK appear to be very concerning and these concerns do not appear to have been sufficiently identified and addressed in the NICE draft guidelines. Tilray requests that NICE	Thank you for your comment. NICE's remit was to assess the clinical and cost effective evidence for cannabis-based medicinal products for the identified 4 conditions. Barriers to access were out of scope and not included in the NICE guidance. The two reports were produced separately, used different methodology and considered different evidence. The committee agreed that the report and the NICE guideline complement each other, as you suggest they should.

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				review the above report and considers how guidances could be streamlined and co-ordinated so that the NICE guidelines and the NHS report work in harmony rather than potentially against each other.	
Tilray	Guideline, Evidence Review A, B, C, D and E	General	General	The draft guidelines only mention plant-derived cannabinoids such as pure cannabidiol (CBD). There is no mention of plant-derived delta-9-tetrahydrocannibinol and cannabidiol (THC:CBD) products. This is a significant omission and is likely lead to people believing that the medicinal cannabis products do not apply to plant-derived THC:CBD products.	Thank you for your comment. The scope of this guideline included the following cannabis-based medicinal products: • cannabis-based products for medicinal use as set out by the UK Government in the 2018 Regulations • the licensed products delta-9-tetrahydrocannibinol and cannabidiol (Sativex) and nabilone • plant-derived cannabinoids such as pure cannabidiol (CBD) • synthetic compounds which are identical in structure to naturally occurring cannabinoids such as delta-9-tetrahydrocannabinol (THC), for example, dronabinol. There is no mention of plant-derived delta-9-tetrahydrocannibinol and cannabidiol (THC:CBD) products in the recommendations due to a lack of data on clinical effectiveness.
Tilray	Guideline, Evidence Review A, B, C, D and E	General	General	Tilray's experience is that there are much lower incidences of adverse events than NICE state. Please see Tilray's associated submission (also included as an Appendix at the end of this document) for further information and thoughts on this point.	Thank you for your comment for providing the additional data but we can only assess the effectiveness of a product based on the consideration of the balance between benefits and harms and relative cost-effectiveness. The report you have provided doesn't contain robust efficacy data (collected by RCT) or cost-effectiveness data and so we are unable to consider the findings.
UKMSSNA	Evidence	10	10	'*Quality assessment of clinical studies included in the evidence review.* ***a.*** *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.'* You say the quality of evidence was 'initially high' but in the guideline you say it was low. We couldn't find out why you downgraded the evidence?	Thank you for your comments, Further clarification has been added to the evidence reviews.
UKMSSNA	Evidence	General	General	We notice in some of the studies weakness is used as an adverse effect – however it may mean it is having an impact by removing spasticity and exposing weakness	Thank you for your comment and the additional information about weakness. Weakness was reported because it was one of the most commonly reported adverse events across studies but did not form a major part of the committee discussion when considering potential harms of cannabis-based medicinal products.
UKMSSNA	Guideline	1	1	**As the guideline is for: '**People taking cannabis-based medicinal products, their families and carers.' We think clarification is needed between a drug that is licensed, non-licensed and has a marketing authority and what this means in reality with regard to whether a drug can be prescribed or not.	Thank you for your comments. The guideline states the licensed products are delta-9-tetrahydrocannibinol and cannabidiol (Sativex) and nabilone. The prescribing requirements for other (unlicensed) cannabis based medicinal products are given in section 1.5 of the guideline. The current practice section of the guideline outlines the licensing status for cannabis-based medicinal products.
UKMSSNA	Guideline	4	4	The guideline is confusing in that it seems not to recommend it for the different symptoms and then it has a section on 'Prescribing' and the criteria for who can prescribe? In reality we are restricted from prescribing.	Thank you for your comments. After publication of the consultation draft of the guideline, the manufacturer reduced the list price of THC:CBD spray, and this had an important impact on our assessment of its cost effectiveness. In light of stakeholder comments, the committee also reviewed their estimates of likely resource use associated with spasticity symptoms. The committee are now able to make a more positive recommendation.
UKMSSNA	Guideline	General	General	We are very disheartened and disappointed that this guidance has remained very limited in its recommendations and scope despite previous recommendations to review this.	Thank you for your comments,
UKMSSNA	Guideline	General	General	QALY data is only a part of the outcomes that we need to consider. Perhaps the guidelines would consider allowing prescription of cannabis based medicinal products and put a caveat of participating in both short term and long term trial.	Thank you for your comments. We acknowledge that there are other measures available to estimate health outcomes among patients. As per NICE guideline manual and NICE reference case, the health effect in the economic model should be expressed as QALYs so that an outcome can be compared between different populations and disease areas.
UKMSSNA	Guideline	General	General	The economic impact of spasticity and chronic pain is huge. a. Several aspects include keeping pwMS at work whether full time or part time. b. There is also the cost of the ever increasing poly pharmacy to manage these symptoms. Most current drugs have a massive impact of cognitive and physical function c. Most patients will require several GP, MS Nurse, MS consultant appointments to help manage the above symptoms. These services are already under strain	Thank you for your comments. As per the manual for Developing NICE guidelines, the costs in a guideline are calculated in line with the NHS and PSS perspective but do not include the wider societal perspective such as loss of productivity. The reason for this is that productivity costs in our analyses would

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					favour those interventions aimed at the working population. We would then discriminate against the elderly, children, unemployed people and people with disabilities. Medicinal cannabis is only considered as the last treatment option as an add-on to the standard of care before the invasive or surgical interventions in the economic model. As such, medicinal cannabis cannot displace any other standard treatments. The economic models included resource use of managing spasticity and chronic pain and compared the impact of strategies with and without medicinal cannabis.
UKMSSNA	Guideline	General	General	PwMS currently are left with no choice but to either buy these products illegally which in itself has ethical and legal consequences. These have unknown drug interactions and potentially harmful due to the lack of regulation and unknown dosages. This puts clinicians at risk who are prescribing other medications to individuals. The only safe practice is to allow wide prescribing.	Thank you for your comments,
UKMSSNA	Guideline	General	General	There needs to be more clarification re the difference between medicinal and over the counter preparations.	Thank you for your comment. In the guideline we have referred to the term 'medicinal' when referring to cannabis-based medicinal products and this is defined in the 'terms used in this guideline' section. Over-the-counter preparations are those that can be purchased from a retail outlet such as a pharmacy. The guideline considered the clinical effectiveness of CBMPs and not over-the-counter products like cannabis oil sold as food supplements.
University College London Hospitals NHS Trust				**Cannabis in Severe Treatment Resistant Epilepsy**	Thank you for your comments. These are addressed in the table below.
University College London Hospitals NHS Trust	Guideline	10	3-20	UCLH supports further research to be conducted in these areas.	Thank you for your comment.
University College London Hospitals NHS Trust	Guideline	15	9-24	It is clear there is no dispute that Sativex is clinically effective with a small increase in quality of life in the 'average' person as stated in the guideline. We have considerable experience in the use of Sativex at UCLH and our data has already been shared with the guidelines committee. It is apparent form our data that although mean responses may be considered as modest there is a subset of patients who gain life changing results from Sativex preventing the need for more invasive procedures such as intrathecal baclofen. We therefore urge the committee to reflect this in their recommendation that referral to a specialist spasticity service is necessary to consider Sativex alongside intrathecal treatments of baclofen or phenol with their inherent risks (and costs) according to each person's needs and situation. We are only talking about a small subset of MS patients including those with moderate to severe spasticity failing two first line treatments. It is interesting that the guideline talks differently about people with MS related spasticity and those with epilepsy. Regarding epilepsy the guideline states on Page 17, line 6; 'specialists, people with epilepsy and their carers should continue to make treatment decisions in the best interests of each person with epilepsy'. However despite Sativex being the only drug in this class which NICE suggests has clinical effectiveness, there is no allowance to treat people with MS in their best interests as individuals. This seems to treat people with MS differently. This inequality should be addressed? The current guideline leaves clinicians in a difficult position. If a patient with MS fails first line treatments and is referred to a specialist centre who have to explain that there are three other licensed treatments; Sativex, intrathecal baclofen or intrathecal phenol. All are clinically effective but intrathecal baclofen involves surgery and a small risk of morbidity and mortality. Phenol causes irreversible paralysis. Sativex may help these patients (50% responder rate) however cannot be trialled (despite the month's trial being provided free from the manufacturer) before invasive treatments as NICE have deemed their quality of life is not	Thank you for your comment. After publication of the consultation draft of the guideline, the manufacturer reduced the list price of THC:CBD spray, and this had an important impact on our assessment of its cost effectiveness. In light of stakeholder comments, the committee also reviewed their estimates of likely resource use associated with spasticity symptoms. The committee are now able to make a more positive recommendation.

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				worth the £3000 cost over 5 years if it works for them (they won't stay on it if it doesn't work and make a meaningful improvement in their quality of life). Please reconsider and we would suggest stating 'Spasticity specialists, people with MS related intractable spasticity and their carers should continue to make treatment decisions in the best interests of each person'.	
University College London Hospitals NHS Trust	Guideline	15	20	The evidence document on spasticity provides information that the £/QALY is £51,321/QALY. We suggest that this specific wording should be used, to provide an understanding of the recommendation at a glance without spending a significant amount of time reading through the evidence document.	Thank you for your comments. The rationale section provided a direct link to the evidence review. The exact ICER results have been included in the economic model section of the main body of the spasticity evidence review. After publication of the consultation draft of the guideline, the manufacturer reduced the list price of THC:CBD spray, and this had an important impact on our assessment of its cost effectiveness. In light of stakeholder comments, the committee also reviewed their estimates of likely resource use associated with spasticity symptoms. The committee are now able to make a more positive recommendation.
University College London Hospitals NHS Trust	Guideline	19	20-21	The wording in this section has the potential to place the onus of prescribing of cannabis-based medicinal products on prescribers in Primary care other than our earlier suggestion of a "skilled and competent clinician". We suggest that the arrangements of shared care with cannabis based products should not include non-medical prescribers, and should be limited to the Specialist and a clinician who is skilled and competent in the condition being treated.	Thank you for your comment. The committee agreed that a non-specialist GP would be in the same situation as a non-medical prescriber with regards to prescribing these cannabis-based medicines and training would be recommended for them all to ensure they are competent to continue the prescribing. Therefore the committee did not change the recommendation.
University College London Hospitals NHS Trust	Guideline	4	4-6	We are concerned that the current wording of "…chemotherapy-induced nausea and vomiting which persists with optimised conventional antiemetics" will encourage the use of nabilone before all suitable antiemetics have been trialled. We would suggest an amendment to the wording (e.g. "chemotherapy-induced nausea and vomiting which persists following optimisation of all suitable antiemetics") to demonstrate that use of nabilone is considered as a sequential line of therapy following optimised conventional antiemetics. See also the comments below for the definition of "optimised conventional antiemetics", (page 9; line 9-11).	Thank you for your comment. After reviewing the evidence, the committee agreed that nabilone may play a role in treating intractable nausea chemotherapy induced nausea and vomiting in people who have not had a full response to optimal antiemetic therapy. This means that people would have had to have tried other antiemetics or combination of antiemetics before nabilone is considered. Additionally, the recommendation also highlights that nabilone should be considered as an add-on to optimised conventional therapy, which means that it should be used alongside other suitable antiemetics. For further information of why committee made the recommendations, please refer to rationale and impact section within the guideline.
University College London Hospitals NHS Trust	Guideline	4	3-10	These statements are compatible with University College London Hospital NHS Foundation Trusts (UCLH's) current position. Nabilone is currently approved in UCLH for management of nausea & vomiting of cancer chemotherapy when conventional antiemetics fail in line with London Cancer Network antiemetic guidelines (http://www.londoncancer.org/media/65597/antiemetic-guidelines-november-2010.pdf).	Thank you for your comment.
University College London Hospitals NHS Trust	Guideline	4	3-10	Should there be a line specifying "Do not offer nabilone to children and young people under 18 years of age for the management of chemotherapy-induced nausea and vomiting unless part of a clinical trial" as this is a research recommendation (page 11 line 1-5) in the draft guideline? This would be consistent with the statement made in section 1.2.2 (page 5 line 1) which reflects a research recommendation for CBD in chronic pain.	Thank you for your comment. Some evidence was identified for the use of CBMPs in children however this evidence was limited and of low quality. Additionally, nabilone is not currently licensed in children as safety and efficacy has not been established. The committee did not think a 'do not use' recommendation was appropriate for this population as more evidence is needed. Therefore, the committee drafted a research recommendation to further explore the clinical and cost effectiveness in this population.
University College London Hospitals NHS Trust	Guideline	4-5	12-16; 1-2	From the section of chronic pain, we are concerned that there is a risk of inferring further research is not encouraged for nabilone, dronabinol, THC or CBD/THC combination. The risk is introduced by making a specific recommendation to offer CBD for chronic pain under a clinical trial but not making a similar recommendation for other cannabis-based medicinal products. If this is not the intention of this guidance, we would ask the Committee to review the wording of this section.	Thank you for your comment. There was no evidence for the use of CBD alone (either as a pure product or containing traces of THC). Therefore, the committee recommended that CBD should not be offered unless as part of a clinical trial. Therefore, the committee also made a research recommendation for CBD in adults with fibromyalgia or treatment-resistant neuropathic pain. There is no RCT data for children with regards to medicinal cannabis. Therefore, the research recommendations for children are less specific.
University College London Hospitals NHS Trust	Guideline	4-5; 1-2	11-16;	These statements are compatible with UCLH's current position. Nabilone, Dronabinol, THC, CBD/THC combination, or CBD only are currently not approved treatments for chronic pain at UCLH.	Thank you for your comments,
University College London	Guideline	5	4	We are concerned that the recommendation primarily references cost rather than clinical efficacy. The report suggests that NICE agree that Sativex is clinically effective for people with Multiple Sclerosis and spasticity but does not allow for specialist judgement on its	Thank you for your comment. After publication of the consultation draft of the guideline, the manufacturer reduced the list price of THC:CBD spray, and this had an important impact on our assessment of its cost effectiveness. In light of stakeholder comments, the committee

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Hospitals NHS Trust				prescription when required clinically. It is considerably more expensive to manage untreated spasticity than to provide Sativex. The first month is provided free by the manufacturer to enable responder status to be ascertained. It may be more appropriate to word it as 'Only offer THC: CBD spray (Sativex) to treat spasticity in people with multiple sclerosis who have failed first line treatments in a Specialist Spasticity Service'.	also reviewed their estimates of likely resource use associated with spasticity symptoms. The committee are now able to make a more positive recommendation.
University College London Hospitals NHS Trust	Guideline	5	13	We would recommend adding a statement of Dravet syndrome here such as 'we are unable to make a recommendation on the use of cannabis-based medicinal products for severe treatment-resistant epilepsy and the use of CBD in Dravet syndrome will be published in 2019' At UCLH, to date, we have used Epidiolex via GWs early access programme in 13 people with Dravet syndrome only. We would therefore agree with the statement- 'we are unable to make a recommendation on the use of cannabis-based medicinal products for severe treatment-resistant epilepsy'	Thank you for your comment. We have made reference to the publication of the technology appraisal guidance in 2019 in the paragraph following on from this.
University College London Hospitals NHS Trust	Guideline	5	3-8	Sativex was approved in UCLH in December 2010 in line with its market authorisation prior to publication of NICE CG186 which states "Do not offer Sativex to treat spasticity in people with MS because it is not a cost effective treatment". Sativex is restricted to UCLH multiple sclerosis clinic, for continuation in secondary care only and only approved under strict initiation criteria as last line therapy delay/prevent initiation of intrathecal baclofen therapy. Patient response data is routinely collected and audited.	Thank you for your comment.
University College London Hospitals NHS Trust	Guideline	5	7-8	The wording used in this section is appropriate and the need for further research does not differentiate between the different cannabis-based medicinal products. We would encourage the use of similar wording in other sections of this guideline where, in contrast, different recommendations are made for individual cannabis-based medicinal products (e.g. page 4 line 11-16, page 5 line 1-2).	Thank you for your comment. The recommendation wording is considered carefully and reflects the quality and quantity of evidence of clinical and cost effectiveness.
University College London Hospitals NHS Trust	Guideline	5	10-22	CBD oral solution (unlicensed) is currently approved in UCLH for treatment refractory seizures under a free of charge scheme provided by GW Pharma for Lennox-Gastaut and Dravet's syndrome (limits on max. patient numbers per centre and strict scheme criteria). No other CBMP is approved within UCLH for the management of severe treatment-resistant epilepsy. This approval status will be reviewed following market authorisation decision and publication of NICE TA's (ID1211 and ID1308).	Thank you for your comment.
University College London Hospitals NHS Trust	Guideline	5	10-20	We feel that section 1.4 would benefit from the insertion of wording demonstrate that cannabis-based medicinal products should not be used unless part of a clinical trial – understandably the NICE TA for pure CBD is coming soon, but there should be a negative statement for the other cannabis-based medicinal products.	Thank you for your comment. Limited evidence was identified for the use of cannabis- based medicinal products for treatment resistant epilepsy and along with the ongoing NICE technology appraisal, the committee agreed that this did not warrant a practice recommendation. The committee also agreed that they should not make a recommendation against the use of CBMPs as this would restrict further research in this area and would prevent people who are currently benefiting from continuing with their treatment. Therefore, the committee opted to make research recommendations to inform future practice.
University College London Hospitals NHS Trust	Guideline	6	2	This considers prescribing and starts with paediatrics. However as the guideline suggests "do not prescribe for anything except nabilone to adults with intractable nausea", it seems a redundant section. Especially as the footnote then excludes nabilone from the prescribing section	Thank you for your comment. Nabilone is a licenced product and therefore does not need to be prescribed by a specialist on the register. Additionally, the SPC does not specify if the product should be prescribed by a specialist. Therefore, nabilone was excluded from this specific recommendation. However clinicians can still make their own individual prescribing decisions in the best interest of their patients.
University College London Hospitals NHS Trust	Guideline	6	21	Please add "Blood tests should be performed at 4 and 8 weeks after initiation".	Thank you for your comment. Details to include in the shared care agreement would be for local determination.
University College	Guideline	6	21	We also suggest recording the frequency of use of rescue medication and hospital admissions due to seizures.	Thank you for your comment. Details to include in the shared care agreement would be for local determination.

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University College London Hospitals NHS Trust	Guideline	6	10-13	The recommendation made here will be challenging in practice because we are concerned with the wording that cannabis-based medicinal products may be issued by "another prescriber". We would suggest that the wording is amended to: a) Specify that the type of clinician who should continue prescribing under a shared care is a prescriber who is a clinician who is skilled and competent in the condition being treated; and The shared care requires acceptance by the clinician before the care of the patient is transferred	Thank you for your comment. The committee considered this and felt that the term 'other prescriber' covered medical and non-medical prescribers. The committee agreed that a non-specialist GP would be in the same situation as a non-medical prescriber, and both would require training to ensure they are competent to continue the prescribing of a CBMP.
University College London Hospitals NHS Trust	Guideline	6	10-23	The detail provided for shared care guidelines is broad and therefore at risk of being heterogeneous across the UK resulting in inequity of access and varying standards of shared care between primary and secondary care. Will more specific details of what is required in a shared care guideline be provided within any positive NICE TA? If this is not the case, NICE will need to consider how variation can be reduced and address the issue in this guidance before it arises in the future.	Thank you for your comment. NICE TAs would not normally include shared care details as this would be determined by local agreement. Recommendation 1.5.2 has been amended to take into account the NHS England document 'Responsibility for prescribing between Primary & Secondary/Tertiary Care', that provides details about arrangements and considerations for shared care.
University College London Hospitals NHS Trust	Guideline	7	7	We would like to clarify the contribution of this section as the guideline previously suggests "Do not prescribe…"	Thank you for your comment. The committee agreed the prescribing recommendations support prescribers with safe and effective prescribing of CBMPs when they are considered for treatment in patients when all treatments options have been exhausted and benefits of treatment outweighs the harm. These prescribing recommendations will be useful when there is more evidence around the use of cannabis-based medicinal products. Furthermore, clinicians can still make their own individual prescribing decisions in the best interest of their patients.
University College London Hospitals NHS Trust	Guideline	7	15	This section should explicitly list interactions with two commonly used anti-convulsants 1) sodium valproate – increased risk of liver dysfunction. Dose adjustments of valproate may be necessary. 2) Interaction with clobazam – Epidiolex increases levels of clobazam and N-desmethylclobazam increasing the risk of clobazam toxicity. Symptoms of this include hypersomnolence and behavioural disruption in some.	Thank you for your comment. The committee agreed to include antiepileptics as an example in this recommendation. It would be difficult to list specific antiepileptics as there will be more than one cannabis-based product that may be prescribed with different drug-drug interactions profile.
University College London Hospitals NHS Trust	Guideline	7	4	Consider inclusion of requirement of communication when patients transition from children & young people services to adult services.	Thank you for your comment. The recommendation has been amended to reflect your comment.
University College London Hospitals NHS Trust	Guideline	7	5	Currently, Section 1.5.4 states that a shared care should include when to stop treatment, such as severe adverse events. We would suggest adding an additional point, to ensure "the management of possible adverse events" is included as a standard in every shared care document produced.	Thank you for your comment. The recommendation has been amended to reflect your comment.
University College London Hospitals NHS Trust	Guideline	7	8-26	In practice, the factors suggested for consideration when prescribing does not take a multi-disciplinary approach. We would suggest adding in advice to consider consultation with other healthcare professionals currently involved in the care of the patient prior to prescribing cannabis-based medicinal products – this could include social workers, substance misuse services and general practitioners.	Thank you for your comment. Consideration for multi-disciplinary approach may be considered locally depending on resources available in local healthcare settings.
University College London Hospitals NHS Trust	Guideline	7	12	The draft guidance does not recommend any THC products (nabilone being structurally distinct from THC). The part of the statement highlighted in **bold** "*potential for dependence, diversion and misuse (**in particular with THC**)*" is contradictory to the preceding recommendations as THC is not a recommended treatment.	Thank you for your comment. The recommendation you refer to is about factors to consider when prescribing these medicines. The committee agreed that these prescribing recommendations will support prescribers when there is more evidence about these medicines in the future and more licensed products are available. Furthermore, clinicians can still make their own individual prescribing decisions in the best interest of their patients.
University College London	Guideline	7	18-23	The only positive treatment recommendation made in the guideline was for nabilone in adults for intractable chemotherapy induced nausea and vomiting. Please review if inclusion of general prescribing considerations for babies, children and young people is relevant to the	Thank you for your comment. The guideline looked at evidence in babies, children and young people as well as in adults. The committee agreed that given that uncertainty about the effects of cannabis-based medicines on neurological development in this population, it would

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Hospitals NHS Trust				current guideline given no treatment recommendations are made within the guideline for this patient group.	be useful to make a recommendation about the potential impact these medicines can have in this population.
University College London Hospitals NHS Trust	Guideline	8	4	We would like to clarify the contribution of this section as the guideline previously suggests "Do not prescribe…"	Thank you for your comment. The committee agreed the prescribing recommendations support prescribers with safe and effective prescribing of CBMPs when they are considered for treatment in patients when all treatments options have been exhausted and benefits of treatment outweighs the harm. These prescribing recommendations will be useful when there is more evidence around the use of cannabis-based medicinal products.
University College London Hospitals NHS Trust	Guideline	8	7	There is a high risk of adverse effects that may be debilitating. We feel this section should list some of the most commonly reported adverse effects. These include anorexia, nausea, vomiting, diarrhoea, hypersomnolence, behavioural changes and deranged liver function tests.	Thank you for your comment. The committee agreed that it would be inappropriate to specify the adverse events due to lack of evidence.
University College London Hospitals NHS Trust	Guideline	8	4-19	We agree with the suggestions made for supporting shared decision making.	Thank you for your comment.
University College London Hospitals NHS Trust	Guideline	8-9	21-22;1-8	UCLH welcomes the broader classification of "Cannabis Based Medicinal Products" which reduces the confusion introduced by the term "Cannabis-Based Products for Medicinal Use (CBPM)" in the October 2018 DHSC document which did not include synthetic versions of naturally occurring cannabinoids (e.g. Dronabinol), any non-natural cannabinoids obtained by chemical synthesis (nabilone) or plant-derived cannabinoids such as pure cannabidiol (CBD).	Thank you for your comment.
University College London Hospitals NHS Trust	Guideline	9	18	This appears to be the same question repeated	Thank you for your comment. These research recommendations have been split by population group to improve clarity.
University College London Hospitals NHS Trust	Guideline	9	9-11	We are concerned that the definition of "optimised conventional antiemetics" does not include the number of lines of sequential therapy trialled prior to nabilone. Upon reviewing the Forest plots taken from the evidence summary for Intractable nausea and vomiting, nabilone has been compared to domperidone, prochlorperazine and placebo in separate analyses (and one analysis versus metoclopramide in the radiotherapy induced nausea and vomiting population); there does not seem to be evidence for nabilone after multiple antiemetics used as a last-line therapy. There is also no Forest plot or GRADE table for nabilone versus ondansetron – ondansetron being one of the most common antiemetics prescribed in patients using chemotherapy. We suggest the following: a) In the absence of evidence to demonstrate a significant improvement in chemotherapy induced nausea and vomiting (including use of multiple lines of therapy), there should be a recommendation to reserve nabilone for use following optimisation of all suitable antiemetic therapy. If there is a desire to use nabilone higher up the treatment pathway, a research recommendation should be made to investigate the benefits of nabilone before all other suitable antiemetics have been trialled.	Thank you for your comment. Forest plots are reflective of the evidence that was identified. No studies were identified that compared nabilone with ondansetron. After reviewing the evidence, the committee agreed that nabilone may play a role in treating intractable nausea chemotherapy induced nausea and vomiting in people who have not had a full response to optimal antiemetic therapy. This means that people would have had to have tried other antiemetics or combination of antiemetics before nabilone is considered. Additionally, the recommendation also highlights that nabilone should be considered as an add-on to optimised conventional therapy, which means that it should be used alongside other suitable antiemetics.
University College London Hospitals NHS Trust	Guideline	9	15-21	The guidance recommends CBD alone in patients with fibromyalgia or treatment-resistant neuropathic pain (a treatment population who may already be heavily dependent on opioids); the guidance agrees that the use of cannabis-based medicinal products to treat chronic pain demonstrates a modest effect. As the evidence suggests some effect seen in low quality evidence, we suggest that research for all cannabis-based medicinal products should be encouraged. This is especially true in the case of the adult population, as research recommendation 2 in children and young people (page 9 lines 22-27) is appropriately broad and has the potential to lead to the use of cannabis-based medicinal products for chronic pain in children in the future. In practice, we	Thank you for your comment. There was no evidence for the use of CBD alone (either as a pure product or containing traces of THC). Therefore, the committee recommended that CBD should not be offered unless as part of a clinical trial. Therefore, the committee also made a research recommendation for CBD in adults with fibromyalgia or treatment-resistant neuropathic pain. There is no RCT data for children with regards to medicinal cannabis. Therefore, the research recommendations for children are less specific.

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				have seen medications become commissioned for childhood use but not for use in adulthood (due to no available evidence), which creates a barrier to treatment as the child progresses to adult services.	
University College London Hospitals NHS Trust	Guideline	9	22-27	The guideline also recommends cannabis-based medicinal products (i.e. inclusive of THC products, nabilone and dronabinol) be trialled in intractable cancer-related pain and painful childhood diseases, where it states there is no evidence. The full evidence review (pg. 257) states "*In addition, there is concern regarding the use of high dose opioids for children and young people because it often causes adverse events*". We suggest that the research question includes an aim to reduce the overall opioid use with cannabis-based medicinal products.	Thank you for your comment. Extra clarification has been added to the guideline.
University College London Hospitals NHS Trust	Guideline	General	General	The guideline does not make a recommendation for unlicensed cannabis-based medicinal products in the document. Problems that have been found in practice is that unlicensed medicines can be more difficult to source in Primary care, they can come with tremendous prices if not within the scope of the drug tariff, and the MHRA Guidance Note 14 states that licensed medicines should be used first to meet the needs of the patient. The majority of cannabis-based medicinal products that are available and have the potential to be prescribed are unlicensed, and it would be pragmatic for the guideline to discuss this. We would suggest that the NICE Guideline Committee provide information on their standpoint on the use of unlicensed products (even if the recommendation is that NICE cannot make a recommendation – with potential signposting to guidance provided by other regulatory bodies to aid clinicians).	Thank you for your comment. The committee considered the clinical and cost effectiveness of licensed and unlicensed CBMPs, however recommendations was not made for unlicensed CBMPs due to a lack of evidence for these products.
University College London Hospitals NHS Trust	Guideline	General	General	There are many "do-not" recommendations in the guideline, however, there are a number of sections that do not specify do-not-do statements for other CBMP agents (e.g. other CBMPs for intractable nausea and vomiting, use of nabilone in children, other CBMPs (except CBD) for epilepsy). We suggest the NICE Guideline Committee make specific recommendations, as this would be useful to aid decision making and managing individual requests in practice.	Thank you for your comment. The recommendation has been amended to improve clarity.
University College London Hospitals NHS Trust	Guideline	General	General	Which areas will have the biggest impact on practice and be challenging to implement? Treatment recommendations within the draft guideline do not introduce any new practice within UCLH requiring implementation. The only recommended treatment in the guideline is nabilone for chemotherapy-induced nausea and vomiting, which is normally only prescribed in Secondary care and prescribing is not undertaken in Primary care, hence the sections on Shared Care does not affect current practice at UCLH.	Thank you for your comment and providing this insight into current practice.
University College London Hospitals NHS Trust	Guideline	General	General	Would implementation of any of the draft recommendations have significant cost implications? Treatment recommendations within the draft guideline do not introduce any new practice or cost implications within UCLH	Thank you for your comments and support.
University College London Hospitals NHS Trust	Guideline	General	General	What would help users overcome any challenges? (For example, existing practical resources or national initiatives, or examples of good practice.) - This overarching NICE guidance for CBMPs being updated to reflect any subsequent NICE TA recommendations - Detailed shared care guidelines for CBMP treatment recommendations made by NICE TA's Linked training to any future NICE TA's with a focus on non-specialist being asked to continue treatment e.g. other specialties providing inpatient care and primary care.	Thank you for your comment.
University of Oxford				I wondered what the science is behind allocating 25% of Dr Stevenson's paper calculations of spasticity cost was and whether a range would be better with best and worst case would be better as this decision will drive the cost effectiveness	Thank you for your comments. Based on committee consensus, the committee agreed that the resource use estimated in Stevenson et al. 2015 cannot be said to be 100% attributable to spasticity alone. The committee felt that the vignette from the health care professional survey could be misleading as it explicitly stated that the disability described in the health states was caused by spasticity only. The committee agreed that some of the physical disability specified in the vignette, particularly in the most severe health states, would have involved multiple other features of the underlying MS. Based on published evidence and the committee's experience, the committee does not think treating spasticity would have a major impact on underlying disability associated with MS (measured by EDSS). Therefore, the

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					committee concluded that Stevenson et al. 2015 overestimated the amount of resource use that is solely attributable to medically modifiable spasticity. However, the committee was sensitive to comments such as this, and did not want to underestimate the possible benefits of THC:CBD spray. Therefore, the committee made a consensus to change this parameter to 50%. The committee agreed that this parameter is highly uncertain, and it should be tested in the sensitivity analysis. This parameter has been modified in the model, tested extensively and reported in the spasticity evidence review chapter (Table 23). When doubling the background management costs (assuming 100% of costs from Stevenson et al. 2015 are attributable to spasticity alone), the cannabis strategy became dominant. When halving the background management costs (assuming 25% of costs are related to spasticity), the ICER is around £35,000. The modelling approach you propose would be attractive if any data were available for either the effectiveness of THC:CBD spray in influencing transit between spasticity health states or for the resource use independently associated with any such health states. As no such data are available, the model structure adopted made use of best-available evidence regarding the effectiveness of THC:CBD spray and the resource use associated with spasticity.
Warwick Clinical Trials Unit	3	Evidence Review B, appendix K	256/7	Detailed recommendation are given for outcomes to assess in any trial of cannabis based medical products for fibromyalgia/neuropathic pain. It is appropriate that that this committee suggest important outcome domains for any future trial. However, the committee has not been constituted to advice on choice of outcomes within each domain. No review of outcome measures appears to have been done to inform choices. We suggest that specific recommendations on outcome measures, e.g. McGill pain questionnaire or brief pain inventory, should be removed. Then researchers can then select most appropriate outcomes and their choices can be assessed by the funding board who will be competent to assess the researchers' choice of measures.	Thank you for your comment. For the research recommendations, the committee acknowledged that favoured functional pain measurement tools change all the time. Therefore, we have included the outcome: "A validated functional pain measurement tool".
Warwick Clinical Trials Unit	3	Evidence Review B, appendix K	256/7	The comparator in the PICO statement, for the research recommendation related to fibromyalgia/neuropathic pain is to be 'Standard treatment (WHO pain ladder step 3: opioids plus adjuvants)'. The committee should be aware that the WHO pain ladder only applies to drug treatment malignant pain and not to the management of non-malignant pain and is thus an inappropriate definition of standard treatment for these patient groups. This is more than a sematic point. As written, the only group of people eligible for a future trial will be people already on opioids. Opioids are, however, inappropriate treatments for these two conditions. 2016 EULAR fibromyalgia guidelines made; '*a 'strong against' evaluation (100% agreement) regarding the use of strong opioids … in patients with fibromyalgia on the basis of lack of evidence of efficacy and high risk of side effects/addiction reported in individual trials'.*[1] 2013 NICE guidelines for neuropathic pain advise that Morphine or Tramadol (and by extension all opioids) should not be initiated as long term treatment except in specialist settings.[2] In light of the overwhelming evidence of serious harms from opioids needing to use these as a prerequisite for inclusion in a trial of cannabis based medicinal products seems inappropriate. We suggest the comparator should be as an addition to usual care, or best usual care as defined by the researchers. Thus, for example, this could then be as an addition to best care including non-drug management [1]Macfarlane GJ, Kronisch C, Dean LE, et al. Ann Rheum Dis 2017;76:318–328. [2] https://www.nice.org.uk/guidance/cg173/chapter/1-Recommendations	Thank you for your comment. For the adult research recommendation, we have changed the comparator to "usual care as defined by the researchers".

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Warwick Clinical Trials Unit	Evidence Review B, appendix K	256/7		It is unclear in the guideline which compound or compounds might be tested. On page nine of the draft guideline the recommendation is to test cannabidiol (CBD). Whilst in appendix K page 256 of the pain evidence review the intervention specified is the PICO states 'Cannabis based product (CBD) with standard treatment. CBD is 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, … ' Here cannabis based product is abbreviated to CBD. Might there have been some confusion by using the same abbreviation to refer to two different but related definitions? The research recommendation does not appear to be consistent with the intervention specified in the PICO. It is, in fact very difficult to isolate pure cannabidiol https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/778357/Factsheet_Cannabis_CBD_and_Cannabinoids_2019.pdf meaning in practical terms that a combination product will be easier and cheaper to source for research purposes. Further the available evidence provided in the evidence review that support the notion that cannabis based medical products may have a small effect on pain (0.44, 95% CI 0.16 to 0.70 on a ten point scale) is based on a meta-analysis of the effect of THC:CBD spray. The research recommendation as currently presented may not accurately represent the committee's intent. If it does accurately reflect the committee's intent then they may wish to look at this again and re-define the intervention as a cannabis based medicinal product.	Thank you for your comment. There was no evidence for the use of CBD alone (either as a pure product or containing traces of THC). Therefore, the committee recommended that CBD should not be offered unless as part of a clinical trial. Therefore, the committee also made a research recommendation for CBD in adults with fibromyalgia or treatment-resistant neuropathic pain. There is no RCT data for children with regards to medicinal cannabis. Therefore, the research recommendations for children are less specific. Revisions have been made to the evidence review and research recommendation PICO to address this.
Warwick Clinical Trials Unit	Guideline	9	16-19	The second sentence in the research recommendation regarding fibromyalgia and neuropathic pain appears to be redundant.	Thank you for your comment. Fibromyalgia and neuropathic pain were identified by the committee as key conditions warranting further research.
Warwick Clinical Trials Unit	Guideline	9	16-19	We are concerned that it is unclear in the guideline which compound or compounds might be tested if the research recommendation is followed. It is not consistent with the PICO recommendation the evidence reviews. The research recommendation as currently presented may not accurately represent the committee's intent. If it does accurately reflect the committee's intent then they may wish to look at this again and re-define the intervention as a cannabis based medicinal product.	Thank you for your comment. With regards to the adult research recommendation, the wording has now been changed to: "CBD (either as a pure product or containing traces of THC)". There was no evidence for the use of CBD alone (either as a pure product or containing traces of THC). Therefore, the committee recommended that CBD should not be offered unless as part of a clinical trial. Therefore, the committee also made a research recommendation for CBD in adults with fibromyalgia or treatment-resistant neuropathic pain
Young Epilepsy	Guideline	10	4	We recommend that research on CBD for severe treatment-resistant epilepsy includes questions on: • Efficacy and safety of long-term use in children and young people • Cognitive, psychological and emotional impact of use in children and young people • Impact of use in children and young people on structural and functional brain development	Thank you for your comments. We have included children and young people within the population for the research recommendation and included reference to changes in cognition. The committee felt that changes in brain development were more relevant to the use of THC and so this was included in the second research recommendation. The full protocols for the research recommendations can be found in the epilepsy evidence review (Appendix J)
Young Epilepsy	Guideline	10	8	We recommend that research on THC in combination with CBD for severe treatment-resistant epilepsy includes questions on: • Efficacy and safety of long-term use in children and young people • Cognitive, psychological and emotional impact of use in children and young people • Impact of use in children and young people on structural and functional brain development	Thank you for your comments. We have included children and young people within the population for the research recommendation and included reference to changes in cognition and brain development. The full protocols for the research recommendations can be found in the epilepsy evidence review (Appendix J).
Young Epilepsy	Guideline	5	14	Young Epilepsy recognises the need for further research into the efficacy and safety of cannabis-based medicines for severe treatment-resistant epilepsy in children and young people. We welcome the inclusion of research recommendations to promote further research and inform future practice.	Thank you for your comments and the support for this guideline.

A number of comments included individual patient data and personally identifying information. This detail has been redacted but we have retained the comments to show how they have been addressed.