National Institute for Health and Clinical Excellence

Opioids in palliative care
Scope Consultation Table
9th May 2011 – 3rd June 2011

Type	Stakeholder	Order No	Section No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
SH	Archimedes Pharma Ltd	3.00	3.1.b	Suggest add Association for Palliative Medicine (APM) Recommendations for breakthrough cancer pain: http://www.breakthroughcancerpain.org/pain-management/apm-recommendations	Thank you. NICE does not cross reference to recommendations from non-NICE guidance in the scope or the final guideline. These recommendations may be assessed as part of the evidence review.
SH	Archimedes Pharma Ltd	3.01	3.1.f	**Re "target audience will be non-specialist healthcare professionals initiating strong opioids for pain...":** Fast-acting fentanyls (FAFs) tend to be initiated by palliative care specialists, pain specialists and oncologists, and are not generally initiated by non-specialists, although education in this area for non-specialists is important as they may write repeat prescriptions and manage side effects, titration, etc. The cited SIGN guideline from 2008 (no. 106) states in section 7.1.2 (top of page 26) that "... some of the newer or less commonly used opioids tend to be initiated in specialist units or following specialist advice". Moreover, SmPCs of the fast-acting fentanyl group of drugs state in section 4.2 (posology) that treatment should be initiated by and remain under the supervision of a physician experienced in the management of opioid therapy in cancer patients.	Thank you for your comment. Although focussed on non-specialists the guideline will also contain recommendations that are relevant to specialists in palliative care**.**

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				This is usually interpreted to mean a specialist. Specialists should therefore not be excluded from this guideline, as it could be argued that they are a group most in need of the guidance as they are the main initiators of these drugs in many cases.	
SH	Archimedes Pharma Ltd	3.02	4.1.2.e	Groups that will not be covered include **"Adults who are unable to take drugs orally":** As this excludes patients who may be able to use the nasal route of administration, and potentially other transmucosal routes as well depending on interpretation of the wording, we believe the statement should be removed.	Thank you for your comment. We have amended the scope to include all routes of administration in the guideline.
SH	Archimedes Pharma Ltd	3.03	4.2	Related to point 2 above, suggest add "hospitals" to statement to read "... including hospitals, hospices, care homes and the community".	Thank you. The current wording will include hospitals.
SH	Archimedes Pharma Ltd	3.04	4.3.1.b	Suggest change statement to read "side effects" instead of "intolerable side effects", as many side effects will not be intolerable, but would still be unpleasant albeit manageable.	Thank you. We have removed the word 'intolerable'.
SH	Archimedes Pharma Ltd	3.05	4.3.2.b	Related to point 3 above, suggest delete point b or add "or by a transmucosal route" to end of sentence.	We have amended the scope to include all routes of administration in the guideline.
SH	Archimedes Pharma Ltd	3.06	4.4	- Part (a): Suggest amend "pain intensity" to "pain", as pain intensity is only one of the efficacy outcomes measured in trials (other measures used include pain intensity difference (PID), summed PID (SPID), pain relief etc.). - Parts (b), (c) and (d): It is unclear what the differences between these outcomes are. Could (b)-	Thank you. We have amended the outcome to pain. We have removed toxicity from the list of main outcomes.

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				(d) be merged? - Patient-centred measures of efficacy are becoming more important and are increasingly being measured in clinical trials, particularly in this therapy area. We would suggest to add an additional outcome of "patient acceptability / satisfaction".	We believe this will be encompassed by HRQOL.
SH	Archimedes Pharma Ltd	3.07	4.5	In the context of end of life care, is QALY the most appropriate measure of cost-effectiveness? For example, we would not expect an opioid to have any effect on patient life expectancy, nor that changing pain intensity levels during episodes of cancer pain would have any effect on life expectancy. If QALY is used, could another measure(s) also be included? Is it worth clarifying the (presumably higher) QALY threshold that would be applied to end of life treatments?	NICE methodology only provides a threshold for cost effectiveness for QALYs. Therefore, we need to adopt this measure in order to determine whether or not particular interventions are cost effective.
SH	Association for Palliative Medicine of Great Britain and Ireland	10.00	4.1.2,4.3.2.b	"unable to take orally" – there are other possible routes of administration, ? why are they excluded	Thank you for your comment. We have amended the scope to include all routes of administration in the guideline.
SH	Association for Palliative Medicine of Great Britain and Ireland	10.01	4.1.2.f, 4.3.2.c	Given the identified groups of patients with non malignant advanced disease, this does not sound coherent.	After considering comments from stakeholders we have amended the scope so that it no longer excludes these patients.
SH	Association for Palliative Medicine of Great Britain and Ireland	10.02	General	No specific statement is made about the use of opioids for indications other than pain	We have amended the title to clarify that the guideline relates to the use of opioids for pain.
SH	British Pain Society	18.00	General	Thank you for asking British Pain Society to give feedback on the draft scope for the proposed guideline ***"Opioids in palliative care: safe and effective prescribing of strong opioids in***	Thank you for your comment. After considering comments from stakeholders we have amended the scope so that it no longer

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				palliative care of adults". We understand that this guidance is intended for 'non-specialist healthcare professionals initiating strong opioids for pain in adults with advanced and progressive disease'. It is meant to 'clarify the clinical pathway'; and that 'adults requiring specialist referral, such as those with kidney failure, liver failure, breathing problems or swallowing problems will not be covered'. In principle, it is reasonable to attempt to restrict the focus of such a guideline to make it workable. However, we believe that for several reasons, this focus is unnecessarily and impractically too narrow and still unclear.	excludes these patients.
SH	British Pain Society	18.01	Title	NICE will be aware that opioids are also used for management of breathlessness in the same patient population as they are used for pain control. Although the title of the guideline does not actually state it, we presume that NICE intends it to cover only the pain indication for opioids. It would be helpful to clarify this in the title.	Thank you. We have amended the title to clarify that the guideline relates to the use of opioids for pain.
SH	British Pain Society	18.02	3	It is hard to see how a new guideline for opioids in pain management would 'clarify the clinical pathway', when there is already so much lack of clarity and misunderstandings about what the clinical pathway currently is; and who it is meant to cover. There are no agreed definitions of what constitutes 'advanced' or 'progressive' disease in cancer, let alone the other non-malignant diseases that the scoping document refers to (organ failures, HIV and neurodegenerative diseases).	The purpose of NICE guidelines is to reduce variation in practice and uncertainty, based on available evidence. It is hoped that the recommendations made by this guideline will reduce this variation and uncertainty by clarifying the clinical pathway.

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				There are currently no parameters defining the scope of what a 'specialist' or 'non-specialist' can or cannot do in this wide range of conditions and stages. The NICE guideline on supportive and palliative care or adults with cancer (2004) did not make this distinction in a way that practically differentiated the roles with respect to clinical interventions. We do not see any reference in this document to how these would be clarified. In the case of cancer, we are aware that non-specialists do see patients with significant pain at earlier stages and we do not see why this guidance should exclude them – especially since it is less likely that such patients would be referred to 'specialists' (presumably palliative care services) at this stage.	The purpose of the remit is to produce a short clinical guideline on safe and effective prescribing of strong opioids in palliatve care of adults, and not to define specialist/non-specialist. It is our intention to produce a guideline that is relevant to non-specialists.
SH	British Pain Society	18.03	4.1.1	*"...who do not have significant kidney failure, liver failure, breathing problems or swallowing problems."* (4.1.1) We find this statement to be confusing and counterproductive for two reasons. It seems paradoxical to define 'advanced and progressive disease' as including several examples of organ failure, and then to immediately exclude patients from the scope if there are 'significant' degrees of failure. Who, then, would be included? In reality much of the difficulty (and dangers) about prescribing opioids comes with just these clinical scenarios of organ failure. As the guideline is, in	After considering comments from stakeholders we have amended the scope so that it no longer excludes these patients.

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				practice, going to be used also by specialists in the field, it would be in our view, better to include general guidance on how to deal with these situations. The guidance would then need to make very clear, the criteria for referral of patients with organ failure to specialist services.	
SH	British Pain Society	18.04	4.1.2.e	*"Adults who are unable to take drugs orally."* (4.1.2.e) We find the exclusion of "Adults who are unable to take drugs orally" to be unnecessarily restrictive and unhelpful, for the following reasons - a. In advancing disease, especially with older people with other reasons for not being able to swallow, eg stroke, the non-oral routes of opioids are especially relevant. b. It is commonplace for non-specialists to prescribe non-oral routes such as transdermal patches and subcutaneous injections and infusions. Indeed, it is often the use of these routes to maintain good pain control as patients approach the end of life that enables GPs to allow patients to remain longer at home and ideally to die at home. Is NICE assuming that all patients actually dying at home would be under the care of specialist teams? Although the scope does later exclude 'Care in the last days of life', it is in the transition to that stage (which is inherently hard to define) that good pain control is essential and we believe that selected non-oral routes play an important role then.	Thank you for your comment. We have amended the scope to include all routes of administration in the guideline. Recommendations made by the guideline development group will be determined by the available evidence.

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				c. Many patients are well controlled on transdermal patches but when pain suddenly increases, even when the patient is not at the end of life, opioid requirement may go up temporarily. It would be essential for non-specialists to know how to handle those situations, eg the importance of not removing the patch if starting a new temporary route; and the dose equivalents between fentanyl and other opioids. d. The scoping document refers to situations where "these problems have led on occasion to patient deaths, and have resulted in doctors facing the General Medical Council or court proceedings." We understand that many of these adverse events actually occur with **inappropriate and uneducated use of non-oral routes** such as transdermal patches and injections. e. We do think that the spinal route for opioids should be excluded as this is purely for specialist use. f. Similarly, the use of the new rapidly acting transmucosal fentanyl products should also be restricted to specialist initiation (although non-specialists should be able to continue them).	
SH	British Pain Society	18.05	4.2	*"All settings in which care commissioned by the NHS is provided, including hospices, care homes and the community."* (4.2) NICE needs to acknowledge that some independent hospices still are not 'commissioned' by local PCTs	Thank you. NICE issues guidance for use by the NHS. It is likely that the charitable sector providing non-NHS

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				but that they should nevertheless be included in the guidance. We take it as given (though not stated) that NHS hospitals are covered, but it is unclear from the statement whether the guidance would extend to private institutions.	commissioned care will take note of our guidance but we have no authority to ensure its implementation in this sector. The current wording will include hospitals.
SH	British Pain Society	18.06	4.3.1.a	*"Key clinical issues that will be covered* *a) First-line treatment with strong opioids in the patient group described in 4.1.1 a, considering:* • *titration schedule* • *formulation* • *breakthrough pain* • *patient information needs".* (4.3.1.a) We believe that the scope is rather restrictive here and we would recommend the following additional areas to be included – a. As already stated, we think that non-oral routes should be covered, which would make the inclusion of 'formulation' more comprehensive. b. As well as titration schedule and breakthrough pain management (both of which need to differ according to the route and formulation), we recommend that 'background pain' should also be covered. c. We hope that carer information needs would be considered alongside patients' needs. d. We believe it is essential that consideration should also be given to adverse effects of opioids, even when used in 'advanced and	We have amended the scope to include all routes of administration in the guideline. Thank you. We consider the areas listed in 4.3.1 (a) are the priorities for investigation. We have amended the scope to include a separate topic on the information needs of patients and carers. Adverse effects are covered in section 4.3.1 (b) and 4.4.

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				progressive disease', eg cognitive, gastrointestinal, endocrine and possible immune effects. (see 6 below) e. How the 'first-line' opioids are chosen is crucially important, and the guidance should cover factors such as future needs, eg the likelihood that certain patients may lose the ability to swallow early on and so the transdermal route may be preferable; or the avoidance of morphine if the patient is likely to develop significant renal impairment. f. There is no mention of 'opioid switching' or 'rotation' – although these are implied as 'first-line' opioids are mentioned, indicating that there must be second- and even third-line choices. In practice this is one of the most difficult aspects of opioid management and especially for non-specialists, guidance on this area, including recommendations on dose equivalence between opioids, should be given. g. We believe the guidance should stress the fact that some of the non-oral routes for opioids are outside of their product license.	Recommendations made by the guideline development group will be determined by the available evidence. Switching will be addressed within section 4.3.1 (b) management strategies of side effects. Recommendations made by the guideline development group will be determined by the available evidence.
SH	British Pain Society	18.07	4.3.1.b	*"Management strategies for intolerable side effects (including patient information needs) in the patient group described in 4.1.1 a."* (4.3.1.b) We believe that the adjective 'intolerable' with reference to side effects introduces an unacceptable degree of subjectivity and is unnecessary. All relevant side-effects should be covered in the	Thank you. We have removed the word 'intolerable'. Recommendations made by the guideline development group will be determined by the

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				guidance, both immediate (eg nausea, constipation, respiratory) and those emerging in the longer term (eg cognitive, endocrine). We also recommend that strategies to prevent, as well as manage, side effects are included, eg starting pre-emptive laxatives, choosing opioids with specific reduced side-effects profile.	available evidence.
SH	British Pain Society	18.08	4.3.2	*"Clinical issues that will not be covered* *a) Assessment before starting strong opioid therapy.* *b) Opioid use in adults who are unable to take drugs orally.* *c) Opioid use in adults with kidney or liver failure, or breathing problems.* *d) Non-opioid pain control.* *e) Care in the last days of life."* (4.3.2) We have already stated that we believe these exclusions to be unduly restrictive and likely to reduce the clinical benefit of the proposed guidance in real practice. We think it is strange to exclude 'assessment before starting strong opioid therapy'. Assessment is surely one of the most important clinical steps before initiating any powerful and potentially dangerous treatment. Guidance needs to be given to non-specialists as to whether strong opioids are needed at all, as well as which opioid to choose for a particular patient. Although it may be expedient to exclude 'non-opioid pain control', some reference should be made to these drugs as they can be as important as opioids and their use can influence the doses of opioids	We have been asked to develop a short clinical guideline and therefore the scope is restrictive in order to make it workable. The remit is to produce a short clinical guideline on safe and effective prescribing of strong opioids in palliative care of adults. Therefore we are unable to cover non-opioid pain control.

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				used. It will be problematic to exclude 'care in the last days of life', because often the transition to 'last days' is clinically unclear, especially to non-specialists; and it is just during this transition that opioid management becomes often difficult. We recommend that opioids for pain control in previous or current IV substance abusers should be identified as an area for specialist management only (and so screening for substance abuse history should be part of the pre-treatment assessment).	We have amended the scope to clarify that this refers to care whilst on the Liverpool Care Pathway or equivalent. This group of patients is not explicitly excluded. However, the evidence will determine whether or not it is possible to make recommendations for this group.
SH	British Pain Society	18.09	4.4	*"Main outcomes* *a) Reduction in pain intensity.* *b) Reduction of opioid side effects.* *c) Adverse events.* *d) Toxicity.* *e) Health related quality of life."* It seems unnecessary to us to differentiate between 'side effects, 'adverse events' and 'toxicity'. These should all be included as 'adverse effects' of opioids and should be categorised according to early or late, common or rare, significant or not. It should be noted that data on 'health-related quality of life' is usually lacking in studies on opioids in this clinical situation. Activities of daily living and interference with these (as measured by Brief Pain Inventory in many studies) should be included.	We have removed toxicity from the list of main outcomes. If this scenario occurs, activities of daily living will be considered as a proxy for HRQOL. We do not feel it is necessary to specify these as an outcome.
SH	British Pain Society	18.10	4.5	We understand that this is a standard NICE	NICE methodology only provides a threshold for cost

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				requirement but are sure that NICE is aware of the problems inherent in attempting to measure quality of life and economic gains in this patient population. Even if 'end of life care' were to be excluded, what are the appropriate metrics for estimating quality and economic benefits in these patients? Will costs of avoiding hospital admission, eg using non-oral routes for patients at home, will included?	effectiveness for QALYs. Therefore, we need to adopt this measure in order to determine whether or not particular interventions are cost effective.
SH	British Pain Society	18.11	5	In addition to the listed existing NICE guidance documents (many of which are actually we find to be of little relevance to the topic), we recommend that NICE should also consult several of the British Pain Society documents that are more relevant, eg on cancer pain; on opioids in non-cancer pain; on drugs used outside of license. NICE should probably also acknowledge frequently used palliative care resources, eg Palliative Care Formulary.	Thank you. This section is for listing NICE guidance, we cannot include non-NICE guidance here.
SH	Cambridge University Hospitals NHS Foundation Trust (Addenbrookes)	8.00	1	Include pain in the title i.e. palliative care of adults i.e. "palliative care of adults with pain".	Thank you. We have amended the title to clarify that the guideline relates to the use of opioids for pain.
SH	Cambridge University Hospitals NHS Foundation Trust (Addenbrookes)	8.01	1.1	Suggest short title should be "opioids for pain in palliative care".	Thank you. We have amended the guideline title and the short title to clarify that the guideline relates to the use of opioids for pain.
SH	Cambridge University Hospitals NHS Foundation Trust (Addenbrookes)	8.02	General	Need to clearly state does not include opioids for breathlessness or other symptoms.	Thank you for your comment. We have amended the title to clarify that the guideline relates to the use of opioids for pain.
SH	Cambridge University Hospitals NHS Foundation Trust (Addenbrookes)	8.03	General	This guidance is likely to be of limited value considering all localities now have symptom control guidance which will be more detailed.	Thank you for this information.
SH	Cambridge University Hospitals NHS Foundation Trust (Addenbrookes)	8.04	4.1.2	Exclusions c and d limit the usefulness of the guidance without information on how to assess the patient	We have been asked to develop a short clinical guideline and therefore the scope is restrictive in order to make it workable.

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SH	Cambridge University Hospitals NHS Foundation Trust (Addenbrookes)	8.05	4.3.1	In 'A' suggested additional bullet point "planning for expected side effects"	Thank you. Side effects are covered under section 4.3.1 (b).
SH	Grunenthal UK Ltd	16.00	4.3.1	For clarity the 'strong opioids' which will be included in the clinical guideline should be named in the final scope.	Thank you. The Guideline Development Group will decide which opioids will be investigated and therefore it is not possible to include this detail in the scope.
SH	Grunenthal UK Ltd	16.01	4.3.1	The choice of 'strong opioid' should take account of the underlying neurophysiological mechanism of pain i.e. nociceptive, neuropathic or mixed pain; the main outcomes of treatment as defined in section 4.4 of the scope; and the anticipated patient compliance / concordance with treatment.	Recommendations made by the guideline development group will be determined by the available evidence.
SH	Grunenthal UK Ltd	16.02	4.3.1	It would be appropriate to include the recently launched tapentadol (Palexia) and tapentadol prolonged release (Palexia SR) in the clinical guideline. Tapentadol is a novel, strong, centrally acting analgesic combining two mechanisms of action, μ-opioid receptor agonism (MOR) and noradrenaline reuptake inhibition (NRI), in a single molecule, providing effective analgesia in nociceptive and neuropathic pain. Palexia is indicated for the relief of moderate to severe acute pain in adults, which can be adequately managed only with opioid analgesics. Palexia SR is indicated for the management of severe chronic pain in adults, which can be adequately managed only with opioid analgesics. Phase III trials have demonstrated that tapentadol provides efficacy in clinical models of acute pain and	Thank you for this information. The Guideline Development Group will decide which opioids will be investigated. Recommendations made by the guideline development group will be determined by the available evidence.

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				tapentadol PR in chronic pain. Tapentadol PR has been shown to have comparable efficacy to oxycodone controlled release (CR). Tapentadol PR demonstrates significant reductions in gastrointestinal side effects (nausea, vomiting and constipation), associated with patients remaining on therapy for longer when compared to oxycodone CR. Tapentadol PR demonstrates significant improvements in patient reported quality of life outcome measures (SF-36 and EQ-5D) compared to oxycodone CR. Tzschentke,T.M. et al. (2007) (-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol hydrochloride (tapentadol HCl): a novel mu-opioid receptor agonist/norepinephrine reuptake inhibitor with broad-spectrum analgesic properties. J. Pharmacol. Exp. Ther., 323, 265-276. Tzschentke,T.M. et al. (2009) Tapentadol hydrochloride: a next-generation, centrally acting analgesic with two mechanisms of action in a single molecule. Drugs Today (Barc)., 45, 483-496. Summary of Product Characteristics: Palexia / Palexia SR. Grunenthal Ltd. February 2011. Accessed at www.emc.medicines.org.uk 03/06/2011 Daniels,S.E. et al. (2009a) A randomized, double-blind, phase III study comparing multiple doses of tapentadol IR, oxycodone IR, and placebo for	

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				postoperative (bunionectomy) pain . Curr. Med. Res. Opin. 25 (3) 765-776 Daniels,S. et al. (2009b) A randomized, double-blind, placebo-controlled phase 3 study of the relative efficacy and tolerability of tapentadol IR and oxycodone IR for acute pain. Curr. Med. Res. Opin., 25 (6) 1551-1561. Afilalo,M. et al. (2010) Efficacy and Safety of Tapentadol Extended Release Compared with Oxycodone Controlled Release for the Management of Moderate to Severe Chronic Pain Related to Osteoarthritis of the Knee: A Randomized, Double-Blind, Placebo- and Active-Controlled Phase III Study. Clin. Drug Investig., 30, 489-505. Buynak,R. et al. (2010) Efficacy and safety of tapentadol extended release for the management of chronic low back pain: results of a prospective, randomized, double-blind, placebo- and active-controlled Phase III study. Expert. Opin. Pharmacother., 11, 1787-804. Schwartz,S. et al. (2011) Safety and efficacy of tapentadol ER in patients with painful diabetic peripheral neuropathy: results of a randomized withdrawal, placebo-controlled trial. Curr. Med. Res. Opin., 27, 151-162. Lange,B. et al. (2010) Efficacy and safety of tapentadol prolonged release for chronic osteoarthritis pain and low back pain. Adv. Ther., 27, 381-399.	

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SH	Grunenthal UK Ltd	16.03	4.3.1	In order to ensure a robust evidence base all RCTs, not just those conducted in palliative care patients, should be included in the systematic review of efficacy and safety. As the guideline excludes care in the last few days of life; patients with significant kidney or liver failure and patients with breathing or swallowing problems it would be appropriate to include studies of a broader group of patients with severe malignant and non-malignant chronic pain.	After considering comments from stakeholders we have amended the scope so that it no longer excludes these patients.
Non SH	Lincolnshire Community Health Services	17.00	3.1.a	Are there any more current statistics regarding deaths from heart failure available from the BHF as the 11,500 quoted is from 2001.	Thank you. We have amended the text.
Non SH	Lincolnshire Community Health Services	17.01	4.1.1.a	It may be appropriate to state heart failure as a disease in itself as it is not always precipitated by heart disease (in the key 1)	Thank you. This is not intended to be an exhaustive list of examples.
SH	Medicines and Healthcare Products Regulatory Agency (MHRA)	13.00	4.1.1 (also: 4.1.2.f 4.3.2.c)	The scope aims to cover patients with advanced and progressive disease; footnote 1 explains that this covers diseases such 'as cancer, heart disease, liver disease, lung disease, kidney disease, HIV and terminal neurodegenerative or neuromuscular conditions'. Somewhat inconsistently, para 4.1.1 goes on to say that the scope only covers those 'who do not have significant kidney failure, liver failure, breathing problems or swallowing problems'. Breathlessness can accompany heart failure, a condition specifically mentioned in section 3.1a of the guideline, but the scope excludes people with breathing problems. Further, dyspnoea is a frequent problem in those receiving palliative care and morphine is often used to alleviate the distressing breathing symptoms. As it stands, the definition of groups that come within the scope of the guideline is ambiguous and, on the	After considering comments from stakeholders we have amended the scope so that it no longer excludes these patients.

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				face of it, excludes a very significant proportion of patients likely to need an opioid.	
SH	Medicines and Healthcare Products Regulatory Agency (MHRA)	13.01	4.1.1 or 4.1.2	It might be useful to specify whether or not the guideline will cover the use of opioids for relieving pain in individuals addicted to opioids	This group of patients is not explicitly excluded. However, the evidence will determine whether or not it is possible to make recommendations for this group.
SH	Medicines and Healthcare Products Regulatory Agency (MHRA)	13.02	4.3.1.a	We believe that the clinical issues to be covered should also include advice on: • How to establish the initial dose (which is then adjusted according to symptoms) • How to switch from one opioid to another or one formulation to another • Anticipating and managing opioid side-effects such as constipation, pruritus, nausea and vomiting,	Switching of opioids and side effects are covered in section 4.3.1 (b). Recommendations made by the guideline development group will be determined by the available evidence.
SH	Medicines and Healthcare Products Regulatory Agency (MHRA)	13.03	4.3.2.d	We recognise that this guideline aims to cover the use of opioids only. However, we expect that the guideline will mention that an opioid might not be the first-choice analgesic for some types of pain (eg bone metastases, nerve compression and neuropathy). The use of specific analgesics for such pain may allow the dose of the opioid to be reduced while maintaining effective pain control.	This guideline is for the management of opioids and will already assume patients have been assessed as suitable for opioid treatment (WHO pain ladder step 3). Recommendations made by the guideline development group will be determined by the available evidence.
SH	Medicines and Healthcare Products Regulatory Agency (MHRA)	13.04	4.4.b, c and d	Outcome measures in 4.4b, c, and d cover the same grounds. We wonder if important outcomes might more simply be covered as:	This section lists outcomes that are likely to be reported by clinical trials.

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				• Adequate pain control • Minimisation of adverse effects of opioids • Health-related quality of life (taking in aspects such as mood, level of consciousness, freedom from distressing effects such as dysponea)	
SH	Napp Pharmaceuticals	12.00	General	Napp Pharmaceuticals is committed to improving the safety of patients taking strong opioids for pain and we fully support the development of this important short guideline driving towards safe and appropriate prescribing of strong opioids without compromising efficacy.	Thank you.
SH	Napp Pharmaceuticals	12.01	1	The guidelines appear to be largely aimed at primary care or non-specialist prescribers and focussed on initiation and titration. Patients requiring specialist advice will fall out of scope. We would recommend that the title be modified to reflect the intended non-specialist focus.	We do not think this is necessary. Although focussed on non-specialists the guideline will also be relevant to specialists in palliative care.
SH	Napp Pharmaceuticals	12.02	General	Consider defining 'strong opioid' – WHO step III? Note that high doses of weak opioids provide equianalgesia with low dose strong opioids and have similar safety profiles.	Thank you for your comment. We have amended the background to reflect this.
SH	Napp Pharmaceuticals	12.03	3.1.f, 4.1.1	The guidelines exclude adults with kidney failure, breathing problems etc but will cover patients with kidney disease and lung disease. Will some guidance be given to when kidney dysfunction is classed as disease rather than failure? A similar comment applies to the distinction between patients with breathing problems (which are excluded from the scope) and patients with lung disease (which are included in the scope). As safety is paramount, further guidance is needed to distinguish which patients can be treated by non-specialists and those	Thank you for your comment. After considering comments from stakeholders we have amended the scope so that it no longer excludes these patients.

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				which require specialist referral.	
SH	Napp Pharmaceuticals	12.04	3.1.b	The current practice section discusses how all opioids are significantly different in terms of bioavailability, metabolism and response between patients and that each patient therefore requires an individualised selection of opioid and dose. We fully support this statement and feel that this should be highlighted again in the clinical management section. This individualised approach to pain relief (reached as a informed discussion or contract between HCP and patient) should be reflected in section 4.3.1a	Thank you for your comment. We disagree. We feel that these issues are adequately encompassed within 4.3.1 (a). This document is the scope and does not make recommendations for how care should be provided. We do not know what recommendations will be made until the evidence has been reviewed.
SH	Napp Pharmaceuticals	12.05	4.3.1	We would strongly recommend an additional subsection capturing the need for the cycle of re-assessment / follow up / monitoring of these patients new to strong opioids. It is important to identify and reduce/stop treatment in those patients who do not have opioid–responsive pain. It is also important to prevent unnecessary suffering if pain is opioid responsive but patients are failing to tolerate the first choice opioid – early switching of opioid could be considered. A dose maximum (and other relevant limitations) could be given for non-specialists to facilitate a prompt referral for the more difficult-to-treat patients, prevent patients having a delayed path to specialist services whilst being on inappropriately high doses of opioid.	Consideration will be given to re-assessment when deciding which opioid to prescribe and choosing an opioid when switching (covered under section 4.3.1 (b). We have made it explicit that switching of opioids will be covered under management strategies for side effects in section 4.3.1 (b) of the scope.
SH	Napp Pharmaceuticals	12.06	4.3.1.b	This section will discuss management strategies for intolerable side effects. We would hope to see the concept of prophylactic management of predictable side effects to improve the patient experience when taking opioids for pain. This may also reduce the likelihood of patients experiencing intolerable side effects requiring switching away from the first line opioid.	Recommendations made by the guideline development group will be determined by the available evidence.

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SH	Napp Pharmaceuticals	12.07	4.5	We note that the economic analysis does not take into account the wider impact on carers. Effective pain control can lead, in some cases, to a previously heavily-dependent patient becoming independent again, with a consequent significant reduction in carer burden.	This is standard text for the scope. It has been created by NICE and we are not able to amend it.
SH	National Council for Palliative Care	11.00	General	The use of opioids in the palliative care setting is an area that causes concern for many clinicians and as such NCPC welcomes the opportunity to contribute to the development of guidelines which will potentially redress some misunderstandings surrounding the use of opioids. NCPC consulted with clinicians on our various expert groups and the response has consistently been that the scope as it stands is far too restrictive. The resulting guidelines will not cover adults who are unable to take drugs orally and those with „significant" kidney failure, liver failure or breathing problems. This was of concern as these groups represent a large proportion of people at the end of life for whom opioids would be appropriate. The scope states that the guidelines will be aimed at generalists, an ambition we very much welcome. Our aim should be to ensure safe, effective palliative care available everywhere it is needed. However, the scope as it stands will provide limited guidance for generalists and narrow the range of clinical problems that can be managed without specialist support.	Thank you for your comment. After considering comments from stakeholders we have amended the scope so that it no longer excludes these patients. It is our intention to produce a guideline that is relevant to non-specialists.
SH	National Council for Palliative Care	11.01	1	**Title** The suggested short title of „Opioids in palliative	Thank you. We have amended the title to clarify that the guideline relates to the use of opioids for pain.

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				care‟ does not reflect the scope which states that the guidance will in fact be limited to strong, oral opioids. The scope is currently limited to opioid analgesia in palliative care and unless the scope is broadened the words „pain‟ or „analgesia‟ should be included in the title.	
SH	National Council for Palliative Care	11.02	3.1.e	**Current practice** Stating that doctors have faced GMC or court proceedings might further alarm a generalist who already has reservations about prescribing opioids.	We disagree. This background text is merely intended to emphasise the need for the guideline.
SH	National Council for Palliative Care	11.03	3.1.f	**Current practice** If the resulting guidelines are intended for non-specialist healthcare professionals care should be taken to ensure the language used is accessible	Thank you.
SH	National Council for Palliative Care	11.04	4.1.1.a	**Groups that will be covered** It is not clear what is meant by 'significant' breathing or swallowing problems‟ Significant‟ needs to be defined in relation to each of the excluding problems.	After considering comments from stakeholders we have amended the scope so that it no longer excludes these patients.
SH	National Council for Palliative Care	11.05	4.1.2.a	**Groups not covered** Physiologically the distinction of who is an adult is hard to define. 18 years is very arbitrary. However, if there are to be parallel guidelines for children and adolescents, this is more acceptable. If not there will be a temptation to extrapolate for post-pubertal teenagers with cancer pain. There are societal and consent issues; however, whilst the physical issues of introducing and titrating opioids in post-pubertal people are similar to adults, the psychological aspects differ. This should be clarified in the document.	The remit from the Department of Health is to produce a short clinical guideline on safe and effective prescribing of strong opioids in palliative care of adults. The agreed definition NICE uses for adults is 18 years and over.

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SH	National Council for Palliative Care	11.06	4.1.2.c	**Groups not covered** Assessing whether an individual is suitable for strong opioids would seem integral to these guidelines. At the very least, a short paragraph and links to relevant more detailed documents would be needed.	We have been asked to develop a short clinical guideline and therefore the scope is restrictive in order to make it workable.
SH	National Council for Palliative Care	11.07	4.1.2.d	**Groups not covered** Focus on strong opioids is unnecessarily limiting. This means missing out a discussion on the use of weak opioids, at the second step of the WHO ladder. As this is the usual step for non-specialists before introducing strong opioids, it is important that this is recognised and specified in this document, unless there is to be a parallel document looking at this.	The remit from the Department of Health is to produce a short clinical guideline on safe and effective prescribing of strong opioids in palliatve care of adults.
SH	National Council for Palliative Care	11.08	4.1.2.e	**Groups not covered** Adults who are unable to take drugs orally **should** be included. Opioid prescribing in the palliative care setting frequently requires a combination of different preparations and different routes - patients may be taking their opioids orally or using transdermal and transmucosal routes, or a combination of the above. The choice of transdermal fentanyl or buprenorphine is generally made because of their side effect profiles – i.e. they tend to be less constipating and have less cerebral side effects than the equivalent doses of other oral opioids. There are price differences – they tend to be more expensive than codeine/dihydrocodeine/morphine – although there is some saving to be made in laxative treatment. This is an area where guidelines would be helpful.	Thank you for your comment. We have amended the scope to include all routes of administration in the guideline. Recommendations made by the guideline development group will be determined by the available evidence. .

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				Transmucosal and transnasal fentanyl products are now available, being marketed for their rapidity of effect and side effect profile rather than use in those unable to take oral medications. Guidance on the cost benefit ratio for these expensive drugs would be welcome, particularly for the palliative care world). Guidelines on the oxycodone/naloxone drug "Targinact" would be welcomed to clarify its cost benefit ratio The rate of change in people with advanced cancer and other life limiting diseases is such that the majority reach a stage at which they are unable to take oral medication and many will need to take opioids via a parenteral route in the end of life setting. It is common for specialist palliative care teams to request that GPs prescribe subcutaneous opioids and to prescribe in anticipation of need in the dying phase. Clear guidelines of when this is clinically appropriate would be helpful for GPs. A parallel document on this topic would seem unnecessarily complex – one document would be preferable and non-specialists should be empowered to use simple subcutaneous opioid regimes It is also felt that including strong non-oral opioids would be an opportunity for NICE to give a national steer on the Morphine vs Diamorphine debate.	
SH	National Council for Palliative Care	11.09	4.1.2.f	**Groups not covered** Adults with kidney failure, liver failure or breathing problems **should** be included in the guidelines. Adults with metabolic failure and/or respiratory problems make up a substantial proportion of patients with advanced disease and non-specialist health care professionals will need to prescribe	After considering comments from stakeholders we have amended the scope so that it no longer excludes these patients.

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				safely and effectively for these patients with appropriate recourse to specialist services. As previously mentioned it is also not clear what is meant by 'significant' kidney failure, liver failure or breathing problems. The term "breathing problems" in particular is very broad, but would likely cover nearly all patients with end stage COPD and chronic heart failure, as well as many of those with cancer, MND or any of the other conditions likely to be eligible for palliative care. The reason for excluding this group is not clear as specific guidelines are needed for respiratory failure. The guidelines need to highlight the need to assess renal function when prescribing as renal failure quite often occurs late in the life of cancer patients, either linked to intra-abdominal tumour or to co-morbidities and requires specific advice on prescribing.	Recommendations made by the guideline development group will be determined by the available evidence.
SH	National Council for Palliative Care	11.10	4.2.a	**Healthcare setting** "Community" should explicitly include extra care housing, sheltered housing and people"s own homes	Thank you. We feel the current wording is appropriate.
SH	National Council for Palliative Care	11.11	4.2.a	**Healthcare setting** The guidelines are intended to be aimed at non-specialists but hospices, who are specialists, are included here.	Although focussed on non-specialists the guideline will also contain recommendations that are relevant to specialists in palliative care.
SH	National Patient Safety Agency	1.00	3.1.d	The guideline should include adherence to the following national mandatory guidance designed to reduce the incidence of medication errors involving dose titration of opiod medicines: Rapid Response Report: Reducing Dosing Errors with Opioid Medicines: NPSA/2008/RRR005	Thank you. NICE does not cross reference to recommendations from non-NICE guidance in the scope or the final guideline. These recommendations may be assessed as part of the evidence review.

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				(Including supporting information) http://www.nrls.npsa.nhs.uk/resources/patient-safety-topics/medication-safety/?entryid45=59888&p=2 Please note that the process for developing Rapid Response Reports has now been accredited by NHS Evidence.	
SH	National Patient Safety Agency	1.01	3.1.e	While fully supporting the need for effective pain control in palliative care, this needs to be provided safely. Patient safety incidents arising from medication errors involving opioid medicines is one of the most frequently reported categories leading to fatal and severe harm outcomes in the National Reporting and Learning System (NRLS). Safety in Dosing Reports 2005-2006 and 2007 http://www.nrls.npsa.nhs.uk/resources/patient-safety-topics/medication-safety/?entryid45=61625	Thank you for this information. We agree.
SH	National Patient Safety Agency	1.02	4.1.1	We would question why the proposal excludes patients with breathing problems, given the proposal is clear that it should include palliative care in cardiac and respiratory disease.	After considering comments from stakeholders we have amended the scope so that it no longer excludes these patients.
SH	National Patient Safety Agency	1.03	4.1.1	We would question why the proposal excludes patients with renal or liver problems, as not many palliative care patients with cancer don't have liver secondaries or generally poor renal and liver function.	After considering comments from stakeholders we have amended the scope so that it no longer excludes these patients.
SH	National Patient Safety Agency	1.04	4.1.2	What is the rationale for excluding patients who are unable to take opioid medicines orally? Many	Thank you for your comment. We have amended the scope to include all routes of administration in the

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				patients move from being able to take their medicines orally to requiring their medicines to be administered by a parenteral route, as their underlying condition gets worse. Clinical management plans incorporate the use of opiod medicine by other routes. Other routes are used in all healthcare settings and are not only restricted to secondary care. Many of the patient safety incidents occur when medicines are changed from the oral route to the parenteral route. It is essential that the NICE guideline includes the use of opioid medicines by all routes of administration. If it is accepted that parenteral opioids be included within the scope of the proposed guidance then the following two pieces of national mandatory guidance, designed to ensure that medication errors involving opioid medicines are reduced, should also be referenced and refered to: Patient Safety Alert 20: promoting safer use of Injectable Medicines: http://www.nrls.npsa.nhs.uk/resources/patient-safety-topics/medication-safety/?entryid45=59812&p=2 Safer Practice Notice 12: Ensuring safer practice with high dose ampoules of diamorphine and morphine: http://www.nrls.npsa.nhs.uk/resources/patient-safety-topics/medication-safety/?entryid45=59803&p=3	guideline. NICE does not cross reference to recommendations from non-NICE guidance in the scope or the final guideline. These recommendations may be assessed as part of the evidence review.
SH	National Patient Safety	1.05	4..3.1	One of the key issues that need to be addressed is	Switching of opioids will be covered under

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	Agency			transfer from oral therapy to parenteral therapy i.e. subcutaneous infusion, or transdermal patch or rectal therapy.	management strategies for side effects in section 4.3.1 (b) of the scope.
SH	National Patient Safety Agency	1.06	4.3.2	We would question why the proposal is to exclude care in the last few days of life as this may well be when patients are most in need of effective analgesia in the form of strong opioids.	The scope does not cover last days of life as the issues for these patients are different.
SH	Palliative Care Pharmacists Network	15.00	1.1	Short title might be misleading as opioids are used in symptom control for other than pain control but this guideline relates to their use in pain	Thank you. We have amended the guideline title and the short title to clarify that the guideline relates to the use of opioids for pain.
SH	Palliative Care Pharmacists Network	15.01	2	Comments as above. Does the remit need to be expanded on prescribing. Is it for initiating strong opioids or initiating titrating and ongoing review?	Thank you. The guideline starts from the point that a decision has been made that a person requires strong opioids for pain control. The remit is produced by the Department of Health and we cannot change it.
SH	Palliative Care Pharmacists Network	15.02	3.d & e	It is good that the guideline will seek to out line the choice of opioid and dosing titration (seecomment 2). Would it be useful to include guidance on doses not to be used as described in the Shipman report?	Thank you. Recommendations on doses not to be used will be dependant upon the review of evidence. It is not possible to determine whether such recommendations will be made at this stage.
SH	Palliative Care Pharmacists Network	15.03	3.f	It is a missed opportunity if patient with certain conditions will not be covered, as health care professionals or patients may be reluctant to accept specialist support. There would not be enough palliative care specialists to support these patients. Initiation of strong opioids should be carried out by generalists or specialists within their own field – it already is & further guidance would be of benefit to them. There would need to be decisions made on degrees of renal failure-(probably easier) , liver failure and breathing problems with signposting to specialist services. By excluding swallowing problems a large number of patients will be excluded-cancer/stroke/dementia etc. There are licensed products which could be initiated for these	Thank you for your comment. After considering comments from stakeholders we have amended the scope so that it no longer excludes these patients**.**

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				patients. To reconsider?	
SH	Palliative Care Pharmacists Network	15.04	4.1.1.a & f	Consider dropping the age to 16? Many adult services look after 16 year olds or signposting will be needed. Commnets as above re swallowing. The guidance now talks about significant kidney failure etc-definitions needed as above	The remit from the Department of Health is to produce a short clinical guideline on safe and effective prescribing of strong opioids in palliative care of adults. The agreed definition NICE uses for adults is 18 years and over. After considering comments from stakeholders we have amended the scope so that it no longer excludes these patients..
SH	Palliative Care Pharmacists Network	15.05	4.1.2.e	Inability to take oral meds-missed opportunity? As above comment4 –licensed products are available which avoid the oral route. They are expensive & can be difficult to titrate & use safely. Guidance would be helpful for non specialists. Again there are not enough palliative care specialist to manage all these patients & NICE would be able support generalists initiate titrate & maintain these patients. Management of patches can be poor & result in both under & over treatment. Non specialists do not always realise the potency of the products available.	Thank you for your comment. We have amended the scope to include all routes of administration in the guideline.
SH	Palliative Care Pharmacists Network	15.06	4.2.a	Can the guidance be extended to private healthcare as many patients who fit the other inclusion criteria are looked after in private healthcare where palliative care provision is scant.	Thank you. NICE guidance is produced for NHS services.
SH	Palliative Care Pharmacists Network	15.07	4.3.1.a	Which defenition of breakthrough pain will be used?-the newer one? If so please be cautious in recommending the newer fentanyl products for use by non specialists. Hopefully this will fall outside the remit set. To include signposting to specialist provision when first line treatment not effective? Rather than including conversion factors?	Recommendations made by the guideline development group will be determined by the available evidence.

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SH	Palliative Care Pharmacists Network	15.08	4.3.2.a	Would be difficult to initiate strong opioids safely without this happening. Also for monitoring ongoing therapy for effect.	We have been asked to develop a short clinical guideline and therefore the scope is restrictive in order to make it workable.
SH	Palliative Care Pharmacists Network	15.09	4.3.2.b	Pity-excludes many patients	We have amended the scope to include all routes of administration in the guideline.
SH	Palliative Care Pharmacists Network	15.10	4.3.2.c	As above point 10 & will need to define	After considering comments from stakeholders we have amended the scope so that it no longer excludes these patients.
SH	Palliative Care Pharmacists Network	15.11	4.3.2.d	the document should include signposting as use of non opioids can reduce the need for opioids	This guideline is for the management of opioids and will already assume patients have been assessed as suitable for opioid treatment (WHO pain ladder step 3). Recommendations made by the guideline development group will be determined by the available evidence.
SH	Palliative Care Pharmacists Network	15.12	4.4.a	If measuring tools to be included please include tool suitable for dementia type illnesses	We are not intending to specify measuring tools in the scope.
SH	Palliative Care Pharmacists Network	15.13	4.4.b &c&d & e	How will this be measured? For point e would have to include the use of adjuvants to be meaningful in palliative care?	We are not intending to specify how these outcomes will be measured in the scope. This will be discussed by the Guideline Development Group.
SH	Palliative Care Pharmacists Network	15.14	5	Also include Cochrane, SIGN, NPSA etc as would be more useful. Exclude drug misuse references-no place in palliative care use of opioids?	Thank you. This section is for listing NICE guidance, we cannot include non-NICE guidance here.
SH	Pancreatic Cancer UK	4.00	General	Pancreatic Cancer UK is unclear whether the guideline will include the use of non-oral opiods in palliative care. It is clear that the guideline does not cover the use of opiods in patients who cannot take opiods orally. However, opiods are available in a range of preparations including liquid injections, suppositories and patches. We seek clarification about whether these different formats will be included in the guideline as we believe it is important	Thank you for your comment. We agree this is confusing and have amended the scope to include routes of administration in the guideline.

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				to include them.	
SH	Pancreatic Cancer UK	4.01	4.3.1.a	Pancreatic Cancer UK believes the guidelines should consider the information needs of carers as well as patients. Family members can be very involved in the care of patients within the palliative care setting and many will want access to clear information about the opiods being used and the effects they may have on the patient.	Thank you. We have amended the scope to include a separate topic on the information needs of patients and carers.
SH	Royal College of General Practitioners	7.00	General	It would be useful if this document could also describe management of opioid side effects	The guideline will cover management strategies for side effects as stated in section 4.3.1 of the scope.
SH	Royal College of General Practitioners	7.01	General	Information regarding swapping between opioids would be advantageous	We have made it explicit that switching of opioids will be covered under management strategies for side effects in section 4.3.1 (b) of the scope.
SH	Royal College of Nursing	14.00	General	The Royal College of Nursing welcomes proposal to develop this guideline. It is timely and comprehensive.	Thank you.
SH	Royal College of Nursing	14.01	3.1.d	The European Association for Palliative Medicine are also about to release guidance on use of opioids/titration	Thank you for this information.
SH	Royal College of Nursing	14.02	3.1.e	There is a need to involve the major pharmaceutical companies regarding the information on the boxes/bottles of the opioids. What is said on the box/bottle is not always what is prescribed which leads to prescribing and administration errors. Focus on what is a legal prescription as opposed to best practice	NICE is not able to dictate practice for pharmaceutical companies.
SH	Royal College of Nursing	14.03	4.1.2.e	The document states it will not include patients who are unable to take drugs orally. This is an important area that should be considered in the document as conversions from one preparation to the other and	Thank you for your comment. We have amended the scope to include all routes of administration in the guideline.

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				changing routes are where many of the prescribing problems occur.	
SH	Royal College of Nursing	14.04	4.1.2.f	The document might want to consider stating that it will not include patients who require opioids who are addicted to strong opioids and who are on rehabilitation programmes.	This group of patients is not explicitly excluded. However, the evidence will determine whether or not it is possible to make recommendations for this group.
SH	Royal College of Nursing	14.05	4.3.1.a	Patient information needs should include information relating to advice on driving	Recommendations made by the guideline development group will be determined by the available evidence.
SH	Royal College of Nursing	14.06	4.3.2.a	Assessment before starting strong opioid therapy: Non-specialist professionals need this guidance or else there is still a great likelihood that opioid prescribing will not be well organised. We would have thought that this was the key area to assist non-specialists in this area. Without guidance on assessment, this guideline may be meaningless as there is a great chance that patients will not be seen as appropriate for the guideline.	We have been asked to develop a short clinical guideline and therefore the scope is restrictive in order to make it workable.
SH	Royal College of Nursing	14.07	4.3.2.c	Non specialists need guidance on this, as not all patients will be referred through to specialist palliative care. If this area is not covered in the scope this may lead to patients being prescribed inappropriate analgesia which may lead to poor symptom management or toxicity without pain relief.	After considering comments from stakeholders we have amended the scope so that it no longer excludes these patients.
SH	Royal College of Nursing	14.08	4.6.2	It is essential that nursing is represented on guideline development group. We have circulated the information for guideline development group recruitment to the relevant networks in the RCN encouraging nurses with interest and expertise to apply.	Thank you. The Guideline Development Group will consist of various health professionals including nurses.
SH	Royal College of Nursing	14.09	General	Overall it is reassuring to see such guidance being produced as it is very much needed.	Thank you.

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				It is important that the substance of the guideline remains within identified parameters.	
SH	Royal College of Paediatrics and Child Health	2.00	General	As the remit and draft scope state that the guideline will cover adults only, the Royal College of Paediatrics and Child Health will not be participating in this consultation	Thank you.
SH	St. Oswald's Hospice	19.00	4.1.2 .c	An individual's sensitivity and tolerance to strong opioids is determined by the pattern of opioid receptor dimmers. There is currently no simple test, sign or symptom that can assess this pattern in an individual and relate the pattern to a specific opioid. This exclusion has no clinical basis and should be removed.	We have been asked to develop a short clinical guideline and therefore the scope is restrictive in order to make it workable.
SH	St. Oswald's Hospice	19.01	4.1.2.e	Non-oral routes are common in palliative care and many errors concern oral to parenteral conversions. It is essential that non-oral routes of strong opioids are considered, otherwise this exclusion means the guideline will fail to meet the needs of a large patient population. This exclusion must be removed.	Thank you for your comment. We have amended the scope to include all routes of administration in the guideline.
SH	St. Oswald's Hospice	19.02	4.1.2.f	Patients with renal, hepatic or respiratory impairment are common in palliative care and opioids can be used with clear guidelines. this exclusion will fail to meet the needs of a large patient population. This exclusion means the guideline will fail to meet the needs of a large patient population. This exclusion must be removed.	After considering comments from stakeholders we have amended the scope so that it no longer excludes these patients.
SH	St. Oswald's Hospice	19.03	4.3.2.a, b & c	See comments above Patients with renal, hepatic or respiratory impairment	After considering comments from stakeholders we have amended the scope so that it no longer excludes these patients.

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				are common in palliative care and opioids can be used with clear guidelines. this exclusion will fail to meet the needs of a large patient population. This exclusion means the guideline will fail to meet the needs of a large patient population. This exclusion must be removed.	
SH	St. Oswald's Hospice	19.04	4.3.2.e	The use of strong opioids at the end of life is a key component of care and causes both anxiety and errors. NICE would be strongly criticised for this exclusion when improving end of life care is such a prominent key target at present.	The scope does not cover last days of life as the pain control issues for these patients are different and complex. This is a short guideline and we have to restrict the scope to reflect the amount of time and resource available to develop it. We have amended the scope to clarify that this refers to care whilst on the Liverpool Care Pathway or equivalent.
SH	United Kingdom Clinical Pharmacy Association (UKCPA) / Royal Pharmaceutical Society of Great Britain	9.00	General	The UK Clinical Pharmacy Association welcomes the development of a guideline on opioids in palliative care, as they are widely used therapies, where prescribing errors are commonplace. Myths (and 'opio-phobia') regarding their use exist among prescribers and patients. With this in mind, reference should be made to the fact that opioids are used as analgesics in situations other than end-of-life such as acute and persistent pain.	Thank you for your comment,. Our remit is to produce guidance for adults with advanced and progressive disease who require strong opioids for pain control as stated in 4.1.1. This is the focus of the scope.
SH	United Kingdom Clinical Pharmacy Association (UKCPA) / Royal Pharmaceutical Society of Great Britain	9.01	1	As opioids are also used for palliation of breathlessness, pain should be included in the title, e.g. "Opioids in palliative care: safe and effective prescribing of strong opioids for pain in palliative care of adults"	Thank you. We have amended the title to clarify that the guideline relates to the use of opioids for pain.
SH	United Kingdom Clinical Pharmacy Association (UKCPA) /	9.02	3.1.d	Reference should be made towards the list of safe prescribing recommendations made by the NPSA in their rapid response report	Thank you. NICE does not cross reference to recommendations from non-NICE guidance in the scope or the final guideline. These

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	Royal Pharmaceutical Society of Great Britain			(http://www.nrls.npsa.nhs.uk/resources/?entryid45=59888) and specific mention should be made of the relative potency of transdermal formulations, as non-pain specialists are often unaware of this	recommendations may be assessed as part of the evidence review.
SH	United Kingdom Clinical Pharmacy Association (UKCPA) / Royal Pharmaceutical Society of Great Britain	9.03	3.1.d	Undeniably, there has been a marked increase in opioid prescribing in the primary care setting, but the majority of this probably relates to use for indications other than cancer pain and palliative care (e.g. musculoskeletal pain and neuropathic pain)	Thank you we agree.
SH	United Kingdom Clinical Pharmacy Association (UKCPA) / Royal Pharmaceutical Society of Great Britain	9.04	3.1.e	Quantity of opioid prescribed may contribute to both under and over treatment of pain. Guidance on appropriate quantities to prescribe would minimise the number of GMC or court proceedings	Thank you, we agree.
SH	United Kingdom Clinical Pharmacy Association (UKCPA) / Royal Pharmaceutical Society of Great Britain	9.05	3.1.f, 4.1.1, 4.1.2.f	Patients with kidney failure, breathing problems and swallowing problems form a significant proportion of the adults with advanced and progressive disease and guidance should be extended to cover these groups. This may be particularly important in renal impairment where the first-line opioids are not widely known, and prescribing errors are commonplace	Thank you for your comment. After considering comments from stakeholders we have amended the scope so that it no longer excludes these patients.
SH	United Kingdom Clinical Pharmacy Association (UKCPA) / Royal Pharmaceutical Society of Great Britain	9.06	4.1.1 & 4.1.2.e	The implication is that only oral opioids are to be considered. Other routes of opioid may be appropriate and necessary for patients with advanced or progressive disease. This will exclude a significant number of patients and reduce the applicability of the guideline	Thank you for your comment. We have amended the scope to include all routes of administration in the guideline.
SH	United Kingdom Clinical Pharmacy Association (UKCPA) / Royal Pharmaceutical Society of Great Britain	9.07	4.1.1 & 4.3.2.a	Some types of pain do not respond to opioid therapy. Only patients for whom opioids have been assessed as suitable are to be included but assessment prior to starting opioid therapy is excluded. To ensure safe and effective prescribing, assessment whilst prescribing opioid therapy should be considered during the guideline development	We have been asked to develop a short clinical guideline and therefore the scope is restrictive in order to make it workable. The guideline will already assume patients have been assessed as suitable for opioid treatment (WHO pain ladder level 3). Consideration will be given to re-assessment when deciding which opioid to prescribe and choosing an

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					opioid when switching (covered under section 4.3.1 (b)).
SH	United Kingdom Clinical Pharmacy Association (UKCPA) / Royal Pharmaceutical Society of Great Britain	9.08	4.3.1	The place of alternative strong opioids when first line treatment fails or is not tolerated despite adequate titration should be considered or the first line treatment is not tolerated despite sensible titration	We have made it explicit that switching of opioids will be covered under management strategies for side effects in section 4.3.1 (b) of the scope.
SH	United Kingdom Clinical Pharmacy Association (UKCPA) / Royal Pharmaceutical Society of Great Britain	9.09	4.4.c	As cancer treatments improve there is increased survival and both short and long term adverse effects of opioid therapy must be considered	Thank you. We will take this into consideration when searching for evidence.
SH	United Kingdom Clinical Pharmacy Association (UKCPA) / Royal Pharmaceutical Society of Great Britain	9.10	5	Some of the related NICE guidance has little relevance to the proposed clinical guideline. The inclusion of TAs and CGs relating to drug misuse may potentially contribute to 'opio-phobic' attitudes	Thank you. We have amended the list as suggested.
SH	Wales Palliative Care Strategy Implementation Board	5.00	4.1.1 4.1.2.f 4.3.2.c	Strong opioids are often required in patients who have some organ impairment and who are managed in non-specialist settings. As different opioids are metabolised/excreted differently, it seems important to consider renal, hepatic failure and also the use of analgesia in those with respiratory failure. If not, these patients risk remaining denied adequate pain relief.	After considering comments from stakeholders we have amended the scope so that it no longer excludes these patients.
SH	Wales Palliative Care Strategy Implementation Board	5.01	4.1.2.d	Opioids are often – or usually – required in the dying patients who are unable to swallow. And they are required for those with head and neck cancers etc during radiotherapy. So to risk denying these patients analgesia is unethical.	Thank you for your comment. We have amended the scope to include all routes of administration in the guideline.
SH	Wales Palliative Care Strategy Implementation Board	5.02	4.2	Private and third sector providers should be added in here as they are increasingly providing NHS services	Thank you. We feel the current wording is appropriate.
SH	Wales Palliative Care Strategy	5.03	4.3.2.e	Conversion to parenteral use is important and there	Recommendations made by the guideline

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	Implementation Board			are varying schedules available so the guideline must decide on a conversion ratio for general use. Otherwise a major part of pain control will be missing from the guidance. Misuse of fentanyl patches at the end of life is also a major concern in practice.	development group will be determined by the available evidence. The scope does not cover last days of life as the issues for these patients are different.
SH	Wales Palliative Care Strategy Implementation Board	5.04	4.4.d and e	Should this read 'recognition of adverse events'? And 'management of toxicity'?	No. We think that adverse events is the measure most likely to be reported in clinical trials and therefore is appropriate to stay as it is. We have removed toxicity from the main outcomes.
SH	Wockhardt UK	6.00	3.1.e	Fear of "facing the General Medical Council or court proceedings" has led to a general tendency to underdosing rather than ensuring adequate dosing for pain control, and to a reluctance to prescribe strong enough opioids for pain control in a primary care setting. This has led to unnecessary suffering, which should be addressed by the provision of specific guidance in this Guideline for adequate pain control for patients under primary care, including those nursed at home.	Thank you, we agree.
SH	Wockhardt UK	6.01	3.1.f and 4.1.1.a	It seems unreasonable to exclude adults with "swallowing problems", significant or otherwise, from this Guideline. A significant proportion of adults requiring strong opioids for pain control in the course of palliative care will have swallowing problems to a greater or lesser degree (including those with oropharangeal cancers, neurodegenerative and neuromuscular conditions, or simply debilitated and weak) and therefore need access to parenterally administered opioids. Their treatment should not be excluded from this Guideline.	Thank you for your comment. After considering comments from stakeholders we have amended the scope so that it no longer excludes these patients.
SH	Wockhardt UK	6.02	4.1.2.e	Similarly, the exclusion of "adults who are unable to take drugs orally" from this Guideline will ignore the	Thank you for your comment. We have amended the scope to include all routes of administration in the

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				needs of a substantial proportion of patients requiring access to strong opioids for control of pain in a palliative care setting.	guideline.
SH	Wockhardt UK	6.03	4.3.1.a & b	With regard to first-line treatment and management strategies for intolerable side effects, consideration should be given to who should be the responsible, decision-making healthcare professional. There is a tendency in the primary care situation for decisions re medication, which frequently need to be made urgently, to be referred to and fro between nursing and medical staff, resulting in unnecessary delays in the management of pain and side effects.	Recommendations made by the guideline development group will be determined by the available evidence.
SH	Wockhardt UK	6.04	4.3.1.a	Another factor that should be considered in relation to first-line treatment is the "route of administration", e.g. nasal, buccal or subcutaneous for patients who cannot take drugs orally or patients with inaccessible veins...	We have amended the scope to include all routes of administration in the guideline.
SH	Wockhardt UK	6.05	4.3.2.b	As per comments 2 and 3, above, the clinical issues described in 4.3.1 should also be applied to patients who are unable to take drugs orally.	We have amended the scope to include all routes of administration in the guideline.
SH	Wockhardt UK	6.06	4.3.2.e	It seems unreasonable to exclude "care in the last days of life" from this Guideline which should surely apply continuously until a patient has no further need for strong opioids, for whatever reason. In any case, at what point and on whose say so, does a patient enter their "last days of life"? Palliative care should be "seamless" and continuous, particularly in relation to pain control.	The scope does not cover last days of life as the pain control issues for these patients are different and complex. This is a short guideline and we have to restrict the scope to reflect the amount of time and resource available to develop it. We have amended the scope to clarify that this refers to care whilst on the Liverpool Care Pathway or equivalent.
SH	Wockhardt UK	6.07	4.4.b, c, & d	"Toxicity" is not a clearly defined entity. It would be better to omit this and simply address: b) reduction in adverse **reactions** (attributable) to opioids	Thank you. We have removed this from the list of main outcomes.

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				c) adverse events (not related to opioids).	

These organisations were approached but did not respond:
Alder Hey Children's NHS Foundation Trust
Association of Chartered Physiotherapists in Oncology and Palliative Care
Association of Paediatric Anaesthetists of Great Britain and Ireland
Barnsley Hospital NHS Foundation Trust
Brains Trust
British Association for Nursing in Cardiovascular Care (BANCC)
British Medical Association (BMA)
British National Formulary (BNF)
British Psychological Society, The
Care Quality Commission (CQC)
Central South Coast Cancer Network
Cerebra
Citizens Commission on Human Rights
Cochrane Pain, Palliative and Support Care Group
Connecting for Health
Croydon Healthcare Services NHS Trust
Department for Communities and Local Government
Department of Health
Department of Health Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infection (ARHAI)
Department of Health, Social Services & Public Safety, Northern Ireland (DHSSPSNI)
East Midlands Cancer Network
English Community Care Association
Faculty of Pain Medicine of the Royal College of Anaesthetists
Flynn Pharma Limited
Gloucestershire Hospitals NHS Trust
Gloucestershire LINk
Great Western Hospitals NHS Foundation Trust
Greater Manchester and Cheshire Cancer Network
Greater midlands cancer network
Healthcare Improvement Scotland
Healthcare Quality Improvement Partnership

Hertfordshire Partnership NHS Trust
Hywel Dda NHS Trust
Inclusive Health
Institute of Biomedical Science
James Whale Fund for Kidney Cancer
Jos Trust
Lambeth Community Health
Leeds Teaching Hospitals NHS Trust
Lincolnshire Teaching PCT
Liverpool Community Health
Lothian University Hospitals Trust
Luton & Dunstable Hospital NHS Foundation Trust
Medtronic Ltd
Ministry of Defence (MoD)
National Treatment Agency for Substance Misuse
NHS Clinical Knowledge Summaries Service (SCHIN)
NHS Direct
NHS Lincolnshire
NHS Plus
NHS Sheffield
NHS Western Cheshire
North East London Cancer Network
Nycomed UK Ltd
Outer North East London Community Services
Paediatric Intensive Care Society
Parkinsons UK
Pelvic Pain Support Network
PERIGON Healthcare Ltd
Pfizer Limited
Pierre Fabre Ltd
Public Health Wales
Rainbows Hospice for Children & Young People
Rotherham NHS Foundation Trust
Royal Brompton & Harefield NHS Foundation Trust
Royal College of Anaesthetists
Royal College of General Practitioners Wales
Royal College of Midwives
Royal College of Obstetricians and Gynaecologists

Royal College of Pathologists
Royal College of Physicians London
Royal College of Psychiatrists
Royal College of Radiologists
Royal College of Surgeons of England
Royal Society of Medicine
Sanctuary Care
Scarborough and North Yorkshire Healthcare NHS Trust
Scottish Intercollegiate Guidelines Network (SIGN)
Sheffield Teaching Hospitals NHS Foundation Trust
Sickle Cell Society
Social Care Institute for Excellence (SCIE)
Social Exclusion Task Force
Society and College of Radiographers
Society for Acute Medicine
Solent Healthcare
South Wales Cancer Network
St Ann's Hospice
Sue Ryder Care
Thames Valley Cancer Network
UCL Partners
UK Clinical Pharmacy Association (UKCPA)
UK Renal Pharmacy Group
University Hospitals Birmingham NHS Foundation Trust
University Hospitals of Leicester NHS Trust
ViroPharma Ltd
Welsh Assembly Government
Welsh Scientific Advisory Committee (WSAC)
Western Health and Social Care Trust
York Teaching Hospital NHS Foundation Trust