**National Institute for Health and Clinical Excellence**

# Neuropathic Pain
## Scope Consultation Table
## 11th June – 9th July 2012

| Stakeholder | Order No | Section No | Comments<br>Please insert each new comment in a new row. | Developer's Response<br>Please respond to each comment |
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| Astellas Pharma | 1 | | Thank-you for the opportunity to comment on the scope for the Neuropathic Pain – Pharmacological Management Guideline. Astellas Pharma do not have any comments at this stage. | Thank you for your comment. |
| Department of Health | 1 | | Thank you for the opportunity to comment on the draft scope for the above clinical guideline.<br><br>**I wish to confirm that the Department of Health has no substantive comments to make, regarding this consultation.** | Thank you for your comment. |
| Pain UK | 5 | | We dread the day when a more limited range of drugs will be approved for e.g. TN, on the basis of what suits others and not every individual. | Thank you for your comment.<br><br>The recommendations set out in NICE clinical guidelines do not cover all possible situations and do not replace clinical judgement.<br><br>Healthcare professionals are encouraged to use the recommendations together with clinical judgement and offer treatment as appropriate for their patient, based on the patient's individual needs. |

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| | | | | The decision on separating or grouping conditions which can cause neuropathic pain will be led by the evidence and decided by the guideline development group in light of the evidence.<br><br>Different recommendations may be made for subgroups if supported by the evidence. |
| MS Trust | 1 | 2 | Commonly in clinical practice, successful management of chronic neuropathic pain often involves pharmacological and non-pharmacological therapies offered in conjunction. Non-pharmacological therapies include CBT, relaxation techniques, TENS, as well as others. There is currently no guidance on the use of non-pharmcological therapies as an adjunct for pain management. Should the scope of this guideline be expanded to include non-pharmacological treatment of neuropathic pain? Alternatively, it may require development of a second guideline. | Thank you for your comment.<br><br>Non-pharmacological management of neuropathic pain is not within the remit of this guideline, which was referred to us by the Department of Health. The remit is specifically the pharmacological management of Neuropathic Pain.<br><br>We recognise that non-pharmacological management of neuropathic pain may be an important issue but we will not be able to look at these areas within the development of this guideline. |

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| **United Kingdom Multiple Sclerosis Specialist Nurses Association (UKMSSNA)** | 2 | 3 1 c) | No MS mentioned or the role MS Specialist Nurses have in managing neuropathic Pain. Incidence/Prevalence; see Treede 2008 (above) | Thank you for your comment.<br><br>This section of the scope is intended to briefly summarise the epidemiology. It is not possible to describe all possible conditions causing neuropathic pain. However, section 3.1 a) has been amended and multiple sclerosis has been added as a possible cause of neuropathic pain.<br><br>Section 4.2 states that all settings other than specialist pain management services are included in this guideline. As a result, individuals who are condition-specific specialists (such as MS Specialist Nurses) are covered by this guideline. |
| Royal College of Nursing | 2 | 3.1 | Multiple Sclerosis is not mentioned but needs to be included as it is a common condition where neuropathic pain is present but under recognised as a symptom of MS. | Thank you for your comment.<br><br>This section of the scope is intended to briefly summarise the epidemiology. It is not possible to describe all possible conditions causing neuropathic pain. However, section 3.1 has been amended and multiple sclerosis has been added as a possible cause of neuropathic pain. |
| Pfizer Ltd. | 1 | 3.1 – c) | It is worth noting that this study may only have looked into | Thank you for your comment. |

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| | | | these pre-defined subgroups of NeP. Other NeP conditions, such as radiculopathy (neck and back pain) and traumatic neuralgia, are more common than PHN, but are often poorly coded by physicians. | We are unable to comment on the prevalence of these conditions because of the lack of literature. Section 3.1 c) highlights that there is limited evidence on the prevalence of neuropathic pain outside specialist management settings. |
| BRITISH PAIN SOCIETY | 2 | 3.1 a | **Epidemiology**<br><br>Chemotherapy-induced peripheral neuropathy is not mentioned. Although it is not common in comparison to DN and PHN, it will be increasingly prevalent as more (and older) patients get chemotherapy. We can't assume that 'specialists' (ie oncologists) will always recognise and treat this appropriately.<br><br>Post-operative/traumatic neuropathic pain is sufficiently common and missed by surgeons and GPs. It should be included. 'Peri-operative' neuropathic pain (as listed in 4.3.2 d) is likely to be identified and managed by specialist acute pain teams in the immediate post-op period, but not thereafter. | Thank you for your comment.<br><br>This section of the scope is intended to briefly summarise the epidemiology. It is not possible to describe all possible conditions causing neuropathic pain. However, section 3.1 a) has been amended and multiple sclerosis has been added as a possible cause of neuropathic pain.<br><br>Cancer pain will be covered by the guideline. We have also amended section 4.3.2 from 'treatment of peri-operative neuropathic pain' to read 'acute post-surgical pain'. Post-operative neuropathic pain will now be included within this guidelines. |
| Association of British | 2 | 3.1 a-d; 4.1 & General | Examples of specific conditions associated with neuropathic Pain include where there is a clearer understanding of the | Thank you for your comment. |

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| Neurologists | | Comment | Epidemiology etc.<br>(a) Cranial Neuropathic pain syndromes i.e. Trigeminal Neuralgia, Glossopharyngeal neuralgia, Occipital Neuralgia, etc.<br>(b) Painful peripheral Neuropathies e.g. Diabetic, HIV related, Toxins etc. | |
| Association of British Neurologists | 3 | 3.1 a-d; 4.1 & General Comment | The guidelines scope Committee needs to reach Consensus and decide **and list which conditions will or will not be considered under the title Neuropathic pain in their terms of reference and state it accordingly to clarify matters** e.g. Is Complex Regional pain syndrome Type I going to be included or not? i.e. What conditions it is addressing with the Neuropathic Pain guideline and what it is not ! | Thank you for your comment.<br><br>The remit is specifically the pharmacological management of Neuropathic Pain. The guideline development group for neuropathic pain will be able to make different recommendations for specific subgroups if supported by the evidence. |
| Association of British Neurologists | 1 | 3.1 a-d; 4.1; 4.5 & General Comment | **There should be a separation of specific neuropathic pain syndromes where there is greater evidence to support therapies** e.g. Trigeminal Neuralgia is the best example within the Neuropathic pain guidance as looking at evidence "as a whole" for a particular drug by "lumping" all types of neuropathic pain together will dilute analysis and potentially miss important data **whereas syndrome specific treatment guidance by evaluating the evidence for each drug in each specific neuropathic pain syndrome will possibly produce better future patient management where data is available.** | Thank you for your comment.<br><br>The decision on separating or grouping conditions which can cause neuropathic pain will be led by the evidence and decided by the guideline development group in light of the evidence.<br><br>Different recommendations may be made for subgroups if supported by the evidence. |
| Association of British Neurologists | 4 | 3.1 b | The definition of Neuropathic pain needs clarification. Is the International Association for the Study of Pain (IASP) classification going to be used or another. | Thank you for your comment.<br><br>The scope has been updated with the International Association for |

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| | | | | the Study of Pain (IASP) definition. |
| The Walton Centre for Neurology and Neurosurgery | 1 | 3.1 Epidemiology | The definition of neuropathic pain has been changed to "Pain caused by a lesion or disease of the somatosensory nervous system" | Thank you for your comment.<br><br>The scope has been updated with this International Association for the Study of Pain (IASP) definition. |
| MS Trust | 2 | 3.1. c) | Paragraph should include multiple sclerosis. The prevalence of pain is high in MS. Some studies suggest up to 90% are affected by pain at some time. An MS Trust survey found that out of 2,265 participants, 81% experienced pain as a symptom of their MS, with 50% classifying their pain as moderate or severe. | Thank you for your comment.<br><br>This section of the scope is intended to briefly summarise the epidemiology. It is not possible to describe all possible conditions causing neuropathic pain. However, section 3.1a) has been amended and multiple sclerosis has been added as a possible cause of neuropathic pain.<br><br>We are unable to comment on the prevalence of these conditions because of the lack of literature. Section 3.1 c) highlights that there is limited evidence on the prevalence of neuropathic pain outside specialist management settings. |
| **MS Society** | 3 | 3.1.a | Within the epidemiology section we would recommend including Multiple Sclerosis as a relevant condition to neuropathic pain. | Thank you for your comment.<br><br>This section of the scope is intended to briefly summarise the |

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| | | | | epidemiology. It is not possible to describe all possible conditions causing neuropathic pain.<br>Section 3.1 a) has been amended and multiple sclerosis has been added as a possible cause of neuropathic pain. |
| **United Kingdom Multiple Sclerosis Specialist Nurses Association (UKMSSNA)** | 1 | 3.1.a) Epidemiology | No mention of MS being a source of Neuropathic pain, although it is a common but under-recognised symptom of MS. Est.8000 PwMS (8%) Treede, R.D. 2008 "Neuropathic Pain.."Neurology,70,1630-5 | Thank you for your comment.<br><br>This section of the scope is intended to briefly summarise the epidemiology. It is not possible to describe all possible conditions causing neuropathic pain. Section 3.1 a) has been amended and multiple sclerosis has been added as a possible cause of neuropathic pain. |
| Grünenthal Ltd | 1 | 3.2 b) | Appropriate guidance on the use of strong centrally acting analgesics and the 5% lidocaine plaster, i.e. as an alternative to / prior to referral, has the potential to reduce the volume of referrals to secondary care specialist pain management clinics. This should be a goal of the guideline, allowing the statement to this effect to be reinstated in this section of the scope. | Thank you for your comment.<br><br>The last statement in section 3.2 b) already states that better management of neuropathic pain in non-specialist settings can ensure only those who need specialist assessment and interventions are referred. |
| MS Trust | 3 | 3.2 b) | Inclusion of referral criteria to specialist pain clinics in this guideline would encourage consistency in practice and reduce unnecessary referral. | Thank you for your comment.<br><br>During the development of this guideline we will not be asking an explicit review question about |

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| | | | | referral. If issues relating to referral are supported by evidence related to the review questions about pharmacological treatments then these will be considered by the guideline development group. |
| Napp Pharmaceuticals Limited | 1 | 3.2b | "However, there is considerable variation in practice in terms of how therapy is initiated, whether therapeutic doses are achieved and whether the different types of drugs are used in the correct sequence".<br><br>Comment:<br><br>4.3.1a suggests that treatment could be with single medicines or with combinations, which is more in line with current practice. We suggest making this clearer in the statement above which is from 3.2b. | Thank you for your comment.<br><br>Section 3.2 b) has been amended to reflect your suggested change. |
| **United Kingdom Multiple Sclerosis Specialist Nurses Association (UKMSSNA)** | 3 | 4 3 1 Key Clinical Issues | Add ( G.) Transcutaneous Nerve Stimulation (TENS) for chronic pain, Cochrane Database 5yst kev 2008 (3) cdoo3222 Nnoaham.K.E.& Kumbang J. "TENS for Chronic Pain | Thank you for your comment.<br><br>This remit of this guideline is to specifically cover the pharmacological management of Neuropathic Pain only. Therefore, transcutaneous nerve stimulation will not be included. |
| Pfizer Ltd. | 2 | 4.1.1 | With regards to the decision to no longer give specific consideration to patients with PHN and PDN from this revised scope:<br><br>Whilst we recognise the heterogeneous nature of neuropathic pain and welcome the intention to give equal consideration to | Thank you for your comment.<br><br>The decision on separating or grouping conditions which can cause neuropathic pain will be led by the evidence and decided by |

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| | | | all subgroups, we urge NICE to be mindful of situations where drugs are studied and licensed only for a clearly defined, specific subgroup of neuropathic pain, such as PHN or PDN. | the guideline development group in light of this evidence.<br><br>Different recommendations may be made for subgroups if supported by the evidence. |
| Pfizer Ltd. | 3 | 4.1.2 | We welcome the change in scope to now include neuropathic pain arising directly from trauma or orthopaedic surgical procedures, as we feel that that this is an important subgroup. | Thank you for your comment. |
| Pfizer Ltd. | 4 | 4.2 | We welcome the broadening of settings where the guidelines are applicable as neuropathic pain patients may be seen in a wide-range of settings. | Thank you for your comment. |
| Pfizer Ltd. | 5 | 4.3.1 | We are concerned by the addition of a large number of medications not licensed specifically for neuropathic pain and with low-grade evidence, according to the GRADE approach utilised by NICE. As noted in section 4.3.1 recommendations should be based on licensed, evidence-based drugs. This is of particular importance, given that these guidelines are aimed towards non-specialists. | Thank you for your comment.<br><br>The guidelines manual does not preclude making recommendations about the use of off-label drugs when there is clear evidence to support this (please see section 9.3.5.1 of the Guidelines Manual). In addition the NICE Guidelines Manual advocates that if the drug is not licensed for the stated use a footnote should make it clear that informed consent should be obtained and documented. |
| Pfizer Ltd. | 6 | 4.3.1 | In part b) it states that "prescribers will use a drug's summary of product characteristics to inform their decisions for individual patients." | Thank you for your comment.<br><br>While it is standard practice to |

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| | | | It is unlikely that the SPC will cover neuropathic pain for those drugs that are not licensed specifically for neuropathic pain and therefore this may not be an appropriate source. Furthermore, for ethical considerations, an informed consent should be obtained from the patient before prescribing an off-label or unlicensed drug. | refer to the summary product characteristics (SPC), dosage information can be provided if there is clear evidence about the effectiveness of different dose levels. In addition the NICE Guidelines Manual advocates that if the drug is not licensed for the stated use a footnote should make it clear that informed consent should be obtained and documented. |
| Royal College of Nursing | 3 | 4.3.1 | Can the guidelines include drug combinations and escalation of drugs? | Thank you for your comment.<br><br>Section 4.3.1 a) highlights that monotherapy and combination therapy will be considered.<br><br>Dose escalation will be considered in the development of this guideline. |
| Faculty of Pain Medicine of the Royal College of Anaesthetists | 1 | 4.3.1 (d) | Flecainide is not an opioid. Include in 4.3.1 (f). | Thank you for your comment.<br><br>This has been amended in the scope. |
| Royal College of Nursing | 4 | 4.3.1 (f) | We are pleased to see that Sativex has been included for review in pain management. | Thank you for your comment. |
| Eli Lilly & Company | 1 | 4.3.1 b | We suggest that the licence description for duloxetine reflect the wording used in the summary of product characteristics. The SPC states duloxetine's therapeutic indication is 'for the treatment of diabetic peripheral neuropathic pain'. | Thank you for your comment.<br><br>We have amended this to reflect the summary of product |

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| | | | | characteristics (SPC) wording. |
| The Walton Centre for Neurology and Neurosurgery | 2 | 4.3.1 b) | Mirtazapine is not a tricyclic antidepressant, trazodone is a tricyclic-related antidepressant, reboxetine is a noradrenaline re-uptake inhibitor | Thank you for your comment.<br><br>This has been amended in the scope. |
| BRITISH PAIN SOCIETY | 3 | 4.3.1 d | Flecainide is not an opioid. It is an anti-arrhythmic with a similar mechanism of action as lidocaine. | Thank you for your comment.<br><br>This has been amended in the scope. |
| Grünenthal Ltd | 2 | 4.3.1 d) | Tapentadol has been added to the list of opioid analgesics to be considered in the guideline. However, tapentadol is a centrally acting analgesic combining two complementary mechanisms of action, μ-opioid receptor agonism (MOR) and noradrenaline reuptake inhibition (NRI), in a single molecule, and therefore should be considered separately from opioid analgesics. The synergistic mode of action of tapentadol[1], targeting both nociceptive and neuropathic pain pathways, but with the potential for reduced reliance on the opioid component, may explain the comparable efficacy, more favourable gastrointestinal (GI) side effect profile and lower rates of abuse compared to oxycodone. These are important differences given the concerns over the use of strong opioids for treating non-malignant chronic pain.<br><br>[1] Schröder W. et al. (2011) Synergistic Interaction between the Two Mechanisms of Action of Tapentadol in Analgesia. J. Pharmacol. Exp. Ther.; 337(1): 312-320. | Thank you for your comment.<br><br>The wording for the review questions (section 4.5 a) ) has been changed so it is clearer that it is not just different classes of drugs that will be compared, but different individual drugs. . |
| The Walton Centre for Neurology and Neurosurgery | 3 | 4.3.1 d) | Flecainide is not an opioid and should go under additional drugs. Before starting long term opioid treatment I would suggest to have the diagnosis confirmed in a specialist setting and evaluate the best tolerated and most effective opioid. A | Thank you for your comment. This has been amended in the scope.<br><br>The remit of this guideline is |

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| | | | long term management plan to respond to tolerance development should be formulated to be followed in primary care and the patient re-referred if there is a change in the painful condition. | specifically the pharmacological management of Neuropathic Pain. The appropriateness of prescribing opioids in non-specialist settings will be discussed by the guideline development group during the development of the guideline. |
| The Walton Centre for Neurology and Neurosurgery | 5 | 4.3.1 e) | As this are guidelines for primary care and non-pain specialists and the scope includes capsaicin patch applications, this should be looked at in conjunction with the capability of assessing neuropathic pain appropriately. A possibility would be to make the diagnosis and map the area to be patched in the specialist setting and continue the treatment after proof of efficacy in primary care. | Thank you for your comment.<br><br>Assessment of neuropathic pain is not within the remit of this guideline, which was referred to us by the Department of Health. The remit is specifically the pharmacological management of Neuropathic Pain.<br><br>We recognise that assessment may be an important issue but we will not be able to look at this area within the development of this guideline. |
| Medtronic Ltd | 1 | 4.3.1. a-g | When considering expensive off label pharmacological interventions it should be borne in mind that spinal cord stimulation for chronic pain is licenced, has a full technology appraisal, and may be a more cost-effective option for neuropathic pain. While it is appreciated the guideline refers to pharmaceutical options it would be appropriate to mention the existing TA in the context of treatment options. | Thank you for your comment.<br><br>This guideline is only looking at the pharmacological management of Neuropathic Pain. Consequently, reference to NICE guidance on other types of interventions for neuropathic pain (including Technology appraisals |

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| | | | | and a number of Interventional procedures guidance) have not been listed. |
| **MS Society** | 4 | 4.3.1.e | In addition to the topical therapies listed we would recommend that the scope considers non-steroidal anti-inflammatory agents; and buprenorphine patches. | Thank you for your comment.<br><br>In NICE clinical guidelines we are not always able to cover all possible interventions and situations.<br>Non-steroidal anti-inflammatory drugs will not be considered as part of this guideline.<br><br>Healthcare professionals are encouraged to use the recommendations together with clinical judgement and offer treatment as appropriate for their patient, based on the patient's individual needs.<br><br>Buprehorphine is already included in the section on opioid analgesics (now section 4.3.1 e). This is not restrictive for different preparations of this drug. To be clearer that lidocaine and capsaicin are not the only possible drugs which will be considered topically, these have been moved to the 'additional drugs section (now section 4.3.1 |

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| | | | | f). |
| **MS Society** | 5 | 4.3.1.f | In addition to those drugs listed we would also suggest including dextromethorphan –quinidine and botox for painful focal spasms. | Thank you for your comment.<br><br>Since the mechanism of these drugs is to treat the spasticity or spasm and not the pain, they are not included in this guideline which is for the treatment of pain, rather than the underlying condition. |
| **United Kingdom Multiple Sclerosis Specialist Nurses Association (UKMSSNA)** | 6 | 4.3.1.f) | We are pleased that Sativex has been included for review in pain management. | Thank you for your comment. |
| United Kingdom Clinical Pharmacy Association (UKCPA) – Pain management group | 4 | 4.3.1a) | Given the small number of trials examining combinations of neuropathic agents, it is highly unlikely that any is likely to be 'clearly supported by evidence' and this statement should be reworded. Perhaps: [This will include use of individual drugs as monotherapy, if clearly supported by evidence. The evidence supporting combinations of therapies should also be considered.] Again, it may be sensible to refer in to specialist services at the same time as initiating combination therapy. | Thank you for your comment.<br><br>This will be addressed during the development of the guideline. Recommendations about combination therapy in neuropathic pain will be led by the evidence and decided by the guideline development group in light of the evidence. |
| Napp Pharmaceuticals Limited | 2 | 4.3.1d | We welcome the consideration of oxycodone / naloxone for the treatment of severe neuropathic pain and would like to provide some additional information for its inclusion within the guideline. Whilst there are no specific studies on the use of | Thank you for these references. Section 4.3.1 a) highlights that individual drugs (such as oxycodone/naloxone) will be |

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| | | | oxycodone / naloxone in neuropathic pain, there are a number of randomised, controlled studies with oxycodone alone or in combination with gabapentin and pregabalin that have demonstrated significant improvements in pain scores for the treatment of severe pain in diabetic neuropathy and post-herpetic neuralgia.[1-6] It is the oxycodone component which provides analgesia, while naloxone, an opioid antagonist, counteracts the potential negative impact that oxycodone can have on the GI function, by the reduction of constipation. All opioid agonists bind to opioid receptors in the gut, causing a significant reduction in peristalsis and subsequent decreased bowel motility. Naloxone has a higher affinity for the opioid receptors than oxycodone, binding preferentially and counteracting the binding of oxycodone.[7] The oxycodone component of oxycodone / naloxone tablets is bioequivalent to prolonged-release oxycodone.[8] Therefore, as it is the oxycodone component that is important in the treatment of severe neuropathic pain, oxycodone / naloxone tablets may also be considered as efficacious in the treatment of neuropathic pain, with the additional benefit of naloxone to counteract opioid-induced constipation.<br><br>References:<br>1. Gatti, A, Fabrizio Sabato, A, Occhioni, R et al. Controlled-release oxycodone and pregabalin in the treatment of neuropathic pain: results of a multicentre Italian study. European Neurology 2009;61:129-137.<br>2. Hanna M, O'Brien C, Wilson M. Prolonged-release oxycodone enhances the effects of existing gabapentin therapy in painful diabetic neuropathy patients. Eur J Pain 2008;12: 804-13.<br>3. Watson CPN, Babul N. Efficacy of oxycodone in neuropathic | considered as monotherapy or in combination with other drugs.<br>We will perform a thorough review of the literature as specified in the review protocol which will be agreed with the guideline development group. The review protocol will include inclusion and exclusion criteria and cut off dates for the evidence review. |

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| | | | pain. A randomised trial in post-herpetic neuralgia. Neurology 1998;50:1837-41.<br>4. Sindrup SH, Jensen TS. Efficacy of pharmacological treatments of neuropathic pain: an update and effect related to mechanism of drug action. Pain 1999;83:389-400.<br>5. Gimbel JS, Richards P, Portenoy RK. Controlled-release oxycodone for pain in diabetic neuropathy. Neurology 2003;60:927-34.<br>6. Watson CPN, Moulin D, Watt-Watson J,et al. Controlled-release oxycodone relieves neuropathic pain: a randomised controlled trial in painful diabetic neuropathy. Pain 2003;105:71-78.<br>7. Summary of product Characteristics. Targinact tablets<br>8. Smith K, Hopp M, Mundin G, et al. Single- and multiple-dose pharmacokinetic evaluation of oxycodone and naloxone in an opioid agonist/antagonist combination in healthy adult volunteers. Clin Ther 2008;30(11):2051-68 | |
| United Kingdom Clinical Pharmacy Association (UKCPA) – Pain management group | 5 | 4.3.1d) | Flecainide is not an opioid and should be included in the miscellaneous section: f) | Thank you for your comment.<br><br>This has been amended in the scope. |
| Pfizer Ltd. | 7 | 4.3.2 – a) | Given the number of comments from stakeholders at the scoping workshop, including KOLs and patient representatives, about the importance of including diagnosis and assessment, we are surprised that this remains out of scope.<br><br>**We suggest that the guideline remit is broadened to include the assessment and diagnosis of neuropathic** | Thank you for your comment.<br><br>Assessment and diagnosis of neuropathic pain are not within the remit of this guideline, which was referred to us by the Department of Health. The remit is specifically the pharmacological |

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| | | | **pain, in addition to pharmacological management, to address the broader clinical guidance required within non-specialist settings**.<br><br>The reasons for the request to include assessment and diagnosis are given as separate comments below. | management of Neuropathic Pain.<br><br>We recognise that assessment and diagnosis may be important issues but we will not be able to look at these areas within the development of this guideline. |
| Pfizer Ltd. | 7a | 4.3.2 – a) (continued) | 1) The early diagnosis of neuropathic pain is crucial in order to prevent irreversible pathology and associated chronic pain (Bennett 2001, Booker 2004). Additionally, there is evidence that neuropathic pain is poorly recognised in non-specialist settings in the UK. The Neuropathy Trust survey of 662 patients with neuropathic pain in the UK found that only 37% of respondents had received a diagnosis for their condition, and that GPs were only able to correctly diagnose in approximately 18% of patients (Booker 2004).<br><br>**We urge NICE to consider the need for simple guidance and consensus on the appropriate tools that non-specialists can use to recognise and diagnose neuropathic pain.** | Thank you for your comment.<br><br>Assessment and diagnosis of neuropathic pain are not within the remit of this guideline, which was referred to us by the Department of Health. The remit is specifically the pharmacological management of Neuropathic Pain.<br><br>We recognise that assessment and diagnosis may be important issues but we will not be able to look at these areas within the development of this guideline. |
| Pfizer Ltd. | 7b | 4.3.2 – a) (continued) | 2) There is evidence of inappropriate referrals to specialist pain clinics for neuropathic pain patients before adequate trials of simple, effective treatments. A cohort study of 703 patients in the UK found that only 22.4% of patients had an adequate trial of an antidepressant before referral to a pain clinic (Davies, 1994). In a UK database study of 16,690 patients with painful neuropathic disorders, only 36.2% of patients received medications recommended for neuropathic pain (Gore 2007).<br><br>Other neuropathic pain guidelines have made | Thank you for your comment.<br><br>Assessment and diagnosis of neuropathic pain are not within the remit of this guideline, which was referred to us by the Department of Health. The remit is specifically the pharmacological management of Neuropathic Pain. |

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| | | | recommendations on assessment, for example the draft British Pain Society guidelines for neuropathic pain (BPS 2011) recommend that patients are reassessed fortnightly until pain is well controlled.<br><br>**Given that these guidelines are aimed at non-specialists, we would expect NICE to include specific guidance on how to assess treatment, when to assess response to treatment, when to change treatment and when to refer.** | We recognise that assessment and diagnosis are important issues but we will not be able to look at these areas within the development of this guideline |
| Pfizer Ltd. | 7c | 4.3.2 – a) (continued) | 3) Finally, we remind NICE of the agreement noted in the annexes of the PPRS negotiation:<br><br>"The Department and industry agree that the purpose of NICE's short clinical guideline process is to examine a small number of clinical questions on a small part of a clinical pathway, rather than be used as a vehicle to appraise new medical technologies"<br>**In the absence of formal submissions of evidence from the manufacturers we would ask the Guideline development group to ensure that this guideline is developed with full consultation with the manufacturers of the products concerned.** | Thank you for your comment.<br><br>All registered stakeholders including drug manufacturers will have the opportunity to comment on the draft clinical guideline during public consultation.<br><br>In line with the NICE guidelines manual, if the guideline development group or technical team staff have good reason to believe that information exists that has not been identified using standard searches of the published literature, a call for evidence may be made to all registered stakeholders. |
| Pfizer Ltd. | 8 | 4.3.2 – d) | We agree with the decision to exclude peri-operative neuropathic pain. | Thank you for your comment. |
| Pfizer Ltd. | 9 | 4.3.2 – e) | Nociceptive pain is typically managed differently to neuropathic | Thank you for your comment. |

| Stakeholder | Order No | Section No | Comments<br>Please insert each new comment in a new row. | Developer's Response<br>Please respond to each comment |
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| | | | pain; nociceptive pain typically responds to conventional analgesics, such as paracetamol, NSAIDs, cyclo-oxygenase (COX)-2 inhibitors or opioids (Kehlet, 2006), whereas neuropathic pain usually responds poorly to conventional analgesics (Serpell 2004). However, many neuropathic pain patients have mixed nociceptive and neuropathic pain.<br><br>**It is important to note that that the presence of nociceptive pain does not exclude the fact that the patient may also have neuropathic pain. We therefore ask NICE to clarify that this guideline will be applicable to the management of the neuropathic component of patients with mixed pain.**<br><br>Furthermore, we suggest that without adequate guidance on how to diagnose neuropathic pain and differentiate it from nociceptive pain, the neuropathic element of mixed pain patients may not be specifically diagnosed. Patients and clinicians will therefore not benefit from the evidence-based recommendations on the pharmacological treatment of neuropathic pain. | Section 4.3.2 e) states that the treatment of pain other than neuropathic pain will not be looked at in this guideline. The scope does not preclude treating neuropathic pain in patients who may also have other types of pain.<br><br>Diagnosis and assessment are not within the remit of this guideline, which was referred to us by the Department of Health. The remit is specifically the pharmacological management of Neuropathic Pain.<br><br>We recognise that assessment and diagnosis may be important issues but we will not be able to look at these areas within the development of this guideline. |
| BRITISH PAIN SOCIETY | 4 | 4.3.2 a | **Clinical issues that will not be covered**<br><br>Diagnosis – still not included in the scope. It is very important to differentiate from Nociceptive pain, as the results will be poorer if neuropathic treatments are applied to non-neuropathic pain conditions (4.3.2 e). **This point was expressed very strongly at the "Scoping" meeting.**<br><br>The guideline is aimed for the non-specialist, so to have a simple tool within the document (saves time searching for it) | Thank you for your comment. Diagnosis and assessment are not within the remit of this guideline, which was referred to us by the Department of Health. The remit is specifically the pharmacological management of Neuropathic Pain.<br><br>We recognise that assessment |

| Stakeholder | Order No | Section No | Comments<br>Please insert each new comment in a new row. | Developer's Response<br>Please respond to each comment |
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| | | | will significantly improve the use of such aids, the rate of correct diagnosis, and the efficacy of response to treatment.<br><br>There are good validated tools; LANSS, DN4 etc., which have high sensitivity and specificity (around 80-85%).1 These diagnostic tools can be added to the appendix and will not require the Guideline document to be expanded much.<br><br>1. Bennett MI et al. Using screening tools to identify neuropathic pain. Pain 2007; 127: 199–203. | and diagnosis may be important issues but we will not be able to look at these areas within the development of this guideline.<br><br>NICE methods avoid directly extracting tools from other clinical guidelines or journal papers so that we are independently able to assess the evidence to support validated tools. To look at validated diagnostic tools we would need to ask a new review question and analyse this evidence. |

| Stakeholder | Order No | Section No | Comments<br>Please insert each new comment in a new row. | Developer's Response<br>Please respond to each comment |
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| BRITISH PAIN SOCIETY | 5 | 4.3.2 a | **Clinical issues that will not be covered**<br><br>Assessment – should include the holistic aspects of anxiety, depression, sleep, physical & mental function, and Quality of Life. These are mentioned in Main Outcomes 4.4 b) & d), so would it not be best to formally itemize them in the assessment phase as they are required to be measured at this time-point?<br><br>These specific secondary parameters will also determine the sequence of order of some monotherapies, or the most appropriate combination therapies ie:<br><br>- co-existent depression may prioritise use of an anti-depressant<br><br>- co-existent anxiety may prioritise use of a gabapentinoid<br><br>- co-existent sleep disturbance may prioritise use of a night time sedating anti-depressant | Thank you for your comment.<br><br>Assessment of neuropathic pain is not within the remit of this guideline, which was referred to us by the Department of Health. The remit is specifically the pharmacological management of Neuropathic Pain.<br><br>If as part of the guideline development process specific evidence on patients with these co-morbidities is available, the guideline development group may choose to consider making specific recommendations about these patients. |
| PRIMARY CARE NEUROLOGY | 1 | 4.3.2 a | **Clinical issues that will not be covered**<br><br>Diagnosis – still not included in the scope. It is dangerous to | Thank you for your comment. Diagnosis and assessment are not within the remit of this |

| Stakeholder | Order No | Section No | Comments<br>Please insert each new comment in a new row. | Developer's Response<br>Please respond to each comment |
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| SOCIETY | | | assume that all patients arrive at the treatment document with the correct diagnosis; diagnostic criteria must be linked to treatment. Despite treatment guidelines being followed, treatments can still fail if a wrong diagnosis is made. For instance, it is very important to differentiate from Nociceptive pain, as the results will be poorer if neuropathic treatments are applied to non-neuropathic pain conditions (4.3.2 e). This fact is the reason why neuropathic pain treatments are a major target of PCT prescribing leads because the GP's cannot prove correct diagnosis.<br><br>The guideline is aimed for the non-specialist, so to have a simple diagnostic tool within the document (saves time searching for it), to confirm the diagnosis, will significantly improve the use of such aids, the rate of correct diagnosis, and the efficacy of response to treatment.<br><br>There are good validated tools; LANSS, DN4 etc., which have high sensitivity and specificity (around 80-85%).1 These diagnostic tools can be added to the appendix and will not require the Guideline document to be expanded much.<br><br>1. Bennett MI et al. Using screening tools to identify neuropathic pain. Pain 2007; 127: 199–203. | guideline, which was referred to us by the Department of Health. The remit is specifically the pharmacological management of Neuropathic Pain.<br><br>We recognise that diagnosis and assessment may be important issues but we will not be able to look at these areas within the development of this guideline.<br><br>NICE methods avoid directly extracting tools from other clinical guidelines or journal papers so that we are independently able to assess the evidence to support validated tools. To look at validated diagnostic tools we would need to ask a new review question and analyse this evidence. |
| PRIMARY CARE NEUROLOGY SOCIETY | 2 | 4.3.2 a | **Clinical issues that will not be covered**<br><br>Assessment – should include the holistic aspects of anxiety, depression, sleep, physical & mental function, and Quality of Life. These are mentioned in Main Outcomes 4.4 b) & d), so would it not be best to formally itemize them in the assessment phase as they are required to be measured at this time-point? | Thank you for your comment.<br><br>Assessment of neuropathic pain is not within the remit of this guideline, which was referred to us by the Department of Health. The remit is specifically the pharmacological management of |

| Stakeholder | Order No | Section No | Comments<br>Please insert each new comment in a new row. | Developer's Response<br>Please respond to each comment |
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| | | | These specific secondary parameters will also determine the sequence of order of some monotherapies, or the most appropriate combination therapies ie:<br><br>- co-existent depression may prioritise use of an anti-depressant<br><br>- co-existent anxiety may prioritise use of a gabapentinoid<br><br>- co-existent sleep disturbance may prioritise use of a night time sedating anti-depressant | Neuropathic Pain.<br><br>If as part of the guideline development process specific evidence on patients with these co-morbidities is available, the guideline development group may choose to consider making specific recommendations about these patients. |
| Royal College of General Practitioners | 2 | 4.3.2 a | **Clinical issues that will not be covered**<br><br>Diagnosis – still not included in the scope. It is dangerous to assume that all patients arrive at the treatment document with the correct diagnosis; diagnostic criteria must be linked to treatment. This fact is the reason why neuropathic pain treatments are a major target of PCT prescribing leads because the GP's cannot prove correct diagnosis. It is very important to differentiate from Nociceptive pain, as the results will be poorer if neuropathic treatments are applied to non-neuropathic pain conditions (4.3.2 e). This point was expressed very strongly at the "Scoping" meeting. NICE should discuss the brief of this document with the government if they believe that it is not within their remit to develop diagnostic criteria.<br><br>The guideline is aimed for the non-specialist, so to have a simple tool within the document (saves time searching for it) will significantly improve the use of such aids, the rate of correct diagnosis, and the efficacy of response to treatment. | Thank you for your comment.<br><br>Diagnosis and assessment are not within the remit of this guideline, which was referred to us by the Department of Health. The remit is specifically the pharmacological management of Neuropathic Pain.<br><br>We recognise that diagnosis and assessment may be important issues but we will not be able to look at these areas within the development of this guideline.<br><br>NICE methods avoid directly extracting tools from other clinical guidelines or journal papers so that we are independently able to |

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| | | | There are good validated tools; LANSS, DN4 etc., which have high sensitivity and specificity (around 80-85%).1 These diagnostic tools can be added to the appendix and will not require the Guideline document to be expanded much.<br><br>1. Bennett MI et al. Using screening tools to identify neuropathic pain. Pain 2007; 127: 199–203. | assess the evidence to support validated tools. To look at validated diagnostic tools we would need to ask a new review question and analyse this evidence. |
| Royal College of General Practitioners | 3 | 4.3.2 a | **Clinical issues that will not be covered**<br><br>Assessment – should include the holistic aspects of anxiety, depression, sleep, physical & mental function, and Quality of Life. These are mentioned in Main Outcomes 4.4 b) & d), so would it not be best to formally itemize them in the assessment phase as they are required to be measured at this time-point?<br><br>These specific secondary parameters will also determine the sequence of order of some monotherapies, or the most appropriate combination therapies ie:<br><br>- co-existent depression may prioritise use of an anti-depressant<br><br>- co-existent anxiety may prioritise use of a gabapentinoid<br><br>- co-existent sleep disturbance may prioritise use of a night time sedating anti-depressant | Thank you for your comment.<br><br>Assessment of neuropathic pain is not within the remit of this guideline, which was referred to us by the Department of Health. The remit is specifically the pharmacological management of Neuropathic Pain.<br><br>If as part of the guideline development process specific evidence on patients with these co-morbidities is available, the guideline development group may choose to consider making specific recommendations about these patients. |
| MS Trust | 4 | 4.3.2 b) | See comment on section 2 above. Would it be appropriate to revise this guideline to include non-pharmacological treatments which are available in non-specialist settings? | Thank you for your comment.<br><br>Non-pharmacological |

| Stakeholder | Order No | Section No | Comments<br>Please insert each new comment in a new row. | Developer's Response<br>Please respond to each comment |
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| | | | | interventions are not within the remit of this guideline, which was referred to us by the Department of Health. The remit is specifically the pharmacological management of Neuropathic Pain<br><br>We recognise that non-pharmacological treatments for neuropathic pain may be an important issue but we will not be able to look at this area within the development of this guideline. |
| The Walton Centre for Neurology and Neurosurgery | 4 | 4.3.2 e) | Would suggest "treatment of chronic pain other than neuropathic", this will include visceral pain and nociceptive pain. | Thank you for your comment.<br><br>This section has been amended to read 'Treatment of pain other than neuropathic pain'. |
| Association of British Clinical Diabetologists | 2 | 4.3.2.a | The diagnosis and assessment of neuropathic pain is to be excluded. This review examines the use of pharmacological agents used in the treatment of neuropathic pain outside a pain clinic setting. It is the view of ABCD that one of the major problems of treating neuropathic pain in this setting is poor and inconsistent assessment of the pain and its response to the various treatments. Treatments are often judged by simple patient report, doses are not appropriately titrated and treatments discontinued without formal assessment. The review would benefit from some comment on tools for use in assessment of symptoms and how they should be interpreted. | Thank you for your comment.<br><br>Diagnosis and assessment are not within the remit of this guideline, which was referred to us by the Department of Health. The remit is specifically the pharmacological management of Neuropathic Pain.<br><br>We recognise that diagnosis and assessment may be important issues but we will not be able to look at these areas within the |

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| | | | | development of this guideline. |
| BRITISH PAIN SOCIETY | 7 | 4.4 | **Main outcomes**<br><br>Duration of outcome parameters is not specified. Should there be a minimum period of proven pain reduction or improvement in functioning? | Thank you for your comment.<br><br>The appropriate timeframe for pain reduction will be considered by the guideline development group during the development of the guideline. |
| Pfizer Ltd. | 13 | 4.4 | We ask NICE to explain the rationale for adding 'probability of treatment failure' to the list of outcomes and ask for clarity on how they intend to assess this outcome.<br><br>We do not feel that this is a valuable addition as there is no clear consensus on how this outcome should be measured and we are concerned about inappropriate interpretation of this outcome.<br><br>We therefore request that 'probability of treatment failure' is removed. | Thank you for your comment.<br><br>This outcome has been removed from the scope. |
| BRITISH PAIN SOCIETY | 6 | 4.4 a | **Main outcomes**<br><br>It may be appropriate to consider more sophisticated methods of assessment of efficacy, such as responder analysis as being developed by Andrew Moore, in addition proportion of patients achieving 30% or 50% pain relief should be considered. | Thank you for your comment.<br><br>We will consider pain outcomes as reported in the literature that is identified (including the proportion of patients that respond at different levels of pain relief as outlined in 4.4 a)). This may include analyses such as those suggested, where they are reported. However, it is unlikely that the guideline developers will |

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| | | | | be able to perform original analyses of this type, as they are dependent on individual patient data, which are seldom available in the published literature. |
| Grünenthal Ltd | 3 | 4.4 c) | Given the anxieties concerning dependence, cognitive impairment, and tolerance associated with use of strong opioids, these should be quantified as main outcome measures. | Thank you for your comment.<br><br>These outcomes are covered in 4.4 b) and d). |
| United Kingdom Clinical Pharmacy Association (UKCPA) – Pain management group | 6 | 4.4a) | More sophisticated methods of assessment of efficacy, such as responder analysis as being developed by Andrew Moore, should be considered in addition to the proportion of patients achieving 30% or 50% pain relief should be considered. | Thank you for your comment.<br><br>We will consider pain outcomes as reported in the literature that is identified (including the proportion of patients that respond at different levels of pain relief as outlined in 4.4 a)). This may include analyses such as those suggested, where they are reported. However, it is unlikely that the guideline developers will be able to perform original analyses of this type, as they are dependent on individual patient data, which are seldom available in the published literature. |
| Grünenthal Ltd | 4 | 4.5 | In light of the comments above an appropriate review question would be:-<br>'What is the clinical effectiveness and safety of tapentadol (MOR agonist and NRI) compared with opioid analgesics for the management of neuropathic pain in adults, in non- | Thank you for your comment.<br><br>The wording for the review questions (section 4.5 a)) has been changed so it is clearer that |

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| | | | specialist settings' | it is not just different classes of drugs that will be compared, but different individual drugs within and between classes. |
| Grünenthal Ltd | 5 | 4.5 | The guidelines should be based on the best available evidence of effectiveness in the non-specialist setting. In accordance with the NICE Guidelines Manual, the review questions should therefore ask 'What is the clinical **effectiveness** of ….', rather than 'What is the clinical **efficacy** of ….'.<br><br>No RCT evidence was obtained for 15 of the 34 interventions in the current guideline. Furthermore, evidence of long-term effectiveness, tolerance, tolerability and abuse are more likely to be obtained from observational studies than formal RCTs. In addition, observational studies, with broader eligibility criteria, extend the findings and consequentially the generalizability of RCTs. Therefore the guideline development group (GDG) should be able to assess and appraise all the available evidence, irrespective as to whether it has been derived from RCTs or observational studies. With this in mind, it is important that the review protocol, approved by the GDG, should not restrict the search criteria to RCT study designs only. | Thank you for your comment.<br><br>Section 4.5 a) has been amended to state 'effectiveness' rather than 'efficacy'. Study design as part of the review protocols for this guideline will be discussed with the neuropathic pain guideline development group and approved by the guideline development group. |
| Grünenthal Ltd | 6 | 4.5 | Enriched enrolment, randomised withdrawal (EERW) study designs are increasingly being employed in the evaluation of treatments for neuropathic pain following their acceptance as an appropriate methodology by regulatory authorities[2]. Such studies provide valuable evidence of effectiveness in routine clinical practice which should be included in the evidence synthesis for this guideline.<br>EERW study designs overcome the shortcomings of conventional RCT designs including:- the failure to address | Thank you for your comment.<br><br>The study designs which will be considered in the guideline will be decided by the guideline development group during the development of the guideline. |

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| | | | heterogeneity in the origin and mechanism of neuropathic pain and the resultant response to an individual therapy, the need with many of these therapies for flexible dose titration to effect and the ethical issue of protracted exposure to placebo treatment[3].<br>The initial phase of the EERW design mirrors what happens in normal clinical practice. After randomisation the comparison with control (placebo, or other active) then gives a conventional test of efficacy and adverse effect incidence. Summary measures of efficacy from these trials are accurate for the selected population studied, reflecting clinical practice, but may overestimate efficacy in an unselected population.<br>The pre-randomization phase provides useful data on proportions of responders versus non-responders, optimum dose and withdrawals due to adverse events or lack of efficacy. From this information the extent of enrichment and its impact on the generalizability of the data can be calculated. A recent assessment of the effect of enrichment on pregabalin / gabapentin studies concluded that any impact of enrichment was masked by the greater impact of dose response to different doses used in the studies[4].<br><br>[2] Dworkin R,H et al. (2010) Research design considerations for confirmatory chronic pain clinical trials: IMMPACT recommendations. Pain 149: 177–193<br>[3] Binder A et al. (2009) Topical 5% Lidocaine (Lignocaine) Medicated Plaster Treatment for Post-Herpetic Neuralgia: Results of a Double-Blind, Placebo-Controlled, Multinational Efficacy and Safety Trial. Clin Drug Invest 29 (6): 393-408<br>[4] Straube S et al. (2008) Enriched enrolment: definition and effects of enrichment and dose in trials of pregabalin and gabapentin in neuropathic pain. A systematic review. Br J Clin | |

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| | | | Pharmacol 66(2): 266 – 275 | |
| Grünenthal Ltd | 7 | 4.5 | A number of relevant studies of tapentadol and the 5% lidocaine plaster have been completed and are in the process of being published but will not be identified in a current search of the published literature. This includes a study evaluating the effectiveness of a combination of tapentadol and pregabalin and a long term efficacy and safety study of the 5% lidocaine plaster. A call for evidence, focused on completed but as yet unpublished evidence, will ensure the recommendations are informed by evidence that will be published during the development of the guideline.<br><br>In addition a number of studies have been published, ahead of full publication, as conference abstracts at Annual Meetings of the American Pain Society, the American Academy of Pain Medicine (AAPM), the Postgraduate Assembly in Anesthesiology (PGA) and at the Congress of the European Federation of the International Association for the Study of Pain (IASP) Chapters (EFIC) and the World Congress of Anesthesia (NWAC). These include a further placebo controlled study of tapentadol in diabetic peripheral neuropathy, 2 year efficacy and safety data on the use of tapentadol and evidence of the rates of abuse and public health burden relative to opioids. Grünenthal would welcome the opportunity to make this information available via a call for evidence | Thank you for your comment.<br><br>The level of evidence which will be considered in the guideline (ie. if only full-text or including conference abstracts) will be decided by the guideline development group during the development of the guideline.<br><br>We will perform a thorough review of the literature as specified in the review protocol which will be agreed with the guideline development group. The review protocol will include inclusion and exclusion criteria and cut off dates for the evidence review.<br><br>In line with the NICE guidelines manual, if the guideline development group or technical team staff have good reason to believe that information exists that has not been identified using standard searches of the published literature, a call for evidence may be made. |

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| Association of British Neurologists | 5 | 4.6 | The QALY needs to be calculated for each specific Neuropathic pain syndrome and once more not just "lumped together" | Thank you for your comment.<br><br>Where the guideline development group believes it is appropriate and the evidence allows, the possibility of analysing the effectiveness (including health-related quality of life) and cost effectiveness of technologies of interest in discrete subgroups of people with neuropathic pain will be considered. |
| MS Trust | 5 | 5.2 | Should include Multiple sclerosis (update). NICE clinical guideline. Publication expected 2014. | Thank you for your comment.<br><br>This has been amended within the scope. |
| Association of British Clinical Diabetologists | 1 | general | ABCD is in broad agreement with the scope of the review and agrees that the list of pharmacological agents to be included is complete | Thank you for your comment. |
| BRITISH PAIN SOCIETY | 1 | General | Can you clarifying whether specific types of neuropathic pain will categorised as in the previous version (diabetic and "all other" peripheral neuropathic pain)? | Thank you for your comment.<br>The decision on separating or grouping conditions which can cause neuropathic pain will be led by the evidence and decided by the guideline development group in light of this evidence.<br><br>Different recommendations may be made for specific subgroups if supported by the evidence. |
| **MS Society** | 1 | General | **About the MS Society**<br>Established in 1953 and with over 38,000 members and 290 | Thank you for your comment. |

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| | | | branches, the MS Society is the UK's largest charity for people affected by multiple sclerosis (MS) and the largest not-for-profit funder of MS research in the UK. There are approximately 100,000 people with MS in the UK and, with 50 new people diagnosed every week, it is one of the most common neurological conditions affecting adults. We are committed to bringing high quality standards of health and social care within reach of everyone affected by MS. | |
| **MS Society** | 2 | General | The MS Society welcomes the opportunity to offer our comments on the draft consultation scope. On the whole the draft scope includes areas of concern for people with MS however we would like to take the opportunity to make some comments and suggestions. | Thank you for your comment. |
| **MS Society** | 6 | General | **Further information:** For further information please contact Daisy Ellis, Senior Policy and Campaigns Officer, dellis@mssociety.org.uk tel: 02084380998. | Thank you for your comment. |
| Pain UK | 1 | General | Pain, and effectiveness of medication for pain, is very individual. The whole suggestion that attempts to assess "clinical effectiveness" based on averages is of concern. E.g. a person on phenytoin for TN finds it the most effective, although this is only prescribed when patients are allergic to the more commonly used drugs - and despite the face that phenytoin is often thought to be not very effective for TN. (And this patient has tried at least 15 of those mentioned in the document). | Thank you for your comment.<br><br>The recommendations set out in NICE clinical guidelines do not cover all possible situations and do not replace clinical judgement.<br><br>Healthcare professionals are encouraged to use the recommendations together with clinical judgement and offer treatment as appropriate for their patient, based on the patient's individual needs. |

| Stakeholder | Order No | Section No | Comments<br>Please insert each new comment in a new row. | Developer's Response<br>Please respond to each comment |
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| Pain UK | 2 | General | There is no mention of any consideration that will be given to the side effects of drugs. This can be a huge practical issue. Many people in severe pain have to prioritise pain relief: this could mean using the one drug that will bring relief to that individual - even if the side effects of that drug mean that their life is dramatically disrupted, e.g. they may be unable to work. | Thank you for your comment.<br><br>Section 4.4 c) highlights that the guideline will consider minor adverse events. This includes any side effects of the administered drugs. |
| Pain UK | 3 | General | Re the suggested questions, there is a problem with "equality" or "anti-discrimination" provisions. These are never exhaustive and therefore can be discriminatory in themselves and can be patronising. Anyone only needs to be classified as someone in pain, other factors are irrelevant, in my view. | Thank you for your comment. |
| Pain UK | 4 | General | It should be considered that clinical effectiveness should NOT be based on generalised data. The guidelines should NOT exclude treatments which only help a minority. Decisions must NOT be taken on what suits significant proportions of people. Effectiveness must be assessed in relation to each individual and decisions about medications must be taken in relation to individuals. "Evidence based" approaches can be a concern because individuals who respond atypically to drugs will get overlooked. | Thank you for your comment.<br><br>The recommendations set out in NICE clinical guidelines do not cover all possible situations and do not replace clinical judgement.<br><br>Healthcare professionals are encouraged to use the recommendations together with clinical judgement and offer treatment as appropriate for their patient, based on the patient's individual needs. |
| Royal College of Nursing | 1 | General | The Royal College of Nursing welcomes proposals to update this guideline.<br><br>The draft scope seems clear and comprehensive and includes all the drugs that we consider would be helpful in having an up | Thank you for your comment. |

| Stakeholder | Order No | Section No | Comments<br>Please insert each new comment in a new row. | Developer's Response<br>Please respond to each comment |
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| | | | to date guidance. | |
| United Kingdom Clinical Pharmacy Association (UKCPA) – Pain management group | 1 | General | The UKCPA welcomes revision of the current guidance, particularly as the HTA on which the original guidance was based, to our knowledge, remains unpublished. | Thank you for your comment. |
| United Kingdom Clinical Pharmacy Association (UKCPA) – Pain management group | 2 | General | It remains unclear from the scope whether NICE will consider specific types of neuropathic pain as in the previous version, or are considering neuropathic pain in its entirety. Given that the guidance is aimed at non-specialists, we would veer towards providing guidance for neuropathic pain generally if this is supported by the evidence, with mention of specific exceptions found in the literature included as deemed appropriate by the GDG (e.g. carbamazepine reserved for trigeminal neuralgia, pregabalin ineffective in HIV neuropathies). | Thank you for your comment.<br><br>The decision on separating or grouping conditions which can cause neuropathic pain will be led by the evidence and decided by the guideline development group in light of this evidence.<br><br>Different recommendations may be made for specific subgroups if supported by the evidence |
| United Kingdom Clinical Pharmacy Association (UKCPA) – Pain management group | 3 | General | Following on from comment no. 2, a range of conditions where support of pain management specialists may also be worth including (ie. initiate treatment and refer). | Thank you for your comment.<br><br>This will be discussed during the development of the guideline. |

| Stakeholder | Order No | Section No | Comments<br>Please insert each new comment in a new row. | Developer's Response<br>Please respond to each comment |
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| United Kingdom Multiple Sclerosis Specialist Nurses Association (UKMSSNA) | 4 | General | No equality and diversity issues identified | Thank you for your comment. |
| United Kingdom Multiple Sclerosis Specialist Nurses Association (UKMSSNA) | 5 | General | Can the guidelines include drug combinations and escalation of drugs? | Thank you for your comment.<br><br>Section 4.3.1 a) highlights that monotherapy and combination therapy will be considered.<br><br>Dose escalation will be considered in the development of this guideline. |
| Eli Lilly & Company | 2 | General / 4.3.1 a | We would like to take this opportunity to make the GDG aware of important clinical data that will become available during the development of this guideline.<br><br>The COMBO-DN Study (Use of duloxetine or pregabalin in monotherapy versus combination therapy of both drugs in patients with painful diabetic neuropathy) investigated the efficacy of a combination treatment of duloxetine + pregabalin compared with the maximal dose of each drug in monotherapy, in patients with diabetic peripheral neuropathic pain (DPNP) who did not respond to the standard recommended dose of either drug. It will provide an answer to a common clinical question, namely, is it better to increase the dose of the current monotherapy or to combine both treatments early on, in patients who do not respond to | Thank you for your comment.<br><br>The level of evidence which will be considered in the guideline (ie. if only full-text or including conference abstracts) will be decided by the guideline development group during the development of the guideline.<br><br>In line with the NICE guidelines manual, if the guideline development group or technical team staff have good reason to believe that information exists that |

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| | | | standard doses of duloxetine or pregabalin.<br><br>Data will be presented at the International Association for the Study of Pain in August 2012 with an abstract currently available for view (click here for link to conference abstracts. Accept terms for 'Guest Access'. Then, type 'COMBO-DN' in the search bar.) | has not been identified using standard searches of the published literature, a call for evidence may be made. |

**These organisations were approached but did not respond:**

Abbott Laboratories
Abertawe Bro Morgannwg University NHS Trust
Action on Pain
Alder Hey Children's NHS Foundation Trust
Allergan Ltd UK
Arden Cancer Network
Ark Therapeutics Ltd
Arthritis Research UK
Association for Palliative Medicine of Great Britain
Association of Anaesthetists of Great Britain and Ireland
Association of British Insurers
Association of Chartered Physiotherapists in Women's Health
Back Care
Black and Ethnic Minority Diabetes Association
Blackpool, Fylde and Wyre Hospitals NHS Foundation Trust
Boehringer Ingelheim

Bolton Primary Care Trust
Boston Scientific
Brain and Spine Foundation
Brighton and Sussex University Hospital NHS Trust
Bristol-Myers Squibb Pharmaceuticals Ltd
British Acupuncture Council
British Association for Counselling and Psychotherapy
British Association of Art Therapists
British Association of Neuroscience Nurses
British Association of Otorhinolaryngologists, Head and Neck Surgeons
British Association of Prosthetists & Orthotists
British Association of Psychodrama and Sociodrama
British Association of Stroke Physicians
British Medical Association
British Medical Journal
British National Formulary
British Orthopaedic Association
British Paediatric Neurology Association
British Psychological Society
British Society of Rehabilitation Medicine
Brunel University
Cambridge University Hospitals NHS Foundation Trust
Cambridgeshire Primary Care Trust
Camden Link
Capsulation PPS
Care Quality Commission (CQC)
Chartered Society of Physiotherapy

Chronic Pain Policy Coalition
Commission for Social Care Inspection
Countess of Chester Hospital NHS Foundation Trust
Coventry and Warwickshire Cardiac Network
Daiichi Sankyo UK
Department for Communities and Local Government
Department of Health, Social Services and Public Safety - Northern Ireland
Diabetes UK
Dudley Primary Care Trust
East and North Hertfordshire NHS Trust
East Lancashire Hospitals NHS Trust
Faculty of Occupational Medicine
Faculty of Pharmaceutical Medicine
FibroAction
Galil Medical
Golden Jubilee Regional Spinal Cord Injuries Centre
GP Care
Hammersmith and Fulham Primary Care Trust
Harrogate and District NHS Foundation Trust
Health Protection Agency
Health Quality Improvement Partnership
Healthcare Improvement Scotland
Heart of England NHS Foundation Trust
Herpes Viruses Association
Hindu Council UK
Hywel Dda Local Health Board
Independent Healthcare Advisory Services

Inspirability
Institute Metabolic Science
Integrity Care Services Ltd.
Kidney Cancer Support Network
Knowsley Primary Care Trust
Lancashire Care NHS Foundation Trust
Leeds Community Healthcare NHS Trust
Leeds Primary Care Trust (aka NHS Leeds)
Lilly UK
Lincolnshire Teaching Primary Care Trust
Livability Icanho
Liverpool PCT Provider Services
Lundbeck UK
Luton and Dunstable Hospital NHS Trust
MASCIP
Maternity and Health Links
MBB Connections Healthcare
McCallan Group, The
Medicines and Healthcare products Regulatory Agency
Ministry of Defence
Motor Neurone Disease Association
Musculoskeletal Association of Chartered Physiotherapists
Myeloma UK
National Cancer Action Team
National Cancer Research Institute
National Diabetes Nurse Consultant Group
National Hospital for Neurology & Neurosurgery

National Institute for Health Research Health Technology Assessment Programme
National Institute for Health Research
National Patient Safety Agency
National Public Health Service for Wales
National Spinal Injuries Centre
National Treatment Agency for Substance Misuse
Neuromodulation Society of UK & Ireland
NHS Clinical Knowledge Summaries
NHS Connecting for Health
NHS Cornwall and Isles Of Scilly
NHS Direct
NHS Manchester
NHS Plus
NHS Plymouth
NHS Sefton
NHS Sheffield
North Lincolnshire and Goole Hospitals NHS Foundation Trust
Northumbria Diabetes Service
Northumbria Healthcare NHS Foundation Trust
Oxleas NHS Foundation Trust
Pain Concern
Pain Relief Unit
Pain Solutions
Pelvic Pain Support Network
PERIGON Healthcare Ltd
PharMAG
Pharmametrics GmbH

Physiotherapy Pain Association
Pseudomyxoma Survivor
Public Health Wales NHS Trust
Queen Victoria Hospital NHS Foundation Trust
Robert Jones & Agnes Hunt Orthopaedic & District Hospital NHS Trust
Royal Berkshire NHS Foundation Trust
Royal Brompton Hospital & Harefield NHS Trust
Royal College of General Practitioners in Wales
Royal College of Midwives
Royal College of Obstetricians and Gynaecologists
Royal College of Paediatrics and Child Health
Royal College of Paediatrics and Child Health , Gastroenetrology, Hepatology and Nutrition
Royal College of Pathologists
Royal College of Physicians
Royal College of Psychiatrists
Royal College of Radiologists
Royal College of Surgeons of England
Royal Free Hospital NHS Foundation Trust
Royal Hallamshire Hospital
Royal Pharmaceutical Society
Royal Society of Medicine
Salford Primary Care Trust
Salford Royal Foundation Hospital
Sandwell Primary Care Trust
Sanofi
Scottish Intercollegiate Guidelines Network
Sheffield Primary Care Trust

Sheffield Teaching Hospitals NHS Foundation Trust
Shingles Support Society
Social Care Institute for Excellence
Social Exclusion Task Force
Society for Back Pain Research
Society of British Neurological Surgeons
South West Yorkshire Partnership NHS Foundation Trust
Special Products Ltd
Spinal Injuries Association
Spinda Bifida . Hydrocephalus . Information . Networking . Equality
St James Priory Project
St Jude Medical UK Ltd.
Staffordshire University
Stockport Primary Care Trust
Sutton and Merton Community Services
Tenscare Ltd
Teva UK
The Association of the British Pharmaceutical Industry
The For All Healthy Living Centre
The Patients Association
Transverse Myelitis Society
Trigeminal Neuralgia Association UK
Trinity-Chiesi Pharmaceuticals
UCB Pharma Ltd
UK Acquired Brain Injury Forum
United Kingdom National External Quality Assessment Service
University College London Hospital NHS Foundation Trust

University Hospital Birmingham NHS Foundation Trust
Welsh Association of ME & CFS Support -
Welsh Government
Welsh Pain Society
Welsh Scientific Advisory Committee
West Herts Hospitals NHS Trust
Western Cheshire Primary Care Trust
Western Health and Social Care Trust
Westminster Local Involvement Network
Wockhardt UK Ltd
Wound Care Alliance UK
York Hospitals NHS Foundation Trust