National Institute for Health and Clinical Excellence

Opioids in Palliative Care
Guideline Consultation Comments Table
2nd Dec 2011 – 6th January 2012

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
SH	Royal Society of Medicine	7.00	Full			This is a general comment about the document as a whole and relates to an area not covered which appear to fall within the scope of the guideline. There is no real reference to the use of opioids when patients have renal impairment. This is an important consideration for the generalist because of the high prevalence of renal impairment in patients with advanced cancer and in the older population – both of which are highly likely to be in the population for which the guideline is intended. The evidence in this area is difficult to assimilate because it is diversely spread across a wide range of sources. However a number of us have made considerable efforts to gather and assess the relevant evidence and we would be very willing to contribute to this as appropriate.	While we did not exclude patients with renal impairment from the scope of this guideline, the evidence review did not find any data specific to this group of patients. Consequently the GDG were unable to make prescriptive recommendations for patients with renal or hepatic impairment. However they have now added a recommendation that specialist advice should be sought before prescribing opioids for this group of patients.
SH	St Ann's Hospice	14.05	general			This guidance is repetitive and unlikely to be read in full by a busy GP. Could key recommendations be presented first and ref to an appendix be used? These recommendations won't really change or aid safe practice	Since this guideline only contains 19 recommendations there is no list of "key priorities for implementation. However a list of all recommendations is presented on pages 6-8. We disagree. We hope that these recommendations will improve practice.
SH	St Ann's Hospice	14.06	general			Evidence statements are relevant but there is little practical advice for generalists (or specialist). Could information about doses for	We have added recommendations in section 3.3 on a safe starting dose for titration.

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						titration in opiate naïve and conversions from codeine and tramadol be included? This is more likely to stop prescribing errors eg diamorphine given at excess doses to an opiate naïve patient or too low a level of analgesia being started for those on weak opioids resulting in inadequate analgesia. Reference to page 1-10 of the Greater Manchester and Cheshire cancer network pain and symptom control guidance may be useful for generalists to use.	
SH	St Ann's Hospice	14.07	general			No mention is given to the need for caution with renal or hepatic impairment. No mention is made for the possible need for dose reduction and increase dosing interval in patients who develop renal failure. This is very relevant as new renal failure may present the generalist with a situation where a dose reduction or opiate switch is required. This would promote safe prescribing.	While we did not exclude patients with renal impairment from the scope of this guideline, the evidence review did not find any data specific to this group of patients. Consequently the GDG were unable to make prescriptive recommendations for patients with renal or hepatic impairment. However they have now added a recommendation that specialist advice should be sought before prescribing opioids for this group of patients.
SH	St Ann's Hospice	14.08	general			Perhaps including a table to show that a 25 microgram patch equates to 60-90mg morphine in 24 hours and should not be used in opiate naïve patients would increase safety and reduce prescribing errors.	We have added a recommendation to section 3.5 about calculating equivalence.
SH	Help the Hospices	43.07	Full	General		The guideline is designed for non-specialist healthcare professionals – however it feels too general to be of use in clinical practice – ie no info on starting doses for opioid naïve patients, no example of a conversion table, no info on switching to syringe driver etc. These are key pieces of data which will promote safer use of opioids in non-specialist settings. Even if there is no high quality evidence for some of these aspects, then reference to established consensus guidelines or extensive clinical	We have added recommendations in section 3.3 on a safe starting dose for titration and a recommendation to section 3.5 about calculating equivalence.

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						experience would be very valuable. It is noted that clinical experience is quoted as "evidence" for some aspects but not others (eg 3.8.5 and 3.10.5 and 3.11.5). If clinical experience IS allowed to influence some of the recommendations, then it seems there are some significant omissions as detailed below. Reference to the BNF is a reasonable option but to have all the info in one place is more useful in practice and for teaching purposes. Also there have been several comments about lack of any advice regarding usage of opioids in the final days of life.	Care during the last days of life is excluded from the scope of the guideline and we are therefore unable to make recommendations on this
SH	Action on Pain	21.00				Dear Sir/Madam We are keen to make our submission regarding the above guidelines however due to problems caused by the poor weather conditions(power lines down at present) we are unable to access your website in order to use the draft format. Under these extreme circumstances we would appreciate if you would accept our submission in e-mail form. Action on Pain is a national charity established in 1998 which provides support and advice for people affected by chronic pain. Run entirely by volunteers we have in-depth experience and knowledge of the issues around providing effective pain management as well as the impact of pain not only on the individual but also their familiy,friends and carers. We have established a reputation for our "down to earth" approach which has become widely	

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						respected both by people affected by pain and healthcare professionals. PainLine- our telephone helpline has received over 42000 calls whilst our mobile information unit provides face to face contact with around 10000 people each year. We work hard to promote the positive side of living with pain. We have carefully considered the draft guidelines for the use of opioids in pallative care which has generated the following observations:	
						We had concerns that in section 3.8 there is reference to use by non-specialist healthcare professionals which would appear to exclude usage by specialists. That a specialist pain team potentially would be prevented by the guidelines from using this form of treatment is inconceivable. That a patient could potentially be left in pain is unacceptable. We refer you to 1.1.7 which states" if pain remains despite optimising first-line therapy, review analgesic strategy, and consider seeking specialist advice". As the draft guidelines read at present they give a clear implication that non-specialists should leave patients in pain if the first line of attack fails. That cannot be right. We strongly urge that the guidelines should give a clear signal that if the first-line of treatment fails(IR morphine) patients should be referred to a specialist pain team who can consider other forms of treatment which may include fast-acting fentanyl.	Unfortunately we are not able to identify text in section 3.8 which implies that specialist healthcare professionals are excluded from following these recommendations. This guideline only covers first line treatment with strong opioids (as defined in the scope) and therefore we are unable to make recommendations about second-line treatment. However there is no intention to leave patients with uncontrolled pain. Recommendation 1.1.7 explicitly states that specialist advice should be sought as does the care pathway on p9.
						We had concerns that in section 3.8.2 IR morphine is regarded as the "gold standard" yet in our opinion this view is deeply flawed. Pain	Section 3.8.2 summarises the available evidence. It compares the effectiveness of IR morphine, fast-acting fentanyls and IR

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						impacts on people in different ways which means that IR morphine is not tolerated by some perhaps due to the nature of the pain, the length of time it takes to take effect or indeed the inability to take oral medication. Again in 3.8 we struggled to find any clear definition of breakthrough cancer pain nor the profile of a typical incident of such pain. Drawing on our experiences we have found a rapid onset with episodes lasting between 30/45 minutes This seemed a strange omission particularly when on Page 54 there is a reference to breakthrough pain. We felt that the panel compiling these guidelines lacked insight as to the impact of breakthrough cancer pain. Looking at 3.8.5 it is difficult to follow the logic of the GDC when they state "felt cost of recommending fentanyl -considerable and could not be justified" How can the GDC come to this conclusion given the contradiction in evidence at 1.1.9 1.1.10 and 3.8.6. Whilst IR morphine may appear to be cost-effective the need to look at the broader picture of the overall cost of providing healthcare to the patient has not been demonstrated in these draft guidelines which to us appears a serious shortcoming.	oxycodone. It does not presume that IR morphine is the most effective opioid. Breakthrough pain is defined in the guideline glossary. We have also added an introductory paragraph to this section. It was not possible to conduct formal cost effectiveness analysis for this topic (which would have investigated the downstream consequences of providing this treatment) due to a lack of clinical data. However the GDG were still required to apply economic thinking when agreeing their recommendations. INFS showed a significant clinical benefit at two out of six time points. At 10 minutes 52.4% of patients taking fentanyl had responded compared to 45% of patients taking morphine. At 15 minutes 75.5% of patients taking fentanyl had responded compared to 69.3% of patients talking morphine. The GDG felt that overall this did not indicate a clinically significant benefit for INFS over IR morphine. In addition the GDG were aware that there is a significant additional cost to using INFS. Consequently the GDG recommended the use of IR morphine. We have amended the

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						In conclusion we feel that the draft guidelines do not demonstrate that sufficient weight has been given to all the available evidence or existing guidelines which adopt a more realistic approach giving a better potential outcome for patients. We further believe that This submission has been compiled by members of the Action on Pain team being based on our experiences of helping people affected by pain. For further information please contact: Ian Semmons Chairman Action on Pain on 0845 6031593 or 07733 168283 5 January 2012	LETR paragraph to clarify the GDGs interpretation of the evidence. We disagree. We believe that sufficient weight has been given to the available evidence. NICE do not base their recommendations on existing guidelines and are unable to endorse such recommendations.
SH	Royal College of General Practitioners in Wales	33.00					Thank you.
SH	RCP	40.00				Just to confirm that the RCP has had sight of and would wish to endorse the response of the APM to the above consultation. I understand that this has been submitted separately by the APM already.	Thank you.
SH	Marie Curie Cancer Care Belfast	41.03	full			3.8.1 general comment: no mention of use of liquid vs tablet preparation for breakthrough pain or that liquid preparations may provide pain relief faster.	Liquid versus tablet preparation was not investigated by the guideline as it was not felt to be a priority area within this short clinical guideline.

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SH	National Patient Safety Agency	8.00	Full	General		We are very disappointed to find that no account seems to have been taken of patient safety in terms of learning from the National Reporting and Learning System in this draft guideline. We would refer again to our previous submission from May 2011. Published national guidance from the NPSA is not referenced or taken account of as detailed in our previous submission (attached as a separate document). Although we accept this is a 'clinical' guideline we feel that delivering care safely should form a fundamental part of such a national document. We would ask that the decision to omit reference to NPSA guidance be reconsidered.	Patient safety is paramount and was taken into consideration when developing all recommendations. We have included an additional paragraph in the guideline introduction to signpost the reader to guidance produced by the NPSA and have also added a cross reference to your website.
SH	Gloucestershire Hospitals NHS Foundation Trust	15.00	Full	General		There is no reference throughout the document that opioid choice should be reviewed once a patients' eGFR is less than 30 ml/min. Although this is a document for generalists in opioid prescribing, this is key to safe prescribing of opioids in palliative care. There should be a comment that, although inappropriate as first line for breakthrough pain, the fast acting fentanyl preparations may have a role in breakthrough pain. This then opens the door for their use in complex patients. The document is long and because of multiple comments regarding lack of evidence, is not likely to be read. It misses the opportunity to put key points across particularly regarding opioid use in renal impairment.	While we did not exclude patients with renal impairment from the scope of this guideline, the evidence review did not find any data specific to this group of patients. Consequently the GDG were unable to make prescriptive recommendations for patients with renal or hepatic impairment. However they have now added a recommendation that specialist advice should be sought before prescribing opioids for this group of patients Second-line management of breakthrough pain is outside the scope of this guideline and we are therefore unable to make recommendations on this issue. We are sorry that you feel this way. We disagree.
SH	St Nicholas Hospice	18.01	full	general		The document does not make clear whether this strong Opioid is to be used in addition to non opioids such as paracetamol.	The scope of this guideline is restricted to strong opioids and does not cover non-opioid pain control or adjuvants. These issues have

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							therefore not been covered.
SH	Target Ovarian Cancer	22.00	Full	General		We support the development of the guideline and feel that the recommendations will offer greater clarity to non-specialist health professionals working in palliative care. We believe the benefits will be improved pain management for patients with advanced and progressive disease.	Thank you.
SH	Marie Curie Cancer Care	24.01	Full	General		The overall review of the existing evidence is useful to remind clinicians of the poor quality of the data. It also confirms that experience which has been accumulated through practice, and which is now available to practitioners in many widely disseminated guidelines, has been able to provide more, much clearer, guidance than that contained here. This aggregated experience in clinical practice has led to a considerable improvement in the overall management of severe pain in the palliative setting over the past few years. The statement, often repeated through the document, that the GDG was '*unable to make recommendations'* risks confusing inexperienced prescribers by suggesting that there is no information at all to support practice.	While we accept that valuable guidance already exists we are unable to cross-reference non-NICE guidance.
SH	Marie Curie Cancer Care	24.02	Full	General		For practicing clinicians, the most useful guidance will always be a single concise document containing all the information required to safely initiate and maintain a patient on treatment. The restriction of this Guideline to a few specific questions, the absence of prescribing detail, especially regarding appropriate dosing and the general lack of clarity of the guidance is not helpful.	This is a short clinical guideline and as such is not intended to be a comprehensive guide to all aspects of opioid pain control. We have added recommendations in section 3.3 on a safe starting dose for titration and a recommendation to section 3.5 about calculating equivalence.
SH	Association for Palliative	25.00	Full	gener		These comments represent the collective view	Thank you for your comment. Stakeholders

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	Medicine of Great Britain and Ireland			al		of the 24 members who responded to our call for comments which went to the whole membership. We found it regrettable that by the time we were able to inform our members there was less than a month in which to gather and collate responses and that this month was interrupted by the festive period. We feel that this probably limited the ability for more members to consider and comment on these guidelines, however the comments of those that have may be taken as representative.	were alerted to the consultation dates in advance of the consultation. In future NICE will ensure that extra time is added to the consultation to accommodate Christmas and August holiday periods.
SH	Association for Palliative Medicine of Great Britain and Ireland	25.01	Full	General		While two respondents liked the simplicity of the guideline most expressed the concern that the guideline was too basic to be useful and would not address the issues of concern over opioid use expressed in the introduction. Specifically our GP member felt that the guideline was too vague to be of any practical use and therefore GP's would look to other sources of guidance rather than this. One correspondent expressed their concerns thus "The NICE document has the feel of guidance rather than a guideline. Given the relative lack of evidence and its quality, if the NICE document is to be based on the available evidence alone it would not be able to be more specific or practical than it is. On occasions though, the GDG do express an opinion based on their clinical experience rather than the evidence alone. I think this may represent an inconsistency of approach. I would prefer a clearer differentiation between guidance and a guideline and if it is to be guidance, then a reference to effective and well developed guidelines such as the Lothian Palliative Care Guidelines (or the SIGN 106 Cancer Pain guidelines) may be helpful. Being clearly	This is a short clinical guideline and as such is not intended to be a comprehensive guide to all aspects of opioid pain control. The GDGs decision on whether or not to make consensus based recommendations when there was a lack of clinical evidence was guided by a wish to address and improve variation in practice. While we accept that valuable guidance already exists we are unable to cross-reference non-NICE guidance.

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						guidelines, these include expert opinion and practical application. Because of this, I suspect guidelines like the Lothian ones may be more useful for the suggested target users of the NICE guidance. This may be particularly relevant for areas where we have very little evidence to guide us, but significant clinical experience, such as the initiation of transdermal opioids when the oral route is unavailable (1.1.8, page 7 of the complete document). Like most palliative medicine specialists, I have experience of transdermal preparations being used without an appreciation of the relative potency of the opioids they contain leading to significant patient harm. This pitfall is very unlikely to emerge within the controlled setting of a clinical trial, but can be clearly described within a guideline based on clinical experience"	
SH	Association for Palliative Medicine of Great Britain and Ireland	25.02	Full	General		There were concerns from a number of respondents that the guideline was written purely from cost perspective and that evidence was interpreted in a way that supports the cost agenda rather than taken on face value. It was felt that where recommendations were based on GDG opinion alone or when GDG opinion has overruled available evidence in making recommendations this should be made clear in the summary recommendations.	The linking evidence to recommendations sections detail how the GDG moved from the evidence (or lack of) to the recommendations. NICE guidelines are required to look at both clinical and cost effectiveness and make recommendations based on this data – this does not necessarily mean recommending the cheapest option.
SH	Association for Palliative Medicine of Great Britain and Ireland	25.03	Full	General		It was felt that this guideline would mainly be used by Medicines Management groups to ration the use of a broader range of opioids and, while intended to discuss the first line use in uncomplicated patients by non-specialists, that this rationing would have implications for second and third line use by specialists such as our members.	This is not the intention of the guideline.

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SH	Department of Health	26.00	Full	General		We are pleased to have the opportunity to comment on this draft guidance. This document presents a helpful review of the available evidence for some aspects of prescribing of strong opioids and confirms both the fact that very little of the existing evidence is of better than 'Low' quality and also that published research has failed to keep pace with developments in clinical practice. The research recommendations could be promoted by national funding agencies so that new evidence could be incorporated to give greater weight to this guidance The draft is not currently a guide for the "safe and effective prescribing" of these drugs which could be used by a generalist clinician. In particular, the deliberate exclusion of the need to assess the patient and make a diagnosis prior to the initiation of treatment is likely to make prescribing less effective.	Thank you. Thank you – this is what we hope will happen. We were tasked with developing a short clinical guideline and therefore the scope was restrictive in order to make this workable. The guideline assumes patients have been assessed as suitable for strong opioid treatment (WHO pain ladder level 3). This was made explicit in the final scope of the guideline.
SH	Department of Health	26.01	Full	General		In several situations throughout the draft guidance 'expert opinion' has been the basis of recommendations when evidence is not available; however the use of such clinical experience is inconsistent, leaving some recommendations more non-specific in content than much of the existing guidance which has driven improvements in practice over the past few years.	We agree, but feel this is a reflection of the limited, poor quality data that is available on this topic area.
SH	Royal College of Nursing	27.00	General	general		The Royal College of Nursing welcomes this document. The guidelines are comprehensive.	Thank you.
SH	Royal College of Nursing	27.09	Full	Gener		It is unclear as to the definition of palliative care	A definition of palliative care is included in the

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				al		here. Many will assume that this is cancer care or end of life care but the guideline does not make this clear. The NICE definition of palliative care includes supportive as well as palliative care and includes any life limiting illness. The guideline could make this clearer for the reader.	glossary.
SH	Grunenthal Ltd	29.00	Full	General		Thank you for the opportunity to comment on the draft guideline. We appreciate that this advice is being developed following the NICE short clinical guideline process and as a consequence is focused on addressing the problems associated with the use of commonly used strong opioids in the non-specialist setting e.g. underdosing leading to avoidable pain and overdosing and the resultant distressing adverse events. However, not all strong centrally acting painkillers rely on the opioid receptor. We highlight the emerging role of tapentadol (Palexia SR) in the management of severe chronic pain associated with advanced and progressive disease and request that, in the future, the institute consider producing broader clinical guidance on the management of pain in palliative care. Tapentadol is a new 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.	You are correct. Since this is a NICE short clinical guideline we have focused on addressing the problems associated with the commonly used strong opioids**.**

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						A meta-analysis of three pivotal trials in osteoarthritis and lower back pain demonstrated significantly reduced incidences of gastro-intestinal side effects (nausea, vomiting, constipation) with tapentadol prolonged-release (PR) compared with oxycodone controlled release (CR) at doses providing similar analgesic effects. Tapentadol PR is associated with fewer treatment discontinuations and with patients remaining on therapy for longer 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. A network analysis within a systematic review of chronic pain treatment with strong opioids and tapentadol showed similar findings regarding efficacy and tolerability of tapentadol compared with morphine as were observed in the head to head studies with oxycodone. Grünenthal propose that tapentadol has a significant role to play in the palliation of pain in primary care.	
SH	Archimedes Pharma Ltd	32.09	Full	General		There are a number of existing guidelines that recommend the use of fast acting fentanyl products in BTCP, such as those from the European Association of Palliative Care (EAPC), the European Oncology Nursing Society (EONs) and the Association of Palliative Medicine of Great Britain (APM). The proposed NICE Guideline is in contradiction with these, in part due to what appears to be narrow inclusion	This topic compared the effectiveness of IR morphine, fast-acting fentanyl and IR oxycodone. It did not presume that IR morphine was the most effective opioid. INFS in breakthrough pain showed a significant clinical benefit at a minority of time points. At 10 minutes 52.4% of patients taking fentanyl had responded compared to 45% of patients taking morphine. At 15 minutes 75.5% of patients taking fentanyl had

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						criteria for clinical evidence, and a starting assumption that IRMS is the standard by which all other therapies should be judged, irrespective of its suitability for the treatment of a typical BTCP episode. This is not helpful to the prescribing clinician trying to manage a patient with BTCP, and we suggest that NICE considers this guideline in the broader context of other guidelines to clinical practice in the UK and encourages the non-specialist to refer this subpopulation of patients for specialist review.	responded compared to 69.3% of patients talking morphine. The GDG felt that overall this did not indicate a clinically significant benefit for INFS over IR morphine. In addition the GDG were aware that there is a significant additional cost to using INFS. Consequently the GDG recommended the use of IR morphine. We have amended the LETR paragraph to clarify the GDGs interpretation of the evidence. GDG based their recommendations on a review of the available clinical and cost-effectiveness evidence. Since this guideline examined cost-effectiveness but the guidelines from the professional organisations did not, this may have contributed to different recommendations being made
SH	Teva UK	34.00	Full	General		The guideline would be more complete if further consideration was given to those cancer patients with breakthrough pain (despite appropriate daily doses of strong opioids) who are not managed *via* the first line approach advocated within the draft. For instance, what does the Team recommend as second line treatment under these circumstances? Should such patients be referred back to specialist care or should advice be sought in other ways? Should practitioners in the community continue medication prescribed within the secondary care environment (including fast acting fentanyls) and under what circumstance?	This guideline only covers first line treatment with strong opioids (as defined in the scope and guideline introduction) and therefore we are unable to make recommendations about second-line treatment. There is no intention to leave patients with uncontrolled pain. Recommendation 1.1.7 explicitly states that specialist advice should be sought as does the care pathway on p9.
SH	Teva UK	34.01	Full	General		The guideline appears to have been written for general practitioners, however, we are concerned that these guidelines may be applied outside this group (*i.e.* to Palliative Care and	Although the guideline is aimed at non-specialists, we hope that these guidelines would be of some value to all healthcare professionals.

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						Pain specialists) unless the intended audience is made clearer	
SH	Napp Pharmaceuticals Ltd	35.00	Full	General		Napp Pharmaceuticals strongly supports the valuable work of NICE in producing these guidelines for opioid prescribing which will improve safety and outcomes for patients.	Thank you.
SH	Royal College of General Practitioners & British Pain Society	36.00	Full	General		Please note that the consultation time for this very extensive set of documents has been unreasonably short – the guidance came to BPS in mid-December with a deadline for 6 January. One working week was effectively lost from these four weeks because of the holiday period.	Thank you for your comment. Stakeholders were alerted to the consultation dates in advance of the consultation. In future NICE will ensure that extra time is added to the consultation to accommodate Christmas and August holiday periods.
SH	Royal College of General Practitioners & British Pain Society	36.03	Full	General		The guideline is clearly about the use of so-called 'strong' opioids. However, it was disappointing to see no reference anywhere in the document to other pain medications that should always be considered alongside – or even before – strong opioids. This is especially important as the careful use of other agents (eg non-steroidal anti-inflammatory drugs, calcium-channel blocking agents for neuropathic pain) may improve the pain control and help to minimise opioid side-effects by keeping the dose lower. As a result, this document is actually narrower than the WHO cancer pain ladder, which at least does mention non-opioid drugs. It would be a pity if this led to less rational drug management of pain in advanced disease!	The scope of this guideline is restricted to strong opioids and does not cover non-opioid pain control or adjuvants. These issues have therefore not been covered.
SH	Royal College of General	36.12	Full	Gener		We are disappointed that there is no specific	There is no intention to leave patients with

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	Practitioners & British Pain Society			al		reference to the benefits of referring patients with moderate to severe pain in advanced disease, to pain specialists or others who can assist in pain management. For example, pain interventions such as neurolytic blockade, spinal analgesia (including with strong opioids), vertebroplasty, or surgery in some cases of bone cancer pain. Although it would normally be the responsibility of palliative medicine specialists to initiate such referrals, it seems a missed opportunity to not inform non-specialists about the role of these non-drug interventions. We believe that, together with the clear bias for economic reasons to advocate oral morphine before any other evidence-based opioid or route, could lead to inadequate pain control and/or unacceptable side-effects, in the hands of 'non-specialists'	uncontrolled pain. The recommendations and care pathway explicitly state that specialist advice should be sought.
SH	British Pain Society	38.00	Full	General		Please note that the consultation time for this very extensive set of documents has been unreasonably short – the guidance came to BPS in mid-December with a deadline for 6 January. One working week was effectively lost from these four weeks because of the holiday period.	Thank you for your comment. Stakeholders were alerted to the consultation dates in advance of the consultation. In future NICE will ensure that extra time is added to the consultation to accommodate Christmas and August holiday periods.
SH	British Pain Society	38.01	Full	General		This response has been coordinated with those from the Association for Palliative Medicine and the Royal College of General Practitioners. Although each organisation will be submitting separate responses as distinct stakeholders, all three share the same views and concerns with the draft guidance. This response will focus more on the concerns from the point of view of	Thank you.

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						the British Pain Society.	
SH	British Pain Society	38.04	Full	General		The guideline is clearly about the use of so-called 'strong' opioids. However, it was disappointing to see no reference anywhere in the document to other pain medications that should always be considered alongside – or even before – strong opioids. This is especially important as the careful use of other agents (eg non-steroidal anti-inflammatory drugs, calcium-channel blocking agents for neuropathic pain) may improve the pain control and help to minimise opioid side-effects by keeping the dose lower. As a result, this document is actually narrower than the WHO cancer pain ladder, which at least does mention non-opioid drugs. It would be a pity if this led to less rational drug management of pain in advanced disease!	The scope of this guideline is restricted to strong opioids and does not cover non-opioid pain control or adjuvants. These issues have therefore not been covered.
SH	British Pain Society	38.13	Full	General		We are disappointed that there is no specific reference to the benefits of referring patients with moderate to severe pain in advanced disease, to pain specialists or others who can assist in pain management. For example, pain interventions such as neurolytic blockade, spinal analgesia (including with strong opioids), vertebroplasty, or surgery in some cases of bone cancer pain. Although it would normally be the responsibility of palliative medicine specialists to initiate such referrals, it seems a missed opportunity to not inform non-specialists about the role of these non-drug interventions. We believe that, together with the clear bias for	This guideline only covers first line treatment with strong opioids (as defined in the scope) and therefore we are unable to make recommendations about second-line treatment. There is no intention to leave patients with uncontrolled pain. Recommendation 1.1.7 explicitly states that specialist advice should be sought as does the care pathway on p9.

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						economic reasons to advocate oral morphine before any other evidence-based opioid or route, could lead to inadequate pain control and/or unacceptable side-effects, in the hands of 'non-specialists'	
SH	Birmingham St Marys Hospice	39.01	Full	general		Should there be some evidence or reference to the one sixth of regular dose that is stated in the document. Our understanding is that there is not good evidence for this.	We assume you are referring to the health economic evaluation on p62. The dose of fentanyl has also been calculated as one sixth of the regular dose. Given that the patch release is 25µg/hour, this is equivalent to a daily dose of 600µg. Thus a dose of 100µg is one sixth of the regular dose. For further clarity the footnote will be changed to "typically one sixth of regular daily dose". Note that in the case of actiq, doses begin at 200µg, so this is the closest equivalent that could be used.
SH	National Council for Palliative Care	42.00	full	general		We are pleased to have the opportunity to respond to the draft guideline. We consider the document to be clear and straight-forward to read.	Thank you.
SH	National Council for Palliative Care	42.01	full	general		We believe the guideline has significantly benefitted from the change in title and scope, following comments from stakeholders including NCPC in June. We do, however, still find it disappointing that assessment (and re-assessment) is not covered. The clinicians we consulted with found this to be a major area of concern. This point was also raised by the Pain Society, RCN, United Kingdom Clinical Pharmacy Association	We were tasked with developing a short clinical guideline and therefore the scope was restrictive in order to make this workable. The guideline assumes patients have been assessed as suitable for opioid treatment (WHO pain ladder level 3). This was made explicit in the final scope of the guideline.

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						(UKCPA) / Royal Pharmaceutical Society of Great Britain and Napp Pharmaceuticals in the first round of consultation.	
SH	Royal College of Nursing	27.08	Full	General	General	Although the guideline mentions the patient's fear of addiction regularly, it does not seem to say that the risk is extremely low if not impossible in palliative care	We agree that the risk of addiction is low. However it is common for patients to have this misapprehension. Therefore we have made the recommendations in 1.1.1
SH	UK Clinical Pharmacy Association	20.00	Full	General	n/a	The United Kingdom Clinical Pharmacy Association welcomes the development of the guideline on opioids in palliative care and feels that the GDG have produced an excellent short clinical guideline	Thank you.
SH	UK Clinical Pharmacy Association	20.01	Full	General	n/a	We welcome the recommendations regarding patient information, and feel that these could go some way towards overcoming 'opio-phobia'. The British Pain Society's patient information on managing cancer pain (via http://www.britishpainsociety.org/) may be a helpful resource here.	Thank you.
SH	UK Clinical Pharmacy Association	20.02	Full	General	n/a	We welcome advice regarding the pre-emptive management of opioid-related adverse effects.	Thank you.
SH	Astrazeneca UK Ltd	31.09	Full	General	N/A	As the scope of the guideline covers the management of side effects including switching opioids, we feel would be useful to include information on switching drug and formulation	The guideline concentrates on first line treatment with opioids. Switching opioid was included as part of the management of side effects but we did not investigate what opioid to switch to. Therefore we are not able to make recommendations on this issue.
SH	Astrazeneca UK Ltd	31.00		N/A	N/A	AstraZeneca UK welcome the opportunity to comment on the draft clinical guideline for Opioids in palliative care: safe and effective prescribing of strong opioids for pain in palliative care of adults	Thank you.
SH	Sobell House Hospice Charity	11.00	Full	1-97		Lack of overall guidance mainly due to low grade evidence if any. We would expect more	We agree, but feel this is a reflection of the limited, poor quality data that is available on

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						from clinical experience as suggested in a couple of sections.	this topic area.
SH	Marie Curie Cancer Care	24.00	Full	1	2	Marie Curie Cancer Care is pleased to have the opportunity to comment on this draft. The concept as outlined in the introduction is welcome. However, the Guideline's title is misleading as it will **not** assist generalist clinicians in either safe or effective prescribing of strong opioids. In particular the absence of any recommendation about assessment of the patient and reaching a diagnosis of the causes of pain goes against all current teaching and will prevent effective prescribing.	Thank you for your comment. We disagree that the title is misleading. We were tasked with developing a short clinical guideline and therefore the scope was restrictive in order to make this workable. The guideline assumes patients have been assessed as suitable for opioid treatment (WHO pain ladder level 3). This was made explicit in the final scope of the guideline.
SH	National Council for Palliative Care	42.03	full	3		We **recommend** that you echo your finding that "*Despite the increased availability of strong opioids, published evidence suggests that pain which results from advanced disease, especially cancer, remains under-treated*" in the first page of the Introduction. Doing so would send a stronger message to non-specialists reading the document the urgent importance of addressing pain relief for all people approaching the end of life.	We have inserted this text on p3.
SH	Nycomed UK Ltd	28.00	Full	3	10	The guidance and declaration state the following aims: • '...target to make effective pain control more accessible...' • '...highlight the importance of effective pain control...' • '...control of pain in adults with cancer...' The draft guideline subsequently appears to contradict this by restricting the use of effective medications primarily on the basis of acquisition cost.	NICE guidelines are required to look at both clinical and cost effectiveness and make recommendations based on this data.
SH	Association for Palliative	25.04	Full	3	17	Strong opioids are only one of the principal	The scope of this guideline is restricted to

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	Medicine of Great Britain and Ireland					treatments for pain related to advanced and progressive disease and in fact this guideline risks over emphasising the place of opioids by omitting to mention other methods of pain control. While we appreciate this is because the guideline is about opioids in palliative care the balance could be redressed at this point in the introduction by mentioning that they are only one of the methods and should be used as part of a comprehensive package of pain management.	strong opioids and does not cover non-opioid pain control or adjuvants. These issues have therefore not been covered.
SH	Nycomed UK Ltd	28.01	Full	3	18	This statement implies that oral morphine should be the principal treatment for all types of pain in palliative care. This contradicts evidence published in clinical trials and associated pharmacodynamic data supporting the use of different opioids to treat differing pain states, i.e. chronic pain, acute pain, breakthrough pain etc...	This is the introduction not a recommendation. It is true that morphine is one of the commonly prescribed strong opioids.
SH	Nycomed UK Ltd	28.02	Full	3	20	The text states that, '...the pharmacokinetic profiles of the various opioids are very different with marked differences in bioavailability, metabolism and response between individual patients.' It therefore follows that different opioids with different pharmacokinetic profiles should be used for different pain states, i.e. chronic pain, acute pain, breakthrough pain etc...	This is the introduction. The topics investigated by this guideline tried to compare a variety of opioid preparations.
SH	Nycomed UK Ltd	28.03	Full	3	22	Stating that, 'a suitable opioid must be selected for each patient' is a very worthwhile aim (e.g. Davies et al Eur J Pain 2009,13:331-338). This statement is then contradicted by the rest of the draft guideline which is somewhat prescriptive and narrow in focus.	This is true but the recommendations in the guideline have to be based on evidence of both clinical and cost-effectiveness.
SH	Palliative Care Pharmacists Network	37.00	full	3	23	Sentence doesn't read easily consider just including suitable selection & need for titration	We think the current sentence reads correctly.

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SH	Palliative Care Pharmacists Network	37.01		3	26	Change the word comfort to either symptom control/pain control or management	We have changed "comfort" to "satisfaction".
SH	St. Oswald's Hospice	13.00	Full	3-4	-	Good introduction that promises an effective guidance on prescribing opioids.	Thank you.
SH	National Council for Palliative Care	42.04	full	4		On Drug recommendations, clinicians we consulted felt it was a wasted opportunity to not include prescribing guidance as this was a difficult area for some non-specialists. We **recommend** you lengthen this section.	This is standard text agreed by NICE and we are not able to change it. However we have added recommendations in section 3.3 on a safe starting dose for titration and a recommendation to section 3.5 about calculating equivalence.
SH	St Josephs Hospice	10.00	full	4	1	Clarity required about when the first line opioid suggested might not be appropriate/ or other first line opioids might need to be considered e.g. renal and liver function	While we did not exclude patients with renal impairment from the scope of this guideline, the evidence review did not find any data specific to this group of patients. Consequently the GDG were unable to make prescriptive recommendations for patients with renal or hepatic impairment. However they have now added a recommendation that specialist advice should be sought before prescribing opioids for this group of patients Recommendations for patients unable to take oral opioids have been made in 1.1.8.
SH	ProStrakan Group	30.00	Opioids in Palliative Care – Full Guidance	4	14	The guideline is aimed at 'non specialist' healthcare professionals, however it states that it is likely to be of relevance to palliative care specialists as well. We believe that the proposed guidance will limit choice of prescribing for both groups by this implied broader application, and yet specialist use is not specifically addressed in these guidelines. This will not therefore clarify the clinical pathway and improve pain management.	Whilst the guideline may limit choice for first line treatment with strong opioids, it makes clear recommendations for when patients should be referred for specialist palliative care. The guideline does not make recommendations on second-line or subsequent treatment that may be guided by specialists in palliative care.
SH	UK Clinical Pharmacy Association	20.03	Full	4	15	Given the aim to improve pain management and improve patient safety, we would suggest	We have added recommendations in section 3.3 on a safe starting dose for titration and a

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						providing specific dosing advice, particularly at initiation. This would help address some of the issues highlighted in the current practice section of the final scope (3.1d&e). The scope also says it will consider titration schedule (4.3.1), which is not present in the consultation draft.	recommendation to section 3.5 about calculating equivalence.
SH	Archimedes Pharma Ltd	32.06	Full	4	15	The guideline itself is intended for the use of "...non-specialist healthcare professionals", though it is suggested that the guideline may also be of use to a specialist audience. It is important that there is more clarity provided at the start of the document regarding how the guideline is intended to be used; who is designated a "specialist" in this regard; palliative care, pain, oncologists; or all secondary care consultants? Nurses and pharmacists, or clinicians only? Is this guidance intended to direct prescribing only in primary care or in secondary care as well? The target audience is important when considering the advice given regarding the subpopulation of patients with BTCP, who may not be recognised by the non-specialist prescriber and whose pain may therefore be inadequately managed.	It is not possible for NICE to define whether a healthcare professional is a specialist of non-specialist in the management of patients requiring strong opioids. The individual healthcare professional should be aware whether or not they have specialist knowledge.
SH	Royal College of General Practitioners & British Pain Society	36.01	Full	4	15	*"The target audience is non-specialist healthcare professionals initiating strong opioids for pain in adults with advanced and progressive disease. However, the guideline is likely to be of relevance to palliative care specialists as well."* It is not clear what is meant by 'non-specialists in this context – if it means everyone other than palliative medicine specialists, we presume it would it include GPs, but would it also apply	It is not possible for NICE to define whether a healthcare professional is a specialist or non-specialist in the management of patients requiring strong opioids. The individual healthcare professional should be aware whether or not they have specialist knowledge.

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						oncologists, neurologists, even pain medicine specialists? And in what way could the guidance apply to specialists in palliative medicine?	
SH	British Pain Society	38.02	Full	4	15	*"The target audience is non-specialist healthcare professionals initiating strong opioids for pain in adults with advanced and progressive disease. However, the guideline is likely to be of relevance to palliative care specialists as well."* It is not clear what is meant by 'non-specialists in this context – if it means everyone other than palliative medicine specialists, we presume it would it include GPs, but would it also apply oncologists, neurologists, even pain medicine specialists? And in what way could the guidance apply to specialists in palliative medicine?	It is not possible for NICE to define whether a healthcare professional is a specialist or non-specialist in the management of patients requiring strong opioids. The individual healthcare professional should be aware whether or not they have specialist knowledge.
SH	Association for Palliative Medicine of Great Britain and Ireland	25.06	Full	4	17	Several members expressed the opinion that the guideline did not offer any advice likely to be helpful to palliative care specialists.	Although the guideline is aimed at non-specialists, we hope that these guidelines would be of some value to all healthcare professionals.
SH	St. Oswald's Hospice	13.02	Full	4	19	The BNF is an inconsistent source for doses and just what is a *'drug's summary of product characteristics'*? Surely this guideline was needed precisely because such information is so poor and contradictory. This section suggests the promises of the preceding introductory section may not be realised.	This is standard text agreed by NICE and we are not able to change it. However we have added recommendations in section 3.3 on a safe starting dose for titration and a recommendation to section 3.5 about calculating equivalence.
SH	Isabel Hospice	19.00	Full	4	19	By failing to make any recommendations on drug doses, the guidance becomes of limited practical value to generalists.	We have added recommendations in section 3.3 on a safe starting dose for titration and a recommendation to section 3.5 about

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							calculating equivalence.
SH	Wales Palliative Care Strategy Implementation Board	12.00	Full	4	20	The guideline states that it does not give any guidance on doses and refers the reader to the British National Formulary. The problem is that the information in the British National Formulary is not correct. It does not comply with known best practice and there are some quite serious concerns about the way that it is written. The document also states that it makes the assumption that prescribers will use "a drug summary of product characteristics" to inform decisions; the guideline needs to be very clear what this summary is and where it is to be derived from because it is a complete fallacy to believe that people will be reading in detail the inserts from different manufacturers of drugs.	This is standard text agreed by NICE and we are not able to change it. However we have added recommendations in section 3.3 on a safe starting dose for titration and a recommendation to section 3.5 about calculating equivalence.
SH	Royal College of General Practitioners & British Pain Society	36.02	Full	4	20	*"The guideline does not make recommendations on drug dosage; prescribers should refer to the 'British national formulary' for this information."* We believe that this is a serious missed opportunity, because the BNF does not give adequate current information about drug doses, especially regarding starting strong opioids in patients who are in renal or hepatic failure; about dose titration; and about dose equivalences. Furthermore, we believe it would have been very helpful to indicate the levels of doses of different strong opioids beyond which non-specialists should not prescribe, ie when they should refer to palliative medicine or pain specialists.	This is standard text agreed by NICE and we are not able to change it. However we have added recommendations in section 3.3 on a safe starting dose for titration and a recommendation to section 3.5 about calculating equivalence.
SH	Palliative Care Pharmacists Network	37.03		4	20	BNF capital letters also add in local guidelines PCF4 summary of product characteristics	This is standard text agreed by NICE and we are not able to change it.

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SH	British Pain Society	38.03	Full	4	20	*"The guideline does not make recommendations on drug dosage; prescribers should refer to the 'British national formulary' for this information."* We believe that this is a serious missed opportunity, because the BNF does not give adequate current information about drug doses, especially regarding starting strong opioids in patients who are in renal or hepatic failure; about dose titration; and about dose equivalences. Furthermore, we believe it would have been very helpful to indicate the levels of doses of different strong opioids beyond which non-specialists should not prescribe, ie when they should refer to palliative medicine or pain specialists. For example, in the Guidelines for Supportive Care in Multiple Myeloma published in British Journal of Haematology (Snowden et al, 2011), a recommendation is made that when the dose of opioid reaches 120mg a day of morphine equivalent, the patient should be referred to or discussed with a specialist (palliative care or pain medicine). This is also the dose recommended for specialist referral by the Washington State Agency Medical Directors guidelines (http://www.agencymeddirectors.wa.gov/Files/OpioidGdline.pdf).	This is standard text agreed by NICE and we are not able to change it. However we have added recommendations in section 3.3 on a safe starting dose for titration and a recommendation to section 3.5 about calculating equivalence.
SH	Marie Curie Cancer Care	24.03	Full	4	21	The Guideline provides no information on doses but recommends the use of the BNF. This	This is standard text agreed by NICE and we are not able to change it. However we have

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						formulary is inconsistent in its advice and does not concord with current best practice. It certainly does not provide advice which would be clear to non-specialist prescribers.	added recommendations in section 3.3 on a safe starting dose for titration and a recommendation to section 3.5 about calculating equivalence.
SH	Palliative Care Pharmacists Network	37.04		4	23	Repeat of a statement further up the page- remove?	We have removed the repetition.
SH	Association for Palliative Medicine of Great Britain and Ireland	25.07	Full	4	24	The guideline states that it is principally for non-specialist healthcare professionals. It would be helpful to define who is a specialist and who is a non-specialist in this context.	It is not possible for NICE to define whether a healthcare professional is a specialist or non-specialist in the management of patients requiring strong opioids. The individual healthcare professional should be aware whether or not they have specialist knowledge.
SH	Palliative Care Pharmacists Network	37.02		4	26	Include hydromorphone – licensed for cancer pain unlike a buprenorphine product & is used in palliative care	This is standard text agreed by NICE and we are not able to change it.
SH	St. Oswald's Hospice	13.01	Full	4	3	The omission of hydromorphone is a problem for patients with severe renal impairment who can take oral opioids.	Since this is a NICE short clinical guideline we have focused on addressing the problems associated with the commonly used strong opioids. The GDG felt that hydromorphone would only be prescribed by specialists and therefore was not a priority for investigation in this guideline.
SH	Association for Palliative Medicine of Great Britain and Ireland	25.05	Full	4	9	The guideline rightly highlights errors causing under dosing and avoidable pain or over dosing and distressing side effects. However many members made the point that because there is no guidance on dosing this guideline will do nothing to address this concern and will therefore not achieve its intention of improving pain management and patient safety. .	We have added recommendations in section 3.3 on a safe starting dose for titration and a recommendation to section 3.5 about calculating equivalence.
SH	Teva UK	34.02	Full	5		We are further concerned that, despite the Introduction referring to the importance of patient choice, the current wording relating to	Whilst the guideline may limit choice for first line treatment with strong opioids, it makes clear recommendations for when patients

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						BTcP treatment removes any element of choice despite several specifically designed products being available	should be referred for specialist palliative care.
SH	National Council for Palliative Care	42.05	full	5		It is excellent that a person-centred approach is advocated at the forefront of the document. The requirement to provide verbal and written information to patients and carers, particularly on who to contact out of hours, is very welcome (although this will obviously need monitoring in practice). We agree that good communication between professionals and patients (and carers) is essential in ensuring people benefit from the use of opioids in palliative care. We would **recommend** a small change in wording from *If the patient agrees, families and carers should have the opportunity to be involved in decisions about treatment and care.* to *If the patient agrees, families and carers should have the opportunity to be involved in decisions about treatment and care, and be given the information and support they need. In the event that the patient lacks capacity, the decision to involve families and carers should be based on advance care plans, or in their absence, the best interests of the person in accordance with the Mental Capacity Act.*	This is standard text agreed by NICE and we are not able to change it.
SH	St. Oswald's Hospice	13.04	Full	5	10	The Mental Capacity Act in England and Wales is not a 'code of practice' but an Act of parliament that requires clinicians to follow a specific checklist in someone who lacks capacity for specific decisions.	This is standard text agreed by NICE and we are not able to change it.
SH	Palliative Care Pharmacists Network	37.05		5	19	English to english	We have made this change.

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SH	Nycomed UK Ltd	28.04	Full	5	3	The section on patient care is commendable in that it highlights the fact that patients should have the opportunity to make informed decisions about their care and treatment which in turn is linked with treatment adherence. However, the draft guideline appears to restrict the choices available to patients and removes the opportunity to make an informed decision.	The recommendations in the guideline have to be based on evidence of both clinical and cost-effectiveness. This can sometimes mean that treatment options are limited.
SH	Association for Palliative Medicine of Great Britain and Ireland	25.08	Full	5	4	The guideline rightly says that treatment and care should take into account patient's needs and preferences however the rest of the guideline goes on to ignore exactly those needs and preferences and any evidence relating to this.	The recommendations in the guideline have to be based on evidence of both clinical and cost-effectiveness. This can sometimes mean that treatment options are limited.
SH	Wales Palliative Care Strategy Implementation Board	12.01	Full	5	5	There is a discrepancy between the statement on page 5 extolling patient choice ("People with advanced and progressive disease, who require strong opioids for pain control should have the opportunity to make informed decisions about their care and treatment") and the recommendation 1.1.6 ("Do not routinely offer transdermal patch formulations as first-line maintenance therapy to patients in whom oral opioids are suitable"). This is especially important as the evidence review (p32) suggests that pain relief is as good with a fentanyl patch and is preferred by more patients, although there are known dangers with fentanyl being used inappropriately and its cost is far higher than morphine (page 43).	The recommendations in the guideline have to be based on evidence of both clinical and cost-effectiveness. This can sometimes mean that treatment options are limited.
SH	National Council for Palliative Care	42.06	full	6	1	We feel that the summary of recommendations is rather selective – see, for example, points 7 (p16 1.1.1) and 9 (p16 1.1.13) below. We **recommend** that this section is lengthened, to become more reflective of the document as a whole.	This section contains all of the recommendations in the guideline. We disagree that it is selective.

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SH	Wales Palliative Care Strategy Implementation Board	12.07	Full	9	1	Care Pathway Box 1 implies the communication about concerns as the most important. There needs to be a box in here requiring people to diagnose the cause of the individual pains and assess the individual.	We were tasked with developing a short clinical guideline and therefore the scope was restrictive in order to make this workable. The guideline assumes patients have been assessed as suitable for strong opioid treatment (WHO pain ladder level 3). This was made explicit in the final scope of the guideline.
SH	Isabel Hospice	19.03	Full	9	1	In the first box of the care pathway, it would be sensible to highlight that the patient should have already had trials of WHO ladder step one and two analgesics.	We have made this amendment.
SH	Isabel Hospice	19.04	full	9	1	Whilst diamorphine and parenteral preparations of other drugs are considered elsewhere in the guidance, the lack of comment on initiating continuous subcutaneous infusions of opioids for patients unable to take oral opioids and where patches are not appropriate in the pathway is a definite limitation.	We have added a recommendation on subcutaneous delivery for patients whose analgesic requirements are unstable.
SH	St. Oswald's Hospice	13.06	Full	9	2nd box, 1st bullet point	See 4 above.	See response above.
SH	St. Oswald's Hospice	13.07	Full	9	3rd box, 2nd bullet point	See 6 above *Important note:* enthusiastic wording on transdermal opioids needs to be tempered to avoid an impression that there us a conflict of interest in the CDG regarding these opioids.	The wording used in the care pathway is taken from the recommendations in the guideline. We disagree that recommending transdermal opioids be considered for use is too enthusiastic. We consider it to be pragmatic and based upon the best available evidence.
SH	Wales Palliative Care Strategy Implementation Board	12.08	Full	9	6	Care pathway The comments made about section 1 apply to the boxes in section 2. These are very vague and are not actually clinically useful since they	This care pathway summarises the recommendations in the guideline and is not intended to be a comprehensive description of care. As stated in section 3.9.5, due to the

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			Full	63	10	don't state what should be prescribed (stimulant laxatives, centrally acting antiemetics that have an antidopaminergic effect etc).	lack of evidence, the GDG were not able to specify particular laxatives.
SH	ProStrakan Group	30.02	Opioids in Palliative Care – Full Guidance	9	8	With respect to choice of medication for BTcP FAFs should be also considered for the reasons given above (see point 1).	This topic compared the effectiveness of IR morphine, fast-acting fentanyl and IR oxycodone. It did not presume that IR morphine was the most effective opioid. INFS showed a significant clinical benefit at a minority of time points. At 10 minutes 52.4% of patients taking fentanyl had responded compared to 45% of patients taking morphine. At 15 minutes 75.5% of patients taking fentanyl had responded compared to 69.3% of patients talking morphine. The GDG felt that overall this did not indicate a clinically significant benefit for INFS over IR morphine. In addition the GDG were aware that there is a significant additional cost to using INFS. Consequently the GDG recommended the use of IR morphine. We have amended the LETR paragraph to clarify the GDGs interpretation of the evidence.
SH	Nycomed UK Ltd	28.08	Full	9	All	The proposed care pathway appears to be designed to reduce acquisition costs rather than to give patients an informed choice and allow them to receive the most appropriate treatment based on their specific type of pain.	This care pathway summarises the recommendations in the guideline. The linking evidence to recommendations sections detail how the GDG moved from the evidence to the recommendations. NICE guidelines are required to look at both clinical and cost effectiveness and make recommendations based on this data – this does not necessarily mean recommending the cheapest option.
SH	Palliative Care Pharmacists Network	37.14		9	all	If any of the above is accepted the flow chart will need changing	Thank you.
SH	St Ann's Hospice	14.01	full	9	Box	In the text box "background pain" Instead of	We do not think this needs to be specified.

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					3	"offer a choice of either oral sustained- release or…" this should read "offer a choice of either **regular** oral sustained –release or…"	
SH	St. Oswald's Hospice	13.08	Full	9	Middle box at bottom	See 6 above See important note in 8 above.	Thank you.
SH	St Ann's Hospice	14.02	full	9	Middle box bottom row	In this text box instead of " Offer sustained release morphine as first line oral maintenance therapy" this should read "offer **regular** sustained relase morphine"	We do not think this needs to be specified.
SH	Help the Hospices	43.00		9	2	**2. Care Pathway** This really doesn't have enough detail to be of safe clinical use.	This care pathway summarises the recommendations in the guideline and is not intended to be a comprehensive description of care.
SH	National Council for Palliative Care	42.12	full	10		The evidence section overwhelmingly focuses on cancer. One neurologist we consulted with pointed out that evidence on chronic degenerative neurological conditions was not referenced at all. Similarly, a dementia specialist said that pain often goes untreated in dementia owing to the behavioural challenges associated with this condition; however this is also left unmentioned. The consultation questions ask respondents how the guideline "could be changed to better promote equality of opportunity" Ensuring pain relief is made available to people with all conditions (not just cancer) is an important part of this. We **recommend** that the guideline addresses this point and changes the wording in this section to make clearer that opioids can be used to treat pain in a range of conditions, as	We have removed the term "in cancer" from this background text. The search for evidence was not limited to people with cancer. Our recommendations apply to all patients with advanced and progressive disease.

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						per the Introduction on p. 3.	
SH	Nycomed UK Ltd	28.09	Full	11	14	The statement based on Bender at al. 2008 - '...patients wanted to know about all available options for pain control....' – does not appear to be reflected in this draft guideline.	The recommendations in the guideline have to be based on evidence of both clinical and cost-effectiveness. This can sometimes mean that treatment options are limited.
SH	Astrazeneca UK Ltd	31.06	Appendix E	12	7-11	As recognised within the estimated costs for a constipation event, some patients that receive laxatives concomitantly with strong opioids do not experience relief of constipation. While some of these will go on to receive an enema, there are also some patients that require manual evacuation (also known as manual disimpaction). This is a costly procedure as it is conducted under general anaesthetic. The cost of manual evacuation has not been incorporated into the cost of a constipation event in the cost-effectiveness analysis; however, the cost of manual evacuations should be incorporated as it is likely to have a significant impact on the cost-effectiveness results.	The GDG considered the use of manual evacuation to be rare. Thus, since the model is intended to reflect common practice, it was felt that it was unnecessary to include this cost in the constipation event calculation.
SH	Nycomed UK Ltd	28.10	Full	12	All	More recent surveys are available and should be used in developing an up to date guideline. For example Davies et al Eur J Pain 2011,15:756-763; Bertram et al Schmerz 2010,24(6):605-12)	None of these studies were identified by our search and inspection of them reveals that they do not meet the inclusion criteria for this question on patient/carer information needs.
SH	Association for Palliative Medicine of Great Britain and Ireland	25.32	Full	13	1	One respondent noted "I suspect that non-specialist readers would struggle to find firm and time consuming recommendations based on 3 studies with a total populations of 85 patients"	We agree that the evidence was limited but the expert opinion of the GDG was that these recommendations would improve patient care and experience.
SH	Target Ovarian Cancer	22.01	Full	16	1	We welcome the series of recommendations on communication with patients and carers. Improved information for patients and their family/carers will support them in making an informed choice about the treatment options available to them. We acknowledge that in a small proportion of patients information might	Thank you.

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						heighten anxiety and preclude the use of opioids; however, we feel that in the majority of cases it will alleviate fears and in turn reflect positively on opioid uptake and compliance.	
SH	Pancreatic Cancer UK	23.00	Full	16	1.1.1	We strongly support the recommendation to ask patients about any concerns they have about taking strong opioids such as addiction, side effects and fears that treatment with opioids implies the final stages of life. These can be key concerns for patients with advanced or progressive disease and it is important that they are addressed.	Thank you.
SH	National Council for Palliative Care	42.07	full	16	1.1.1	The Progresive Supranuclear Palsy (PSPA) nurse specialists we received comments from highlighted that a frequent concern of carers was the undue amount of drowsiness experienced by the patient, limiting their quality of life because they are sedated for most of the time. At this stage many carers are more concerned that their loved one is as pain free and responsive as possible, than about addiction or tolerance (though the latter would certainly need to be discussed when initiating opioids). We understand that drowsiness is addressed on p. 70 but would **recommend** that you make this point earlier on in the document, and suggest it is included in the bullet points on line 1.1.1 (and accordingly in 3.1.6)	The issues specified in 1.1.1 are not intended to be an exclusive list. We would anticipate that healthcare professionals would ask patients about all concerns that they have.
SH	Wales Palliative Care Strategy Implementation Board	12.02	Full	16	1.1.1	Recommendation 1.1.1 "When offering a patient pain treatment with strong opioids, ask them about concerns such as: addiction, tolerance, side effects, fears that treatment implies the final stages of life". I worry that this will lead to less-experienced staff asking direct questions to all patients and causing distress.	We disagree. The GDG believes that anxieties about these issues are common and the purpose of this guideline is to educate inexperienced staff on their importance.
SH	Help the Hospices	43.01	full	16		**1.1.1 Communication**	The issues specified in 1.1.1 are not intended

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						In addition to the concerns listed – patients are often concerned about driving and use of alcohol with opioids	to be an exclusive list. We would anticipate that healthcare professionals would ask patients about all concerns that they have.
SH	Help the Hospices		full	16		1.1.2 **Written information** - question reference some existing good guidelines	We are not able to cross-reference non-NICE guidance. However we are aware that a NICE clinical guideline is in development on Patient experience in adult NHS services.
SH	St. Oswald's Hospice	13.03	Full	16	1.1.1	The source of the concern is missing, risking the implication that these are clinician's concerns. Suggest changing to: *When offering a patient pain treatment with strong opioids, ask the patient if they have concerns such as.....*	We feel that the current wording is clear.
SH	Association for Palliative Medicine of Great Britain and Ireland	25.09	Full	16	1.1.1	Most respondents expressed the concern that asking patients about concerns such as addiction from a check list of concerns would be more likely to increase anxiety and opiophobia and what we should be doing is responding to the patient and carer agenda and addressing any concerns. We suggest rewording "when offering a patient pain treatment with strong opioids address patient and carers concerns. These may include:…".	The issues specified in 1.1.1 are not intended to be an exclusive list. We would anticipate that healthcare professionals would ask patients about all concerns that they have.
SH	National Council for Palliative Care	42.09	full	16	1.1.13	PSPA nurse specialists highlighted constipation as a major issue for people with PSP/CBD and as recommended in the guideline, laxatives should be prescribed alongside opioid prescriptions. We understand that constipation is addressed on p. 63 but **recommend** that more could be added to 1.1.3 on the importance of providing guidance and information, particularly for carers, on how to use laxatives to optimum effect. This would help to reduce the needless complications that can arise when laxatives are administered in an ad hoc manner.	We envisage that by giving patients frequent access to review of side effects, appropriate information will be given at this point.
SH	Nottingham University Hospitals NHS Trust	9.00	FULL	16	1.1.2	Although not a clinical issue and probably outside the scope of the review, nevertheless	Storage of opioids was not investigated by the guideline and so the evidence on this has not

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						safe storage is an important patient safety issue. As opioid usage becomes widespread, there is a need to provide advice regarding safe storage. The safe storage advice is to prevent them being accessible not only to children but also to anti-social elements. The patients needing opioids for various symptoms can be vulnerable to actions of drug users and anti-social elements in the community.	been appraised. As such we are not able to make recommendations on this issue.
SH	Sobell House Hospice Charity	11.01	Full	16	1.1.2	Too much to fit in to GP consultation slot. More training for community pharmacists especially in use of unlicensed or off-label applications.	The implementation of these recommendations will be determined locally.
SH	St Ann's Hospice	14.00	full	16	1.1.2	Is there any specific written information to be recommended? Is this for inpatients or outpatients?	We are not able to endorse information produced by other organisations.
SH	Pilgrims Hospices in East Kent	17.00	Full	16	1.1.2	It would be useful if NICE could provide a National, evidence-based leaflet rather than several organisations undertaking a similar piece of work	It is not within NICE's remit to produce leaflets although we would hope that the recommendations guide production of local information. However NICE do produce a lay version of the guideline (Understanding NICE Guidance) which may be a useful source of information.
SH	Pancreatic Cancer UK	23.01	Full	16	1.1.2	We strongly support the recommendation to provide verbal and written information to patients on opioid therapy and their carers. It is particularly important to address questions about how and when to take the therapy, how long the pain relief should last, side effects and signs of toxicity.	Thank you.
SH	Royal College of Nursing	27.01	Full	16	1.1.2	Should specifically mention driving	The issues specified in 1.1.1 are not intended to be an exclusive list. We would anticipate that healthcare professionals would ask patients about all concerns that they have. We have amended recommendation 1.1.23

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							(previously 1.1.17) to include driving and inserted a cross reference to the relevant DVLA guidance
SH	Royal College of General Practitioners & British Pain Society	36.04	Full	16	1.1.2	We believe that information should also be given explicitly about driving when on strong opioids and also on the concomitant consumption of alcohol. It may be best practice to always 'provide verbal and written information' but in practice not necessarily feasible in every case and not necessarily wanted or needed by every patient. There didn't appear to be any evidence presented to justify having to give written information. I'd recommend either the addition of 'as appropriate' or alteration of the wording to 'provide appropriate information (verbal and/or written)'	The issues specified in 1.1.1 are not intended to be an exclusive list. We have added advice about driving to recommendation 1.1.23 (previously 1.1.17) and inserted a cross reference to the relevant DVLA guidance. However information on alcohol consumption is already included in the patient information leaflets provided by the drug manufacturer. We do not feel this needs to be included in a recommendation There was consensus among the GDG based on their clinical experience that providing written information would improve patient experience. Therefore we do not think that the recommendation needs to be changed.
SH	British Pain Society	38.05	Full	16	1.1.2	We believe that information should also be given explicitly about driving when on strong opioids and also on the concomitant consumption of alcohol.	We have added advice about driving to recommendation 1.1.23 (previously 1.1.17) and inserted a cross reference to the relevant DVLA guidance. However information on alcohol consumption is already included in the patient information leaflets provided by the drug manufacturer. We do not feel this needs to be included in a recommendation
SH	Isabel Hospice	19.01	Full	16	1.1.2	Signposting to existing appropriate patient information or development of a standard national patient information leaflet would be useful. If this is not possible it should be specified that any patient information developed goes through an appropriate governance process.	We are not able to endorse information produced by other organisations and it is not within NICE's remit to produce leaflets. We are unaware of any governance process which standardises patient information, which we could recommend is followed.
SH	Association for Palliative	25.10	Full	16	1.1.2	Many respondents were uncertain what the	We have changed this to "how effective they

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	Medicine of Great Britain and Ireland					phase "the potential for non-effectiveness" was intended to convey. We wondered if it was intended to convey the need for individual titration and may be better expressed thus.	are likely to be".
SH	Nycomed UK Ltd	28.05	Full	16	1.1.2	The draft guideline should also consider how rapidly pain relief should start; this is especially relevant when treating breakthrough pain.	We disagree. A patient in pain requires immediate pain management and this does not need to be specified.
SH	Wales Palliative Care Strategy Implementation Board	12.03	Full	16	1.1.2	Should advice on driving be addressed?	We have added advice about driving to recommendation 1.1.23 (previously 1.1.17) and inserted a cross reference to the relevant DVLA guidance
SH	Association for Palliative Medicine of Great Britain and Ireland	25.11	Full	16	1.1.2	Almost all respondents felt that there should be some guidance on advising patients not to drive when initiating or titrating opioids until they were sure that they were not made drowsy or their concentration impaired by opioids.	We have added advice about driving to recommendation 1.1.17 and inserted a cross reference to the relevant DVLA guidance
SH	Astrazeneca UK Ltd	31.01	Full	16	1.1.2	We believe it would be helpful to also include instructions to patients and carers about safe storage and safeguard against abuse.	Storage of opioids was not investigated by the guideline and so the evidence on this has not been appraised. As such we are not able to make recommendations on this issue.
SH	Pancreatic Cancer UK	23.02	Full	16	1.1.3	We strongly support the recommendation to offer patients a frequent review of pain control and side effects. We often hear from people who do not have adequate pain control or are experiencing side effects from pain control. It is important that these needs are addressed so that the patients can be as comfortable as possible. We also strongly support the recommendation for patients and carers to have information about who to contact out of hours.	Thank you. Thank you.
SH	Association for Palliative Medicine of Great Britain and Ireland	25.12	Full	16	1.1.3	There needs to be some instruction to clarify if patients are on weak opioids and then appropriate dosing guidance based on the dose	Management of weak opioids is outside the scope of this guideline and we are therefore unable to make recommendations on this

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						of weak opioids a patient has been exposed to.	issue.
SH	St Josephs Hospice	10.01	full	16	12	Comment about patients avoiding driving/ operating machinery when being titrated	We have added advice about driving to recommendation 1.1.17 and inserted a cross reference to the relevant DVLA guidance
SH	Nycomed UK Ltd	28.11	Full	16	15	Surely one should also consider informing patients of the speed of onset of efficacy as well as the duration? This is especially important in pain such as breakthrough pain.	We think this encompassed within recommendation 1.1.2
SH	Target Ovarian Cancer	22.03	Full	16	19	Agree with the recommendation that patients can access frequent review of pain control and side effects.	Thank you.
SH	Target Ovarian Cancer	22.04	Full	16	19	Welcome the recommendation that patients are given information on who to contact out of hours if they have concerns about their pain relief.	Thank you.
SH	St. Oswald's Hospice	13.09	Full	16	3	See 4 above	See comment above.
SH	Marie Curie Cancer Care	24.05	Full	16	3	Direct questioning, by inexperienced staff, concerning fear of addiction or of hastening death will most probably alarm the patient and certainly risks an incompletely-informed refusal of the medication, to the detriment of the patient's care. This situation is regularly faced by specialists in palliative care on meeting a patient whose confidence in the medication has been undermined by inappropriate 'information'.	We disagree. The GDG believes that anxieties about these issues are common and the purpose of this guideline is to educate inexperienced staff on their importance.
SH	Department of Health	26.02	Full	16	3	The first recommendation for patient information should be to provide verbal and written information which addresses practical concerns such as if and when it is safe to drive or to consume alcohol while taking strong opioids. Although no evidence was found, these are questions which practicing clinicians are asked on a regular basis. This might be an appropriate place to use an 'expert opinion' recommendation.	We have added advice about driving to recommendation 1.1.17 and inserted a cross reference to the relevant DVLA guidance. However information on alcohol consumption is already included in the patient information leaflets provided by the drug manufacturer. We do not feel this needs to be included in a recommendation.

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SH	Target Ovarian Cancer	22.02	Full	16	8	We support the recommendation for the provision of verbal and written information. However, we feel there should be specific reference made to constipation as it is the side effect experienced by the majority of patients receiving opioid pain relief. Constipation is a particularly worrying symptom for women with ovarian cancer because it is often a sign of more serious bowel obstruction. In addition to the acknowledgement of this side-effect clear information and guidance should be given to patients and carers on how constipation will be managed.	This list is not exhaustive and we would anticipate that written information would cover all side effects.
SH	St Ann's Hospice	14.03	full	17	2nd last line	Should hydromorpone be included in the list with bupenorphone, diamorphine, fentanyl, morphine and oxycodone? Also, are these research recommendation for these drugs relevant to the generalist?	The GDG felt that hydromorphone would only be prescribed by specialists and therefore was not a priority for investigation in this guideline. Research recommendations are intended to provide evidence which would inform future recommendations to the generalist
SH	Royal College of Nursing	27.03	Full	18	3.3.2	'IV and IM' were not included, but do have a place in managing acute exacerbation of pain - particularly when patients are admitted to hospital	IV and IM routes are not commonly used in people starting strong opioids and therefore were not investigated by the guideline. Therefore we are unable to make recommendations on this issue.
SH	St Ann's Hospice	14.04	full	18	8	Breakthrough definition? Incident, titration or episodic?	A definition of breakthrough pain is included in the glossary. We have also added an introductory paragraph to this section.
SH	Association for Palliative Medicine of Great Britain and Ireland	25.33	Full	19	2	"Strong-opioid-naive" may be a bit too much jargon for a non-specialist, and would benefit from clarification if it is to be used repeatedly, although the point is, of course, important.	We have amended this text to make it clearer.
SH	Department of Health	26.04	Appendix D	20	1	In a document promoting guidance for safe and effective prescribing it would be helpful to	The GDG felt the issue of patient switching opioid because of side effects was a higher

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						address a more general question such as what class of laxative is the most effective in preventing and treating opioid induced constipation. Without this there is a risk of continued ineffective prescribing of inappropriate laxatives.	priority for investigation than comparing laxatives.
SH	Nycomed UK Ltd	28.12	Full	21	All	This table is incomplete and omits key clinical studies published since 2003.	We are unclear which key clinical studies you are referring to.
SH	Astrazeneca UK Ltd	31.05	Appendix E	22	1-16	This section describes the limitations of the analysis conducted by the GDG. A limitation that has not been noted is that key data inputs in the model have been estimated by the GDG, and therefore, there is considerable uncertainty in these estimates and the subsequent results from the cost-utility model. Examples of estimated data inputs include the rate of spontaneous resolution of pain (5%, page 10, line 4), the percentage of patients requiring an enema (10%, page 12, line 9). We request that this limitation is noted in the document; firstly, as it is unclear whether all of these estimated values have been tested in the one-way sensitivity analyses and PSA; and secondly, for those readers not familiar with economic evaluations.	The limitations of the data have been explained in appendix F. However we will also add this to section 3.4.4. Most data inputs have been tested by sensitivity analysis. For those that haven't we do not believe it would affect the results of the model.
SH	Wales Palliative Care Strategy Implementation Board	12.04	Full	24	26	Should an economic analysis be done comparing subcutaneous diamorphine and morphine?	No clinical evidence was found for this comparison (as documented in section 3.6.3) Therefore it was not possible to conduct economic analysis (as documented in section 3.6.4)
SH	Sobell House Hospice Charity	11.03	Full	28	3.3.5	Very poor evidence therefore no reason why can't start on one then switch. Logical to start with IR and titrate before prescribing MR	The GDG felt that for patients with stable pain it was reasonable to start with a sustained release preparation.
SH	Royal College of Nursing	27.04	Full	28	3.3.5	Most trials are old, perhaps not all relevant	This was the evidence found from the literature search.

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SH	St. Oswald's Hospice	13.10	Full	28	6	The comfort/patient costs of erratic and missed doses of IR opioids outside clinical trials is not mentioned.	No evidence was identified on the costs of missed doses to the patient.
SH	Help the Hospices	43.02		29		1.1.4 **First-line treatment - titration** Would be useful to include examples of starting doses in opioid naïve patients or where starting dosing and opioid choice is more critical e.g. renal patients or those with advanced respiratory disease. Would be useful to note that titration with transdermal opioids is not appropriate as too slow – if a patient needs titration and cannot swallow, then a subcutaneous infusion is the best way to titrate. The evidence review states there is no evidence for the subcutaneous route – however the guidelines need to include common-sense advice? It seems a significant omission not to mention considering adjuvants during titration as opioid-sparing options. In practice, we see opioids rapidly titrated to toxic levels and no adjuvants have been considered. The evidence that sustained release titration is as effective as immediate release is interesting. This will be a new approach to clinical practice and is potentially dangerous without any dosage guidelines	We have added recommendations in section 3.3 on a safe starting dose for titration and a recommendation to section 3.5 about calculating equivalence. Transdermal opioids were investigated in this topic but oral preparation was recommended. We do not think it is necessary to specify that transdermal opioids should not be used. We have added a recommendation on subcutaneous delivery for patients whose analgesic requirements are unstable The scope of this guideline is restricted to strong opioids and does not cover non-opioid pain control or adjuvants. These issues have therefore not been covered. We have added recommendations in section 3.3 on a safe starting dose for titration and a recommendation to section 3.5 about calculating equivalence.
SH	Sobell House Hospice Charity	11.02	Full	29	1.1.4	Is the term IR or immediate release recognised outwith palliative care circles?	Immediate release has been added to the glossary.
SH	Astrazeneca UK Ltd	31.02	Full	29	1.1.4	Should recommend reference to the SMPC for starting dose and also provide titration	We have added recommendations in section 3.3 on a safe starting dose for titration and a

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						instructions, i.e., when and how to titrate.	recommendation to section 3.5 about calculating equivalence.
SH	National Council for Palliative Care	42.08	full	29	1.1.4	Did NICE consider the issue of offering patients a choice of ways to administer medication, to improve adherence? PSPA nurse specialists highlighted that oral therapies may not be the most appropriate route of administration for people experiencing swallowing difficulties, for example.	Recommendation 1.1.8 covers patients who are not able to take oral medication.
SH	Association for Palliative Medicine of Great Britain and Ireland	25.13	Full	29	1.1.4	As morphine has been recommended in the next bullet point it seems to be counter intuitive to simply say "regular oral sustained release or immediate release preparations" without specifying morphine. Also one respondent suggested switching the order to "IR or SR."	We have amended recommendation 1.1.4 to clarify that the information on rescue dose relates to morphine. We disagree that the order of IR and SR needs changing.
SH	Association for Palliative Medicine of Great Britain and Ireland	25.14	Full	29	1.1.4	There needs to be some advice to review renal function.	Long term monitoring of patients is not the focus of the guideline.
SH	Association for Palliative Medicine of Great Britain and Ireland	25.15	Full	29	1.1.4	There needs to be a caveat saying "in patients who do not have contraindications to morphine and can absorb via the oral route."	Recommendation 1.1.8 covers patients who are not able to take oral medication.
SH	Wales Palliative Care Strategy Implementation Board	12.05	Full	29	1.1.4	It is not safe to start patients who are opioid naïve on sustained release preparations without initially titrating them on immediate release preparations. It also is not safe to write this without any kind of guidance on starting doses. This section should also have something in about trying to diagnose the cause of the pain and managing the underlying cause as well as the symptoms.	The GDG felt that for patients with stable pain it was reasonable to start with a sustained release preparation
SH	Palliative Care Pharmacists Network	37.06		29	1.1.4	Remove word breakthrough there seems to be confusion between the definitions of types of pain-the new definition of breakthrough pain vs titration pain or rescue painkillers. This seems to	Given that a variety of different terminology is used in practice, the GDG had to be consistent in the terminology used in the guideline. The terminology used in this

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						happen throughout the document & could cause confusion. Also affects the flow chart	guideline is "rescue dose" for "breakthrough pain".
SH	Nycomed UK Ltd	28.06	Full	29	1.1.4	Pharmacokinetic and pharmacodynamic profiles together with expert opinion (e.g. Davies et al. Eur J Pain 2009,13:331-338; Zeppetella Clin Oncol 2011,23:393-389; Coluzzi et al. Pain 2001, 91(1):123-130) highlight the limitations of and do not support the use of immediate release morphine as a rescue medication for spontaneous episodes of breakthrough pain. The available information concerning the limitations of morphine for spontaneous breakthrough pain goes against the principles stated in the introduction about making sure effective pain relief is more accessible for cancer patients.	INFS showed a significant clinical benefit at two our of six time points. At 10 minutes 52.4% of patients taking fentanyl had responded compared to 45% of patients taking morphine. At 15 minutes 75.5% of patients taking fentanyl had responded compared to 69.3% of patients talking morphine. The GDG felt that overall this did not indicate a clinically significant benefit for INFS over IR morphine. In addition the GDG were aware that there is a significant additional cost to using INFS. Consequently the GDG recommended the use of IR morphine. We have amended the LETR paragraph to clarify the GDGs interpretation of the evidence.
SH	Nycomed UK Ltd	28.13	Full	29	13	The draft guideline cites 'expert opinion' but does not clearly identify who these experts are. Can NICE please identify the experts consulted.	We have amended to clarify that it is the expert opinion of the GDG.
SH	Association for Palliative Medicine of Great Britain and Ireland	25.34	Full	29	17	It should be made clear that the GDG failed to explore literature on sustained release opioids versus patches first line and it is that failure to explore the literature fully that makes the GDG unable to make a recommendation on the use of patches as first line treatment.	Because the GDG felt that it was reasonable to start a patient with stable pain on a sustained release preparation, this is included in recommendation 1.1.4 under titration. However the evidence review is in section 3.4.2 under first line maintenance therapy where it would be more commonly used.
SH	Isabel Hospice	19.05	Full	29	22	No clear guidance is given with respect to what "clinical presentation" may make either immediate or sustained release opioids more appropriate, making this comment of limited benefit to generalists.	We have deleted the phrase "clinical presentation"
SH	Marie Curie Cancer Care	24.04	Full	29	25	Patient preference is quoted as the first determinant of the method and drug choice for	The wording in the recommendation is "offer" which implies that the patient has a choice

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						titrating analgesic requirement. While patient choice will probably enhance compliance with a treatment regime, the primary consideration of the patient will be to achieve rapid pain control. To do this, the evidence quoted here suggests that they would take the clinician's advice on the method to be adopted.	whether or not to take the clinicians advice.
SH	Nycomed UK Ltd	28.14	Full	29	26	The recommendation to use rescue doses of oral immediate-release preparations for breakthrough pain goes against the current accepted guidelines for treating breakthrough pain.	We are not clear which guidelines you are referring to. The GDG based their recommendations based on the available evidence, not recommendations made in other guidelines.
SH	Palliative Care Pharmacists Network	37.15		29	26	In the box take out for breakthrough & change to rescue or titration	Given that a variety of different terminology is used in practice, the GDG had to be consistent in the terminology used in the guideline. The terminology used in this guideline is "rescue dose" for "breakthrough pain".
SH	Sobell House Hospice Charity	11.04	Full	29	3.3.6	Opioid naïve, frail and elderly, impaired renal function should start with IR first. Caution with fentanyl patch initiation in opioid naïve. Expert opinion needed due to low quality evidence and referral to approves texts eg PCF4 or websites or apps eg palliative adult network guidelines 2011	While we did not exclude patients with renal impairment from the scope of this guideline, the evidence review did not find any data specific to this group of patients. Consequently the GDG were unable to make prescriptive recommendations for patients with renal or hepatic impairment. However they have now added a recommendation that specialist advice should be sought before prescribing opioids for this group of patients. We do not recommend initiation with patch formulations unless patients are unable to take opioids via the oral route (1.1.8) which also recommends having specialist support.
SH	Association for Palliative Medicine of Great Britain and Ireland	25.36	Full	38	10	There should also be statements that patients were more likely to discontinue sustained release morphine due to adverse effects and	These are summaries of what was reported in the evidence.

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						that patient preference was for transdermal Fentanyl particularly as patient preference is rated as an important factor in the introduction to the guideline.	
SH	Association for Palliative Medicine of Great Britain and Ireland	25.35	Full	38	14	The statement that sustained release morphine is associated with statistically significantly better pain relief in patients with cancer pain is taken from a Meta-analysis which ignored the largest body of evidence from cross over studies where no difference in pain relief was found and if it is to be left in should be given that caveat in the summary evidence statement.	We have now changed the evidence statement to reflect the evidence more explicitly.
SH	Association for Palliative Medicine of Great Britain and Ireland	25.37	Full	38	17	There should be a statement that patients were more likely to discontinue sustained release morphine	These are summaries of what was reported in the evidence.
SH	Sobell House Hospice Charity	11.05	Full	38	3.4.3.3	Buprenorphine patches blacklisted in many PCTs	Thank you for this information.
SH	St. Oswald's Hospice	13.11	Full	39	3	This statement implies that this substantial rise of TD opioids is good practice. While the use of TD opioids has increased, is there any evidence that this is coming from palliative care specialists? See important note in 8 above.	This is background for why cost effectiveness analysis was required for this topic. It is not a summary of the evidence or a recommendation.
SH	St. Oswald's Hospice	13.12	Full	39	5	*"Transdermal opioid therapies may be preferred over oral therapies because of better patient adherence, fewer treatment-related adverse events and the preference of the patient."* Preferred by whom? Where is the evidence? What about opioid hyperalgesia of which fentanyl may the commonest cause? What about the serious drug alerts on fentanyl issued in Canada, the US and the UK? See important note in 8 above.	This is background for why cost effectiveness analysis was required for this topic. It is not a summary of the evidence or a recommendation.
SH	Nycomed UK Ltd	28.15		39	5	As a first-line approach to moderate-to-severe	This is background for why cost effectiveness

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						pain, 'transdermal therapies may be preferred over oral therapies because of better patient adherence, fewer treatment-related adverse events and the preference of the patient'. However, this has not been taken into account as transdermal therapies are not recommended for first-line use. The first chapter of this draft guideline emphasised the importance of patient choice, better access to more effective therapies and acknowledged that adherence is improved after an informed choice. However, here, even though it is acknowledged that patients are likely to prefer (and therefore are likely to have better adherence to) transdermal therapy, this is still not recommended as a first-line choice.	analysis was required for this topic. It does not come from a summary of the evidence and so cannot be used to support making a recommendation.
SH	Association for Palliative Medicine of Great Britain and Ireland	25.38	Full	40	8	The use of a clinical panel of experts to estimate key model parameters such as efficacy and resource use has been used in many NICE economic analyses. It therefore seems perverse to use this as a reason to reject other economic analyses unless NICE is moving away from this model itself.	The quality of economic evaluations is assessed using a NICE checklist, in which the estimation of model parameters is considered a limitation. However, this does not negate the use of parameter estimation as it is often necessary because of a lack of data. Indeed, the use of parameter estimation alone does not necessarily mean that a study will be rejected. In this particular instance, the previous economic evaluations were considered not to adequately address the decision problem because of potential conflicts of interest and the use of parameter estimation. The use of parameter estimation for quality of life values is also highlighted as a particular concern because these should ideally be reported directly by patients.

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SH	Nycomed UK Ltd	28.16		41	All	The rationale why only transdermal fentanyl and SR oral morphine were considered in the economic model is not clear. Reasons given are: • 'Given the limitations of the evidence base for SR oral morphine and transdermal buprenorphine, it was decided that this comparison would not be considered in the economic evaluation' • 'given that SR oral morphine and SR oral oxycodone were equivalent in effectiveness terms (as had been decided for all considered treatments), it was decided that this comparison would not need to be modelled.' There are individual data available for buprenorphine and SR oral morphine which could be used to develop a more meaningful economic model. There are also differences in the side effect profiles of morphine vs. oxycodone that should be considered in the economic model. This approach seems inconsistent. The Markov model clearly includes QoL that is affected by adverse effects.	A consistent approach has been adopted that places emphasis on the use of evidence of the highest possible quality that has been identified in the clinical review. The rationale for not modelling each of the comparisons is given below: **SR oral morphine vs transdermal buprenorphine:** The only evidence identified in the clinical review was adjudged to be of very low quality, with a patient population of only 52 subjects. This was not considered an adequate base for an economic evaluation. We are not sure of the specifics of the individual data to which you refer but it's likely that if it wasn't picked up by the evidence review (or was rejected at some stage) then it also wouldn't be considered to be of a high enough standard on which to base an economic evaluation. **SR oral morphine vs SR oral oxycodone**: the point that you have added into the brackets is not strictly correct. Treatments were assumed to be equivalent in terms of pain relief but effectiveness (at least in terms of the economic model) also encompasses the occurrence of adverse events. Thus the reason for modelling against fentanyl was the evidence for differences in the occurrence of adverse events. However, the comparison of oxycodone and morphine didn't show significant differences in adverse events, with the exception of nausea (in one small study with 22 subjects, while other larger studies did not show significant differences) and dry

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							mouth (which was adjudged to be fairly inconsequential economically).
SH	Royal College of Nursing	27.05	Full	42		There could be a cost associated with switching – admission to hospital is fairly common when initial treatment fails/side effects are not managed effectively.	A cost associated with switching is included within the model. This cost encompassed the resource use identified by the GDG. However, it was recognised that the true cost of switching is actually difficult to correctly estimate. As you point out it is possible that patients may be admitted to hospital but without knowing the frequency of this occurrence it is difficult to estimate the cost. **He**nce, the GDG felt it would be useful to perform a threshold analysis on this parameter (whereby we ascertain how high the switching cost needs to be for fentanyl to be cost-effective). The result of this analysis showed that the switching cost needs to be unreasonably high for fentanyl to be cost-effective.
SH	Association for Palliative Medicine of Great Britain and Ireland	25.40	Full	43	22	Since we are by guideline definition dealing with end of life drugs here why was the threshold not set at £50,000 as for other end of life drug therapies?	The threshold of £50,000 is not relevant in this case as the current guideline doesn't match the criteria of being *life extending*, and the population is too large.
SH	Association for Palliative Medicine of Great Britain and Ireland	25.39	Full	43	4	It is unclear how the key resource use parameters such as admission due to opioid complications, laxative costs, district nurse visits for enemas, costs of initiating non-oral routes when the patient is no longer able to take orals, have been factored into this model.	The resource use included in the model is fully described in technical appendix F. Further detail regarding resource use will be added to the full guideline.
SH	Nycomed UK Ltd	28.17		43	All	Does this model take into account the reduced number of patients discontinuing due to adverse events on transdermal fentanyl vs. SR morphine and the recent price reduction for fentanyl patches?	The model does take into account the reduced number of patients discontinuing fentanyl treatment due to adverse events in comparison to morphine. As mentioned in the guideline, prices were

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							obtained from the most recent version of the British National Formulary (BNF 61) at the time of analysis. If price changes have been made since then or if price changes would not be captured by BNF then they have not been included in the economic evaluation.
SH	St. Oswald's Hospice	13.13	Full	44	1	Sensible recommendations, but ones that have ignored patients with severe renal impairment who will need hydromorphone or fentanyl as first line opioids.	While we did not exclude patients with renal impairment from the scope of this guideline, the evidence review did not find any data specific to this group of patients. Consequently the GDG were unable to make prescriptive recommendations for patients with renal or hepatic impairment. However they have now added a recommendation that specialist advice should be sought before prescribing opioids for this group of patients.
SH	Association for Palliative Medicine of Great Britain and Ireland	25.41	Full	44	23	Given the difficulties of research in the palliative care population it is unlikely that even with significant investment studies of much higher quality could be achieved. Therefore we need to accept what limited evidence is available and be guided by that or state very clearly that these guidelines are not evidence based but merely GDG opinion.	Section 3.4.5 makes clear the relative value placed on the low quality evidence and GDG clinical opinion in developing the recommendations.
SH	Nycomed UK Ltd	28.18		44	All	Patients should be able to make an informed choice and, based on the evidence that transdermal fentanyl had fewer patient discontinuations, less constipation (which is a significant problem in patients on opioids), better adherence and patient preference, this is not reflected in the recommendations. The recommendations do not appear to reflect the evidence available in a thorough or consistent manner.	These recommendations are based on evidence of both clinical and cost-effectiveness. The text acknowledges that morphine may result in an increase in GI side effects, but the GDG believed these could be managed by adjunctive treatments. The text also states that the ICER for fentanyl was £107,533/QALY which is higher than the threshold considered by NICE to be cost effective.
SH	Royal College of General Practitioners & British	36.05	Full	45	1.1.5	We believe that there should be some recognition of situations when initiating oral	We have re-organised sections 3.5-3.7 and added introductory text to clarify which

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	Pain Society					morphine would NOT be appropriate: previous morphine or codeine intolerance; renal failure; severe hepatic failure; inability to take oral medications.	patients would not be suitable for oral opioids.
SH	British Pain Society	38.06	Full	45	1.1.5	We believe that there should be some recognition of situations when initiating oral morphine would NOT be appropriate: previous morphine or codeine intolerance; renal failure; severe hepatic failure; inability to take oral medications.	We have re-organised sections 3.5-3.7 and added introductory text to clarify which patients would not be suitable for oral opioids.
SH	St. Oswald's Hospice	13.05	Full	45	1.1.6	Transdermal opioids have never been first line in patients who are vomiting or have temporary dysphagia. These would do better on SC opioid infusions to avoid the delays of reaching steady state with TD opioids. This section contradicts section 1.1.6 and implies that cost takes precedence over patient comfort.	We have added a recommendation on subcutaneous delivery for patients whose analgesic requirements are unstable and for whom oral opioids are unsuitable.
SH	Association for Palliative Medicine of Great Britain and Ireland	25.19	Full	45	1.1.6	Many respondents expressed the concern that lowest acquisition cost was the sole parameter that was advised for choosing a transdermal opioid given that the two products available are not equivalent either in dose range or in evidence base in palliative care.	These recommendations were based on clinical and cost effectiveness evidence – not on the lowest acquisition cost.
SH	Association for Palliative Medicine of Great Britain and Ireland	25.21	Full	45	1.1.6	This guideline also seems to suggest that other oral opioids should be tried as second line before transdermal opioids being used, where the evidence presented does not demonstrate any benefit of other oral opioids over first line morphine but does suggest benefits of transdermal opioids. If this is to be an evidence based guideline then transdermal fentanyl would be at least the second line choice.	Second-line treatment is outside of the scope of this guideline and recommendations have not been made on this issue.
SH	Association for Palliative Medicine of Great Britain and Ireland	25.22	Full	45	1.1.6	There was concern that subcutaneous opioids are not referred to as an alternative for patients in whom oral opioids are unsuitable and do not	We have added a recommendation on subcutaneous delivery for patients whose analgesic requirements are unstable and for

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						feature in these recommendations.	whom oral opioids are unsuitable.
SH	Association for Palliative Medicine of Great Britain and Ireland	25.16	Full	45	1.1.6	Should read "transdermal opioid patch formulations" and may be improved by the caveat "unless the patient has significant renal impairment, specific contraindications to morphine or there are reasons why the transdermal route is preferred". For example in patients with recurrent episodes of oesophageal or gastrointestinal obstruction more stable analgesia with a non-oral route may be preferred even though at times the oral opioids are suitable.	We do not agree that this change is needed and believe that the patients you are referring to would be covered by recommendation 1.1.7.
SH	Pancreatic Cancer UK	23.03	Full	45	1.1.7	We support the recommendation of seeking specialist advice if the pain remains uncontrolled despite optimising first line therapy because it is essential that patients receiving palliative care receive good pain control.	Thank you.
SH	Royal College of General Practitioners & British Pain Society	36.06	Full	45	1.1.7	*"If pain remains uncontrolled despite optimising first-line therapy, review analgesic strategy and consider seeking specialist advice ."* We found this to be unhelpful, because of two reasons: a. There is no guidance given in the document about how to assess, measure and monitor pain, or pain response to analgesics. Thus it would be difficult for non-specialists to know what is meant by pain being 'uncontrolled'. Furthermore, what amount of adverse effects are acceptable with a degree of pain control? b. The term 'optimising' pain therapy has no meaning in pain medicine that we know of, especially in the absence of guidance on dosing and scheduling. Taken together, these two reasons lead us to	The GDG anticipates that if a non-specialist did not know if pain was controlled, they would seek specialist advice as stated in the recommendation.

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						believe that the guidance as it stands could lead to unnecessary variation in opioid prescribing and potentially some patients having to endure unacceptable side effects before being considered for second line therapy.	
SH	British Pain Society	38.07	Full	45	1.1.7	*"If pain remains uncontrolled despite optimising first-line therapy, review analgesic strategy and consider seeking specialist advice ."* We found this to be unhelpful, because of two reasons: a. There is no guidance given in the document about how to assess, measure and monitor pain, or pain response to analgesics. Thus it would be difficult for non-specialists to know what is meant by pain being 'uncontrolled'. Furthermore, what amount of adverse effects are acceptable with a degree of pain control? b. The term 'optimising' pain therapy has no meaning in pain medicine that we know of, especially in the absence of guidance on dosing and scheduling. Taken together, these two reasons lead us to believe that the guidance as it stands could lead to unnecessary variation in opioid prescribing and potentially some patients having to endure unacceptable side effects before being considered for second line therapy.	The GDG anticipates that if a non-specialist did not know if pain was controlled, they would seek specialist advice as stated in the recommendation.
SH	Association for Palliative Medicine of Great Britain and Ireland	25.17	Full	45	1.1.7	"inadequately controlled" may be better than "uncontrolled."	We have made this change.
SH	Association for Palliative Medicine of Great Britain and Ireland	25.18	Full	45	1.1.7	Should say "specialist palliative care advice." Some guidance has suggested a dose limit at which specialist palliative care advice should be	We think specialist advice is adequate.

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						sought of 120mgs of oral morphine equivalent daily dose. (http://www.ukmf.org.uk/documents/August-2011/MM-supportive-guidelines-2011.pdf http://www.agencymeddirectors.wa.gov/Files/OpioidGdline.pdf http://www.dao.health.wa.gov.au/DesktopModules/Bring2mind/DMX/Download.aspx?EntryId=168&Command=Core_Download&PortalId=0&TabId=211) Several members felt that guidance similar to this would be most likely to prevent problems of over dosing with opioids.	
SH	Nycomed UK Ltd	28.19		45	All	The evidence presented does not justify the recommendation that transdermal patch formulations should not be offered as first-line maintenance therapy to patients.	We disagree. Our analysis showed that transdermal fentanyl is not cost effective compared to oral morphine.
SH	Napp Pharmaceuticals Ltd	35.02	Full	45	Rec 1.1.5	The draft guidelines recommend the use of SR morphine as first-line and provide clarity that transdermal preparations should not be considered for first-line treatment. However, further guidance may be needed for the non-specialist to take account of patients intolerant of first-line morphine but able to take oral medications (which may be up to 25% of patients (Riley, 2006)). The GDG may wish to make a recommendation to cover this scenario (particularly if they consider that an alternative oral opioid would be preferred to second-line transdermal patch therapy).	This guideline only covers first line treatment with strong opioids (as defined in the scope) and therefore we are unable to make recommendations about second-line treatment.
SH	St Josephs Hospice	10.03	full	46	1	Need more clarity around when an oral opioid would be unsuitable, comment on prescribing in the last few days of life when oral route may be lost in a patient who may be opioid naive	We have re-organised sections 3.5-3.7 and added introductory text to clarify which patients would not be suitable for oral opioids. Care during the last days of life is excluded from the scope of the guideline and we are therefore unable to make recommendations on this.

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SH	St. Oswald's Hospice	13.14	Full	46	1	This evidence has ignored patients unable to take oral opioids because of temporary problems such as nausea & vomiting, reversible dysphagia (eg. mucositis), or while awaiting a non-oral route of hydration/feeding. Consequently the title is incorrect and has nothing to do with first-line therapy. It should simply state: *Treatment with opioid patches if oral opioids are unsuitable.* See important note in 8 above.	Patients who have been taking oral opioids but become unable to take them because of the reasons you specify, would be classed as receiving second-line treatment which is outside the scope of this guideline. We have re-organised sections 3.5-3.7 and added introductory text to clarify which patients would not be suitable for oral opioids.
SH	St Ann's Hospice	14.09	full	46	5	Does bupenorphine mean butrans or transtec? Please clarify as they differ.	The buprenorphine drug in question would be Transtec (reflecting clinical practice when dealing with higher buprenorphine doses). However NICE do not specifically name drugs by brand name and hence we have referred to "buprenorphine"
SH	Nycomed UK Ltd	28.20		46	All	If there is a lack of evidence, in terms of trials looking specifically at comparing fentanyl patch treatment with buprenorphine patch treatment, the evidence for the patches individually should be examined.	The purpose of this topic was to investigate the most effective patch formulation. Comparative data is needed to do this.
SH	Association for Palliative Medicine of Great Britain and Ireland	25.42	Full	47	1	As the evidence has not shown superiority of other oral opioids other than morphine the review question should be first line treatment with opioid patches if oral morphine is not suitable.	The restricted development timescale for a short clinical guideline meant that it wasn't always possible to get the answer to one question before starting to appraise the evidence for the next question.
SH	Association for Palliative Medicine of Great Britain and Ireland	25.43	Full	50	5	Should read "and statistically significantly lower rates of a few side effects". It is also appropriate to comment here that Fentanyl has a larger dose range and in general a greater evidence base. These factors put together would suggest to many of us that transdermal Fentanyl should be preferred over buprenorphine in this setting.	We disagree. The current wording is correct.
SH	Royal College of General	36.07	Full	7	1.1.8	*"Consider initiating transdermal opioids with the*	While we did not exclude patients with renal

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	Practitioners & British Pain Society					*lowest acquisition cost for patients in whom oral opioids are unsuitable and analgesic requirements are not changing rapidly, supported by specialist advice where needed."* In addition, transdermal opioids should be considered as first line therapy if the patient has severe renal or hepatic failure.	impairment from the scope of this guideline, the evidence review did not find any data specific to this group of patients. Consequently the GDG were unable to make prescriptive recommendations for patients with renal or hepatic impairment. However they have now added a recommendation that specialist advice should be sought before prescribing opioids for this group of patients.
SH	British Pain Society	38.08	Full	51	1.1.8	*"Consider initiating transdermal opioids with the lowest acquisition cost for patients in whom oral opioids are unsuitable and analgesic requirements are not changing rapidly, supported by specialist advice where needed."* In addition, transdermal opioids should be considered as first line therapy if the patient has severe renal or hepatic failure.	While we did not exclude patients with renal impairment from the scope of this guideline, the evidence review did not find any data specific to this group of patients. Consequently the GDG were unable to make prescriptive recommendations for patients with renal or hepatic impairment. However they have now added a recommendation that specialist advice should be sought before prescribing opioids for this group of patients.
SH	Help the Hospices	43.03		51		1.1.8 **Opioid patches** Using the patch with the lowest acquisition cost suggests the cheapest generic formulation – however there has been advice in the past to prescribe by brand for opioids to guarantee dose equivalence and safety? Also it seems that the potential potency of opioid patches (particularly fentanyl which is widely used in primary care) needs to be highlighted.	We have added a recommendation to section 3.5 about calculating equivalence.
SH	Palliative Care Pharmacists Network	37.07		51	1.1.8	Take out the word consider & change seeking to seek. This repeats later in the document. If someone is struggling with pain control they meust seek help	"Consider" is the correct directive term for NICE recommendations and as such we have retained it. We cannot find the word "seeking" in this recommendation.
SH	Association for Palliative Medicine of Great Britain	25.20	Full	51	1.1.8	Many felt that broader concerns rather than simply oral opioids being unsuitable were	We have added a recommendation on subcutaneous delivery for patients who are

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	and Ireland					reasons to choose transdermal products such as issues of compliance, renal failure, risk of swallowing difficulty, oral compromise and absorption issues and higher risks associated with constipation in particular individuals. Also if patient preference is valued by NICE then this should be stated here as a reason. If not then it should be explained in the introduction why patient preferences are not considered important in this area of prescribing.	unable to take oral opioids and whose analgesic requirements are unstable. Therefore patients now have a choice.
SH	Palliative Care Pharmacists Network	37.16		51	box	Need to separate opioid naive vs patient on opioids as fentanyl 25 should not be initiated in opioid naïve. Generic fentanyl patches might be cheaper than branded buprenorphine (7 day product). Cannot go on cost alone must look at patient factors & advice that patient initiated on fentanyl 25 should have been on 60mg morphine a day or equivalent for 7 days (despite what the SPC says). Please review statement in the box	In addition to offering patches we have added a recommendation on subcutaneous delivery for patients who are unable to take oral opioids and whose analgesic requirements are unstable. We have also added a recommendation to section 3.5 about calculating equivalence.
SH	St Josephs Hospice	10.04	Full	52	1	Need more clarity around when an oral opioid would be unsuitable	We have re-organised sections 3.5-3.7 and added introductory text to clarify which patients would not be suitable for oral opioids.
SH	Sobell House Hospice Charity	11.06	Full	52	3.6.5	Lack of crucial advice e.g. cheapest is morphine	We have added a recommendation on subcutaneous delivery for patients whose analgesic requirements are unstable.
SH	St Josephs Hospice	10.05	Full	53	1	Need more clarity around when an oral opioid would be unsuitable	We have re-organised sections 3.5-3.7 and added introductory text to clarify which patients would not be suitable for oral opioids.
SH	St. Oswald's Hospice	13.15	Full	53	25	Since diamorphine is several times more expensive than morphine, why was an economic comparison of the two thought unnecessary?	We have amended the text to clarify why this topic was not prioritised for economic evaluation.
SH	Royal College of Nursing	27.06	Full	54		The standard definition is 3 or more point reduction	This text reports what was in the evidence of Davies et al. 2011.
SH	Teva UK	34.03	Full	54		The guidance as written might unintentionally	We disagree. We are not aware of any group

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						leave a sub-group of vulnerable cancer patients who are experiencing breakthrough pain without fuller guidance being provided on their appropriate management	of patients that will be disadvantaged by these recommendations.
SH	Teva UK	34.04	Full	54		Section 3.8 is headed **Breakthrough pain**, however, the Section refers to breakthrough cancer pain – this is an important distinction to make as the two terms are different. Breakthrough Cancer Pain (BTcP) is a specific type of pain and requires careful description in order for the non-specialist reader to apply the guidelines correctly. We suggest, therefore, that the title be changed to 'Breakthrough cancer pain'	We acknowledge that the evidence reviewed in this guideline on breakthrough pain relates only to patients with cancer (as no evidence for other conditions was found in the literature search). However the GDG agreed it was appropriate to extrapolate this evidence to the wider population because the available literature on non-cancer related breakthrough pain is consistent with results from the cancer population. We have amended the LETR paragraph to clarify this. However, since this guideline makes recommendations on the use of opioids for adults with advanced and progressive disease, it would not be appropriate to restrict this section to only patients with breakthrough cancer pain.
SH	Marie Curie Cancer Care Belfast	41.04	full	54		3.82 Highlight that in trials of IR morphine compared with FAFentanyl, morphine tablet was used rather than morphine liquid.	We have added "capsules" to the evidence review to specify the formulation of immediate-release morphine used in the evidence.
SH	Marie Curie Cancer Care Belfast	41.05	full	54		3.81Definition of breakthrough pain not clear with regard to EAPC guidance. In particular no mention of incident pain for which the FA fentanyl preparations may have a role	This is a summary of the evidence that was appraised.
SH	St Ann's Hospice	14.10	full	54	12	Does breakthrough mean incident, titration or episodic here? Needs clarification	A definition of breakthrough pain is included in the glossary. **We have also added an introductory paragraph to this section**
SH	Archimedes Pharma Ltd	32.02	Full	54	12	Section 3.8 refers to "Breakthrough pain". However, no definition or description of this type of pain is provided. This is important, as the	A definition of breakthrough pain is included in the glossary. We have also added an introductory paragraph to this section.

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						needs of some patients with breakthrough cancer pain (BTCP) are not currently being addressed within this guideline. BTCP, according to experts in palliative care, is typically of rapid onset (over a few minutes), of severe intensity and of relatively short duration (median 30-45 minutes per episode). This is clearly of relevance where data are discussed assessing the relative effectiveness of analgesics with various pharmacokinetic profiles, and especially when the suitability of immediate release morphine sulphate (IRMS) is being considered as a therapy for BTCP. IRMS may indeed be suitable for a patient with pain of slow onset and relatively long duration; however for a patient who suffers from BTCP episodes which are more typical, (rapid onset and short duration), an analgesic with a faster onset and shorter duration of action than IRMS would be required.	We acknowledge that the evidence reviewed in this guideline on breakthrough pain relates only to patients with cancer (as no evidence for other conditions was found in the literature search). However the GDG agreed it was appropriate to extrapolate this evidence to the wider population because the available literature on non-cancer related breakthrough pain is consistent with results from the cancer population. We have amended the LETR paragraph to clarify this.
SH	Archimedes Pharma Ltd	32.01	Full	54	21	Section 3.8 refers to "Breakthrough pain". However the evidence review is only of studies of therapies for breakthrough *cancer* pain. No evidence for other types or causes of breakthrough pain is discussed, and so it is important for the guideline to address this point and to suggest whether the conclusions drawn from the data can be extrapolated to apply to breakthrough pain in general. If guidance can only be offered for breakthrough cancer pain this should be made explicit.	We acknowledge that the evidence reviewed in this guideline on breakthrough pain relates only to patients with cancer (as no evidence for other conditions was found in the literature search). However the GDG agreed it was appropriate to extrapolate this evidence to the wider population because the available literature on non-cancer related breakthrough pain is consistent with results from the cancer population. We have amended the LETR paragraph to clarify this.
SH	Archimedes Pharma Ltd	32.00	Full	54	22	Missing reference: please note publication of the primary manuscript for the PecFent 044 study (Fentynl Pectin Nasal Sray vs IMRS) is Fallon at el., J Support Oncol 2011;9:224-231 in	The publication by Davies et al. (2011) was included in the evidence review instead of Fallon et al. (2011) because Davies et al. (2011) was identified by our search which

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						addition to Davies e al which is a secondary publication. Fallon et al should also be referenced in table 12 page 57 and listed in the reference section on page 77	Fallon et al. (2011) was not . This is most likely the case because the publication date of Fallon et al. (2011) was after the completion of our search (Fallon et al. (2011) was accepted for publication on 18 July 2011). Secondly, as the two publications report the same data, only one of the studies can be included.
SH	Archimedes Pharma Ltd	32.04	Full	54	25	Section 3.8.2 reviews the evidence for opioids in breakthrough pain The time to onset of efficacy of PecFent (FPNS) is not addressed. Fully published data from both PecFent RCTs (fully published as papers by Davies, Fallon, Portenoy and Taylor) demonstrate that PecFent begins to have an effect (statistically significant difference from both placebo and from IRMS) within 5 minutes of dosing. This is specifically included within the PecFent product licence. A rapid onset of action is of major importance in the management of BTCP. IRMS has a slow, 30-minute onset of effect, which is not fast enough to meet a patient's needs, when they experience a typical BTCP episode with a rapid onset over 3-5 minutes.	It is correct that time to onset of efficacy of FPNS is not addressed in the clinical question on breakthrough pain. INFS showed a significant clinical benefit at two our of six time points. At 10 minutes 52.4% of patients taking fentanyl had responded compared to 45% of patients taking morphine. At 15 minutes 75.5% of patients taking fentanyl had responded compared to 69.3% of patients talking morphine. The GDG felt that overall this did not indicate a clinically significant benefit for INFS over IR morphine. In addition the GDG were aware that there is a significant additional cost to using INFS. Consequently the GDG recommended the use of IR morphine. We have amended the LETR paragraph to clarify the GDGs interpretation of the evidence.
SH	Palliative Care Pharmacists Network	37.18		54	26	There is a difference between statistically significant & clinically significant changes in pain scores when choosing therapies for patient pain control & see below (37.19, 37.20, 37.21)	Yes, we agree. There is a difference between statistically and clinically significant changes in pain scores. This distinction is referred to several places in the guideline section on breakthrough pain.
SH	Sobell House Hospice Charity	11.07	Full	54	3.7.5	No advice for best practice	We have added a recommendation on subcutaneous delivery for patients whose

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							analgesic requirements are unstable and for whom oral opioids are unsuitable.
SH	Nycomed UK Ltd	28.21	Full	54	4	A more expansive definition of breakthrough pain is required here otherwise there is little context to the following sections.	A definition of breakthrough pain is included in the glossary. We have also added an introductory paragraph to this section.
SH	Palliative Care Pharmacists Network	37.17		54	4	3.8 should the heading be breakthrough pain given the new definition	The title of section 3.8 is currently "Breakthrough pain".
SH	Archimedes Pharma Ltd	32.03	Full	54	9	Section 3.8.2 "Evidence review" states that only studies comparing IRMS with other treatments for breakthrough pain would be included in the review. IRMS is known to take approx. 30 minutes to begin to have any analgesic effect. In contrast to fast-acting fentanyl products, which are specifically approved for the treatment of BTCP, a) there is little or no clinical trial evidence to support the effectiveness of IRMS in BTCP, and b) IRMS is not specifically approved for this indication. In this context, to review *only* studies which used IRMS as a comparator excludes a large part of the evidence base in this therapy area. Many palliative care clinicians consider IRMS to be unsuitable for some patients with BTCP, due to its inappropriate pharmacokinetic profile for the typical episode of breakthrough pain, as well as the fact that some patients cannot tolerate orally administered therapy for their pain either due to swallowing difficulties or oral pathologies. All RCTs studying effectiveness of therapies for BTCP, including those using placebo as a comparator, should be included in the review of evidence; the exclusion of studies which have been specifically designed to investigate the effectiveness of fast-acting fentanyl therapies for breakthrough cancer pain is a major	During guideline development, the GDG decided on the specific questions they wanted to answer for this guideline, including the interventions they wanted to compare. In the context of breakthrough pain, the GDG did not want to compare any strong opioids to placebo, but preferred to concentrate on active drug comparisons in order to ascertain the comparative effectiveness of the strong opioids under consideration. The GDG also chose not to specifically consider 'onset of action' as an outcome, although this information was reported to the GDG when it was included in the studies that directly addressed this clinical question (i.e., the studies that met the inclusion criteria). Within the context of the clinical question each included study has been assessed for risk of different biases according to the NICE Guidelines Manual 2009.

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						omission, particularly as no placebo-controlled RCT data exist for IRMS in this population. In excluding placebo-controlled studies, important evidence regarding rapid (5 and 10 minute) onset of action and achievement of pain relief, as well as overall length of clinical effect, is excluded from consideration in this review and this is a source of bias. This has led to an overestimation of the benefits of IRMS in the management of patients with BTCP.	
SH	ProStrakan Group	30.03	Opioids in Palliative Care – Full Guidance	55	21	The GDG findings indicate that the network meta-analysis showed that statistically significant larger pain intensity differences were associated with intranasal fentanyl (INFS) and IR-Morphine at 15, 30, 45 and 60 minutes. This is in contradiction to the comments made on page 61 of the full document which indicate that there was no clinically significant difference between the two formulations.	We disagree that the meta-analysis showed the difference in pain intensity was clinically significant. INFS showed a significant clinical benefit at a minority of time points. At 10 minutes 52.4% of patients taking fentanyl had responded compared to 45% of patients taking morphine. At 15 minutes 75.5% of patients taking fentanyl had responded compared to 69.3% of patients talking morphine. The GDG felt that overall this did not indicate a clinically significant benefit for INFS over IR morphine. In addition the GDG were aware that there is a significant additional cost to using INFS. Consequently the GDG recommended the use of IR morphine. We have amended the LETR paragraph to clarify the GDGs interpretation of the evidence.
SH	Nycomed UK Ltd	28.22	Full	55	22	This section acknowledges that INFS offered significantly larger pain intensity differences than IR morphine at all time points from 15 minutes up to 60 minutes. (Vissers et al CMRO 2010,26(5):1037-1045; Zeppetella et al. Poster presented at the European Multidisciplinary Cancer Congress	INFS showed a significant clinical benefit at a minority of time points. At 10 minutes 52.4% of patients taking fentanyl had responded compared to 45% of patients taking morphine. At 15 minutes 75.5% of patients taking fentanyl had responded compared to 69.3% of patients talking morphine. The GDG felt that

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						(16th ECCO, 36th ESMO, and 30th ESTRO). September 23–27, 2011, Stockholm, Sweden). Some commentators (e.g. Coluzzi et al Pain 2001, 91(1):123-130; Davies et al Eur J Pain 2009,13:331-338) have indicated that orally administered medications may yield a time-action profile that may not be the optimal rescue medication for breakthrough pain , citing the observation that morphine sulphate immediate release may take more than 30 minutes to take effect and peak pharmacological effect may occur only after 40-60 minutes. This onset may not be fast enough to relieve breakthrough cancer pain adequately and, moreover, the duration of effect may be too long for breakthrough pain episodes. Ideal rescue or breakthrough medications have been cited as being efficacious, patient friendly, having a rapid onset of action, a relatively short duration of action, minimal adverse effects and being cost effective. Breakthrough pain can place significant physical and economic burdens on both patients and care givers. Inadequately relieved breakthrough pain can place additional burdens on the healthcare system, with increases in emergency admissions, medical visits, more hospital admissions and longer stays and increased expenses for the patient.(Zeppetella Clin Oncol 2011,23:393-389). Such factors are pertinent considerations to overall costs, rather than just drug acquisition costs.	overall this did not indicate a clinically significant benefit for INFS over IR morphine. In addition the GDG were aware that there is a significant additional cost to using INFS. Consequently the GDG recommended the use of IR morphine. We have amended the LETR paragraph to clarify the GDGs interpretation of the evidence.
SH	Archimedes Pharma Ltd	32.05	Full	60 61 62		The statement in section 3.8.3.1 that "fentanyl nasal spray [PecFent] is associated with a statistically significantly better improvement in pain at 15 and 30 minutes ... but not at 45 and 60 minutes ... compared with immediate-release morphine" is factually incorrect. Only one study	INFS showed a significant clinical benefit at a minority of time points. At 10 minutes 52.4% of patients taking fentanyl had responded compared to 45% of patients taking morphine. At 15 minutes 75.5% of patients taking fentanyl had responded compared to 69.3% of

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						compared Pecfent with IRMS. As reported by Fallon at el., J Support Oncol 2011;9:224-231(page 228), a statistically significant improvement in pain intensity difference (PecFent vs IRMS) was recorded at 15, 30, 45 and 60 minutes, and the level of statistical significance was actually greater at 60 minutes (P<0.01) than at the other time points (P<0.05), with no indication over the 60-minute observation period of a decrease in the difference in pain scores between PecFent and IRMS. The guideline has considered that the size of this statistically significant difference is not clinically significant. Basing a judgment of clinically significant efficacy of PecFent vs IRMS solely on the 2 or more point reduction at 10 and 15 minutes, which was not the primary endpoint for which this study was powered, is misleading. The % of episodes with clinically meaningful pain relief (≥2 point reduction in pain intensity) was statistically significantly greater for PecFent than IRMS at 10 and 15 minutes, and the difference in the numbers of episodes for which patients experienced meaningful pain relief is indeed statistically and clinically significant. The conclusion on page 62 of the draft guidance that "… there was no evidence to suggest that fentanyl is more clinically effective than immediate-release morphine" is therefore not valid. As Fallon et al. conclude the RCT evidence demonstrates that PecFent provided a clinically	patients talking morphine. The GDG felt that overall this did not indicate a clinically significant benefit for INFS over IR morphine. In addition the GDG were aware that there is a significant additional cost to using INFS. Consequently the GDG recommended the use of IR morphine. We have amended the LETR paragraph to clarify the GDGs interpretation of the evidence.

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						significant benefit in pain relief more quickly than IRMS, and maintains clinically significant efficacy at a significantly greater level than IRMS throughout 60 minutes.	
SH	Palliative Care Pharmacists Network	37.19		60		It doesn't state whether morphine is liquid or tablets. The study used tablets, is it right to include the study as Oramorph liquid has a time to peak plasma levels faster than tablets due to the tablets having to dissolve before absorption. This was raised as an issue at the advanced course in symptom management july 2011	We have added "capsules" to the evidence statement to specify the formulation of immediate-release morphine used in the evidence. The included studies have been included because they met the inclusion criteria as per the pre-specified review protocols (see Appendix D)
SH	ProStrakan Group	30.05	Opioids in Palliative Care – Full Guidance	60	10	The GDG noted that oral transmucosal fentanyl citrate (OTFC) is associated with statistically significant better improvement in pain at 15, 30, 45, and 60 minutes compared with IR-Morphine. This is indicative of the pharmacokinetics of OTFC which mimic the pain profile of BTcP and which is most effective during acute onset of pain.	Thank you for this information.
SH	ProStrakan Group	30.06	Opioids in Palliative Care – Full Guidance	60	24	The GDG identified breakthrough and background pain, opioid side effects, adverse events, and health related quality of life to be the most relevant outcomes. We wish to bring to the attention of the GDG the results published in the Überall study. During the phase IV study, (n= 217) 3163 episodes were treated with a mean dose of 401.4 µg per episode. The study recorded a significant improvement in maximum BTcP intensity with sublingual fentanyl ODT, compared with baseline ($p<0.0001$). Patients reported the time to first effect following administration of sublingual fentanyl ODT was	The Überall study was not included as it did not meet inclusion criteria for the clinical questions (i.e., it is not an RCT).

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						≤10 minutes in 82.8% of episodes. mPDI (modified pain disability index) and HADS (hospital anxiety and depression scale) scores significantly improved during the observation period (p<0.0001). Sublingual fentanyl ODT was well-tolerated, with 12 patients (5.5%) experiencing ≥1 study drug-related adverse event. The majority of patients reported that, compared to previous medication, sublingual fentanyl ODT was better in terms of speed of action (87.7% of patients), strength of action (85.7%), duration of action (83.9%), tolerability (88.6%) and ease of handling (87.3%). This study has revealed that patients preferred this formulation and that the Sublingual fentanyl demonstrated that there was an improvement in mPDI and HADS scores, a positive effect on improved QOL. (Überall, MA et al, Curr Med Res Opin 2011, 19 April 2011; published online)	
SH	Nycomed UK Ltd	28.24		60	3.8.5	'The GDG agreed based on its clinical experience, that both oxycodone and morphine had very similar efficacies and side-effect profiles when used to manage breakthrough pain'. This draft guideline should be based on objective evidence and not on 'clinical experience'	NICE guidelines are based on evidence where this is available. However it is also within NICE methodology for expert opinion to inform the development of recommendations.
SH	Nycomed UK Ltd	28.23	Full	60	4	This statement is inaccurate as it combines INFS and FPNS – two different intranasal fentanyl sprays with significantly different formulations. Published clinical studies show that INFS demonstrates statistically significant better pain relief vs IR at 15, 30, 45, 60 minutes.	INFS showed a significant clinical benefit at a minority of time points. At 10 minutes 52.4% of patients taking fentanyl had responded compared to 45% of patients taking morphine. At 15 minutes 75.5% of patients taking fentanyl had responded compared to 69.3% of patients talking morphine. The GDG felt that overall this did not indicate a clinically significant benefit for INFS over IR morphine.

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							In addition the GDG were aware that there is a significant additional cost to using INFS. Consequently the GDG recommended the use of IR morphine. We have amended the LETR paragraph to clarify the GDGs interpretation of the evidence.
SH	ProStrakan Group	30.04	Opioids in Palliative Care – Full Guidance	60	5	The GDG noted that intranasal fentanyl spray (INFS) is associated with a statistically significant better improvement in pain at 15 and 30 minutes but not at 45 and 60 minutes compared with IR-Morphine. This is indicative of the pharmacokinetics of INFS which mimic the pain profile of BTcP and which is most effective during acute onset of pain.	Thank you for this information.
SH	Palliative Care Pharmacists Network	37.20		60	9	Add word tablet or take out completely as above	We have added "capsules" to the evidence statement to specify the formulation of immediate-release morphine used in the evidence.
SH	Nycomed UK Ltd	28.25	Full	61	1	This recommendation appears to be based on cost and ignores the definition of breakthrough cancer pain and the patients' requirements for rapid onset of efficacy – something that is not provided by oral morphine.	We disagree. INFS showed a significant clinical benefit at a minority of time points. At 10 minutes 52.4% of patients taking fentanyl had responded compared to 45% of patients taking morphine. At 15 minutes 75.5% of patients taking fentanyl had responded compared to 69.3% of patients talking morphine. The GDG felt that overall this did not indicate a clinically significant benefit for INFS over IR morphine. In addition the GDG were aware that there is a significant additional cost to using INFS. Consequently the GDG recommended the use of IR morphine. We have amended the LETR paragraph to clarify the GDGs interpretation of the evidence.
SH	ProStrakan Group	30.07	Opioids in	61	18	The statement '..although this difference was statistically significant it was not found to be	INFS showed a significant clinical benefit at a minority of time points. At 10 minutes 52.4%

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			Palliative Care – Full Guidance			clinically significant; that is there was no clinically important difference in the proportions of patients experiencing a reduction in pain intensity of 2 or more points...'. This statement is incorrect as Davies 2011 demonstrated that there was a significant proportion of patients experiencing 2 point or more reduction in pain intensity at both the 10 minute and 15 minute time points. In addition there was statistically significant pain relief (≥ 2 points) at the 15 and 30 minute time points. (Davies A. Journal of Pain and Symptom Management, Vol 41, No. 2, February 2011, 358-366) In a phase IV study conducted by Überhall et al, the study recorded a significant improvement in maximum BTcP intensity with sublingual fentanyl ODT, compared with baseline ($p<0.0001$). Patients reported the time to first effect following administration of sublingual fentanyl ODT was ≤10 minutes in 82.8% of episodes. (Überall, MA et al, Curr Med Res Opin 2011, 19 April 2011; published online) The proposed guideline goes against current EAPC guidelines which state that breakthrough pain (ie incident pain) can be effectively managed with oral immediate release opioids or oral fentanyl preparations. In addition it was noted that in some cases, these fast acting fentanyl preparations may be preferred to immediate release oral opioids. The proposed guideline also goes against the British Pain Society guidance on managing	of patients taking fentanyl had responded compared to 45% of patients taking morphine. At 15 minutes 75.5% of patients taking fentanyl had responded compared to 69.3% of patients talking morphine. The GDG felt that overall this did not indicate a clinically significant benefit for INFS over IR morphine. In addition the GDG were aware that there is a significant additional cost to using INFS. Consequently the GDG recommended the use of IR morphine. We have amended the LETR paragraph to clarify the GDGs interpretation of the evidence. The Überall study was not included as it did not meet inclusion criteria for the clinical questions (i.e. it is not an RCT). The GDG based their recommendations on a review of the available clinical and cost-effectiveness evidence. Since this guideline examined cost-effectiveness but the guidelines from the professional organisations did not, this may have contributed to different recommendations being made.

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						cancer pain, in which fast acting fentanyls delivered via buccal, transmucosal or intranasal routes are seen as an essential part of the armamentarium available to HCPs to manage pain which is in addition to normal background pain. The APM guidelines state that the management of breakthrough pain should be individualised, and that management of BTcP depends on a variety of patient –related factors, including the personal preferences of the patient. (Davies AN et al, European Journal of Pain 13 (2009) 331-338). The guidelines proposed by NICE do not take this important aspect of patient choice into consideration.	NICE do not base their recommendations on existing guidelines and are unable to endorse such recommendations.
SH	Palliative Care Pharmacists Network	37.21		61	18	Add word tablet or take out completely as above	We have added "capsules" to the evidence statement to specify the formulation of immediate-release morphine used in the evidence.
SH	Association for Palliative Medicine of Great Britain and Ireland	25.44	Full	61	20	Research in this area is fraught with difficulties as patients tend to adapt their behaviour to within the freedom that their analgesia gives them. This contributes to a large placebo response (20.1% patients rated pain relief at >=2 at 5 mins even with morphine when pharmacologically the drug could not have been having an effect in the Davies study.) Therefore to find any effect, even smaller effect, may be more significant in the clinical context. This may be why patient preference is greater for fentanyl in this study	Thank you for this information.
SH	Nycomed UK Ltd	28.26		61	20	Pain Intensity Differences (PID) have been employed as a measure of efficacy for analgesia and a PID>2 has been suggested as	Our evidence review looked at data on both FPNS and INFS. INFS showed a significant clinical benefit at a minority of time points. At

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						being clinically significant (Farrar et al. Pain 2000,88:287-294). Currently there are two commercially available intranasal fentanyl preparations- intranasal fentanyl spray (INFS) and fentanyl pectin nasal spray (FPNS). A recent network meta-analysis has compared the efficacy of opioids for the treatment of breakthrough pain and included the two licensed intranasal fentanyl presentations, INFS and FPNS. The analysis demonstrated that INFS produced an absolute Pain Intensity Difference (PID) $\geq$2 at 15 minutes whereas other medications only achieved this value at later time points (Zeppetella et al. Poster presented at the European Multidisciplinary Cancer Congress (16th ECCO, 36th ESMO, and 30th ESTRO). September 23–27, 2011, Stockholm, Sweden). Other comparisons including their pharmacokinetics and pharmacodynamic profiles drawn from the Summaries of Product Characteristics also serve to differentiate between the currently available intranasal fentanyl preparations.	10 minutes 52.4% of patients taking fentanyl had responded compared to 45% of patients taking morphine. At 15 minutes 75.5% of patients taking fentanyl had responded compared to 69.3% of patients talking morphine. The GDG felt that overall this did not indicate a clinically significant benefit for INFS over IR morphine. In addition the GDG were aware that there is a significant additional cost to using INFS. Consequently the GDG recommended the use of IR morphine. We have amended the LETR paragraph to clarify the GDGs interpretation of the evidence.
SH	Nycomed UK Ltd	28.27		61	26	This statement is incorrect as not all FAFs require a spray canister.	We have amended the text to clarify that not all FAFs require a spray canister.
SH	Teva UK	34.05	Full	62		We refer principally to the section within the guidelines which states that fast acting fentanyl products (which have been specifically developed and licensed for management of breakthrough cancer pain) should not be used as a first line treatment.	INFS showed a significant clinical benefit at a minority of time points. At 10 minutes 52.4% of patients taking fentanyl had responded compared to 45% of patients taking morphine. At 15 minutes 75.5% of patients taking fentanyl had responded compared to 69.3% of patients talking morphine. The GDG felt that overall this did not indicate a clinically significant benefit for INFS over IR morphine. In addition the GDG were aware that there is

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						This is contrary to advice given by the European Association for Palliative Care (EAPC), and, more importantly, the statement does not provide further advice as to circumstances where these drugs may benefit those patients who are not managed adequately by conventional opioids. Furthermore, there is a concern that the guidance document asks non-specialists to deviate from the EAPC guidelines (2011) where fast acting fentanyls are recommended above oral morphine for the treatment of BTcP due to their shorter onset of action. It is our belief that the EAPC guidelines have been arrived upon following a long process of review by key European specialists in Palliative Care, and should, therefore, be referred to in the guidelines in support of the fast acting fentanyl as a treatment for BTcP	a significant additional cost to using INFS. Consequently the GDG recommended the use of IR morphine. We have amended the LETR paragraph to clarify the GDGs interpretation of the evidence. NICE do not base their recommendations on existing guidelines and are unable to endorse such recommendations. This guideline only covers first line treatment with strong opioids (as defined in the scope) and therefore we are unable to make recommendations about second-line treatment.
SH	Teva UK	34.06	Full	62		Recommendation 1.1.9 reads: 'Offer immediate-release oral morphine for the first-line rescue medication of breakthrough pain' and Recommendation 1.1.10 reads: 'Do not offer fast-acting fentanyls as first-line rescue medication'. We wish to raise serious concerns that the guidance risks excluding the important special patient group whose pain is not controlled by oral morphine. Evidence suggests that 68% of breakthrough cancer pain episodes last 30 min or less[1] and the onset of action of oral morphine is approximately 35 min[2,3], therefore those patients whose pain is of shorter duration *i.e.* less than 30 min may not have their pain adequately treated. The current guidance does not recommend an alternative or second line treatment if oral morphine does not provide adequate symptom control in this sub-group of	This guideline only covers first line treatment with strong opioids (as defined in the scope) and therefore we are unable to make recommendations about second-line treatment. Recommendation 1.1.8 and the care pathway make it clear that healthcare professionals should seek specialist advice if patients pain remains uncontrolled.

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						patients. We would advocate that 'In the event of poor symptom control with oral morphine, specialist advice should be sought through referral to a Palliative Care service and consideration should be given to commencing a fast acting fentanyl as a rescue treatment in these patients	
SH	Association for Palliative Medicine of Great Britain and Ireland	25.45	Full	62	1	It would be more accurate to say that there was "limited evidence to suggest that fentanyl is more clinically effective"	The text will be edited to reflect your comment.
SH	Nycomed UK Ltd	28.28	Full	62	1	Please explain how these doses and costs were calculated – without this information this table is not useful. In addition the two intranasal formulations, INFS and FPNS, should be presented separately as they are priced differently, i.e. INFS is flat priced across all dose strengths whereas the cost of FPNS is dose dependent.	As mentioned in the footnote to the table, the breakthrough doses are taken to be one sixth of the regular 'maintenance' dose. For clarity, this will be made clearer in the text. Regarding the second point, it is usual practice to use the average price of the available drugs within a particular class. Furthermore, since the costing is concerned with the price at a particular dose (100µg), we see no reason why the pricing structure should be an issue. All that matters is the price of INFS and FPNS at the doses specified. For clarity, a footnote will be added to the table making it clear that the fentanyl price is based on INFS and FPNS. It should also be mentioned that even if the drugs were priced separately, it wouldn't change the recommendations, as fentanyl would still be more expensive than morphine and oxycodone.
SH	Palliative Care	37.09		62	1.1.1	?confusion with definitions of pain as above.	Page 62 is in section 3.8 which covers

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	Pharmacists Network				0	Fentanyl products are not intended for titration pain but breakthrough	breakthrough pain, not titration.
SH	Sue Ryder Care	16.00	Full	62	1.1.10	We agree with the Guideline Development Group that 'rapid onset' fentanyls should not be 1st line treatment in this setting. However, it is unclear whether NICE are recommending them for second line use. It might be helpful to say something more about their place (e.g. "They should be considered for selected patients with *opioid-responsive* episodic pain where the underlying cause cannot be addressed [e.g. through orthopaedic or oncology intervention] and a non-opioid adjuvant cannot be used [e.g. a neuropathic agent]). Alternatively, you could say "only initiating on specialist advice"	Thank you This guideline only covers first line treatment with strong opioids (as defined in the scope) and therefore we are unable to make recommendations about second-line treatment. We have added a recommendation that specialist advice should be sought if pain remains inadequately controlled despite optimising therapy.
SH	Association for Palliative Medicine of Great Britain and Ireland	25.24	Full	62	1.1.10	Even amongst those who supported the recommendations to try oral morphine first there were concerns that the statement in line 17 was too strong and should say "do not routinely offer fast acting Fentanyl as first line rescue medication unless the patient has significant renal impairment or has reasons why oral opioids are unsuitable or alternative routes are preferred.	The question investigated by this guideline was the most effective opioid for patients with breakthrough pain who are able to take oral opioids. Therefore the evidence on patients with breakthrough pain who are unable to take oral opioids has not been reviewed and we are unable to make recommendations on this issue.

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						Fast acting Fentanyls should be considered in those in whom oral morphine provides inadequate relief under advice from specialist palliative care."	We have added a recommendation that specialist advice should be sought if pain remains inadequately controlled despite optimising therapy.
SH	ProStrakan Group	30.01	Opioids in Palliative Care – Full Guidance	62	1.1.10	BTcP is a transitory exacerbation of pain that occurs on a background of otherwise stable, persistent pain in patients receiving chronic opioid therapy (1), BTcP is characterised by a sudden onset of pain that reaches peak intensity within as little as three minutes and lasts for an average of 30 minutes. (1,2) The guidance does not provide a clear definition of Breakthrough Cancer Pain, which should be defined in terms of its characteristics, onset and duration. (1.1.10) Both fast-acting fentanyls (FAF) and immediate-release oral morphine (IR-Morphine) could be used as first line medication for breakthrough cancer pain (BTcP). IR-Morphines do not reach peak activity until 30-45 minutes after administration (2) and are therefore unable to match the timing of BTcP episodes. (1) Portenoy RK. Pain, 1990; 41: 273-81 (2) Simmonds MA. Oncology (Williston Park) 1999; 13:1103-8 By limiting the choice of opioids to only IR-morphine, this non specialist healthcare group do not have clear guidance in terms of a suitable alternative in the event that IR-morphine fails to resolve the patient's pain. Nor is the group at which this guidance is aimed,	We acknowledge that the evidence reviewed in this guideline on breakthrough pain relates only to patients with cancer (as no evidence for other conditions was found in the literature search). However the GDG agreed it was appropriate to extrapolate this evidence to the wider population because the available literature on non-cancer related breakthrough pain is consistent with results from the cancer population. We have amended the LETR paragraph to clarify this. However, since this guideline makes recommendations on the use of opioids for adults with advanced and progressive disease, it would not be appropriate to give particular emphasis to patients with breakthrough cancer pain. We have added a recommendation that specialist advice should be sought if pain remains inadequately controlled despite optimising therapy.

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						given a clear directive in terms of seeking specialist advice, or referring the patient into secondary care for urgent reassessment and resolution of their pain. This will defeat the goals of the guidance which was to clarify the clinical pathway and improve pain management (see page 4, line 14).	
SH	Association for Palliative Medicine of Great Britain and Ireland	25.23	Full	62	1.1.9	A significant number of respondents expressed concerns over the treatment of breakthrough pain in the guideline, The concern most fully being expressed by these quotes from two correspondents: "The clinical guideline does not adequately define "breakthrough pain", which is a specific type of pain (and not any exacerbation of pain). It doesn't mention the most important aspect, i.e. controlled background pain The clinical guideline does not discuss the pharmacokinetic / pharmacodynamic characteristics of oral opioids (which mean that oral opioids are inappropriate for most episodes of true breakthrough pain – see below). The Review Question is "what is the most effective opioid treatment for breakthrough pain in patients with advanced and progressive disease who receive first-line treatment with strong opioids (for background pain)? However, the Evidence Review "focused on the effectiveness of immediate-release (IR) morphine compared with fast-acting fentanyls or IR oxycodone as treatment for breakthrough pain in patients with advanced and progressive disease who are currently being treated with	A definition of breakthrough pain is included in the glossary. We have also added an introductory paragraph to this section. The pharmacokinetics/pharmacodynamics of oral opioids was not investigated by the guideline. INFS showed a significant clinical benefit at two out of six time points. At 10 minutes 52.4% of patients taking fentanyl had responded compared to 45% of patients taking morphine. At 15 minutes 75.5% of patients taking fentanyl had responded compared to 69.3% of patients talking morphine. The GDG felt that overall this did not indicate a clinically significant benefit for INFS over IR morphine. In addition the GDG were aware that there is a significant

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						strong opioids for background pain".	additional cost to using INFS. Consequently the GDG recommended the use of IR morphine. We have amended the LETR paragraph to clarify the GDGs interpretation of the evidence.
						The disparity between the Review Question and the Evidence Review is a fundamental flaw within the guideline. Oral morphine does not have a marketing authorisation ("licence") for the management of breakthrough pain, and the evidence to support its use in the management of breakthrough pain is, to say the least, limited. Hence, it is difficult to justify its position as the "gold standard" within the guideline. Moreover, the narrow focus of the Evidence Review means that most of the evidence for the fentanyl-based formulations has been excluded from the guideline (i.e. 8 randomised controlled trials; 1 mixed treatment comparison /network meta-analysis) [1-9].	Oral morphine is licensed for moderate to severe cancer pain. As the license does not break down into type, manifestation or class of pain the GDG agreed that the use of oral morphine to treat breakthrough pain is included within this licence indication. Since this is a NICE short clinical guideline we have focused on addressing the problems associated with the commonly used strong opioids.
						The Evidence Statement states: "fentanyl nasal spray is associated with a statistically significantly better improvement in pain at 15 and 30 minutes (in two out of two studies; MODERATE QUALITY), but not at 45 and 60 minutes (in one out of two studies; LOW QUALITY) compared with immediate-release morphine". It is, therefore, somewhat surprising / confusing to see that the recommendation is "do not offer fast acting fentanyl as first-line rescue medication".	INFS showed a significant clinical benefit at two out of six time points. At 10 minutes 52.4% of patients taking fentanyl had responded compared to 45% of patients taking morphine. At 15 minutes 75.5% of patients taking fentanyl had responded compared to 69.3% of patients talking morphine. The GDG felt that overall this did not indicate a clinically significant benefit for INFS over IR morphine. In addition the GDG were aware that there is a significant additional cost to using INFS. Consequently the GDG recommended the use of IR morphine. We have amended the LETR paragraph to clarify the GDGs interpretation of

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							the evidence. The GDG based their recommendations on a review of the available clinical and cost-effectiveness evidence. Since this guideline examined cost-effectiveness but the guidelines from the professional organisations did not, this may have contributed to different recommendations being made.
						The conclusions of the guideline contradict those of the European Association of Palliative Care (EAPC) [10], and the Association for Palliative Care of Great Britain and Ireland (APM) [11]. The EAPC guidance on breakthrough pain states: "the time to peak effect for orally administered opioids is approximately 60 minutes and is not suitable for pains with a short onset and duration" (i.e. most episodes of breakthrough pain) [10]. The APM guidance states: "the pharmacokinetic / pharmacodynamic profiles of oral opioids do not tend to mirror the temporal characteristics of most breakthrough pain episodes. Thus the slow onset of action (onset of analgesia: 20-30 min; peak analgesia 60-90 min) results in delayed / ineffective analgesia, whilst the prolonged duration of effect (3-6 hr) results in ongoing adverse effects. In other words, oral opioids are not the optimal rescue medication for most breakthrough pain episodes. Nevertheless, oral opioids do have a role in the management of breakthrough pain episodes lasting more than 60 min, and may be considered in the pre-emptive management of volitional incident pain or procedural pain. However, if oral opioids are uses in the latter scenario, then they need to be taken at least 30 min before the relevant precipitant of the pain" [11]. References	Procedural pain is a specialist area and is not covered by this guideline.

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						Farrar JT, Cleary J, Rauck R et al. Oral transmucosal fentanyl citrate: randomized, double-blinded, placebo-controlled trial for treatment of breakthrough pain in cancer patients. J Natl Cancer Inst 1998; 90 (8): 611–616. Portenoy RK, Taylor D, Messina J, Tremmel L. A randomized, placebo-controlled study of fentanyl buccal tablet for breakthrough pain in opioid-treated patients with cancer. Clin J Pain 2006; 22 (9): 805–811. Slatkin NE, Xie F, Messina J, Segal TJ. Fentanyl buccal tablet for relief of breakthrough pain in opioid-tolerant patients with cancer-related chronic pain. J Support Oncol 2007; 5 (7): 327–334. Kress HG, Orońska A, Kaczmarek Z et al. Efficacy and tolerability of intranasal fentanyl spray 50 to 200 µg for breakthrough pain in patients with cancer: a Phase III, multinational, randomized, double-blind, placebo-controlled, crossover trial with a 10-month, open-label extension treatment period. Clin Ther 2009; 31 (6): 1177–1191. Mercadante S, Radbruch L, Davies A et al. A comparison of intranasal fentanyl spray with oral transmucosal fentanyl citrate for the treatment of breakthrough cancer pain: an open-label, randomised, crossover trial. Curr Med Res Opin 2009; 25 (11): 2805–2815. Rauck RL, Tark M, Reyes E et al. Efficacy and long-term tolerability of sublingual fentanyl orally disintegrating tablet in the treatment of breakthrough cancer pain. Curr Med Res Opin 2009; 25 (12): 2877–2885. Portenoy RK, Burton AW, Gabrail N et al. A multicenter, placebo-controlled, double-blind,	

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						multiple-crossover study of Fentanyl Pectin Nasal Spray (FPNS) in the treatment of breakthrough cancer pain. Pain 2010; 151: 617–624. Rauck R, North J, Gever LN et al. Fentanyl buccal soluble film (FBSF) for breakthrough pain in patients with cancer: a randomized, double-blind, placebo-controlled study. Ann Oncol 2010; 21: 1308–1314. Zeppetella G, Davies A, Rios C, Eijgelshoven I, Jansen J. The efficacy of intranasal fentanyl spray and other opioids for the treatment of breakthrough cancer pain. In: Proceedings of European Multidisciplinary Cancer Conference (16th ECC0, 36th ESMO and 30th ESTRO), 23-27th September 2011, Stockholm Mercadante S, Radbruch L, Caraceni A et al. Episodic (breakthrough) pain: consensus conference of an expert working group of the European Association for Palliative Care. Cancer 2002; 94 (3): 832–839. Davies AN, Dickman A, Reid C et al. The management of cancer-related breakthrough pain: recommendations of a task group of the Science Committee of the Association for Palliative Medicine of Great Britain and Ireland. Eur J Pain 2009; 13 (4): 331–338." "***The analgesic efficacy of immediate release morphine*** We carried out the first clinical studies of oral controlled release morphine (marketed as MST-1). At the time there had been only one previous study in humans, an investigation of the pharmacokinetics of MST-1 in six healthy volunteers. There were no data in humans on	Thank you for this information. INFS showed a significant clinical benefit at two out of six time points. At 10 minutes 52.4% of patients taking fentanyl had responded compared to 45% of patients taking morphine. At 15 minutes 75.5% of patients taking fentanyl had responded compared to 69.3% of patients talking morphine. The GDG felt that overall this did

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						the pharmacodynamic effects of MST-1. The product had been licensed on the basis off its demonstrable sustained release characteristics in vitro and the fact that the active component was morphine. The main aim of our study was to measure the duration of analgesia produced by MST-1 in an RCT comparing its effects with those of oral morphine in solution (the control). We used a post-operative dental surgery model commonly favoured at that time to evaluate new analgesics (Hanks GW et al 1981a). We administered a fixed dose of 20mg and patients were randomly allocated to receive the modified release formulation or oral morphine in solution. Blindness was maintained by using a double dummy technique. The response of the patients in both groups was poor and we were forced to abandon the study because eight of 16 patients in the MST-1 arm and six of 13 patients in the control group had to withdraw from the study because of unrelieved pain. In a Letter to the Editor of the Lancet we drew attention to the misleading advertising for MST-1 which implied that it could serve as a substitute for parenteral morphine (Hanks GW et al 1981b) in acute pain. We went on to complete an RCT of MST-1 in cancer pain (Hanks GW et al 1983) which is discussed in the guideline. Our abandoned study was the first investigation of the analgesic effect of single oral doses of morphine for some thirty years. In the early 1950s Beecher and his colleagues at Harvard had conducted a series of studies of single doses of morphine and other drugs given to patients with acute pain and showed that	not indicate a clinically significant benefit for INFS over IR morphine. In addition the GDG were aware that there is a significant additional cost to using INFS. Consequently the GDG recommended the use of IR morphine. We have amended the LETR paragraph to clarify the GDGs interpretation of the evidence.

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						morphine 10mg was "decidedly inferior" to aspirin 600mg. Houde and Wallenstein at Sloan-Kettering cancer centre carried out relative potency assays for all of the common strong opioids and much of their data are still applicable today. However they found that the oral to parenteral potency ratio for morphine was in the region of 1:6 or 1:8 . This was why "in most countries morphine was usually given parenterally, because you have to give so much more by mouth to achieve the same effect" (Lasagna 1979). Morphine given orally in single doses is a poor analgesic but there appears to be a change in analgesic effectiveness when moving to repeated dose administration (Lasagna, 1981). The oral to parenteral relative potency ratio changes from 1:6 to 1:3. There may be a pharmacokinetic explanation for this (Hanks GW et al 1987) but we still do not understand exactly what role the metabolites of morphine play in its therapeutic effects. However it seems clear that single oral doses are not a reliable way to use the drug: you need to keep giving it to achieve its full therapeutic effect. The problem with this is that many patients experience a feeling of being 'doped' which clouds their every waking moment as long as they take regular oral opioids. ***The analgesic efficacy of fast acting fentanyls*** The relief of acute on chronic pain is a particular challenge for oral morphine , not because it lacks analgesic efficacy but because of its pharmacokinetics which do not match the time course of the pain. Very often morphine by mouth takes too long to work but then	

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						exacerbates unwanted effects because it lasts for too long after the pain has subsided. The fast acting fentanyls have a profile of action which more closely matches the profile of breakthrough pain in cancer, particularly incident bone pain. Incident bone pain has long been identified as one of the most difficult pains to treat in cancer patients and because of its consequent impairment of mobility it has profound deleterious effects on quality of life. Immediate release oral morphine is the most widely used analgesic remedy but its inadequacies in this situation have perhaps been underestimated. As described here there are fundamental problems in using immediate release morphine for breakthrough pain. There is sufficient evidence to make a case for the careful use of fast acting fentanyls based on a selection of particular patients with a temporal pattern of pain matching the time course of their analgesic action. It does not seem logical to exclude the use of these new formulations on the grounds of cost when the potential gains have not been fully assessed and when the standard treatment has such limitations. These brief comments highlight the generally poor effects of immediate release morphine in cancer breakthrough pain which are widely underestimated. It seems illogical to advise against the use of fast acting fentanyls thus reducing the options for patients and their clinicians. ***References*** Beecher HK, Keats AS, Mosteller F, Lasagna L, The effectiveness of oral analgesics	

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						(morphine, codeine, acetylsalicylic acid) and the problem of placebo "reactors" and "non-reactors" Journal of Pharmacology and Experiment al Therapeutics 1953;109:393-400. Hanks GW, Rose NM, Aherne GW, Piall EM, Fairfield S, Trueman T Controlled release morphine tablets. A double blind trial in dental surgery patients. **British Journal of Anaesthesia 1981a;** 53: 1259-1264. Hanks GW, Rose NM, Aherne GW, Piall EM. Analgesic effect of morphine tablets. **Lancet 1981b;** i: 732-733 Hanks GW, Rose NM, Aherne GW, Piall EM Controlled release morphine. **Lancet 1981**; i: 1104-1105. Hanks GW, Hoskin PJ, Aherne GW, Turner P, Poulain P. Explanation for potency of repeated oral doses of morphine? **Lancet 1987**; ii: 723-725. Hanks GW, Twycross RG, Bliss JM. Controlled release morphine tablets: a double-blind trial in patients with advanced cancer. **Anaesthesia 1987**; 42: 840-844. Houde RW, Wallenstein SL, Beaver WT Clinical measurement of pain. In de Stevens G, ed. Analgesics.New York: Academic Press, 1965:75-122 Lasagna L Drugs for pain **British Medical Journal** 1979; ii: 333 Lasagna L Heroin: a medical "me-too". **New England Journal of Medicine** 1981;304: 1539-40"	
SH	Palliative Care	37.08		62	1.1.9	"Breakthrough pain". This seems to be talking	For the purpose of this guideline the GDG has

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	Pharmacists Network					about titration pain management or use of rescue medication not breakthrough pain	defined rescue dose as the treatment of breakthrough pain. Section 3.8.1 makes it clear this topic is about breakthrough pain not titration.
SH	Nycomed UK Ltd	28.07	Full	62	1.1.9	As oral morphine is generally accepted as not being effective for spontaneous breakthrough pain (e.g. Zeppetella Clin Oncol 2011,23:393-389; Davies et al. Eur J Pain 2009,13:331-338) the recommendation that it should be used first-line and that fast acting fentanyls should not be offered first-line ignore the needs and requirements of patients experiencing breakthrough pain.	We disagree. The GDG's interpretation of the evidence was that oral morphine was the most clinical and cost-effective intervention for treating breakthrough pain.
SH	Royal College of General Practitioners & British Pain Society	36.08	Full	62	1.1.9 & 1.1.10	*1.1.9 Offer immediate-release oral morphine for the first-line rescue medication of breakthrough pain.* *1.1.10 Do not offer fast-acting fentanyl as first-line rescue medication."* In patients with renal failure, immediate release oral morphine would be contra-indicated and either immediate release oxycodone or a fasting acting fentanyl product should be offered instead. We also believe that the guideline has not fairly evaluated the evidence for fast-acting fentanyl products and that for many patients, these would provide a better solution for predictable and short-lived breakthrough pains, eg to cover nursing procedures, bathing, having Xrays, scans or radiotherapy. It is true that the fast-acting fentanyl drugs should not be initiated by non-specialists, but the guideline should make it clearer that such patients should be referred to a pain or palliative medicine specialist for this consideration.	The question investigated by this guideline was the most effective opioid for patients with breakthrough pain who are able to take oral opioids. Therefore the evidence on patients with breakthrough pain who are unable to take oral opioids has not been reviewed and we are unable to make recommendations on this issue. INFS showed a significant clinical benefit at a minority of time points. At 10 minutes 52.4% of patients taking fentanyl had responded compared to 45% of patients taking morphine. At 15 minutes 75.5% of patients taking fentanyl had responded compared to 69.3% of patients talking morphine. The GDG felt that overall this did not indicate a clinically significant benefit for INFS over IR morphine. In addition the GDG were aware that there is a significant additional cost to using INFS. Consequently the GDG recommended the use of IR morphine. We have amended the LETR paragraph to clarify the GDGs

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							interpretation of the evidence. We have added a recommendation that specialist advice should be sought if patients breakthrough pain remains inadequately controlled.
SH	British Pain Society	38.09	Full	62	1.1.9 & 1.1.10	*1.1.9 Offer immediate-release oral morphine for the first-line rescue medication of breakthrough pain.* *1.1.10 Do not offer fast-acting fentanyl as first-line rescue medication."* In patients with renal failure, immediate release oral morphine would be contra-indicated and either immediate release oxycodone or a fasting acting fentanyl product should be offered instead. We also believe that the guideline has not fairly evaluated the evidence for fast-acting fentanyl products and that for many patients, these would provide a better solution for predictable and short-lived breakthrough pains, eg to cover nursing procedures, bathing, having Xrays, scans or radiotherapy. It is true that the fast-acting fentanyl drugs should not be initiated by non-specialists, but the guideline should make it clearer that such patients should be referred to a pain or palliative medicine specialist for this consideration.	The question investigated by this guideline was the most effective opioid for patients with breakthrough pain who are able to take oral opioids. Therefore the evidence on patients with breakthrough pain who are unable to take oral opioids has not been reviewed and we are unable to make recommendations on this issue. We have added a recommendation that specialist advice should be sought if patients breakthrough pain remains inadequately controlled. INFS showed a significant clinical benefit at a minority of time points. At 10 minutes 52.4% of patients taking fentanyl had responded compared to 45% of patients taking morphine. At 15 minutes 75.5% of patients taking fentanyl had responded compared to 69.3% of patients talking morphine. The GDG felt that overall this did not indicate a clinically significant benefit for INFS over IR morphine. In addition the GDG were aware that there is a significant additional cost to using INFS. Consequently the GDG recommended the use of IR morphine. We have amended the

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							LETR paragraph to clarify the GDGs interpretation of the evidence.
SH	Nycomed UK Ltd	28.30	Full	62	1.1.9 -10	These recommendations do not appear to be evidence based in that IR morphine has been shown not to be the optimal treatment for many episodes of breakthrough pain (Davies et al. Eur J Pain 2009,13:331-338, Zeppetella Clin Oncol 2011,23:393-389; Coluzzi et al Pain 2001, 91(1):123-130). In addition data for some FAFs has clearly shown efficacy over IR morphine at 15-60 minutes (e.g. Vissers et al. CMRO 2010,26(5):1037-1045; Zeppetella et al. Poster presented at the European Multidisciplinary Cancer Congress (16th ECCO, 36th ESMO, and 30th ESTRO). September 23–27, 2011, Stockholm, Sweden). This recommendation seems to contradict initial aims of ensuring better access to effective pain relief for patients as well as denying patients an informed choice. It also does not give any recommendation as to second-line actions or treatments.	INFS showed a significant clinical benefit at a minority of time points. The GDG felt that overall this did not indicate a clinically significant benefit for INFS over IR morphine. In addition the GDG were aware that there is a significant additional cost to using INFS. Consequently the GDG recommended the use of IR morphine. We have amended the LETR paragraph to clarify the GDGs interpretation of the evidence. This guideline only covers first line treatment with strong opioids (as defined in the scope) and therefore we are unable to make recommendations about second-line treatment.
SH	Archimedes Pharma Ltd	32.07	Full	62	14	The final paragraph of section 3.8.5 (page 62) states that the GDG "...felt the cost impact of recommending fentanyl ....would be considerable and could therefore not be justified. Therefore, the GDG agreed to recommend that fast-acting fentanyls are not offered". However, section 3.8.4 Health	We have amended section 3.8.4 to clarify why this topic was not prioritised for health economic evaluation.

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						Economic Modelling (page 60) states "This topic was not considered a health economic priority; the cost-effectiveness literature on this topic was reviewed but no evidence was found". It is therefore not appropriate for the CDG to form a conclusion on cost impact regarding he use of fentanyls in BTCP if no such health economic review has been undertaken. The statement that fentanyls should not be used is misguided, and the breadth of this statement precludes consideration of the important subpopulation of patients with BTCP whose needs are not met by IRMS.	
SH	ProStrakan Group	30.08	Opioids in Palliative Care – Full Guidance	62	15	In a phase IV study (Überall, 2011) on sublingual fentanyl citrate, the study recorded a significant improvement in maximum BTcP intensity with sublingual fentanyl ODT, compared with baseline ($p<0.0001$). Patients reported the time to first effect following administration of sublingual fentanyl ODT was ≤10 minutes in 82.8% of episodes. (Überall, MA et al, Curr Med Res Opin 2011, 19 April 2011; published online) We believe that there is significant evidence to indicate that Intranasal Fentanyl Citrate (INFC) is more suited to match the pharmacokinetic/dynamic profile of BTcP than IR-Morphines. (Davies 2011) Davies's analysis revealed that INFC consistently provided relief from pain more rapidly than IR-Morphines; by 10 minutes, there were significant differences in pain intensity difference scores and in the percentages of episodes showing clinically	The Überall study was not included as it did not meet inclusion criteria for the clinical questions (i.e. it is not an RCT). INFS showed a significant clinical benefit at a minority of time points. At 10 minutes 52.4% of patients taking fentanyl had responded compared to 45% of patients taking morphine. At 15 minutes 75.5% of patients taking fentanyl had responded compared to 69.3% of patients talking morphine. The GDG felt that overall this did not indicate a clinically significant benefit for INFS over IR morphine. In addition the GDG were aware that there is

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						meaningful pain relief (P < 0.05). Overall acceptability scores were significantly greater for INFC than for IR-Morphine at 30 (P < 0.01) and 60 (P < 0.05) minutes. (Davies A. Journal of Pain and Symptom Management, Vol 41, No. 2, February 2011, 358-366) It would appear that despite having a pharmacokinetic profile which matches that of breakthrough cancer pain, fast acting fentanyls are being excluded from consideration on the basis of acquisition cost. The APM guidelines (Davies AN et al, European Journal of Pain 13 (2009) 331-338) also state that the absolute cost of intervention should always be balanced against the total cost of uncontrolled breakthrough pain, which could include increased use of healthcare services (eg unplanned admissions), direct expenditure (eg other pharmacotherapeutic agents), and indirect expenditure (eg transport etc) for patients and their carers.	a significant additional cost to using INFS. Consequently the GDG recommended the use of IR morphine. We have amended the LETR paragraph to clarify the GDGs interpretation of the evidence.
SH	Archimedes Pharma Ltd	32.08	Full	62	19	The recommendations 1.1.9 and 1.1.10 (section 1 recommendations on page 7 and repeated in section 3.8.6 on page 62) are incomplete. They state that IRMS should be used as first line rescue medication in breakthrough pain, but do not go on to advise what the non-specialist should do if that first line treatment is considered unsuitable, proves ineffective or is poorly tolerated; this is a major omission. The treatment of patients suffering BTCP cannot be a "one size fits all" approach. Therapy selection needs to be individualised to the patient, to	This guideline only covers first line treatment with strong opioids (as defined in the scope) and therefore we are unable to make recommendations about second-line treatment. However, we have added a recommendation that specialist advice should be sought if pain remains inadequately controlled despite optimising therapy.

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						optimise the likelihood of success and patient satisfaction. In the recommendations 1.1.5 to 1.1.7 for *maintenance* therapy (pages 7 and 45), recommendation 1.1.7 specifically states, "If pain remains uncontrolled despite optimising first-line therapy, review analgesic strategy and consider seeking specialist advice". The draft guideline as it stands is effectively instructing non-specialists to leave patients with their *breakthrough* pain if the first line treatment doesn't work. A statement should be added as recommendation 1.1.11 to the breakthrough pain recommendations to the effect that, should IRMS be considered unsuitable, ineffective or poorly tolerated, this subpopulation of patients with poorly controlled BTCP should be referred to a specialist for consideration of other analgesia, such as a fast-acting fentanyl product.	
SH	Target Ovarian Cancer	22.05	Full	62	26	We are disappointed that fast-acting fentanyl could not be recommended for the management of breakthrough pain as we feel it could offer significant fast acting pain relief to some patients with cancer. We feel this is an area that warrants further research, particularly the nasal spray delivery system.	We agree that further research would be desirable but the limited data available did not indicate a clinically significant benefit for INFS over IR morphine. In addition the GDG were aware that there is a significant additional cost to using INFS. Consequently the GDG recommended the use of IR morphine.
SH	Nycomed UK Ltd	28.29	Full	62	3	How can the GDG be satisfied that IR morphine/oxycodone is as effective as fast acting fentanyls when the guideline previously refers to the faster onset of action for INFS?	INFS showed a significant clinical benefit at a minority of time points. At 10 minutes 52.4% of patients taking fentanyl had responded compared to 45% of patients taking morphine. At 15 minutes 75.**5%** of patients taking fentanyl had responded compared to 69.3% of patients talking morphine. The GDG felt that

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							overall this did not indicate a clinically significant benefit for INFS over IR morphine. In addition the GDG were aware that there is a significant additional cost to using INFS. Consequently the GDG recommended the use of IR morphine. We have amended the LETR paragraph to clarify the GDGs interpretation of the evidence.
SH	Sobell House Hospice Charity	11.08	Full	62	3.8.6	No second line suggested	This guideline only covers first line treatment with strong opioids (as defined in the scope) and therefore we are unable to make recommendations about second-line treatment.
SH	St Josephs Hospice	10.02	full	62	bottom	Statement about not offering fast acting fentanyl as first line rescue feels too absolute – may be occasions for example incident pain from a fracture and pain on weight bearing	INFS showed a significant clinical benefit at a minority of time points. At 10 minutes 52.4% of patients taking fentanyl had responded compared to 45% of patients taking morphine. At 15 minutes 75.5% of patients taking fentanyl had responded compared to 69.3% of patients talking morphine. The GDG felt that overall this did not indicate a clinically significant benefit for INFS over IR morphine. In addition the GDG were aware that there is a significant additional cost to using INFS. Consequently the GDG recommended the use of IR morphine. We have amended the LETR paragraph to clarify the GDGs interpretation of the evidence.
SH	Napp Pharmaceuticals Ltd	35.03		62	Rec 1.1.9	Recommendation 1.1.9 states that oral IR morphine should be used as first-line rescue medication. We would welcome the GDG's consideration of whether further clarification is needed for patients taking background SR oral opioids other than morphine. For example, for patients taking background oxycodone SR, an	Further clarification has been added to recommendation 1.1.9 that if morphine is used for background pain it should also be used as rescue medication.

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						IR formulation of oxycodone would provide the molecular continuity considered good practice amongst clinicians and therefore may be considered first line in this group of patients. (Twycross R and Wilcock A. Palliative Care Formulary, Fourth Edition. 2011. Page 355.)	
Non reg SH (have contacted	Birmingham St Marys Hospice	39.00	Full	62	table	Although this table relates to cost it is confusing in that the footnote b states' Typically one sixth of regular dose' – this only relates to morphine and oxycodone not fentanyl and actiq	The dose of fentanyl has also been calculated as one sixth of the regular dose. Given that the patch release 25µg/hour, this is equivalent to a daily dose of 600µg. Thus a dose of 100µg is one sixth of the regular dose. For further clarity the footnote will be changed to "typically one sixth of regular daily dose". Note that in the case of actiq, doses begin at 200µg, so this is the closest equivalent that could be used.
SH	Association for Palliative Medicine of Great Britain and Ireland	25.46	Full	63	1	It is regrettable that the GDG fails to explore the evidence base around the use of opioid antagonists in the treatment of constipation.	This guideline is aimed primarily at generalists. Since opioid antagonists are used in the specialist setting, they were not included in this guideline.
SH	Napp Pharmaceuticals Ltd	35.01	Full	63	1	We welcome the appropriate attention to the management of constipation given that constipation is often one of the most troublesome and persistent side-effects of opioid therapy. However, we were disappointed to note that oxycodone/naloxone, an improvement on the oxycodone formulation specifically developed to counteract this most common opioid side-effect, was not reviewed and considered within the oxycodone literature review. Although it is widely recommended that patients receiving opioids should also receive optimised laxative regimens, evidence for the efficacy of	This guideline is aimed primarily at generalists. Since opioid antagonists are used in the specialist setting, they were not included in this guideline. In addition the guideline recommends the use of morphine not oxycodone.

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						laxatives in treating opioid induced constipation is limited (Ahmedzai 2009). Many patients (especially the elderly with co-morbiditites) fail to tolerate sufficiently high enough doses to ensure effective laxation. This may be due to administration issues, such as patients being unable to ingest the significant volumes required for some liquid laxative preparations, or due to the poor palatability of several laxatives (Panchal 2007). In other patients, laxation may only be achieved with doses that are higher or more frequent than the licensed posology for the product, and in 1/3 of patients rectal measures are required in order to sufficiently manage constipation. (Twycross R and Wilcock A. Palliative Care Formulary, Fourth Edition. 2011. Page 35) It should also be noted that significant side-effects may further limit the effectiveness of laxatives, (Panchal 2007) and concordance with the regular laxative regimens suggested by the GDG may be poor. The GDG highlighted the importance of making recommendations on this common side effect in order to improve patient care; we feel that oxycodone/naloxone aligns with the aims of the GDG by offering an improved patient experience in appropriately selected individuals in whom laxative treatment fails. Oxycodone/naloxone has proven efficacy (published RCTs) in non-malignant pain and, of more relevance, in cancer pain (Ahmedzai SH et al Palliative Medicine 2011.A randomized, double-blind, active-controlled, double-dummy, parallel-group study to determine the safety and efficacy of oxycodone/naloxone prolonged-release tablets in patients with moderate/severe, chronic cancer pain). A recent	

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						health economic article (in press) has demonstrated the cost-effectiveness of oxycodone/naloxone, with the cost per QALY being well below the commonly accepted threshold (paper available on request). In patients with persistent constipation despite the highest tolerated dose of laxative, where quality of life may be significantly impaired, oxycodone/naloxone provides analgesia equivalent to oxycodone but with significantly improved bowel function (enabling laxatives to be reduced or stopped). We would encourage the GDG to review the RCT data for oxycodone/naloxone and to assess whether they consider that oxycodone/naloxone fulfills an unmet need for those patients who experience this common side-effect but fail on optimised laxative regimens.	
SH	Nottingham University Hospitals NHS Trust	9.01	FULL	63	3.9	District nurses might be able to help with enemas and prevent unnecessary, costly and distressing hospital admissions. A mention of this in NICE guidance would be helpful for non-specialist healthcare professionals	Enemas are included in the background text on p63. This issue was not investigated by the guideline and so the evidence on this has not been appraised. As such we are not able to make recommendations on this issue.
SH	Nottingham University Hospitals NHS Trust	9.02	FULL	63	3.9	Relistor is licensed for 'Treatment of opioid-induced constipation in advanced illness patients who are receiving palliative care when response to usual laxative therapy has not been sufficient'. A randomised published in NEJM has shown it to be beneficial. CDG opinion on this drug would be helpful for specialists and non-specialists. (Thomas et al. Methylnaltrexone for Opioid-Induced Constipation in Advanced Illness.N Engl J Med 2008; 358:2332-2343)	This guideline is aimed primarily at generalists. Since opioid antagonists are used in the specialist setting, they were not included in this guideline. In addition methylnaltrexone is the subject of an ongoing Technology Appraisal and therefore cannot be investigated by this guideline.
SH	Astrazeneca UK Ltd	31.03	Full	63-65	Secti	The discussion and review question focuses	The GDG felt the issue of patient switching

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					on 3.9	only on two options – use of laxatives or switching opioids. Although we realise that this may fall outside of the guideline scope we believe a more appropriate clinical question would be: How should opioid induced constipation (OIC) be managed and what treatment strategies should be considered if laxative treatment is not adequate for patients. Given the patient population, a range of options should be discussed prior to considering opioid switching given the potential negative outcomes (documented within the draft guidelines) associated with switching opioids. We would highlight that not all laxative failures are due to lack of adherence but may be because of a lack or efficacy or tolerability, this should also be considered. The discussion regarding laxatives should include alternative classes of therapy such as mu opioid antagonists which may be an appropriate option prior to consideration of opioid switching.	opioid because of side effect issues was a higher priority for investigation than comparing laxatives. Recommendation 1.1.14 covers what to do if laxative therapy doesn't work. This guideline is aimed primarily at generalists. Since opioid antagonists are used in the specialist setting, they were not included in this guideline.

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SH	Royal College of Nursing	27.07	Full	64		Fast acting fentanyl should be recommended for patients who cannot take oral medications	The question investigated by this guideline was the most effective opioid for patients with breakthrough pain who are able to take oral opioids. Therefore the evidence on patients with breakthrough pain who are unable to take oral opioids has not been reviewed and we are unable to make recommendations on this issue.
SH	Marie Curie Cancer Care Belfast	41.06	full	64		3.9 no mention of use of Naloxone containing preparations for reduction in constipating effects of opiods i.e. either Relistor@ or TARGINACT@	This guideline is aimed primarily at generalists. Since opioid antagonists are used in the specialist setting, they were not included in this guideline. In addition the guideline recommends the use of morphine not oxycodone.
SH	Marie Curie Cancer Care Belfast	41.07	full	64		3.9 No mention of evidence for use of alfentanyl/fentanyl preparations vs morphine or other opioid	The evidence on constipation with fentanyl versus other strong opioids is reviewed in section 3.4.2. We have inserted a cross-reference to this section.
SH	Marie Curie Cancer Care	24.06	Full	64	25	The recommendations on managing constipation are based on clinical experience as no evidence specifically comparing the use of laxatives with switching opioids was found. This was a very specific question which risks overlooking the fact that many patients are started on opioids without any preventative treatment. In this situation it would be helpful to describe the patho-physiology of opioid induced constipation as a guide to which classes of laxatives are like to be most effective.	Recommendation 1.1.12 is clear that laxative therapy should be prescribed to all patients initiating strong opioids. As stated in section 3.9.5, due to the lack of evidence, the GDG were not able to specify particular laxatives.
SH	Association for Palliative Medicine of Great Britain and Ireland	25.28	Full	65		A further recommendation "if patients are constipated despite laxatives consider peripheral opioid antagonists and referral for specialist palliative care advice." should be made	This guideline is aimed primarily at generalists. Since opioid antagonists are used in the specialist setting, they were not included in this guideline.
SH	Royal College of General	36.09	Full	65	1.1.1	*1.1.11 Inform patients that constipation affects*	

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	Practitioners & British Pain Society				1 – 1.1.14	*nearly all patients receiving strong opioid therapy. 1.1.12 Prescribe laxative therapy (to be taken regularly at an effective dose) for all patients initiating strong opioids.* *1.1.13 Inform patients that treatment for constipation takes time to work and adherence is important.* *1.1.14 Optimise laxative therapy for the management of constipation before considering switching opioids."* We believe that this and subsequent sections on the management of opioid adverse effects are inaccurate and could lead to poor prescribing. For example, the statement (p 63) *"Some opioids are thought to be more constipating than others."* is wrong. There is ample evidence, both clinical and pre-clinical in animal models, that certain opioids, notably fentanyl and buprenorphine, cause less constipation and other gastrointestinal adverse effects, for the same level of pain control. For patients in whom constipation is already a problem or who could be at risk of significant impairment of quality of life, eg through faecal impaction, it would make good sense to avoid morphine and initiate a less constipating opioid at the outset. Re the statement (p 63): *"The GDG wanted to investigate the evidence on whether laxative treatment or switching the type of opioid medication would be a more effective intervention in reducing constipation for patients with troublesome constipation on opioids."* And further: *"Is laxative treatment more effective with*	The evidence in section 3.4.2 shows that some opioids do cause more constipation than others, which is further supported by your comments on fentanyl and buprenorphine. These recommendations are based on evidence of both clinical and cost-effectiveness. The text on p44 acknowledges that morphine may result in an increase in GI side effects, but the GDG believed these could be managed by adjunctive treatments. The text also states that the ICER for fentanyl was £107,533/QALY which is far beyond the threshold considered by NICE to be cost effective.

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						opioid switching, or without opioid switching, in reducing constipation in patients with advanced and progressive disease who are taking strong opioids and experience constipation as a side effect?" We believe that this asking the wrong question, and it not surprising that the evidence team found no papers to answer it. The GDG should have been presented with evidence from existing RCTs, systematic reviews and meta-analyses that fentanyl and buprenorphine are less constipating in themselves. It seems unreasonable to insist that patients have to take large amounts of (not inexpensive) laxatives and undergo invasive procedures such as rectal suppositories or enemas, when less constipating drugs are available. It seems to us that this decision was made primarily on economic, rather than clinical, or evidence-based grounds. Furthermore, we found it surprising and disappointing that there was no reference to or guidance on two other researched and published methods of dealing with opioid-induced constipation. These are a. the use of subcutaneous methylnaltrexone as a peripherally acting, non-systemically bioavailable opioid antagonist. b. The use of the combination of sustained release oxycodone and naloxone (Targinact).	The GDG felt the issue of patients switching opioid therapy because of side effect issues was a higher priority for investigation. This guideline is aimed primarily at generalists. Since opioid antagonists are used in the specialist setting, they were not included in this guideline. Methylnaltrexone is the subject of an ongoing Technology Appraisal and therefore cannot be investigated by this guideline. The guideline recommends the use of morphine not oxycodone, so Targinact would not be appropriate.

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SH	British Pain Society	38.10	Full	65	1.1.11 – 1.1.14	*1.1.11 Inform patients that constipation affects nearly all patients receiving strong opioid therapy. 1.1.12 Prescribe laxative therapy (to be taken regularly at an effective dose) for all patients initiating strong opioids.* *1.1.13 Inform patients that treatment for constipation takes time to work and adherence is important.* *1.1.14 Optimise laxative therapy for the management of constipation before considering switching opioids."* We believe that this and subsequent sections on the management of opioid adverse effects are inaccurate and could lead to poor prescribing. For example, the statement (p 63) *"Some opioids are thought to be more constipating than others."* is misleading, as '*thought to be'* implies some uncertainty about the evidence regarding constipation. There is in fact ample evidence, both clinically and in pre-clinical animal models, that certain opioids, notably fentanyl and buprenorphine, cause less constipation and other gastrointestinal adverse effects such as nausea, for the same level of pain control. For patients in whom constipation is already a problem or who could be at risk of significant impairment of quality of life, eg through faecal impaction, it would therefore make good sense to avoid morphine and initiate a less constipating opioid at the outset. Re the statement (p 63): *"The GDG wanted to investigate the evidence on whether laxative treatment or switching the type of opioid medication would be a more effective*	The evidence in section 3.4.2 shows that some opioids do cause more constipation than others, which is further supported by your comments on fentanyl and buprenorphine. These recommendations are based on evidence of both clinical and cost-effectiveness. The text on p44 acknowledges that morphine may result in an increase in GI side effects, but the GDG believed these could be managed by adjunctive treatments. The text also states that the ICER for fentanyl was £107,533/QALY which is far beyond the threshold considered by NICE to be cost effective.

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						intervention in reducing constipation for patients with troublesome constipation on opioids." And further: *"Is laxative treatment more effective with opioid switching, or without opioid switching, in reducing constipation in patients with advanced and progressive disease who are taking strong opioids and experience constipation as a side effect?"* We believe that this asking the wrong question, and it not surprising that the evidence team found no papers to answer it. The GDG should have been presented with evidence from existing RCTs, systematic reviews and meta-analyses that fentanyl and buprenorphine are less constipating in themselves. It seems unreasonable to insist that patients have to take large amounts of (not inexpensive) laxatives and undergo invasive procedures such as rectal suppositories or enemas, when less constipating drugs are available. It seems to us that this decision was made primarily on economic, rather than clinical, or evidence-based grounds. Furthermore, we found it surprising and disappointing that there was no reference to or guidance on two other researched and published methods of dealing with opioid-induced constipation. These are c. the use of subcutaneous methylnaltrexone as a peripherally acting, non-systemically bioavailable opioid antagonist. d. The use of the combination of sustained release oxycodone and naloxone (Targinact).	The GDG felt the issue of patient switching opioid because of side effect issues was a higher priority for investigation.

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						e.	
SH	Pancreatic Cancer UK	23.04	Full	65	1.1.11-14	We support these recommendations as it is essential that patients receive good information and support to help them manage the side effects of constipation.	Thank you.
SH	Palliative Care Pharmacists Network	37.10		65	1.1.12	? to be more prescriptive as for non specialists eg by adding stimulant +/- softener	As stated in section 3.9.5, due to the lack of evidence, the GDG were not able to specify particular laxatives.
SH	Help the Hospices	43.04		65		1.1.11 **Constipation** Examples of appropriate laxatives based on clinical experience would be helpful – even with a poor evidence base.	As stated in section 3.9.5, due to the lack of evidence, the GDG were not able to specify particular laxatives.
SH	Association for Palliative Medicine of Great Britain and Ireland	25.25	Full	65	1.1.12	Might be better as "prescribed stimulant laxative therapy..". Also this may be better with a caveat "unless the patient has a high out put stoma, inflammatory bowel disease or is being started on transdermal Fentanyl where as required laxatives may be more appropriate".	As stated in section 3.9.5, due to the lack of evidence, the GDG were not able to specify particular laxatives.
SH	Association for Palliative Medicine of Great Britain and Ireland	25.26	Full	65	1.1.13	May be better as "advise patients that if treatment for constipation has not worked within 24-48 hours they should seek advice on titrating or combining laxatives."	We feel recommendation 1.1.3 adequately covers this.
SH	Association for Palliative Medicine of Great Britain and Ireland	25.27	Full	65	1.1.14	May be better to "optimise laxative therapy for the management of constipation before switching to transdermal opioids" (there is no evidence that switching to other oral opioids will reduce constipation).	This guideline only covers first line treatment with strong opioids (as defined in the scope) and therefore we are unable to make recommendations about second-line treatment.
SH	Target Ovarian Cancer	22.06	Full	65	8	We welcome the series of recommendations on the management of constipation as a side effect of opioid pain relief. We feel it is particularly important that patients are made aware that treatment for constipation can take time to work and that good adherence will improve relief.	Thank you.
SH	Department of Health	26.03	Full	66	26	Guidance on safe and effective prescribing might more usefully be focussed on the general efficacy of non-drug measures and the various	The GDG felt the issue of patient switching opioid because of side effect issues was a higher priority for investigation than comparing

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						classes of anti-emetics in controlling opioid induced nausea than in addressing only the question of opioid switching. This focus, leading to 2 very general recommendations, may result in non-specialist prescribers believing that there is no clinical evidence about which anti-emetics are less effective in this situation.	anti-emetics or non-drug measures. Because of the lack of evidence, the GDG were not able to specify particular anti-emetics.
SH	Palliative Care Pharmacists Network	37.11		68		Us there evidence for recurrence of nausea when increasing doses of opioids? I have never seen this & cant find it in any standard texts books. Is there a role for recommending short courses of anti emetics prophylactically as per some text books?	It was the opinion of the GDG, based on their clinical experience that this happens. Prophylactic anti-emetics were not recommended because nausea is likely to be transient.
SH	St Nicholas Hospice	18.00	full	68		Advice on not driving during dose adjustment phases may be useful. Driving can continue when dose is stable if concentration is not affected.	We have added advice about driving to recommendation 1.1.17 and inserted a cross reference to the relevant DVLA guidance
SH	Help the Hospices	43.05		68		1.1.15 **Nausea** Suggestion of examples of appropriate antiemetics for opioid induced nausea – there is an evidence base. Also highlight that if nausea persists, then an alternative to the oral route may be appropriate (common problem in practice that analgesia is ineffective as oral opioids are not being absorbed) Similarly – with profuse diarrhoea or short bowel (resection) syndrome, sustained release preparations are likely to be less effective.	The question we addressed was the issue of opioid switching versus optimising anti-emetic use. We did not compare effectiveness of different anti-emetics. Therefore we are unable to specify particular drugs as we have not examined this evidence. Recommendation 1.1.16 does not exclude switching opioid to a non-oral route.
SH	Palliative Care Pharmacists Network	37.12		68		Add in about reviewing patients as there might be other causes of n & v at this point some of which are emergencies	We feel this issue is covered by recommendation 1.1.3.
SH	Marie Curie Cancer Care Belfast	41.00	full	68	1.1.15	1.1.15 and 1.1.16 pragmatic approach would be to ensure anti-emtics are available for regular or prn use before stage of nausea is reached	Our recommendations do not preclude this from happening.

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SH	Palliative Care Pharmacists Network	37.13		68	1.1.15	Take out the word consider	We do not think this is required.
SH	Royal College of General Practitioners & British Pain Society	36.10	Full	68	1.1.15 & 1.1.16	*1.1.15 Advise patients that nausea may occur when starting opioid therapy or at dose increase, but that it is likely to be transient. 1.1.16 If nausea persists, prescribe and optimise anti-emetic therapy before considering switching opioids."* Once again, as with constipation, the question set was unhelpful (p66) *"Is anti-emetic treatment more effective with opioid switching, or without opioid switching, in reducing nausea in patients with advanced and progressive disease who are taking strong opioids and experience nausea as a side effect?"* Not surprisingly, no publications were found which answered this pointless question. There is published evidence that fentanyl transdermal patches cause less emesis than morphine and this should be a reason to start fentanyl earlier in patients with persistent nausea or vomiting with morphine. Furthermore, the phrase *"If nausea persists, prescribe and optimise anti-emetic therapy*" is unclear. First, how long should nausea be allowed to persist for? Second, what is meant by optimising anti-emetic therapy (we are unaware of any other current evidence-based	The GDG felt the issue of patient switching opioid because of side effect issues was a higher priority for investigation. These recommendations are based on evidence of both clinical and cost-effectiveness. The text on p44 acknowledges that morphine may result in an increase in GI side effects, but the GDG believed these could be managed by adjunctive treatments. The text also states that the ICER for fentanyl was £107,533/QALY which is far beyond the threshold considered by NICE to be cost effective. These recommendations were based on the expert clinical opinion and experience of the GDG as there was no published evidence base. Therefore we were unable to define the length of time the nausea should be allowed to persist. If a patient remains nauseas they

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						guidance on this).	should take an anti-emetic and if it doesn't work then it should be changed to an alternative anti-emetic.
SH	British Pain Society	38.11	Full	68	1.1.15 & 1.1.16	*1.1.15 Advise patients that nausea may occur when starting opioid therapy or at dose increase, but that it is likely to be transient. 1.1.16 If nausea persists, prescribe and optimise anti-emetic therapy before considering switching opioids."* Once again, as with constipation, the question set was unhelpful (p66) *"Is anti-emetic treatment more effective with opioid switching, or without opioid switching, in reducing nausea in patients with advanced and progressive disease who are taking strong opioids and experience nausea as a side effect?"* Not surprisingly, no publications were found which answered this pointless question. There is published evidence that fentanyl transdermal patches cause less emesis than morphine and this should be a reason to start fentanyl earlier in patients with persistent nausea or vomiting with morphine. Furthermore, the phrase *"If nausea persists, prescribe and optimise anti-emetic therapy*" is unclear. First, how long should nausea be allowed to persist for? Second, what is meant by optimising anti-emetic therapy (we are unaware of any other current evidence-based guidance on this).	The GDG felt the issue of patient switching opioid because of side effect issues was a higher priority for investigation. These recommendations are based on evidence of both clinical and cost-effectiveness. The text on p44 acknowledges that morphine may result in an increase in GI side effects, but the GDG believed these could be managed by adjunctive treatments. The text also states that the ICER for fentanyl was £107,533/QALY which is far beyond the threshold considered by NICE to be cost effective.
SH	Pancreatic Cancer UK	23.05	Full	68	1.1.15-16	We support these recommendations as it is important for patients to receive good	Thank you.

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						information and support to help them manage any nausea associated with opioid therapy.	
SH	Royal College of Nursing	27.02	Full	68	1.1.16	Start prophylactic anti-emetics as nausea at an early stage can put patients off opioids - preferring pain to side effects. Mention other side effects that patients find a problem – pruritus and hallucinations	Our recommendations do not preclude this from happening. These side effects were not investigated by the guideline and so the evidence on them has not been appraised. As such we are not able to make recommendations on this issue.
SH	Wales Palliative Care Strategy Implementation Board	12.06	Full	68	1.1.16	Again here the antiemetic should be specified as being a centrally acting antiemetic such as Metoclopramide or Haloperidol. Without specifying this, the mis-prescribing of Ondansetron and similar antiemetics will continue.	The question we addressed was the issue of opioid switching versus optimising anti-emetic use. We did not compare effectiveness of different anti-emetics. Therefore we are unable to specify particular drugs as we have not examined this evidence.
SH	Association for Palliative Medicine of Great Britain and Ireland	25.29	Full	68	1.1.16	Most respondents felt that a recommendation to consider prescribing prophylactic as required anti-emetics should be made and some felt specifically that prokinetic antiemetics or Haloperidol should be advised as the drugs of choice.	Our recommendations do not preclude this from happening. The question we addressed was the issue of opioid switching versus optimising anti-emetic use. We did not compare effectiveness of different anti-emetics. Therefore we are unable to specify particular drugs as we have not examined this evidence.
SH	Marie Curie Cancer Care	24.07	Full	68	19	Clinical experience of the GDG was used to create the recommendations on managing nausea since no evidence was found. Long experience in managing opioid related nausea has shown that some classes of anti-emetic medication are less effective and more expensive. **If** this draft document is intended to guide effective prescribing, some comment on this subject would have been helpful.	The question we addressed was the issue of opioid switching versus optimising anti-emetic use. We did not compare effectiveness of different anti-emetics. Therefore we are unable to specify particular drugs as we have not examined this evidence.
SH	Palliative Care	37.22		68	2	Us there evidence for recurrence of nausea	It was the opinion of the GDG, based on their

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	Pharmacists Network					when increasing doses of opioids? I have never seen this & cant find it in any standard texts books. Is there a role for recommending short courses of anti emetics prophylactically as per some text books?	clinical experience, that this happens. Prophylactic anti-emetics were not recommended because nausea is likely to be transient.
SH	Nottingham University Hospitals NHS Trust	9.03	FULL	68	3.10	Macmillan nurses in community (where available) would be able to provide advice to the patient. District nurses could also help with antiemetic administration via Syringe driver at home. . A mention of this in NICE guidance would be helpful for non-specialist healthcare professionals	We feel this is an issue that can be dealt with at implementation. We did not examine the evidence on who should administer antiemetics and therefore are not able to make recommendations on this issue.
SH	St Ann's Hospice	14.11	full	68	Recommendation 1.1.15	Could transient be defined (ie 1 week)	A definition of transient has been included in the glossary.
SH	Target Ovarian Cancer	22.07	Full	69	3	We agree that this is an appropriate research recommendation that would potentially benefit the management of nausea.	Thank you.
SH	Association for Palliative Medicine of Great Britain and Ireland	25.47	Full	70	1	It is regrettable that the GDG failed to explore the role of psychostimulants in the management of opioid induced drowsiness.	This is a short clinical guideline and topics had to be prioritised for inclusion. The GDG prioritised strategies which were used in general practice and since psychostimulants are only used in specialist settings, there were not investigated by this guideline.
SH	St Josephs Hospice	10.06	Full	70	bottom	Need to think about signs of toxicity	This section reports what was found in the evidence review.
SH	Sobell House Hospice Charity	11.09	Full	71	3.11.5	Assumption that pain is opioid responsive whereas may need specialist assessment and adjuvant therapy. Side effects of drowsiness should be balanced against pain control as may not have choice for non-intervention. Clinical	This section describes how the GDG went from the evidence to their recommendations. We do not understand how your comment relates to this.

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						experience is quoted here.	
SH	Marie Curie Cancer Care Belfast	41.01	full	72		1.1.18 Advise patients to avoid driving or similar activites whie doses are being adjusted or newly introduced.	We have added advice about driving to recommendation 1.1.17 and inserted a cross reference to the relevant DVLA guidance
SH	Marie Curie Cancer Care Belfast	41.02	full	72		general comment: no mention of driving advice	We have added advice about driving to recommendation 1.1.17 and inserted a cross reference to the relevant DVLA guidance
SH	Help the Hospices	43.06		72		1.1.17 **Drowsiness** Need to highlight that this may be due to the fact that the underlying pain has been treated eg with recent radiotherapy – and that dose reduction is now appropriate.	We believe this issue is covered in recommendation 1.1.18.
SH	Sue Ryder Care	16.01	Full	72		The Guideline Development Group have again produced a clinically sensible synthesis here. However, it might be helpful to expand the 2nd bullet point to encourage the prescriber to consider opioid-responsiveness, before they opioid switch. For example: • Consider reducing the opioid dose and adding a non-opioid adjuvant analgesic if opioid-poorly responsive pain components are present (e.g. neuropathic pain, skeletal or smooth muscle spasm, bony pain) • Otherwise, consider switching opioids, or seeking specialist advice, if pain is not controlled	Thank you. We believe this is adequately covered in the current wording.
SH	Association for Palliative Medicine of Great Britain and Ireland	25.30	Full	72		Many felt would be better "in patients with persistent central nervous system effects."	The GDG felt it was important that both patients with persistent CNS effects and those with moderate-severe effects should have their symptoms managed.
SH	Isabel Hospice	19.02	Full	72	1.1.17	Advice should be included in the section on drowsiness on driving with reference to DVLA guidance.	We have added advice about driving to recommendation 1.1.17 and inserted a cross reference to the relevant DVLA guidance

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SH	Royal College of General Practitioners & British Pain Society	36.11	Full	72	1.1.17 & 1.1.18	*1.1.17 Advise patients that mild drowsiness or impaired concentration may occur when starting opioid therapy or at dose increase, but that it is often transient.* *1.1.18 In patients with either persistent or moderate-to-severe central nervous system side effects:* *consider dose reduction if pain is controlled* *consider switching opioids if pain is not controlled."* Once again, the question asked was of the form (p 70): "*Is opioid dose reduction or switching opioid more effective in reducing drowsiness in patients with advanced and progressive disease who are taking strong opioids and experience drowsiness as a side effect?"* However, compared to the questions on constipation and nausea, the comparator to switching opioids was not a specific intervention for drowsiness, but rather dose reduction. For non-specialists, this is unhelpful because dose reduction done in isolation (eg, without adding or increasing other non-opioid medication or performing a non-pharmacological intervention) could lead to an unnecessary increase in pain. It was surprising that there is no mention of the use of psychostimulants (methylphenidate or modafanil) to counter unacceptable drowsiness caused by opioids. Furthermore, the guideline does not acknowledge that there is evidence that fentanyl	The GDG believe that the recommendation is correct as worded and would not lead to patients experiencing unnecessary pain This is a short clinical guideline and topics had to be prioritised for inclusion. The GDG prioritised strategies which were used in general practice and since psychostimulants are only used in specialist settings, there were not investigated by this guideline. This evidence was reviewed in section 3.4.2

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						and oxycodone are associated with a reduced level of sedation (and possibly other CNS adverse effects such as hallucinations.	but no difference was found.
SH	British Pain Society	38.12	Full	72	1.1.17 & 1.1.18	*1.1.17 Advise patients that mild drowsiness or impaired concentration may occur when starting opioid therapy or at dose increase, but that it is often transient.* *1.1.18 In patients with either persistent or moderate-to-severe central nervous system side effects:* *consider dose reduction if pain is controlled* *consider switching opioids if pain is not controlled."* Once again, the question asked was of the form (p 70): "*Is opioid dose reduction or switching opioid more effective in reducing drowsiness in patients with advanced and progressive disease who are taking strong opioids and experience drowsiness as a side effect?"* However, compared to the questions on constipation and nausea, the comparator to switching opioids was not a specific intervention for drowsiness, but rather dose reduction. For non-specialists, this is unhelpful because dose reduction done in isolation (eg, without adding or increasing other non-opioid medication or performing a non-pharmacological intervention) could lead to an unnecessary increase in pain. It was surprising that there is no mention of the use of psychostimulants (methylphenidate or modafanil) to counter unacceptable drowsiness caused by opioids. Furthermore, the guideline	The GDG believe that the recommendation is correct as worded and would not lead to patients experiencing unnecessary pain.

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						does not acknowledge that there is evidence that fentanyl and oxycodone are associated with a reduced level of sedation (and possibly other CNS adverse effects such as hallucinations.	
SH	National Council for Palliative Care	42.10	full	72	1.1.18	We **recommend** NICE add □ for opiate equivalence consider seeking specialist advice □ consider a non-opiate medication Palliative Adult Network Guidelines (PANG) should also be referenced (http://book.pallcare.info).	We have added a recommendation to section 3.5 about calculating equivalence. Non-opiate mediation is outside the scope of this guideline While we accept that valuable guidance already exists we are unable to cross-reference non-NICE guidance.
SH	National Council for Palliative Care	42.11	full	72	1.1.18	We **recommend** NICE reference Driver and Vehicle Licensing Agency / Pain Society guidance in reference to safety and driving when initiating opiates	We have added advice about driving to recommendation 1.1.17 and inserted a cross reference to the relevant DVLA guidance
SH	Association for Palliative Medicine of Great Britain and Ireland	25.31	Full	72	1.1.19	"if side effects remain inadequately controlled despite optimising therapy seek specialist palliative care advice for consideration of psychostimulants."	This is a short clinical guideline and topics had to be prioritised for inclusion. The GDG prioritised strategies which were used in general practice and since psychostimulants are only used in specialist settings, there were not investigated by this guideline.
SH	St. Oswald's Hospice	13.16	Full	72	14	A lack of response to opioids is not a reason to switch opioids! This should read: *" consider switching opioids if pain drowsiness persists in the presence of good pain control.*	We agree but the recommendation to switch opioids only relates to uncontrolled pain after dose reduction because of drowsiness.
SH	Napp Pharmaceuticals Ltd	35.04		72	Rec 1.1.18	In determining recommendation 1.1.18, the information scientists were unable to find any literature relating to the efficacy of opioid switching in patients with CNS effects. We wish to draw attention to a paper by Riley et al (Support Care Cancer 2006) describing an open label study of switching morphine-intolerant patients to oxycodone and other opioids (if a	Thank you for providing these references. Unfortunately these studies do not meet the inclusion criteria for the topic investigated and therefore were not included in the evidence appraisal.

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						subsequent switch was required). Although patients experienced a range of side effects on morphine, many were CNS-based. The GDG may be interested in reviewing the attached PDF copy of this article.	
SH	St Ann's Hospice	14.12	full	72	Recommendation 1.1.17	Again could transient be defined as this would allow a generalist to consider after what time period an opioid may need to be switched or reduced	We think this term is commonly understood.
SH	Wales Palliative Care Strategy Implementation Board	12.09	Full	73	1	Overall this guidance is <u>not</u> guidance on the prescribing of opioids in patients with severe pain but it is guidance on ways of improving patient compliance with strong opioids when there are prescribed for severe pain. The research review is about the fears that patients have and the reason that they do not take their analgesia.	Thank you for your view.
SH	Wales Palliative Care Strategy Implementation Board	12.10	Full	73	1	The review is not about the way the analgesic should be prescribed and other drugs that should be prescribed with them. Without specifying that the opioids should be stated at low dose and titrated up, the emerging problem in recent years of opioids toxicity being confused with clinical deterioration will continue. There should at the very least be guidance on doses at the start of opioid titration.	We have added recommendations in section 3.3 on a safe starting dose for titration and a recommendation to section 3.5 about calculating equivalence.
SH	Wales Palliative Care Strategy Implementation Board	12.11	Full	73	1	This guideline should have a title that more accurately reflects its content, for example, "Improving Patient Compliance when Opioids are Prescribed as Analgesics in Advanced Disease". These are guidelines on how to increase compliance of patients on opioids but are not prescribing guidelines.	The title was specified by the Department of Health and we are not able to change it.
SH	St. Oswald's Hospice	13.17	Full	73	1	***This guideline has***	Thank you.

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						- emphasised the use of oral morphine as the first line opioid - outlined the challenges in prescribing opioids and helping patients achieve concordance in taking opioids - an over enthusiastic wording regarding transdermal opioids ***The guideline will not*** - provide any advice regarding opioid doses (surprising considering the GMC case of GMC v Martin 2010) - clear the confusion over titration (starting doses, rate and what dose to ask for help) ***Unfortunately the guideline has*** - ignored all patients with severe renal impairment risking serious adverse events if the guideline's recommendations are followed - provided the wrong sources of advice on opioid prescribing	Thank you We disagree that recommending transdermal opioids be considered for use is too enthusiastic. We consider it to be pragmatic and based upon the best available evidence. We have added recommendations in section 3.3 on a safe starting dose for titration and a recommendation to section 3.5 about calculating equivalence. While we did not exclude patients with renal impairment from the scope of this guideline, the evidence review did not find any data specific to this group of patients. Consequently the GDG were unable to make prescriptive recommendations for patients with renal or hepatic impairment. However they have now added a recommendation that specialist advice should be sought before prescribing opioids for this group of patients
SH	Association for Palliative Medicine of Great Britain and Ireland	25.48	Full	91	1	The declarations of interest do not seem to be complete.	This is a complete record of all interests that the GDG members declared.
SH	Astrazeneca UK Ltd	31.04	Appendix E	General	n/a	A systematic review of literature was undertaken to identify relevant published economic evaluations (page 1 of appendix E). It is considered good practice to report the date the search was conducted, the databases used	The search strategy for economic evaluations was conducted in June 2011. This information is available in appendix D.

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						and the search strategy to enable readers to assess the appropriateness and for other researchers to use the information for further analyses. Therefore, we request that this information is added to the Appendix.	
SH	Astrazeneca UK Ltd	31.08	CUA Model	'Cost and utilities' sheet	Cell D16	As stated in Appendix F (page 11), patients receiving opioids are assumed to receive laxatives concomitantly in the model to reflect clinical practice. In the Excel-based model, the cost for laxatives (£2.10, Cell D16 on 'Costs and utilities' page) does not appear to be included in the costs calculated in the Markov traces for fentanyl or morphine. Either the text or model should be amended accordingly.	Thank you for your comment, the model will be amended to include the cost of concomitant laxatives. Note that this change is not expected to alter the conclusions of the model.
SH	Astrazeneca UK Ltd	31.07	CUA Model	'Cost and utilities' sheet	Cells F24	Under the "Health state costs and utilities" table, the last column includes monitoring costs, based on one GP visit every 4 weeks. For those patients which have terminated their opioid use ("opioids terminated" health state), which is due to the spontaneous resolution of pain, the model assumes these patients also require monitoring and therefore a cost of £8 per week has been used. However, if a patient is no longer taking opioids, is this monitoring necessary?	It is assumed that patients that have discontinued opioids would still be monitored monthly. Given the likely severity of the underlying condition that caused the pain symptoms, it is assumed that the GP would want to continue to check the patient's progress and ensure that pain symptoms haven't re-emerged.

These organisations were approached but did not respond:

Alder Hey Children's NHS Foundation Trust

Amdipharm plc

Association of Chartered Physiotherapists in Oncology and Palliative Care

Association of Paediatric Anaesthetists of Great Britain and Ireland

Barnsley Hospital NHS Foundation Trust

Basildon and Thurrock University Hospitals NHS Foundation Trust

Bowel Cancer UK

Bradford District Care Trust

Brainstrust

British Association for Nursing in Cardiovascular Care

British Liver Trust

British Medical Association

British Medical Journal

British National Formulary

British Psychological Society

Cambridge University Hospitals NHS Foundation Trust

Cambridgeshire Community Services NHS Trust

Camden Link

Camden Provider Services

Care Quality Commission (CQC)

Central South Coast Cancer Network

Cephalon UK Ltd

Cerebra

Childrens Hospices UK

Chronic Pain Policy Coalition

Citizens Commission on Human Rights

Clatterbridge Centre for Oncology

Cochrane Pain, Palliative Care and Supportive Care Group

Commission for Social Care Inspection

Community District Nurses Association

Croydon Health Services NHS Trust

Dementia UK

Department for Communities and Local Government

Department of Health, Social Services and Public Safety - Northern Ireland

Dorset Primary Care Trust

East Midlands Cancer Network

English Community Care Association

Equalities National Council

Faculty of Pain Medicine of the Royal College of Anaesthetists

Farleigh Hospice

Flynn Pharma

George Eliot Hospital NHS Trust

Gloucestershire LINk

Great Western Hospitals NHS Foundation Trust

Greater Manchester and Cheshire Cancer Network

Greater Manchester West Mental Health NHS Foundation Trust

Greater Midlands Cancer Network

Health Protection Agency

Health Quality Improvement Partnership

Healthcare Improvement Scotland

Heart of England NHS Foundation Trust

Hertfordshire Partnership NHS Trust

Humber NHS Foundation Trust

Hywel Dda Local Health Board

Inclusive Health

Institute of Biomedical Science

International Neuromodulation Society

James Whale Fund for Kidney Cancer

Jo's Trust

Lambeth Community Health

Lancashire Care NHS Foundation Trust

Leeds Teaching Hospitals NHS Trust

Lincolnshire Teaching Primary Care Trust

Liverpool Community Health

Liverpool Primary Care Trust

Lothian University Hospitals Trust

Luton and Dunstable Hospital NHS Trust

Medicines and Healthcare products Regulatory Agency

Medtronic

Ministry of Defence

National Cancer Research Institute

National Clinical Guideline Centre

National Institute for Health Research Health Technology Assessment Programme

National Public Health Service for Wales

National Radiotherapy Implementation Group

National Treatment Agency for Substance Misuse

Neonatal & Paediatric Pharmacists Group

Nester Healthcare Group Plc

NHS Clinical Knowledge Summaries

NHS Connecting for Health

NHS Direct

NHS Milton Keynes

NHS Plus

NHS Sheffield

NHS Warwickshire Primary Care Trust

NHS Worcestershire

North East London Cancer Network

North East London Community Services

Northamptonshire Primary Care Trust

Nottingham City Hospital

Paediatric Intensive Care Society

Papworth Hospital NHS Foundation Trust

Parkinson's UK

Pelvic Pain Support Network

PERIGON Healthcare Ltd

Pfizer

Pierre Fabre Ltd

Pilgrim Projects

Public Health Wales NHS Trust

Queen Elizabeth Hospital King's Lynn NHS Trust

Rainbows Childrens Hospice

Royal Berkshire NHS Foundation Trust

Royal Brompton Hospital & Harefield NHS Trust

Royal College of Anaesthetists

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 Marsden NHS Foundation Trust

Royal National Institute of Blind People

Royal Pharmaceutical Society

Sanctuary Care

Sandwell and West Birmingham Hospitals NHS Trust

Sarcoma UK

Scarborough and North Yorkshire Healthcare NHS Trust

Scottish Intercollegiate Guidelines Network

Sheffield Teaching Hospitals NHS Foundation Trust

Sickle Cell Society

Social Care Institute for Excellence

Society and College of Radiographers

Society for Acute Medicine

Society of British Neurological Surgeons

Solent Healthcare

South Asian Health Foundation

South East Coast Ambulance Service

South East Wales Cancer Network

South Staffordshire Primary Care Trust

South Western Ambulance Service NHS Foundation Trust

St Clare Hospice

St Gemma's

St Helena Hospice

St Lukes Hospice

Sutton and Merton Community Services

Thames Valley Cancer Network

The Children's Trust

The Rotherham NHS Foundation Trust

Trinity Hospice

UCL Partners

UK Renal Pharmacy Group

University Hospital Birmingham NHS Foundation Trust

University Hospitals of Leicester NHS Trust

Velindre NHS Trust

ViroPharma Ltd

Welsh Government

Welsh Scientific Advisory Committee

Western Cheshire Primary Care Trust

Western Health and Social Care Trust

Wockhardt UK Ltd

Worcestershire Acute Hospitals Trust

Wye Valley NHS Trust

York Hospitals NHS Foundation Trust