National Institute for Health and Clinical Excellence

Neutropenic Sepsis
Scope Consultation Table
7 June – 5th July 2010

Stakeholder	Order No	Section No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
Guys and St Thomas NHS Trust	1.00	4.31 Page 5 i	We are not good at educating patients about the risk of neutropenic sepsis. Although this symptom is mentioned many times, the risk does not appear to register with patients and their carers. This may be one reason patients present late with this complication. We also do not routinely monitor high risk patients.	Thank you for this information. We will take this suggestion into consideration when developing the clinical question for topic 4.3.1.i
Guys and St Thomas NHS Trust	1.01	4.31 j	Training for healthcare professionals should include how to prepare patients and carers to react if symptoms of NS occur	Until we have examined the evidence for this topic we do not know what recommendations we will be able to make
Guys and St Thomas NHS Trust	1.02	4.4 Outcomes	Should include delayed patient presentation	This is covered by 4.4.e
Royal College of General Practitioners Wales	2.00	General	There is lack of recognition that first point of contact is often Primary care or Out Of Hours service. Need to ensure standardisation of advice available to Health care professionals re management of side effects, access to specialist service.	Thank you for identifying this issue. We will consider this when setting the clinical questions for topics 4.3.1.a and 4.3.1.j of the scope
Royal College of General Practitioners Wales	2.01	General	Communication of a care plan to Primary care should be included	Thank you for identifying this issue. We will consider this when setting the clinical questions for topics 4.3.1.a and 4.3.1.j of the scope
Breast Cancer Care	4.00	3.2 c	There is also noticeable national variation on the use of (when, with which regimens, duration) of GCSF	We have added growth factors to section 3.2.c
Breast Cancer Care	4.01	4.3.1 i	Patients with breast cancer have told us that their information and support needs include understanding their risk of neutropenia (likely incidence with their	Thank you for this information. We will take this suggestion into consideration when developing the clinical question for topic 4.3.1.i

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			specific chemotherapy regimen); whether there is anything they can do to minimise this risk; which symptoms to report, when and to who; the implications for them if they develop (febrile) neutropenia, specifically with regards to delays in treatment or dose reduction which may adversely affect their prognosis	
Breast Cancer Care	4.02	4.3.1 f	We support the inclusion of primary prophylaxis as this can have a significant effect and we know that having one event of neutropenia significantly increases the chances of another event. GCSF incurs extra costs but it can reduce the risk of febrile neutropenia and hence might save significant resources (hospital stays, antibiotic use) in the longer term	Thank you for your comment.
Breast Cancer Care	4.03	4.3.1 j	It is important that training of healthcare professionals includes primary care. Patients with breast cancer tell us that their GP's are often reluctant to intervene when they report symptoms and are unlikely to instigate antibiotic cover without the input of the hospital	We are including all healthcare professionals in this topic.
Breast Cancer Care	4.04	4.3.2 e	We are disappointed about the omission of the effects of neutropenic sepsis on subsequent chemotherapy scheduling and doses. We understand that this may be difficult to apply to such a wide patient population and a breadth of treatment regimens. However general principles about the effects of delays would be valuable. Patients with breast cancer have told us that they are very concerned about the implications of developing (febrile) neutropenia, specifically with regards to delays in treatment or dose reduction which may adversely affect their prognosis	We agree that this is a very important issue but felt that it was not possible to investigate such a vast and complicated area as a single topic within the scope. Therefore it has been specifically excluded (see section 4.3.2.e) in terms of topics.
Breast Cancer Care	4.05	general	Patients with breast cancer tell us that the experience	Thank you for this information. We will take this

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			of febrile neutropenia is terrifying and can it have a significant impact on health related quality of life. Importantly, the experience can impact on their adherence with chemotherapy and may be a major factor in their choosing not to complete their full course of treatment. As neutropenia can be worse early on (commonly occurring by the 3rd chemotherapy cycles), stopping treatment will result in the potential for half the course to be omitted. This in turn impacts on treatment success rates and survival figures, so it is crucial to understand the implications for the patient beyond merely the clinical management	suggestion into consideration when developing the clinical question for topic 4.3.1.i
Breast Cancer Care	4.06	general	Patients with breast cancer tell us that the experience of neutropenia prior to developing sepsis can have a significant impact on health related quality of life. There may have experienced infections in the lungs, mouth, throat and skin. Some patients experience painful mouth ulcers, gum infections, ear infections, periodontal disease or infections of the urinary tract, colon, rectum, or reproductive tract. All of these can influence adherence and therefore there are wider implications than clinical management of the acute episode	We appreciate that there are wider toxicities than just neutropenic sepsis associated with chemotherapy, but unfortunately these are not within the remit of this guideline, so cannot be included in the scope.
Breast Cancer Care	4.07	general	Patients with breast cancer tell us that the experience of neutropenia can be broader in that other toxicities are likely to be worse in the presence of neutropenia resulting in an even greater impact on health related quality of life	We appreciate that there are wider toxicities than just neutropenic sepsis associated with chemotherapy, but unfortunately these are not within the remit of this guideline, so cannot be included in the scope.
United Clinical Pharmacy Association (UKCPA)	5.00		UKCPA welcomes the proposal for NICE guidance for the management of neutropenic sepsis. Although we recognise that the management of infectious complications due to fungal pathogens has been explicitly excluded from this consultation, we would	We agree that fungal infections are an important potentially avoidable cause of death in patients with cancer and neutropenia, particularly those who have acute leukaemia and have received high-dose chemotherapy and stem cell replacement. The

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			ask NICE to reconsider this decision, or to give urgent future consideration towards guideline development in this area, perhaps once the current process is completed. Resource implications in this area are significant involving diagnostic imaging, newer investigative techniques, and complex antifungal treatments and prophylaxis, and the ongoing controversies in therapeutic decision making affecting this area make this a key topic for consensus guidance.	diagnosis and management of fungal infection is extremely complex and resource intensive. The relative merits of diagnostic techniques (including, but not limted to, CT scans of thorax +/-sinuses, serum antigen assays, and assays of broncheoalvaolar lavage fluid) and early options of empirical or targeted treatment are a considerable part of this pathway. To adequately address fungal infection would require us to omit a large proportion of our current scope. Based on priority, guided by the NCAG/NCEPOD reports and supported by stakeholder responses, we have decided to exclude the management of non-bacterial infections from this guideline.
North London Cancer Network	7.00	General	We completely welcome this document and feel that the scope is wholly appropriate	Thank you for your comment.
Royal College of Paediatrics and Child Health	8.00	General	The College representative at the scoping workshop in Manchester understands this scope incorporates the discussions at the workshop.	Thank you for your comment.
Royal College of Paediatrics and Child Health	8.01	General	We think there needs to be more emphasis placed on the necessary communication between tertiary centre and admitting hospital.	We will consider this issue when setting the clinical question for topic 4.3.1.j
Royal College of Paediatrics and Child Health	8.02	3.2 a	We note that neutropenic sepsis does not just describe a significant inflammatory response to **bacterial** infection in a person with neutropenia, but can be bacterial, viral, fungal or mixed.	The text you refer to has now been deleted. We have amended the scope to clarify that we will be including definitions of the various terms in the guideline
Royal College of Paediatrics and Child Health	8.03	3.2 b	We think that whether the chemotherapy is given in a day-case or outpatient setting is largely irrelevant, as patients usually present with fever a week or so after chemotherapy (i.e. once they have been discharged) when their counts are at their nadir.	We feel it is important to include this sentence because it emphasises that the vast majority of anti-cancer treatments in the UK are given on a day-case, outpatient basis. We feel that the current text is explicit that patients with neutropenia will predominantly present in the community.
Royal College of Paediatrics and	8.04	3.2 d	We suggest rewording as follows: Evidence-based	We have changed "will" to "are expected to".

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Child Health			recommendations on the prevention, identification and management of this life threatening complication of cancer treatment should improve outcomes.	
Royal College of Paediatrics and Child Health	8.05	4.1.1	We think that the guideline should explicitly cover patients with cancer **and associated conditions** receiving anti-cancer treatment. Anecdotal evidence supports that many patients who do not officially have malignant conditions (e.g. Langerhans cell histiocytosis, benign brain tumours such as pilocytic astrocytoma, myelodysplastic syndromes, etc.) are treated by oncologists or haematologists with chemotherapy or bone marrow transplants as if they have a malignant condition. We think that the guideline should cover these patients.	The remit of the guideline specifically limits it to looking at neutropenic sepsis in cancer patients therefore we are not able to look at associated conditions
Royal College of Paediatrics and Child Health	8.06	4.1.1	We think that patients with aplastic anaemia, autoimmune neutropenia, drug related neutropenia and bone marrow failure could be considered as a separate group.	The remit of the guideline specifically limits it to looking at neutropenic sepsis in cancer patients therefore these groups can not be included in the scope.
Royal College of Paediatrics and Child Health	8.07	4.1.1	We think that bone marrow transplant patients could be considered as a separate group.	We acknowledge that bone marrow transplant patients could be considered as a separate group . However, as the differences in management relate largely to the management of fungal/non-bacterial infections and Graft versus Host Disease, and their primary management would be similar to that of other patients with febrile neutropenia, we have not included them as a separate group.
Royal College of Paediatrics and Child Health	8.08	4.3.1 a	We think that children should be assessed/discussed directly with treating unit rather than primary care.	We have amended the text to read "secondary/tertiary care"
Royal College of Paediatrics and Child Health	8.09	4.3.1 c	We recommend adding emergency assessment within specialist unit.	We have amended the text to read "secondary/tertiary care"
Royal College of Paediatrics and Child Health	8.10	4.3.1 d	We agree that it is very important to have agreed definitions of neutropenia and significant fever. We think that the guideline should clarify that patients	Thank you Until we have examined the evidence for this topic

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			do not necessarily have to be febrile with neutropenic sepsis and that they do not have to be neutropenic to be treated for neutropenic sepsis. If a patient's counts are non-neutropenic but on the way down, and the patient is unwell, anecdotal evidence supports that they are generally treated as if they are neutropenic.	we do not know what recommendations we will be able to make.
Royal College of Paediatrics and Child Health	8.11	4.3.1 d	Regarding routine investigations, we note that peripheral blood cultures are standard in adult practice, but that they are not universal in paediatric practice. There is a strong argument for not inflicting unnecessary pain by taking peripheral cultures if there is a central line in situ. If central cultures are positive then a decision has to be made about how likely the organisms are to be responsible for the sepsis. However, that is also the case with peripheral cultures and, depending on the technique used to take peripheral cultures, the contamination rate may be high.	Until we have examined the evidence for this topic we do not know what recommendations we will be able to make
Royal College of Paediatrics and Child Health	8.12	4.3.1 e	We recommend adding guidance on monitoring of antibiotic levels.	Until we have examined the evidence for the use of antibiotics for which levels can be routinely measured we do not know what recommendations we will be able to make
Royal College of Paediatrics and Child Health	8.13	4.3.1 e	We note that common pitfalls in the management of suspected infection are **not** addressed. These include: 1. Understanding of empiric treatment, i.e. where no source/organism is identified. Patients with infiltrate on CXR, for example, should follow pneumonia/BTS guidelines not the "empiric" neutropenic fever regimen. Significant isolates should be treated according to antimicrobial susceptibility, etc.	The potential scope of this guideline is broad and it is not possible to cover all topics within the limited development time. Therefore the topics covered by the guideline had to be prioritised. It is likely that the background to this section of the guideline will mention fungal infections as part of the differential diagnosis but their investigation and management will not be covered.

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			2. Differentiation between neutropenic fever and neutropenic sepsis with appropriate care bundles for sepsis management. 3. Definition of response to antibiotics. There is an unrealistic expectation that fever settles rapidly whereas anecdotal evidence supports that the duration in documented bacterial infection is 7-10 days. This leads to inappropriate additions and switching of antimicrobials. Markers of response should include reducing fever pattern, haemodynamic stability, normalisation of acute phase response markers.	We have expanded and slightly modified our definitions in Section 3.2a to clarify. As we want to focus the guideline on the management of neutropenic sepsis rather than the broader issue of intensive/critical care, we have not made reference to sepsis management. Until we have examined the evidence for this topic we do not know what recommendations we will be able to make
Royal College of Paediatrics and Child Health	8.14	4.3.1 e	While the treatment of fungal infection is beyond this guideline, we think that the pre-emptive therapy and necessary investigations of fungal infection need to be included. We note that the addition of empirical antifungals is common practice. Much of it is unnecessary and results in inappropriate use of resources, adverse events and drug interactions.	The potential scope of this guideline is broad and it is not possible to cover all topics within the limited development time. Therefore the topics covered by the guideline had to be prioritised. It is likely that the background to this section of the guideline will mention fungal infections as part of the differential diagnosis but their investigation and management will not be covered..
Royal College of Paediatrics and Child Health	8.15	4.3.1 f	Anecdotal evidence supports that quinolone (or septrin) prophylaxis has been found to be beneficial in certain groups, and therefore a review of the literature may well lead to a recommendation to use prophylaxis. However, we are concerned that the high resistance rates now present for quinolones would reduce any beneficial effect if the studies were performed now (the studies do not generally give	Until we have examined the evidence for this topic we do not know what recommendations we will be able to make

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			rates of background quinolone resistance, but it was likely to have been approx 5% - resistance in E. coli from blood cultures in Cardiff is now 32%). We think therefore the GDG should account for current resistance rates when judging whether prophylaxis is likely to be beneficial.	
Royal College of Paediatrics and Child Health	8.16	4.3.1 f	We think this will depend on chemotherapy protocol. See Children's Cancer and Leukaemia Group. Therapy based long term follow up, 2nd ed, April 2005. http://www.cclg.org.uk/researchandtreatment/content.php?3id=29&2id=19	Until we have examined the evidence for this topic we do not know what recommendations we will be able to make
Royal College of Paediatrics and Child Health	8.17	4.3.1 g	We would like clarification on whether this refers to line related infection? If so, we think the guideline should cover the use of line locks with antibiotics. We note the empiric use of teicoplanin/vanc if suspected but not proven coagulase-negative staphylococci infection.	Yes 4.3.1.g does cover line related infection but does not cover central line management.
Royal College of Paediatrics and Child Health	8.18	4.3.1 h	We note this may differ between adults and children.	Thank you for this comment
Royal College of Paediatrics and Child Health	8.19	4.3.1 i	We think that the information and support issues specific to patients with neutropenic sepsis and their carers or families are: • Method of checking temperature at home • Patient/parent information on significant pyrexia/signs • Appropriate contact information • Transport issues addressed in advance	Thank you for this information we will take this suggestion into consideration when developing the clinical question for topic 4.3.1.i
Royal College of Paediatrics and Child Health	8.20	4.4	We note that the effects of chemotherapy scheduling and doses with overall effects on rate of mortality from disease may be a significant outcome.	We agree that this is a very important issue but felt that it was not possible to investigate such a vast and complicated area as a single topic within the scope. Therefore it has been specifically excluded in

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				terms of topics. However we have amended section 3.1.b to acknowledge this issue
Royal College of Paediatrics and Child Health	8.21	General (GDG)	We note that medical and clinical oncologists have very little experience of treating febrile neutropenia and sepsis compared to haematologists both adult and paediatric, and paediatric oncologists, who treat patients with leukaemia and lymphoma (diseases affecting the bone marrow) and give highly myelosuppressive chemotherapy (compared to what oncologists administer), resulting in profound neutropenia. Many oncology patients (outside paediatrics) have their febrile episodes managed by general medical teams and not those that give the chemotherapy. Only in paediatrics do the children consistently get treated for their febrile neutropenia by those that actually give the chemotherapy. Why paediatric haematologists are not included in the list of people with appropriate experience other than as a paediatric haematologist/oncologist with experience at a shared care centre is difficult to understand. We would like clarification on whether this means a paediatrician working at a shared care centre who liaises with the Principal Treatment Centre (PTC). Paediatric haematologists and paediatric oncologists only work in teaching hospitals and at PTCs and not in shared care units (St Mary's Paddington being the exception). This guideline scope seems to ignore the possibility of input from experienced paediatric oncologists (unless the term medical and clinical oncologists includes paediatric oncologists) and paediatric haematologists (as only adult haematologists are	We disagree. The proportion of patients in the paediatric field who experience febrile neutropenia is higher than that within adults. However there are vastly more adults receiving anti-cancer chemotherapy. The intensity and complexity of chemotherapy in adult oncology is also increasing. Adult oncologists take the lead in managing patients with neutropenic sepsis within cancer centres in a similar way to their colleagues in paediatric haematology/oncology. We consider that expertise in paediatric haematology/oncology is essential to the development of this guideline. We expect the GDG to include four healthcare professionals with expertise in paediatric haematology/oncology.

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			mentioned) who actually deal with febrile neutropenia and sepsis on an hourly basis in PTCs.	
Royal College of Nursing	9.00	General	The Royal College of Nursing welcomes proposals to develop this guideline. It is timely and the draft scope is comprehensive and appropriate and is very relevant to clinical practice.	Thank you for your comment.
Royal College of Nursing	9.01	Page 5: 4.3.1 i)	This statement does not seem clear *'information and support for patients and carers that is*'	Thank you for your comment – 'that is' has been removed.
Royal College of Nursing	9.02	General	There is no reference to the 'Surviving Sepsis Campaign' which has been running since 2004.	While we accept that a proportion of patients will have intensive/critical care requirements, we want to focus the guideline on the management of neutropenic sepsis rather than the broader issue of intensive/critical care. Therefore we have not made reference to the 'Surviving Sepsis Campaign'
Royal College of Nursing	9.03	General	There is no reference also to the sepsis care bundle.	While we accept that a proportion of patients will have intensive/critical care requirements, we want to focus the guideline on the management of neutropenic sepsis rather than the broader issue of intensive/critical care. Therefore we have not made reference to the 'sepsis care bundle'.
Royal College of Nursing	9.04	4.3.1 j)	We expect this to be addressed under 4.3.1 j) *training of all care professionals on the identification and management of neutropenic sepsis.*	We are unsure which section you are referring to as you refer to the same section.
Royal College of Nursing	9.05	General	From reviewing the invitation for professional representatives, we welcome the fact that provision has been made for nurse representation on the group. We are however, disappointed that invitations are not being asked from any intensive care representative. This is particularly relevant as these patients are often admitted to ICU due to previous sub-optimal care in the ward environment. In addition to this, the scoping terms of reference makes frequent reference	Thank you We agree that a proportion of patients will have intensive/critical care requirements but we want to focus the guideline on the management of neutropenic sepsis rather than the broader issue of intensive/critical care. We have amended the text of section 4.3.2.d to clarify this. Because intensive/critical care is not covered by the guideline

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			to neutropenic sepsis and its relationship to Intensive Care. We would like to see the invitations be extended to include a general Intensivist and a representative from critical care outreach (nurse specialist).	we did not feel that representation on the GDG from intensive/criticial care clinicians was required.
Airedale Acute Trust/NHS foundation trust (name change)	10.00	3.2 (b) and 4.3.1 (a)	The presenting emergency whose signs and symptoms need to be recognised is neutropenic fever which may or may not proceed to neutropenic sepsis. The distinction cannot be made outside secondary care so the policy needs to be developed around the lower level of illness.	Thank you for identifying this issue. We will consider this when setting the clinical questions for topics 4.3.1.a and 4.3.1.c of the scope
Airedale Acute Trust/NHS foundation trust (name change)	10.01	4.3.1 (d)	Parallels need to be drawn with the *surviving sepsis campaign* or the *sepsis care bundle;* patients presenting within the acute care setting sometimes present as acute sepsis without the background of chemotherapy being apparent. The process should be the same whether or not neutropenia is known to be likely and the timed pathways of sepsis care should be expected to apply.	Until we have examined the evidence for this topic we do not know what recommendations we will be able to make.
Airedale Acute Trust/NHS foundation trust (name change)	10.02	4.3.1(e)	"Management of unresponsive fever (excluding fungal infection)". Notwithstanding section 4.3.2 (a), this should cover 'ruling out fungal infection'. This NICE guidance is not restricting itself to the initial management, so should include the whole process.	The potential scope of this guideline is broad and it is not possible to cover all topics within the limited development time. Therefore the topics covered by the guideline had to be prioritised. It is likely that the background to this section of the guideline will mention fungal infections as part of the differential diagnosis but their investigation and management will not be covered.
Airedale Acute Trust/NHS foundation trust (name change)	10.03	4.3.1 (h)	The continuing use of other implants may need to be considered.	Thank you for this comment
Airedale Acute Trust/NHS foundation trust (name change)	10.04	4.3.1 (i)	The first sentence is incomplete. On starting chemotherapy patients and their supporting families need education about the risks of chemotherapy among which neutropenia and risk of sepsis are	Thank you for your comment – 'that is' has been removed. Thank you for this information we will take this

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			predominant. Following an episode which has been survived, patients and carers are educated by experience. Their onward care and associated information needs depend on how the episode affects future treatment decisions.	suggestion into consideration when developing the clinical question for topic 4.3.1.i
Airedale Acute Trust/NHS foundation trust (name change)	10.05	4.3.1 (j) and general	Whilst education for patients is obligatory as in 4.3.1 (i) the lessons from NCEPOD include the fact that some patients come to attention via emergency departments or by contacting their GPs. Commissioners and some clinicians are sometimes naive about the effect of education! Neutropenic fever and sepsis may be expected in patients who are known to have received chemotherapy but the service should be as good for those who are admitted ill with sepsis that turns out to be due to chemotherapy-related neutropenia.	Thank you for your comment. We are including all healthcare professionals in this topic.
Airedale Acute Trust/NHS foundation trust (name change)	10.06	4.1.2	Given comment (6) above, the pathway of management of neutropenic fever & sepsis should be the same when chemotherapy is not the cause; subsequent haematological management will be different and therefore outside this scope but the initial pathway cannot be separated.	We appreciate that the management pathway may be the same but we are limited by the remit to focus on neutropenic sepsis in cancer patients
Society for Acute Medicine	11.00	4.3.1.	a) Signs and symptoms in people with suspected neutropenic sepsis in the community that necessitate referral to secondary care. Define swift referral pathways for patients in/from Intermediate Care settings (specifically those with beds in a community setting).	Thank you for identifying this issue. It will be considered when setting the clinical question for topic 4.3.1.a.
RCGP Wales	12.00	4.3.1.j	Training of all healthcare professionals on the identification and management of neutropenic sepsis – This is essential but needs to be focused in the community	Until we have examined the evidence for this topic we do not know what recommendations we will be able to make

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			at District Nurse, GPs and Out of Hours services..	
RCGP Wales	12.01	General	The scoping document is extensive and seems fit for purpose.	Thank you for your comment.
North Tees & Hartlepool NHS Foundation Trust	13.00	4.1.1	Patients with haematological cancers do acquire neutropenic sepsis without anticancer treatment. Should these patients not have same treatment pathway as those receiving anticancer treatment?	We appreciate that the management pathway may be the same but we are limited by the remit to focus on neutropenic sepsis in cancer patients
North Tees & Hartlepool NHS Foundation Trust	13.01	4.3.2	Patients with neutropenic sepsis may require treatment on intensive care units (critical care units?). Needs the exclusion more explicit.	We agree that a proportion of patients will have intensive/critical care requirements but we want to focus the guideline on the management of neutropenic sepsis rather than the broader issue of intensive/critical care.
Royal College of Physicians London & Association of Cancer Physicians (Dr Alan Anthoney)	14.00	4.3.2. (e)	Clinical issues that will not be covered: Effect of neutropenic sepsis on subsequent chemotherapy scheduling and doses. We are concerned that this exclusion is unrealistically strict and may lead to inappropriate guidance. Cancers that are curable using platinum-based chemotherapy (testicular cancer is the paradigm) are highly dependant on preservation of renal function to enable curative doses of drugs to be given. Many centres are still routinely using aminoglycosides in combination with penicillins as first-line therapy for febrile neutropenia (this is in spite of meta-analyses that show no benefit to this practice). The random use of aminoglycosides in neutropenic patients with testis cancer may seriously compromise their chance of cure. We believe that this issue should be within the scope	We agree that this is a very important issue but felt that it was not possible to investigate such a vast and complicated area as a single topic within the scope. Therefore it has been specifically excluded in terms of topics. However we have amended section 3.1.b to acknowledge this issue These issues are covered in 4.3.1.e. Until we have examined the evidence for this topic we do not know what recommendations we will be able to make

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			of this proposed guidance.	
LYMPHOMA ASSOCIATION	15.00	3.1.b	Another important clinical outcome of neutropaenia – and neutropaenic sepsis – is that doses of chemotherapy may need to be delayed or reduced subsequently. This results in reduction of dose intensity, which can jeopardise the success of treatment. Although life threatening side effects of treatment are clearly an issue for patients, the success of their treatment is also of paramount concern.	We agree that this is a very important issue but felt that it was not possible to investigate such a vast and complicated area as a single topic within the scope. Therefore it has been specifically excluded (see section 4.3.2.e) in terms of topics. However we have amended section 3.1.b to acknowledge this issue.
LYMPHOMA ASSOCIATION	15.01	4.3.1 b	'Education and support for patients and carers on the identification of neutropenic sepsis'. We would add: '...to include emphasis on the fact that this is a medical emergency requiring immediate hospital intervention'.	We agree this is a medical emergency (see section 3.1a, 3.2b and 3.2c) but feel it is unnecessary to re-iterate this here.
LYMPHOMA ASSOCIATION	15.02	4.3.1.i)	What in your view are the information and support issues specific to patients with neutropenic sepsis and their carers or families? We receive a lot of calls to our helpline from patients and carers who are uncertain about what to do if they start to feel unwell. It is difficult to overstate the importance of clear patient information in this context. Such episodes happen when the person is away from hospital, so it is vital that people have a clear understanding of what to be aware of and what to do. They need to know that neutopaenic sepsis is a medical emergency requiring immediate intervention. They need to know to contact the hospital, not the GP. They need to know what to do if they are away from home eg on business or holiday.	Thank you for this information. We will take this suggestion into consideration when developing the clinical question for topic 4.3.1.i

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			However, not all hospitals' A&E departments have staff who fully understand the urgency. The guidance could usefully include something about alerting other health professionals to the importance of immediate intervention, and perhaps this is something that scoping could discuss. Patients need clear information about the signs and symptoms of neutropaenic sepsis. They should know at what point in the treatment cycle they are most vulnerable, although it should be stressed that it might happen at other times too. They should be advised about taking their own temperature and shown how to do this accurately. However they also need to know that a temperature isn't always present. This can become something that patients concentrate on with the risk of overlooking other serious indications of infection. They need telephone numbers for round the clock support, seven days a week. Information should be written down, not passed on as a set of verbal instructions. It should be made accessible to carers and close family members. Particular care should be taken to identify someone to charge with this information if the patient is someone who lives alone.	
LYMPHOMA ASSOCIATION	15.03	4.3.2.e)	See comment 1 above.	We agree that this is a very important issue but felt that it was not possible to investigate such a vast and complicated area as a single topic within the scope. Therefore it has been specifically excluded in terms of topics. However we have amended section 3.1.b to acknowledge this issue

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Roche Diagnostics	16.00	4.3.1 (d)	Under appropriate initial investigations and routine investigations it is important to capture the value of new technologies, e.g. polymerase chain reaction (PCR), pre-calcitonin (PCT). This point was raised at the Scoping Workshop. One such technology is SeptiFast. The CE-marked LightCycler SeptiFast assay from Roche Diagnostics first became available in the UK in 2006. A key advantage of the test – which detects and identifies 25 different bacterial and fungal species pathogens directly from the blood sample – is its speed. Prior incubation or culture steps are not required, and a laboratory can provide a result within six hours (from sample preparation to final report). Therefore, this can allow for faster therapy with a specific antibiotic and the detection of fungal pathogens (which currently can take up to eight days to detect using blood culture). With its PCR technology, speed and high sensitivity, SeptiFast has the potential to enable early assessment of sepsis thereby affecting mortality, morbidity, hospitalisation and recurrence rates, and the time to treatment of neutropenic sepsis with appropriate antibiotics. There is good evidence to show the impact of PCR technology on diagnosis of sepsis. The danger is just limiting the scope to the traditional diagnostic techniques. This will not incentivise the incorporation of new and better technologies into routine practice. Some of the key clinical papers highlighting the usefulness and advantages of PCR technology are listed below: Varani S, Stanzani M, Paolucci M, Melchionda F, Castellani G, Nardi L, Landini MP, Baccarani M, Pession A and Sambri V. Diagnosis of bloodstream infections in immunocompromised patients by real-time PCR. *Journal of Infection* 2009; **58**: 346-351. Mancini N, Carletti S, Ghidoli N, Cichero P, Burioni R and Clementi M. The Era of Molecular and Other	Until we have examined the evidence for this topic we do not know what recommendations we will be able to make We have removed the list of examples Thank you for this information.

Stakeholder	Order No	Section No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
	16.00	4.3.1	Von Lilienfeld-Toal M, Lehmann LE, Raadts AD, Hahn-Ast C, Orlopp KS, Marklein G, Purr I, Cook G, Hoeft A, Glasmacher A and Stuber F. Utility of a Commercially Available Multiplex Real-Time PCR Assay To Detect Bacterial and Fungal Pathogens in Febrile Neutropenia. *Journal of Clinical Microbiology* 2009; **47(8)**: 2405-2410. Lehmann LE, Alvarez J, Hunfeld KP, Goglio A, Kost GJ, Louie RF, Raglio A, Regueiro B, Wissing H and Stuber F. Potential clinical utility of polymerase chain reaction in microbiological testing for sepsis. *Critical Care Medicine* 2009; **37(2)**: 3085-3090. Lamoth F, Jaton-Ogay K, Calandra T, Prodhom G, Senn L, Bille J and Marchetti O. Septifast PCR for the Microbilogical Documentation of Infections in Febrile Neutropenic Patients. *Abstracts of the 15th International Symposium on Infections in the Immunocompromised Host – International Journal of Infectious Diseases* 2008; **12(2)**: S31-S32. Mancini N, Clerici D, Diotti R, Perotti M, Ghidoli N, De Marco D, Pizzorno B, Emrich T, Burioni R, Ciceri F and Clementi M. Molecular diagnosis of sepsis in neutropenic patients with haematological malignancies. *Journal of Medical Microbiology* 2008; **57**: 601-604.	Thank you for this information.
Roche Diagnostics	16.01	4.3.2 (a)	Not including non-bacterial infection could be crucial, particularly as a good number of neutropenic sepsis cases are caused by fungal organisms. Because fungal organisms are difficult to detect they often tend to be overlooked. The new technologies have a big role to play in this area. For example, SeptiFast	We agree that fungal infections are an important potentially avoidable cause of death in patients with cancer and neutropenia, particularly those who have acute leukaemia and have received high-dose chemotherapy and stem cell replacement. The diagnosis and management of fungal infection is

Stakeholder	Order No	Section No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
			can detect the presence of fungal organisms, and therefore guide clinicians to the right treatment options. Currently, if the causative organism is thought to be fungal a whole array of expensive anti-fungal treatments are used empirically. Therefore, inclusion of prophylaxis, investigation and management of fungal infection should be included within the scope.	extremely complex and resource intensive. The relative merits of diagnostic techniques (including, but not limted to, CT scans of thorax +/-sinuses, serum antigen assays, and assays of broncheoalvaolar lavage fluid) and early options of empirical or targeted treatment are a considerable part of this pathway. To adequately address fungal infection would require us to omit a large proportion of our current scope. Based on priority, guided by the NCAG/NCEPOD reports and supported by stakeholder responses, we have decided to exclude the management of non-bacterial infections from this guideline.
Amgen UK Ltd	17.00	General	We feel it is important to define the terms neutropenic sepsis and febrile neutropenia. Neutropenic sepsis implies patients need intensive in-patient management in a high dependency or intensive care unit. Febrile neutropenia is defined in the EORTC guidelines[1] as "fever is defined as a single oral temperature of ≥38.3^{o}C or a temperature of ≥38.0^{o}C for ≥1 h. Neutropenia is defined as a neutrophil count of <500 cells/mm^{3} or <1000 cells/mm^{3}, predicted to fall below 500 cells/mm^{3}." It is important to note that these guidelines and the associated clinical issues for consideration relate to patients at risk of febrile neutropenia and not patients who are overtly septic. 1. Aapro MS, Cameron DA, Pettengell R, at al. EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphomas and solid tumours. European Journal of Cancer 42: 2433–2453	We have amended the scope to clarify that we will be including definitions of the various terms in the guideline We disagree that neutropenic sepsis implies patients need intensive in-patient management and think this would only apply for severe sepsis or septic shock.
Amgen UK Ltd	17.01	General	The remit for this guideline is the production of a	The remit from the Department of Health asked us to

Stakeholder	Order No	Section No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
			clinical guideline for the prevention and management of neutropenic sepsis in cancer patients. Whilst the appropriate management of neutropenic sepsis is critical for patient outcomes in those undergoing anti-cancer treatment, adequate and appropriate preventative measures are also equally important to ensure the risk of neutropenic sepsis is reduced in patients at greatest risk and thereby reduce the burden of management. We feel that there is currently a disproportionate focus on the management of neutropenic sepsis compared to that of prevention. This is reflected within all aspects of the current draft scope (epidemiology, current practice and clinical management). We recommend that relevant information and clinical issues for consideration for the prevention of neutropenic sepsis is reflected in these sections of the draft scope.	develop a guideline on both the prevention and management of neutropenic sepsis, therefore we have to cover both aspects. We feel that the major issues related to prevention have been covered by the topics included in the scope. However we have clarified that there is variation in the use of primary and secondary prophylaxis in section 3.2c.
Amgen UK Ltd	17.02	3.2.c	The draft scope states that "There is national variation in use of risk stratification, and also in oral/intravenous antibiotics and in/outpatient management policies." Additional to these elements associated with the management of neutropenic sepsis, we would like to iterate there is also widespread national variation with regard to prophylaxis (primary or secondary) policies for patients at risk of neutropenic sepsis during anti-cancer treatment. This national variation in appropriate prophylaxis results in disparities in neutropenic sepsis rates. These disparities in neutropenic sepsis incidences are primarily associated with either inappropriate primary or secondary prophylaxis policies or	We have now clarified that there is variation in the use of primary and secondary prophylaxis in section 3.2c.

Stakeholder	Order No	Section No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
			inappropriate timing of administration and duration of treatment with granulocyte colony stimulating factors (G-CSFs).	
Amgen UK Ltd	17.03	4.1.1.a	The draft scope states that the population of interest will include children, young adults and adults with cancer. Elderly patients (aged ≥65 years) are a population at higher-risk of neutropenic sepsis during anti-cancer treatment and therefore a distinction for this age group would be appropriate as provided for both children and young adults.	We appreciate that age may be an important factor. If the literature search reveals any evidence on the effect of age, this will be reported.
Amgen UK Ltd	17.04	4.3.1.f	Firstly, appropriately agreed definitions of primary and secondary prophylaxis should be included and adopted in the guideline to ensure that the respective strategies are clearly defined throughout the clinical guideline development. Secondly, this key clinical issue within the draft scope is structured to provide a recommendation related to the use of primary and secondary prophylaxis in people at risk of neutropenic sepsis during anti-cancer treatment. However, we would like to comment that the clinical risk assessment that informs the need for use of G-CSF prophylaxis in clinical practice is a key component that is currently absent from this proposed clinical issue. The appropriate use of (either primary or secondary) G-CSF prophylaxis should be based on the identification of the at risk patient population. Published international clinical guidelines for the use of G-CSFs describe the relevant populations with respect to anti-cancer treatment regimens and associated risk of febrile eutropenia as well as additional patient characteristics.[1,2]	Thank you for your comment. We agree. Thank you for your comment. Until we have examined the evidence for this topic we do not know what recommendations we will be able to make.

Stakeholder	Order No	Section No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
			1. Smith TJ, Khatcheressian J, Lyman GH, et al. 2006 Update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. Journal of Clinical Oncology. 24(19):3187-3205 Aapro MS, Cameron DA, Pettengell R, at al. EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile eutropenia in adult patients with lymphomas and solid tumours. European Journal of Cancer 42: 2433–2453	
Amgen UK Ltd	17.05	4.4	The current key clinical issues consider the use of antibiotics for primary and secondary prophylaxis of febrile neutropenia. The current EORTC guidelines state that "general antibiotic prophylaxis could lead to the emergence of resistance, so it is essential that a balance is achieved between potential harms and benefits to patients".[1] We recommend that the main outcomes should therefore also include the emergence of antibiotic resistance if primary or secondary prophylaxis with antibiotics are considered within this clinical guideline. Aapro MS, Cameron DA, Pettengell R, at al. EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphomas and solid tumours. European Journal of Cancer 42: 2433–2453	Thank you for this information. We will take this suggestion into consideration when developing the clinical questions for specific topics. However, we do not feel section 4.4 needs to be altered.
Chugai Pharma UK LTD	18.00	4.1.1	Lenograstim (Granocyte) The safety and efficacy of GRANOCYTE have been established in patients older than 2 years in BMT (Ref. http://www.medicines.org.uk/emc/medicine/8347/SPC/Granocyte+13+million+IU,+and+34+million+IU/#IN	Thank you for this information. This section does not make reference to interventions as this refers to groups that will be covered by the scope.

Stakeholder	Order No	Section No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
			DICATIONS	
Chugai Pharma UK LTD	18.01	4.3.1 f	There is strong and consistent evidence for the use of daily Lenograstim (rHuG-CSF) prophylaxis in order to maintain chemotherapy at the desired dose intensity and density and to minimise delays. Thatcher N, Girling DJ, Hopwood P, Sambrook RJ, Qian W, Stephens RJ. Improving survival without reducing quality of life in small-cell lung cancer patients by increasing the dose-intensity of chemotherapy with granulocyte colony-stimulating factor support results of a British Medical Research Council Multicenter Randomized Trial. Medical Research Council Lung Cancer Working Party. *J Clin Oncol* 2000;18:395–404 Gisselbrecht C, Haioun C, Lepage E, et al. Placebo-controlled phase III study of lenograstim (glycosylated recombinant human granulocyte colony-stimulating factor) in aggressive non-Hodgkin's lymphoma: factors influencing chemotherapy administration. Groupe d'Etude des Lymphomes de l'Adulte. *Leuk Lymphoma* 1997;**25**:289–300	Thank you for this information. Until we have examined the evidence for this topic we do not know what recommendations we will be able to make
Chugai Pharma UK LTD	18.02	4.3.1 f	Level III evidence from the INC-EU prospective European neutropenia study supports the use of G-CSF to reduce the incidence of FN in lymphoma and patients with breast cancer Pettengell R, Schwenkglenks M, Leonard R, et al. Neutropenia occurrence and predictors of reduced chemotherapy delivery: results from the INC-EU prospective observational European neutropenia study. *Support Care Cancer* 2008;**16**:1299–309 and confirms that patients scheduled to receive certain chemotherapy regimens obtain the most benefit from G-CSF prophylaxis. In multivariate analysis, clinically	Thank you for this information.

Stakeholder	Order No	Section No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
			relevant factors that were significantly associated with cycle 1 FN included increasing planned cyclophosphamide dose and increasing planned etoposide dose. An analysis for cycle 1 FN in 240 patients with lymphoma showed that prophylactic G-CSF was strongly protective (OR 0.18; 95% CI 0.03, 0.94; *P* = 0.042). Pettengell R, Bosly A, Szucs TD, et al. Multivariate analysis of febrile neutropenia occurrence in patients with non-Hodgkin lymphoma: data from the INC-EU Prospective Observational European Neutropenia Study. *Br J Haematol* 2009;**144**:677–85	
Chugai Pharma UK LTD	18.03	4.3.1 f	Level III evidence from a further prospective observational study in elderly patients (age ≥70 years) with lymphoma or solid tumours has also confirmed benefits of G-CSF. Shayne M, Culakova E, Poniewierski MS, et al. Dose intensity and hematologic toxicity in older cancer patients receiving and hematologic toxicity in older cancer patients receiving systemic chemotherapy. *Cancer* 2007;**110**:1611–20. In this study, primary CSF prophylaxis significantly decreased neutropenic complications, defined as the occurrence of severe or FN in cycles 1 to 4, by 64% (OR 0.36; 95% CI 0.21, 0.62; *P* = 0.0002). This study also confirmed that anthracycline or platinum-based regimens were associated with an increased risk of FN. Level IV evidence from audit data of patients with breast cancer treated with FEC-D in clinical practice demonstrated a reduction in rates of FN from 46% to 8.6% with the use of primary daily G-CSF prophylaxis, usually given from days 5 to 10. The	Thank you for this information

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			authors comment that this course may not be optimal, and further improvements may be possible with early or prolonged treatment. Gohil S, Sharma A, Harper-Wynne C. Comparison of rates of febrile neutropaenia using FEC100/Docetaxel100 chemotherapy in breast cancer patients with and without primary GCSF prophylaxis. In: National Cancer Research Institute Cancer Conference, 4–7 October, Birmingham, UK, 2009. (abstract B75).	
Chugai Pharma UK LTD	18.04	5.3.1.f	In a meta-analysis of patients with lymphoma or solid tumours across 15 randomised controlled trials (five with Lenograstim) in which the overall underlying risk of FN was 37%, the RR reduction with G-CSF was 46% (RR 0.54; 95% CI 0.43, 0.67; *P* = <0.001). Kuderer NM, Dale DC, Crawford J, Lyman GH. Impact of primary prophylaxis with granulocyte colony-stimulating factor on febrile neutropenia and mortality in adult cancer patients receiving chemotherapy: a systematic review. *J Clin Oncol* 2007;**25**:3158–67.	Thank you for this information
Chugai Pharma UK LTD	18.05	5.3.1.f	The role of daily G-CSF (Lenograstim) to reduce the incidence of febrile neutropenia in Small Cell Lung Cancer has been demonstrated Woll PJ, Hodgetts J, Lomax L, Bildet F, Cour-Chabernaud V, Thatcher N. Can cytotoxic dose-intensity be increased by using granulocyte colony-stimulating factor? A randomized controlled trial of lenograstim in small-cell lung cancer. *J Clin Oncol* 1995;**13**:652–9	Thank you for this information
Chugai Pharma UK LTD	18.06	5.3.1. f	A previous episode of febrile neutropenia predisposes to further occurrence, it is important that the risk of FN and related complications are assessed at each cycle, and where appropriate,	Thank you for this information

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			secondary prophylaxis with G-CSF is initiated. Level III evidence shows that the use of daily G-CSF as primary or secondary prophylaxis not only reduces risk of FN but also decreases the duration of those grade 4 neutropenia events which can occur despite prophylaxis. Crawford J, Glaspy JA, Stoller RG, et al. Final results of a placebo-controlled study of filgrastim in small-cell lung cancer: exploration of risk factors for febrile neutropenia. *Support Cancer Ther* 2005;**3**:36–46	
Chugai Pharma UK LTD	18.07	4.3.1 f	Within the NCCN Guidelines for myeloid growth factors secondary prophylaxis with CSFs is recommended for patients who experienced a neutropenic complication from a prior cycle of chemotherapy (for which primary prophylaxis was not received), in which a reduced dose may compromise disease-free or overall survival or treatment outcome. In many clinical situations, dose reduction or delay may be a reasonable alternative http://www.nccn.org/professionals/physician_gls/PDF/myeloid_growth.pdf	Thank you for this information
Chugai Pharma UK LTD	18.08	4.3.1 f	Daily G-CSF (Lenograstim) has demonstrated efficacy and safety to reduce the impact of chemotherapy induced neutropenia in the paediatric setting in lymphoma and sarcoma http://www.ncbi.nlm.nih.gov/pubmed/11786572 http://www.ncbi.nlm.nih.gov/pubmed/19148579	Thank you for this information
Chugai Pharma UK LTD	18.09	4.4 a	Daily G-CSF (e.g. Lenograstim) has been demonstrated to reduce mortality rates following a variety of chemotherapy combinations. Kuderer NM, Dale DC, Crawford J, Lyman GH. Impact of primary prophylaxis with granulocyte colony-stimulating factor on febrile neutropenia and mortality in adult cancer patients receiving	Thank you for this information.

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			chemotherapy: a systematic review. *J Clin Oncol* 2007; **25**:3158–67.	
Chugai Pharma UK LTD	18.10	4.4 c	Hospitalisation rates and length of hospital stay has been demonstrated to be reduced following daily Lenograstim (rHuG-CSF). Lenograstim-treated patients had fewer days of infection, and of antibiotic administration, and also spent less time in hospital. http://www.ncbi.nlm.nih.gov/pubmed/7510813	Thank you for this information.
Chugai Pharma UK LTD	18.11	4.5	Using Synovate data it has been shown that the average number of dayspatients in the UK require Lenograstim support is 5.07 (NHL), 4.36 (breast), 3.4 (lung), 8 (AML), 4 (CLL) Synovate Oncology Monitor June 2008 – May 2009. *Total UK Cancer Patients Body Surface Area and Weight (kg)*	Thank you for this information.
Chugai Pharma UK LTD	18.12	4.5	In a study undertaken by the BENEFIT study group the use of Lenograstim to prevent CIN in patients with NHL was associated with a reduction in total direct medical costs as a result of reduced patient morbidity. http://www.ncbi.nlm.nih.gov/sites/pubmed	Thank you for this information.
Hospira UK Ltd	19.00	General	Febrile neutropenia (FN) predisposes cancer patients to serious and potentially life-threatening infections and can lead to a decision to reduce or delay subsequent chemotherapy doses, with implications for treatment efficacy. Hospira believes FN rather than neutropenic sepsis should be the primary focus of the guideline, particularly as sepsis is unlikely to be confirmed at the time of presentation when treatment may be initiated. Similarly, the decision to use prophylactic interventions, including granulocyte-colony stimulating factors (G-CSFs) is typically based on the risk of development of FN, rather than neutropenic sepsis.	We have amended the scope to clarify that we will be including definitions of the various terms in the guideline The remit from the Department of Health asked us to develop a guideline on both the prevention and management of neutropenic sepsis, therefore we have to cover both aspects.

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Hospira UK Ltd	19.01	4.3.1	Patient-related and treatment regimen-related risk factors for development of chemotherapy-induced neutropenia should be included in the scope to ensure appropriate patients receive G-CSF prophylaxis. These are defined in international evidence-based practice guidelines for G-CSF from Europe (ESMO, EORTC) and the United States (ASCO, NCCN), and include older age (≥65 years), advanced stage of disease, previous episodes of febrile neutropenia and lack of prior G-CSF use.	These factors will be considered when setting the clinical question for topic 4.3.1.f
Hospira UK Ltd	19.02	4.3.1	Prophylactic antibiotics are not necessary for all patients and risk factors for their use should be included in the scope. The EORTC Infectious disease group strongly suggest that caution be used as general antibiotic prophylaxis could lead to the emergence of resistance; it is essential that a balance is achieved between potential harms and benefits to patients. US NCCN guidelines on the prevention and treatment of cancer-related infections recommend prophylactic fluoroquinolones for high-risk and intermediate-risk groups. For most solid tumours undergoing standard outpatient chemotherapy, in which the anticipated duration of neutropenia is <7 days, prophylactic fluoroquinolones are not recommended due to the risk of microbial resistance.	Until we have examined the evidence for this topic we do not know what recommendations we will be able to make
Hospira UK Ltd	19.03	4.3.2	The effect of febrile neutropenia on subsequent chemotherapy scheduling and dosing should be considered as part of the guideline scope as this is a major neutropenic complication which can compromise cancer treatment outcome. Such treatment modifications are a particular concern when chemotherapy is given with curative intent. Evidence from studies in breast cancer patients,	We agree that this is a very important issue but felt that it was not possible to investigate such a vast and complicated area as a single topic within the scope. Therefore it has been specifically excluded in terms of topics. However we have amended section 3.1.b to acknowledge this issue

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			particularly in the adjuvant setting, indicates that reductions in chemotherapy dose intensity may negatively affect survival.	
Hospira UK Ltd	19.04	4.4	Main outcomes should also include the duration of neutropenia as this determines a patient's ability to receive anticancer treatment according to the prescribed course. Extended duration of neutropenia can lead to increased length of hospitalisation and dose delay which may compromise treatment outcome and lead to increased treatment costs.	Duration of neutropenia alone, if important, will be observed as variation in outcomes a, b, c and therefore we do not feel it needs to be included separately.
Association of Cancer Physicians	20.00	3.1 (b)	This paragraph is fairly meaningless. It should talk about the possible consequences of *infection in a neutropenic person* (as neutropenic fever and neutropenic sepsis already have connotations of different levels of severity) and might better illustrate this in an ascending fashion. That is - no adverse effect; localised or systemic bacterial infection requiring ward based support; multi-system impairment requiring intensive (e.g. ITU) support; death.	We have amended the text to refer to "The consequences of an episode of infection in a neutropenic person". We do not feel that changing the order of adverse effects is necessary.
Association of Cancer Physicians	20.01	3.2 (a)	Last two sentences of this paragraph should be in the previous section 3.1 as they are descriptive of neutropenic sepsis and fever. This section may also want to mention that the risk and likelihood of neutropenia varies widely with the type of chemotherapy given. May also mention that the risk of neutropenic infection is greater the longer the period of neutropenia.	The text you refer to has now been deleted. We have amended the scope to clarify that we will be including definitions of the various terms in the guideline
Association of Cancer Physicians	20.02	3.2 (b) 1st sentenc e	Even chemotherapy given as an in-patients over a few days give rise to neutropenia when the patient is back in the community. Should this not just say that the great majority of cases of neutropenic fever and sepsis will arise when patients are in the community and not in hospital.	We disagree., We feel that the current text is explicit that patients with neutropenia will predominantly present in the community.

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Association of Cancer Physicians	20.03	4.1.1 (a)	Sorry for pendantry but why not just say " Patients of all ages with cancer ". As currently written "young people" is meaningless and you could equally say "elderly people" who are also a group with individual and specific needs.	Current NICE guidance refers to children and young people with cancer and our terminology is consistent with this.
Association of Cancer Physicians	20.04	4.3.1 (a)	Although no sub-groups requiring special consideration have been defined (4.1.1 b) it may be that the presentation of neutropenic sepsis will differ between age groups and require different advice. This section needs also to indicate that the timing of symptoms in relationship to treatment needs to be considered and may differ depending on the anti-cancer therapy (chemotherapy regimen) involved.	We appreciate that age intensity and time since chemotherapy may be important factors. If the literature search reveals any evidence on the effect of these, this will be reported. However we do not feel it is necessary to specify them in the topic.
Association of Cancer Physicians	20.05	4.3.1 (b)	? Should also include education and support for medical and nursing staff in primary care and the community.	We felt this issue was so important that we have made it a separate topic (see 4.3.1.j)
Association of Cancer Physicians	20.06	4.3.1.(d)	Should just mention routine investigations and not start pre-empting the decisions on which ones are required e.g. there is some evidence that routine chest X-ray is not always required in a neutropenic febrile patient.	We have removed the examples.
Association of Cancer Physicians	20.07	4.3.1 (e)	Not quite sure what is meant by "(excluding fungal infection)" under the section on Management of Unresponsive Fever. I assume it means guidance on searching for non-bacterial causes of fever.	We have deleted this text
Association of Cancer Physicians	20.08	4.3.1 (i)	This section is really the same as 4.3.1(a). Most patients and carers should / will be given verbal and written information on the fact that there is a risk of infection happening and that if neutropenic it can be life threatening. However, as the early manifestations of sepsis can be non-specific instilling into the patients a low-threshold for contacting their hospital team will be required. One common problem is when patients get admitted to their local hospital (not their	Thank you for this information. We will take this suggestion into consideration when developing the clinical question for topic 4.3.1.i

Stakeholder	Order No	Section No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
			treating hospital) and for whatever reason the local hospital do not contact the treating team to inform (or for information). Giving patients or carers guidance on when this might be appropriate and the permission to do it themselves if the local hospital team have not might be useful. Ideas on information in formats other than paper based ones would also be useful. In this day and age it should be considered that information for patients in a visual form (CD; on a web page etc) might be more helpful in putting across important messages.	
Association of Cancer Physicians	20.09	4.3.2 (a)	Is it not a bit short-sighted for these guidelines not to include some information on management of non-bacterial infections in the neutropenic person? In the first instance it will not be known that it is not a bacterial infection initially and only by a matter on exclusion will it become more obvious that it may be a fungaemia or viraemia. IN these circumstances there should be some guidance on the further management of such patients even in directing further investigations and other resources for their management.	We agree that fungal infections are an important potentially avoidable cause of death in patients with cancer and neutropenia, particularly those who have acute leukaemia and have received high-dose chemotherapy and stem cell replacement. The diagnosis and management of fungal infection is extremely complex and resource intensive. The relative merits of diagnostic techniques (including, but not limted to, CT scans of thorax +/-sinuses, serum antigen assays, and assays of broncheoalvaolar lavage fluid) and early options of empirical or targeted treatment are a considerable part of this pathway. To adequately address fungal infection would require us to omit a large proportion of our current scope. Based on priority, guided by the NCAG/NCEPOD reports and supported by stakeholder responses, we have decided to exclude the management of non-bacterial infections from this guideline. It is likely that the guideline will include fungal infection in the differential diagnosis of unresponsive fever but will not address its investigation or management.
Association of Cancer Physicians	20.10	4.4 (a),	How are these to be defined? For example a patient	The definitions for these may vary between different

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		(b), (c), (d)	may be admitted with neutropenic fever as one component of a number of complications of anti-cancer therapy. The neutropenia and sepsis may resolve but the patient develop morbidity or die from another complication (essentially unrelated to the neutropenic fever). With recurrence rate - if this is to be used to determine the effectiveness of measures to reduce repeated episodes of neutropenic fever/sepsis then it has to be considered that modification of the patients subsequent chemotherapy regimen / intensity is the predominant method used (particularly in patients treated with palliative intent).	topics. Therefore the GDG will give more precise definitions when they agree the clinical questions.

Organisations who did not respond:

Alder Hey Children's NHS Foundation Trust
Association for Clinical Biochemistry
Association of Chartered Physiotherapists in Oncology and Palliative Care
AstraZeneca UK Ltd
BMJ
Breakthrough Breast Cancer
British National Formulary (BNF)
British Nuclear Medicine Society
British Society for Haematology
British Thoracic Society
Cambridge University Hospitals NHS Foundation Trust (Addenbrookes)
Cancer Network Pharmacists Forum
Cancer Research UK
Care Quality Commission (CQC)
Central South Coast Cancer Network
Commission for Social Care Inspection
Connecting for Health

Department for Communities and Local Government
Department of Health
Department of Health Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infection (ARHAI)
Dorset Cancer Network
East Lancashire Hospitals NHS Trust
East Midlands Cancer Network
Gilead Sciences Ltd
Gloucestershire Hospitals NHS Trust
Greater midlands cancer network
Insitute of Biomedical Science
Intensive Care Society
Intensive Care Society
Jos Trust
Kidney Research UK
Leukaemia & Lymphoma Research
Leukaemia CARE
Luton & Dunstable Hospital NHS Foundation Trust
Macmillan Cancer Support
Maidstone and Tunbridge Wells NHS Trust
Medicines and Healthcare Products Regulatory Agency (MHRA)
Medway NHS Trust
Ministry of Defence (MoD)
Myeloma UK
National Lung Cancer Forum for Nurses
National Patient Safety Agency (NPSA)
National Public Health Service for Wales
National Treatment Agency for Substance Misuse
NETSCC, Health Technology Assessment
NHS Direct
NHS Plus
NHS Quality Improvement Scotland
NHS Sheffield
NHS Western Cheshire
North Cumbria Acute Hospitals NHS Trust
North East London Cancer Network

North West London Cancer Network
Northern Ireland Cancer Network
Paediatric Intensive Care Society
PERIGON Healthcare Ltd
Pfizer Limited
Poole and Bournemouth PCT
Royal College of Anaesthetists
Royal College of General Practitioners Wales
Royal College of Obstetricians and Gynaecologists
Royal College of Pathologists
Royal college of Pathologists - lay advisory committee
Royal College of Radiologists
Royal Marsden Hospital NHS Trust
Royal Society of Medicine
Royal United Hospital Bath NHS Trust
Scottish Intercollegiate Guidelines Network (SIGN)
Sheffield Teaching Hospitals NHS Foundation Trust
Social Care Institute for Excellence (SCIE)
Social Exclusion Task Force
South Tees Hospitals NHS Trust
Southampton University Hospitals NHS Trust
Teenage Cancer Trust
Teenagers and Young Adults with Cancer (TYAC)
United Kingdom Chemotherapy Redesign Group
United Kingdom Oncology Nursing Society (UKONS)
Welsh Assembly Government
Welsh Scientific Advisory Committee (WSAC)
Western Health and Social Care Trust
Whipps Cross University Hospital NHS Trust
Wirral University Teaching Hospital NHS Foundation Trust
York NHS Foundation Trust